Pathology

Pathology

From the Tissue Level to Clinical Manifestations and Inter-professional Care

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Introduction

JENNIFER KONG

Welcome to this ever-evolving learning **Pathology** resource for students and learners interested in and/or involved in Health Care Professions and Health Care Professional programs.

The goals of this resource are to:

- explain the pathology underlying a selection of common **diseases**,
- link the **clinical manifestations** to the pathology
- introduce interprofessional collaboration between health professionals that are involved in a patient's diagnosis and treatment.

This resource is a result of a collaboration between British Columbia Institute of Technology (BCIT), and the University of British Columbia on both the Vancouver and Okanagan campuses (UBC-V and UBC-O, respectively). We gratefully acknowledge the financial support for this project provided by the BCIT Open Education Grant, UBC-V OER Fund, UBC-O Aspire 2040 Learning Transformations (ALT2040) Grant, and the UBC-O Irving K. Barber Faculty of Science Curricular and Teaching Innovation Grant (CTIG).

Do I need to pay for this online text?

NO!! This resource is part of Open Education, thus making it available to everyone for free.

How was this resource funded and created?

The authors were awarded funding by BCIT, UBC-V Open Education groups, UBC-O Provost's Office and the UBC-O Irving K. Barber Faculty of Science to prepare this resource. This funding made videorecording and editing possible by BCIT Video & Digital Media producer Ian Whittlesey. As well, this funding also allowed students from UBC-V and UBC-O to contribute to this resource (see Authors and Contributors at the back of this resource). Some UBC-V students also volunteered to contribute, out of a passion for pathology & education.

Do I require a lot of prior medical knowledge to understand the information in this book?

No. You can think about this resource as a beginner's guide to a disease. Each section on a disease starts with going over the normal structure and function of an organ and then what changes occur with a particular disease. We demonstrate the changes at the structural gross (macroscopic), and microscopic levels, and functional levels. We then bring in various health professionals to talk about how they participate in either diagnosing or treating patients with a particular disease.

How will I know what I am looking at?

We have provided videos with descriptions pointing out what you are to look for. The examples used in this book often show severe instances of a disease as in these cases the changes are obvious enough for everyone to see and appreciate.

What if I come across a term I don't understand?

Terms that are bolded in red lettering are defined in the glossary. You can hover over one of these terms and the definition will pop-up below the word or term.

It seems like there would be a lot information presented. How do I know what is important? How will I know if I am actually learning anything?

Each chapter has a section outlining the key points you should learn and interactive exercises to reflect on what you are learning. Each Chapter also has a quiz at the end where you can test your knowledge.

There are a lot of videos in this resource. Why is that?

A lot of pathology is describing the changes in appearance of an organ brought about by a disease process. It is easier to point out how to look for these changes using a moving image than a still one.

I found that I wanted to learn more about a disease. Where can I find more information?

Each Disease section has links to other resources that are available under "Further Reading". This resource isn't meant to be an in-depth examination of a disease but to highlight the main features of a disease and its impact on the function of an organ and how that will affect the person with a disease.

Where are the specimens from? Can I explore more on my own?

All pathology specimens shown are from the David Hardwick Pathology Learning Centre (DHPLC) within the Department of Pathology and Laboratory Medicine at UBC. Further exploration of the DHPLC (either virtually or in-person) can be accessed through https://pathology.ubc.ca/dhplc/



DHPLC- *UBC's David Hardwick Pathology Learning Centre at Vancouver General Hospital*

Please contact the manager of DHPLC at dhplc.info@ubc.ca to arrange for an in-person tour or access to the virtual collection.

Media Attributions

- DHPLC

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Every single specimen at the David Hardwick Pathology Learning Centre (DHPLC) has been donated from a patient (or their family) for the sole purpose of education. It was their (and our) hope that these specimens will educate current and future health-care providers in disease – from the tissue level, to what can be seen clinically. We thank each donor for their generosity.

We ask the reader to please honour and respect the people behind these specimens and to use their images appropriately. For licensing information about the DHPLC images, go the Licensing Information page.

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Adaptions

Several Open Education resources were adapted and included in this resource. Where indicated, these resources are in their original format or an abbreviated version. The following resources are used and noted at the appropriate part of the text in the adaption statement at the bottom of the page.

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Using this Resource

JENNIFER KONG

Bridging the Gap Between Normal Anatomy and Physiology and Clinical Education

This multimedia resource is intended to 'bridge the gap' between normal anatomy and physiology (A&P) and clinically-oriented resources. Thus, this resource requires a basic understanding of normal A&P that is taught at the post-secondary level. Where possible, this resource includes links to the Open education resource, Anatomy and Physiology by JG Betts *et al*, should the reader need a refresher on A&P before learning about pathology.

Similarly, this resource is intended to provide the science behind the disease a health care professional is managing. When appropriate, this resource mentions clinical skills associated with the assessment, management and treatment of the disease and relating to why these clinical skills work. To correlate the clinical skills mentioned in this resource, the authors have tried to include relevant links to the open educational resource Clinical Procedures for Safer Patient Care by GR Doyle & JA McCutcheon.

When working with people who have diseases it is important to discuss the required and recommended communication strategies and supportive relationships: between patient and provider, provider & family, and patient and family. This resource was created to provide the science behind the well-written stories in Health Case Studies by G Rees, R Kruger, & J Morrison.

Working with patients while on their health journey is a team affair, and this resource highlights the interprofessional collaboration that occurs between health care providers. As in real life, this resource includes contributions from many health care disciplines and how they interact with other care providers. Thus, this resource is intended for multidisciplinary studies in the health care field. For more information on BCIT & UBC's mandate on interprofessional education, please visit both BCIT interprofessional collaboration education & UBC interprofessional education & collaborative practice.

Self-Directed Lesson Format

This resource can be read in any order desired. With the exception of the Preface and Conclusion sections, each lesson contains:

- a pre-test at the start of each disease
- an introduction to the A&P involved
- discussion on the pathological process involved
- video lesson on describing the differences between normal health and pathological tissues
    - where appropriate, the catalogue number of the DHPLC pathology specimen will be provided for the reader to view in greater magnification in the DHPLC virtual collection.
- a written or video lesson from Dr. Jennifer Kong & Helen Dyck teaching pathology from the tissue level to physiological changes to clinical manifestations
- interviews with health care providers with their clinical experience with patients with this pathology
- a post-test at the end of each pathology

As a Template for Course Development or Use within an Existing Course

This resource is intended for instructors to use at any level or specialization of teaching human health and disease. This resource can be used as a template to designing lessons from either perspective of clinical manifestations link to the underlying cellular cause. This resource focusses on explaining the rationale behind each sign and symptom from the level of tissues.: thus it may be useful to any branch of health science to adapt for their own purpose, whether it be a professional program (e.g. medical radiography) or a theoretical base (e.g. 1st-year biology).

Finally, interprofessional collaboration is a reality in clinical life and there is a need to introduce it in the classroom before students enter their clinical education. This resource strives to bring in voices from as many health care professions as possible to highlight the myriad of health care professionals a patient will encounter in their health journey. Thus, this resource – in conjunction with the aforementioned Open Ed Resource Health Case Studies – will be beneficial to interprofessional education.

Instructional Guide

An accompanying instructor guide for this textbook is under development. The guide will be made available here upon completion.

Abbreviations

MEIHUA E. SU

The following abbreviations are used throughout the text.

A&P	Anatomy and Physiology
AAT	Alpha-1-Antitrypsin
ACTH	Adrenocorticotropic Hormone
ADH	Antidiuretic Hormone
AKI	Acute Kidney Injury
ANS	Autonomic Nervous System
ATN	Acute Tubular Necrosis
BMI	Body Mass Index
BPH	Benign Prostatic Hypertrophy
CBC	Complete Blood Count
CCT	Certified Cardiographic Technician
CDK	Cyclin-Dependent Kinase
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	SARS-CoV-2 Virus
CPAP	Continuous Positive Airway Pressure
CPR	Cardiopulmonary Resuscitation
CRAT	Certified Rhythm Analysis Technician
CRP	C-Reactive Protein
CT	Computed Tomography
CVD	Cardiovascular Disease
DCT	Distal Convoluted Tubule
DHPLC	David F. Hardwick Pathology Learning Centre at UBC (VGH Site)
DKA	Diabetic Ketoacidosis
DRG	Dorsal Respiratory Group
EKG	Electrocardiogram
ERV	Expiratory Reserve Volume
ESR	Erythrocyte Sedimentation Rate
FACC	Fellow Of The American College Of Cardiology
FEV1	Forced Expiratory Volume In 1 Second
FRC	Functional Residual Capacity
G1	Gap 1 Phase
G2	Gap 2 Phase
GFR	Glomerular Filtration Rate
H&E	Hematoxylin and Eosin
HDL	High-Density Lipoprotein
hESCs	Human Embryonic Stem Cells
Hib	Haemophilus Influenzae Type B
HPIV	Human Parainfluenza Virus
HRVC	Human Rhinovirus C

IC	Inspiratory Capacity
IDL	Intermediate-Density Lipoproteins
IFN- γ	Interferon-γ
IgA	Immunoglobulin A
IL-1	Interleukin-1
INR	Placeholder
iPSCs	Induced Pluripotent Stem Cells
IRV	Inspiratory Reserve Volume
IVC	Inferior Vena Cava(e)
IVC	Placeholder
LA	Left Atrium
LAD	Left Anterior Descending Artery
LDL	Low-Density Lipoprotein
LFTs	Liver Function Tests
LoH	Loop of Henle
LPS	Lipopolysaccharide
LV	Left Ventricle
MAP	Mean Arterial Pressure
MI	Myocardial Infarction
MSH	Melanocyte-Stimulating Hormone
NFP	Net Filtration Pressure
oxLDL	Oxidized Ldl
P_{alv}	Intra-Alveolar Pressure
P_{atm}	Atmospheric Pressure
PCT	Proximal Convoluted Tubule
PCV13	Pneumococcal Conjugate Vaccine
PGE_2	Prostaglandin E_2
P_{ip}	Intrapleural Pressure
PP	Pancreatic Polypeptide
PRG	Pontine Respiratory Group
PRRs	Pattern Recognition Receptor
PTT	Placeholder
RA	Right Atrium
RAAS	Renin-Angiotensin-Aldosterone
RCCS	Registered Congenital Cardiac Sonographer
RCES	Registered Cardiac Electrophysiology Specialist
RCIS	Registered Cardiovascular Invasive Specialist
RCS	Registered Cardiac Sonographer
RPhS	Registered Phlebology Sonographer
RSV	Respiratory Synyctial Virus
RV	Residual Volume

RV	Right Ventricle
RVS	Registered Vascular Specialist
S phase	Synthesis Phase
STEMI	ST-Elevated MI
SVC	Placeholder
SVC	Superior Vena Cava
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TLC	Total Lung Capacity
TMAO	Trimethylamine N-Oxide
TNF	Tumour Necrosis Factor
TV	Tidal Volume
UBC	University of British Columbia
UTIs	Urinary Tract Infections
UV	Ultraviolet
VC	Vital Capacity
VLDL	Very Low-Density Lipoproteins
VRG	Ventral Respiratory Group
VSMCs	Vascular Smooth Muscle Cells
WSS	Wall Shear Stress

PREFACE

Preface Overview

Learning Objectives

By the end of this chapter, you will be able to:

- Define the terms: pathology, pathophysiology, and pathologist.
- Find more specimens similar to those presented in this textbook.
- Describe, at a basic level, how specimens are obtained and prepared for examination.
- Describe the different characteristics examined during specimen analysis.
- Identify and describe the basic characteristics of epithelial tissue.
- Describe the various forms epithelial cells.
- Identify epithelial cells under the microscope.

This part of the book has information that is helpful to know before you delve into the Disease Chapters that follow.

Abbreviations

The following abbreviations are used throughout the chapter.

DHPLC	David Hardwick Pathology Learning Centre
H&E	Hematoxylin and Eosin
UBC	University of British Columbia

What Is Pathology, Pathophysiology, and a Pathologist?

HELEN DYCK AND JENNIFER KONG

Learning Objectives

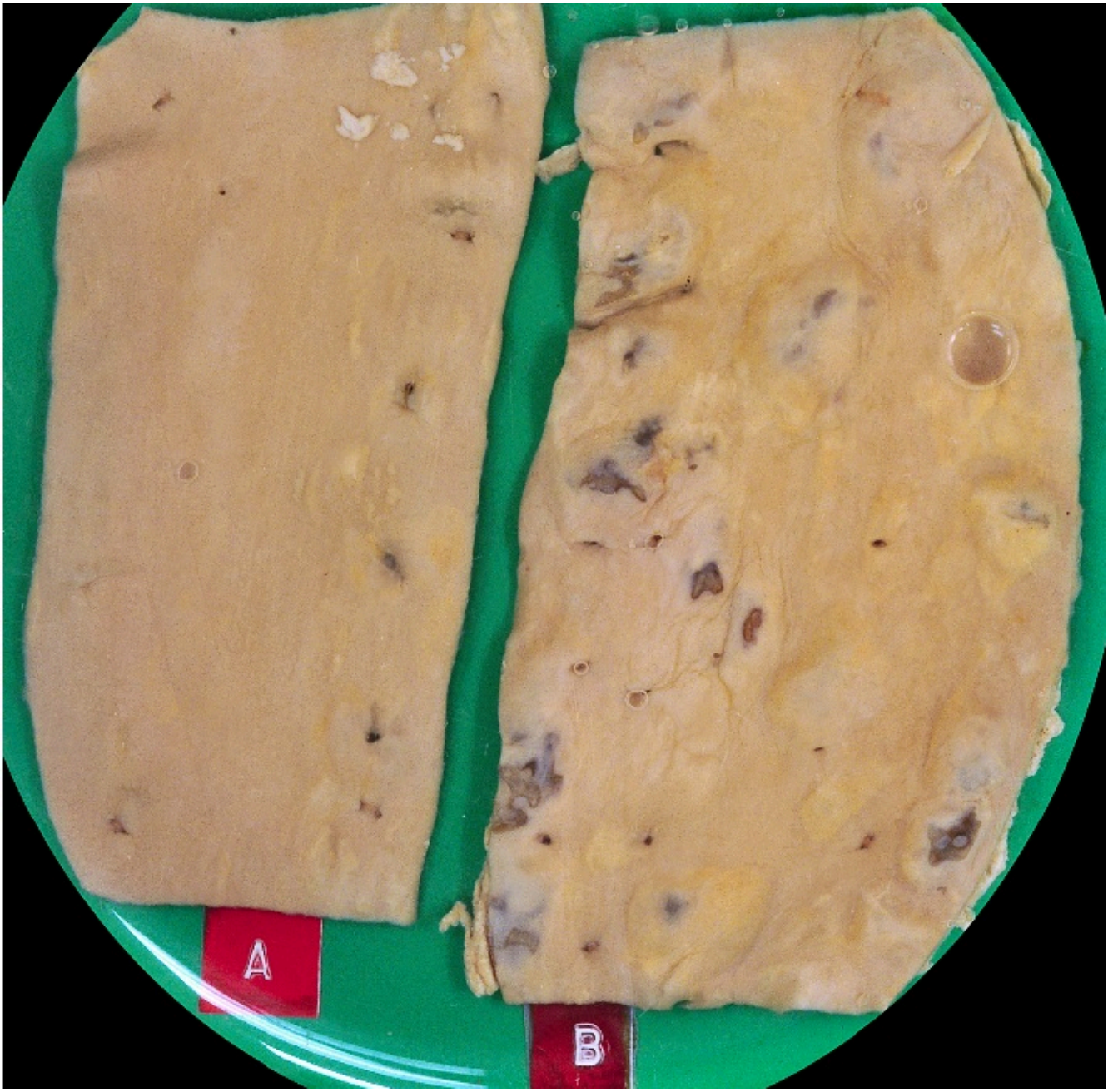
By the end of this section you will be able to:

- Define and differentiate disease, pathology, and pathophysiology.
- Briefly describe how a primary care provider collaborates with various health care professionals to determine the cause of a disease.

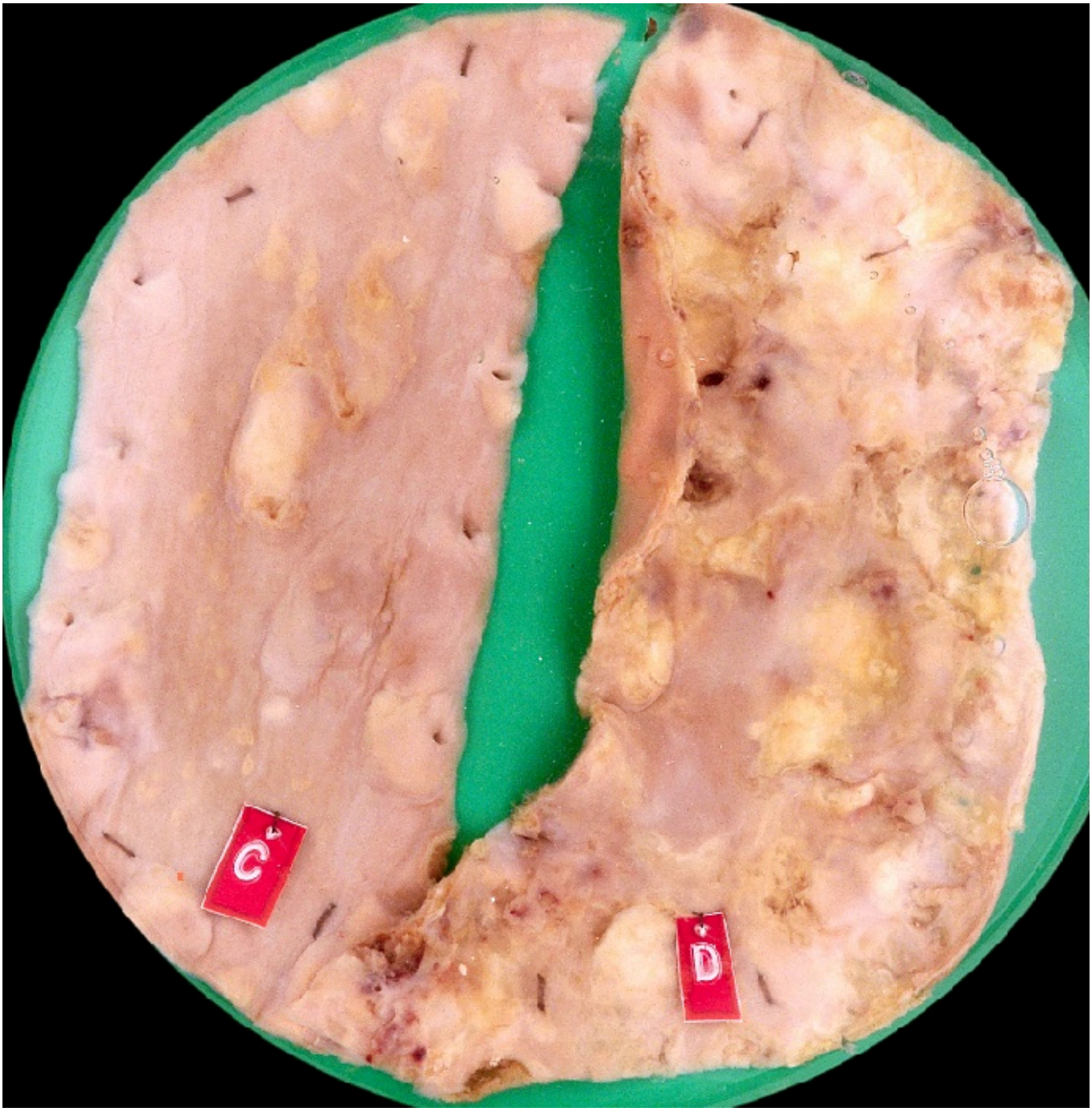
All organisms, composed of cells, tissues, and organs, undergo changes in response to environmental or genetic signals. Some of these changes are beneficial to an organism, such as when muscles enlarge due to increased workload, or when a callus forms to protect against constant rubbing. But what happens when the changes are not beneficial, and instead impair the structure or function of a part of or the whole organism? These abnormal changes are grouped by their associated signs and symptoms and are defined as a **disease** when they are not caused by a direct external injury.

Pathology is the study of abnormal changes in cells, tissues and organs that negatively affect their structure or function. These studies involve recognizing and identifying abnormal changes, trying to determine their underlying causes and describing their potential effects. Because of this, **pathologists** play an important role in the identification of disease processes and the confirmation of disease.

Changes can occur at the macroscopic or gross level, which means you can see the changes with your eyes, or they can happen at the microscopic level, which means you need a light microscope or an electron microscope to see the changes. **Histopathology** is the study of tissues to identify changes at the cellular or microscopic level.



DHPLC Specimen C0327 – *Pathological changes at the gross level – Aorta: progression of atherosclerosis*



DHPLC Specimen C0333 *– Pathological changes at the gross level – Aorta: progression of atherosclerosis*

DHPLC E-slide PATH 425-175 *– Pathological changes at the microscopic level – Cervical Cancer***Physiology** is the study of the function of cells, tissues ,and organs and so **pathophysiology** looks at the detrimental changes in these functions. Impaired function can have a big impact on overall quality of life, and it is often these changes that lead us to go see a doctor to find out what is wrong.

An Example From Everyday Life

Let's use the analogy of a bicycle to illustrate these terms.

A bicycle is made of many parts: wheels, chain, gears, seat, etc. However, for a bike to function properly, every single part has to be made properly and work in cooperation with the other parts.



Normal bicycle

Imagine one day you went to ride your bike, but it wouldn't move. You phone up your bike doctor and say, "My bike won't move. Can you fix it?" You are describing a symptom affecting your bike that relates to a loss of function (pathophysiology).

The bike doctor might ask, "Can you turn the pedals?" This question helps narrow down the reasons for the malfunction. The options are: the pedals function normally (they turn with a bit of resistance), the pedals turn too easily, or the pedals don't turn at all.

If the pedals turn too easily, it usually indicates a problem with the chain or the gears not being engaged. If the pedals don't turn at all, it might indicate a problem with the brakes or something impeding the wheel.

You check the bike, and the pedals do turn. You relay that information to your bike doctor. They ask you to take a picture of the bike and send it to them so that they can see what is going on for visual assessment. This is the equivalent to your doctor sending you for x-ray or ultrasound imaging to see if the pictures will shed light on the problem.

You send the following image:



Broken bike

You don't have to know much about bikes to recognize that the front wheel is bent. This bent wheel represents the underlying pathology for the disease this bike has. The fact that the bike won't go and yet the pedals can turn are the changes in function or the pathophysiology of this bike disease. The treatment would involve getting a new wheel. If only we could replace our broken parts so easily!

When Are Other Health Professionals Brought In?

Some types of pathology are unique or obvious enough that your primary care provider (your family doctor, nurse-practitioner, ER doctor) is able to recognize what is going on without involving other health care providers. More commonly, however, as with pedals that won't turn, there might be more than one underlying cause. A primary care provider will take your presenting signs and symptoms, and compare them to those of known diseases. They will then collect more information through visual observation (changes in appearance, colour); through palpation (for difference in size, position, and pain indicators); auscultation (listening with a stethoscope for changes in sounds) and simple measurements such as temperature, blood pressure, pulse, and oxygen saturation. These will give them more information to determine what other health professionals Careers in Health Care in BC need to be involved to identify the underlying disease process, or pathology, or if the changes are just a normal variation.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=409#h5p-36

How Does Pathology Fit into a Visit to the Doctor by Jennifer Kong, Adrian Marcuzzi, & Theo Lam, licensed under All Rights Reserved

A Clinical Example

Let's say you go to the doctor because you are more thirsty than normal and urinating much more frequently than normal. The signs and symptoms you are presenting with are of an increase in thirst and urination. An increase in thirst is a symptom because it is subjective while an increase in urination can be a sign because you can objectively measure an increase in volume or urine or the number of times you need to urinate in a day (or night). Of the three most common causes of increased thirst and urination, one is a medical emergency (potentially fatal if not treated right away); one needs you to see a specialist; and one the doctor can treat. How does the doctor figure out the underlying pathology (cause) responsible for your pathophysiology (change in function)? There are three diseases we are looking at here: Type 1 diabetes, which can be fatal if untreated; Type 2 diabetes, which the primary care provider can treat; and diabetes insipidus, which needs further testing and specialist involvement. All three have increased urine output, which results in increased thirst. The first two have increased thirst and urination because there is too much sugar in the urine. In Type 1 diabetes, the sugar in the blood and urine is too high because the body has destroyed the pancreatic beta cells that produce insulin, which allows the body to store glucose in cells. In Type 2 diabetes, the body produces insulin, but the cells have a harder time recognizing it. As a result, the body cannot store glucose in the cells as readily, leaving excess in the blood (and urine). On the other hand, diabetes insipidus has nothing to do with sugar levels; instead, the body cannot concentrate the urine because it is missing or unable to recognize the protein vasopressin (antidiuretic hormone), which is produced by the hypothalamus and stored in the posterior pituitary gland. A simple dip-stick test of your urine can rule out diabetes insipidus if there is too much glucose in the urine. Lethargy, unresponsiveness, confusion, and coma are all symptoms that point towards Type 1 diabetes as opposed to Type 2. Therefore, the primary care provider has to evaluate at the overall clinical picture, recognize the potential differentials and determine the necessary steps to distinguish different underlying pathologies. Often, they will order blood work or send samples for testing, both of which involve medical laboratory technologist and pathologists. Alternatively, they might order imaging, which involves radiation technologists, ultrasound technologists, radiologists, and etc.

Pathology as a Medical Specialty

We saw from the previous example that pathology is also a medical specialty (you need to be a doctor). There are different specialties within Pathology. **Anatomic Pathologists** look at tissues and organs to determine disease based on changes in the appearance of cells, tissues and organs, both grossly and microscopically, and often specialize in a particular organ system. **Forensic Pathologists** determine the cause of death by examining the entire body, specific tissues and organs, and ordering toxicological tests for foreign substances that may have contributed. **Neuropathologists** specialize in the nervous system and muscle pathology. **Hematopathologists** specialize in changes to the blood cells and has **Transfusion medicine** as a subspecialty. **Medical Microbiologists** isolate, grow and identify micro-organisms that cause disease, along with which treatments may be effective against them. They work with **Infectious Disease** specialists to identify, treat communicable diseases, and prevent their spread in the community. **Medical Biochemists** and **Clinical Chemists** oversee the laboratory testing of chemical substances in the body, either produced by the body (endogenous) or ingested (exogenous), including selecting the optimal methods to use, identify the test limitation, and establishing normal reference ranges for a given test.

Pathologists do not work in isolation. They are supported by a team of Medical Laboratory Technologists, who prepare specimens, perform the tests, and troubleshoot problems with techniques and instrumentation. Medical Laboratory Technologists cover a wide range of areas from phlebotomy (drawing blood), to preparing histological samples, to growing up microorganisms, to running complex chemical analysis equipment. Therefore, they tend to specialize as well.

Section Review

The fact that we live with injury and disease has led to disciplines focused on studying changes happening at the cellular, tissue, and organ levels. Pathophysiology looks at the functional changes, while pathology as a whole looks at both functional and structural changes associated with injury and disease. Pathologists and Medical Laboratory Technologists are closely involved with confirming the diagnosis of diseases and monitoring ongoing changes with disease progression or remission.

Media Attributions

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- broken bike © mikicon is licensed under a CC BY (Attribution) license

Where Do the Specimens Come From? The David Hardwick Pathology Learning Centre (DHPLC)

HELEN DYCK AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Briefly describe what the David Hardwick Pathology Learning Centre (DHPLC) is and how it is used in health education.
- List the different pathology collections within DHPLC

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=414#h5p-37

Introduction to the David F. Hardwick Pathology Learning Centre (DHPLC) by Jennifer Kong & Adrian Marcuzzi, licensed under All Rights Reserved

The specimens, both gross and microscopic, come from the collections of the David F. Hardwick Pathology Learning Centre.



UBC's David Hardwick Pathology Learning Centre at Vancouver General Hospital

The David F. Hardwick Pathology Learning Centre (DHPLC) is an educational resource of the University of British Columbia's (UBC) Department of Pathology and Laboratory Medicine. It has been set up as a resource for people to learn about diseases and the changes that they introduce into organs at both the macroscopic (gross) and microscopic levels.

The DHPLC has a physical presence at the Vancouver General Hospital Campus of UBC located in the Gordon and Leslie Diamond Health Care Centre at 2201-2775 Laurel Street, Vancouver, BC. It houses several specimen collections, two of which are open to the public: The Boyd Museum of Pathology and the Betty Poland Collection.

It also has a virtual presence where several of its collections are available for public viewing at DHPLC virtual collections

Access is free but you need to have a user ID and password to access the database. Please contact DHPLC.info@ubc.ca to arrange for access.

There are also several atlases and other educational materials in the virtual collections that are appropriate for use in the teaching of health professions.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=414#h5p-39

History of Collections Housed in DHPLC by Jennifer Kong & Adrian Marcuzzi, licensed under All Rights Reserved

Section Review

The DHPLC is a collection of both microscopic and gross anatomical pathology specimens. Originally started by Dr. William Boyd, multiple pathologists have contributed pathology specimens which are organized and presented in the DHPLC. Access to the DHPLC (both in person and virtual) are free; however, contact with DHPLC manager is required.

Media Attributions

- DHPLC

How Are the Specimens Obtained and Prepared?

HELEN DYCK

Learning Objectives

By the end of this section, you will be able to:

- Briefly describe how pathology specimens are obtained, prepared, preserved, and presented in the DHPLC.

Obtaining Specimens

There are three main ways of obtaining specimens for pathological examination: 1) biopsies, where small amounts of tissue are removed, often using a wide bore needle; 2) surgical resection, where parts or whole organs are removed during surgery; and 3) autopsy, where specimens are obtained after a person has died to try and determine the cause of death.

Preservation

When cells, tissues, and organs are removed from the body and deprived of their normal environment and blood supply, they start to die, and will release enzymes that start to break down the cellular and tissue structures. Therefore, in order to distinguish any pathological changes to the organ, these artificially induced changes must be prevented from occurring. The main method of preserving the tissue and preventing these changes is using a chemical fixative.

Chemical Fixatives

The most common chemical fixative is formalin, which is a buffered solution of formaldehyde. There are other chemical fixatives that can be used that are better at preserving specific components of the tissue, but their use is specialized. An important limitation of a fixative is the slow penetration rate, which requires the specimens to be thinly sliced to make sure they get complete penetration before degradation occurs. When a specimen is cut up for fixation, care must be taken to retain the features that you want to look at (e.g. perpendicular to the surface if you want to look at the layers).

Preparing for Viewing

Specimens intended to be examined under the microscope need more extensive preparation than those to be viewed grossly, or macroscopically.

Specimens for Gross Examination

Pathologists will examine specimens before fixation to mark any changes on the outside of the specimen before dissecting and viewing the inside of the specimen. They will usually then select areas of the organ that they want to view microscopically to see the changes occurring at that level. They will then remove a block of tissue, which will be processed for microscopic viewing.

Specimens for Viewing in the Museum

Specimens that show interesting features of a disease, with consent obtained from the individual or family for educational use, may be processed for viewing in the museum. The specimens are already sliced and fixed in formalin. The specimens are soaked in a series of solutions to try to remove excess red blood cells, which tend to cloud the solutions, restore colour as much as possible, and to replace the water-based solutions with a glycerol-based solution to provide the right refractive index so that there is no distortion when viewing the specimen through plexiglass or glass. This final solution, Kaiserling III, is non-toxic.

The specimens are then mounted in a plexiglass case with a stopper that allows the fluid to be topped up and replaced when it gets depleted, cloudy or discoloured.

Specimens for Viewing Under the Light Microscope

In order to view tissue under the light microscope, the tissue must be thin enough to: a) allow light to pass through, and b) thin enough to distinguish features (i.e. not have too many cells piled up on one another so you don't know which features belong to which cell). They also need to be coloured, or **stained**, in some way. Otherwise, you are looking at a clear specimen, making the details hard to distinguish. They are then covered with a coverslip to preserve and allow viewing at high magnification with oil immersion.

Paraffin Embedding

If you have ever tried to cut into fresh chicken or a steak, you will notice how 'wobbly' the tissue is and how the skin has a different consistency from the muscle below. These characteristics make it difficult to section tissue thinly and consistently without embedding in a supportive medium. Paraffin wax is the most commonly used medium to provide this support. However, if we just placed a tissue directly into paraffin, it would pop out of the paraffin during sectioning as paraffin cannot penetrate into the water-based tissue (paraffin is immiscible with water). Therefore, we need to put the tissue through a series of solutions where we replace water with alcohol, then alcohol with xylene and finally xylene with melted paraffin wax. This process is known as tissue processing.

Fortunately, processing has been automated, or you would be there all night.

Once tissue is completely infiltrated with paraffin wax, it can be brought to the tri-console embedding machine, where it is placed into the molten wax in the cassette holding tank. The technician then removes the tissue from the cassette and embeds the specimen completely into molten wax. Placing the final product on the cold plate solidifies the wax in preparation for cutting (sectioning).

Paraffin Sectioning

There are several types of microtomes, depending on what it is that you need to cut. Smaller rotary microtomes are used to cut paraffin embedded specimens into thin sheets (typically 5 – 8 µm thick) that can be placed in a warm water bath and picked up on glass slides. So why are we doing all of this work and completing all of these steps? We need to cut VERY THIN pieces of tissue in order to see them with a microscope.

Staining

Unstained tissues cannot be viewed using a standard light microscope so we must use different dyes to stain the tissue and distinguish components. Unfortunately, these dyes cannot bind to the tissue when it is full of paraffin, so we must remove the paraffin completely. Basically, what happens is we reverse the process we used to infiltrate the tissues with wax using xylene to remove the wax, alcohol to remove the xylene, and if it is a water-based stain, we use water to remove the alcohol.

Using multiple dyes makes it easier to distinguish between components. The most commonly used stain combination is Hematoxylin and Eosin (H&E).

Coverslipping

We are now almost ready to view the tissue under the microscope, but first we need to put on a coverslip, which is a thin piece of glass or plastic that is 0.17mm thick to maximize resolution. This won't stick by itself, so we need to use an adhesive to attach it. This adhesive cannot interfere with the dye or the viewing of the specimen. They are usually dissolved in toluene or xylene. So, guess what? We get to replace the water from the dye baths with alcohol and then the alcohol with xylene.

Section Review

Pathology specimens are obtained from patients (given with consent and permission) during their health journey. The specimens can be a block of tissue, which is preserved in chemicals (to prevent tissue degradation) before mounting in a plexiglass case, for viewing the gross anatomy. Tissue specimens, which are to be viewed microscopically, have the additional step of being solidified (paraffin wax embedding) and sliced thinly before staining and covering with a coverslip.

How do we Look at a Pathology Specimen?

HELEN DYCK

Learning Objectives

By the end of this section, you will be able to:

- Explain why preserved organs may look different in size and colour between in the body versus when on display.
- List the changes a pathologist looks for when examining an organ/tissue.

Observations

Now that we are ready to look at our specimen, what are we looking for?

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=423#h5p-42

How to View Pathology Specimens by Jennifer Kong and Adrian Marcuzzi, licensed under All Rights Reserved

Macroscopic Observation (Gross Specimens)

Remember that we are looking to see how the specimen differs from normal. For gross specimens, the pathologist is looking for changes in:

- Size:
  - Is it larger? Indicating extra growth of either normal tissue or abnormal tissue
  - Is it smaller? Indicating cell death or destruction of tissue
- Shape:
  - Does it have the proper shape?
  - Is it distorted in any way?
- Colour*: (this is best evaluated before fixation)
  - Is there a change in colour in parts of the specimen that are unusual? This often happens with infection

(white blood cells), tumours where the cells are different, and loss of certain tissues.

- Texture:
  - Is the specimen firmer than usual? Indicating perhaps extra fluid or perhaps a tumour or deposits of something that is normally not there
  - Is it squishier than usual? Usually a sign of tissue destruction
- Structure:
  - Is the structure what we expect?
  - Was it formed properly?
  - Has it been modified through the disease process?

*Colour: The DHPLC specimens no longer retain their original colour due to fixation, oxidation and bleaching over time.

Microscopic Observation

Remember that tissue is normally clear, so we stain it to be able to distinguish the various parts of the tissue (e.g. H&E stain). The colour and intensity of the stain gives us hints about the makeup of the cells that form the tissue.

To prepare for your video lesson on histology, we first need a primer on the tissue we are examining: epithelial tissue. Epithelial tissue is made from tightly connected cells, forming a 'sheet,' covering all the surfaces exposed to the outside world OR lining the outside or inside of hollow organs. Epithelial tissue can be classified based on the shape of the outermost layer of cells (squamous, columnar, cuboidal, pseudostratified) and whether the sheet is a single layer (simple) or multiple layers (stratified). As skin is the most exposed layer, skin is an epithelial tissue. Epithelial tissue is quite varied, based on their function and location within the body.

For a deeper understanding, consider the following chapter – paying particular attention to their cellular makeup (i.e. with or without a gland), avascularity, and functions of epithelial tissue, as they provide the histological background for many of our video lessons on histology.

Section Review

To get a hint of what is going wrong in the disease process, a pathologist can look at a block of tissue or whole organ for changes in size, shape, colour, texture, and structure. These changes can suggest underlying problems in cellular changes. Microscopic analysis of tissue is possible using thin slices that are stained to enable visibility of cellular organelles and cytosol.

Epithelial Tissue

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

This section gives the background of how many cells make up epithelial tissue and key features. This background will be instrumental for the subsequent videos of histological examination of normal and pathological tissue. By the end of this section, you will be able to:

- Explain the structure and function of epithelial tissue.
- Distinguish between tight junctions, anchoring junctions, and gap junctions.
- Distinguish between simple epithelia and stratified epithelia, as well as between squamous, cuboidal, and columnar epithelia.
- Describe the structure and function of endocrine and exocrine glands and their respective secretions.

Most epithelial tissues are essentially large sheets of cells covering all the surfaces of the body exposed to the outside world and lining the outside of organs. Epithelium also forms much of the glandular tissue of the body. Skin is not the only area of the body exposed to the outside. Other areas include the airways, the digestive tract, as well as the urinary and reproductive systems, all of which are lined by an epithelium. Hollow organs and body cavities that do not connect to the exterior of the body, which includes, blood vessels and serous membranes, are lined by **endothelium** (plural = endothelia), which is a type of epithelium.

All epithelia share some important structural and functional features. This tissue is highly cellular, with little or no extracellular material present between cells. Adjoining cells form a specialized intercellular connection between their cell membranes called a **cell junction**. The epithelial cells exhibit polarity with differences in structure and function between the exposed or **apical** facing surface of the cell and the basal surface close to the underlying body structures. The basal lamina, a mixture of glycoproteins and collagen, provides an attachment site for the epithelium, separating it from underlying connective tissue. The basal lamina attaches to a **reticular lamina**, which is secreted by the underlying connective tissue, forming a **basement membrane** that helps hold it all together.

Epithelial tissues are nearly completely avascular. For instance, no blood vessels cross the basement membrane to enter the tissue, and nutrients must come by diffusion or absorption from underlying tissues or the surface. Many epithelial tissues are capable of rapidly replacing damaged and dead cells. Sloughing off of damaged or dead cells is a characteristic of surface epithelium and allows our airways and digestive tracts to rapidly replace damaged cells with new cells.

Generalized Functions of Epithelial Tissue

Epithelial tissues provide the body's first line of protection from physical, chemical, and biological wear and tear. The

cells of an epithelium act as gatekeepers of the body controlling permeability and allowing selective transfer of materials across a physical barrier. All substances that enter the body must cross an epithelium. Some epithelia often include structural features that allow the selective transport of molecules and ions across their cell membranes.

Many epithelial cells are capable of secretion and release mucous and specific chemical compounds onto their apical surfaces. The epithelium of the small intestine releases digestive enzymes, for example. Cells lining the respiratory tract secrete mucous that traps incoming microorganisms and particles. A glandular epithelium contains many secretory cells.

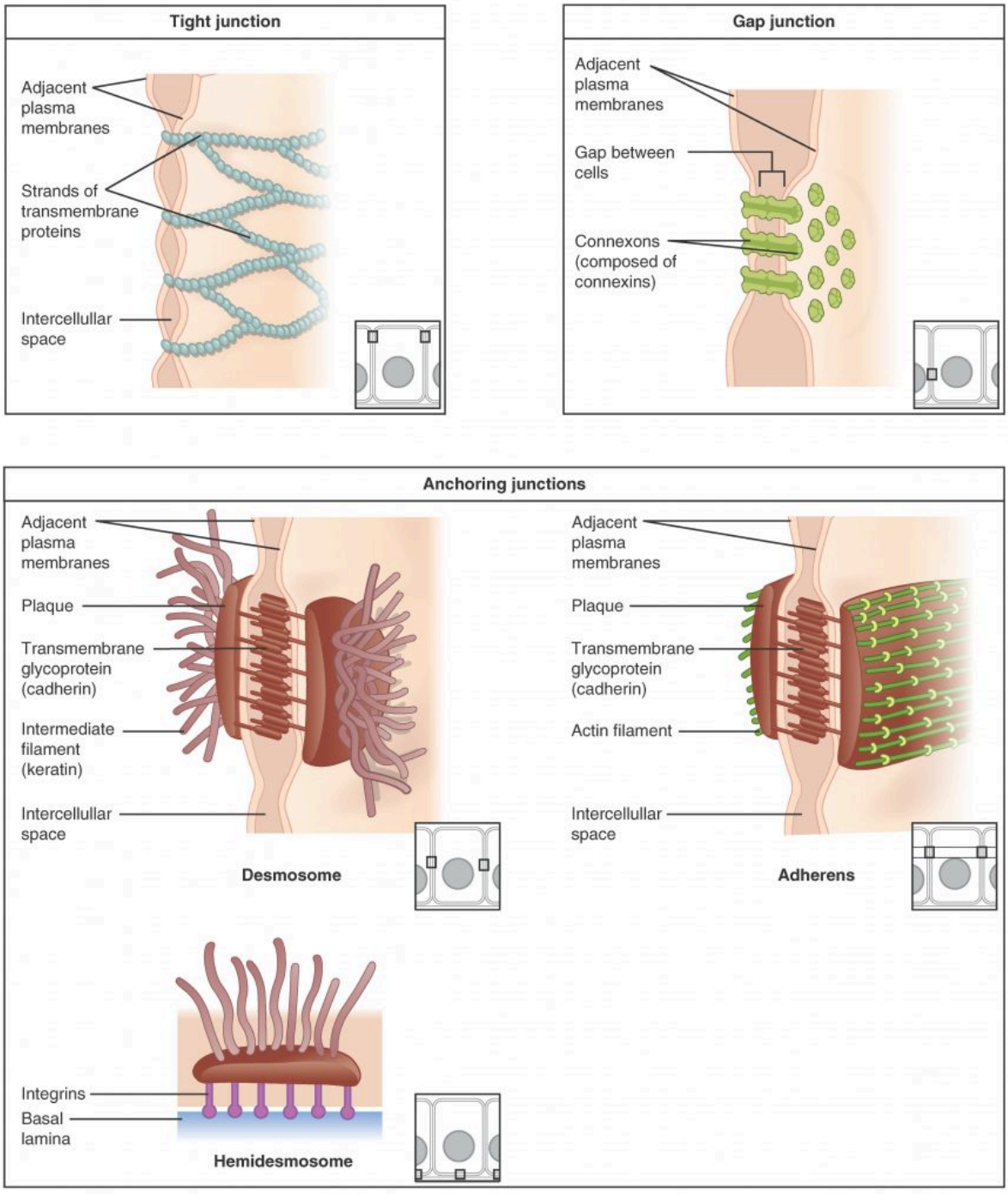
The Epithelial Cell

Epithelial cells are typically characterized by the polarized distribution of organelles and membrane-bound proteins between their basal and apical surfaces. Particular structures found in some epithelial cells are an adaptation to specific functions. Certain organelles are segregated to the basal sides, whereas other organelles and extensions, such as cilia, when present, are on the apical surface.

Cilia are microscopic extensions of the apical cell membrane that are supported by microtubules. They beat in unison and move fluids as well as trapped particles. Ciliated epithelium lines the ventricles of the brain where it helps circulate the cerebrospinal fluid. The ciliated epithelium of your airway forms a mucociliary escalator that sweeps particles of dust and pathogens trapped in the secreted mucous toward the throat. It is called an escalator because it continuously pushes mucous with trapped particles upward. In contrast, nasal cilia sweep the mucous blanket down towards your throat. In both cases, the transported materials are usually swallowed, and end up in the acidic environment of your stomach.

Cell to Cell Junctions

Cells of epithelia are closely connected and are not separated by intracellular material. Three basic types of connections allow varying degrees of interaction between the cells: tight junctions, **anchoring junctions**, and gap junctions.



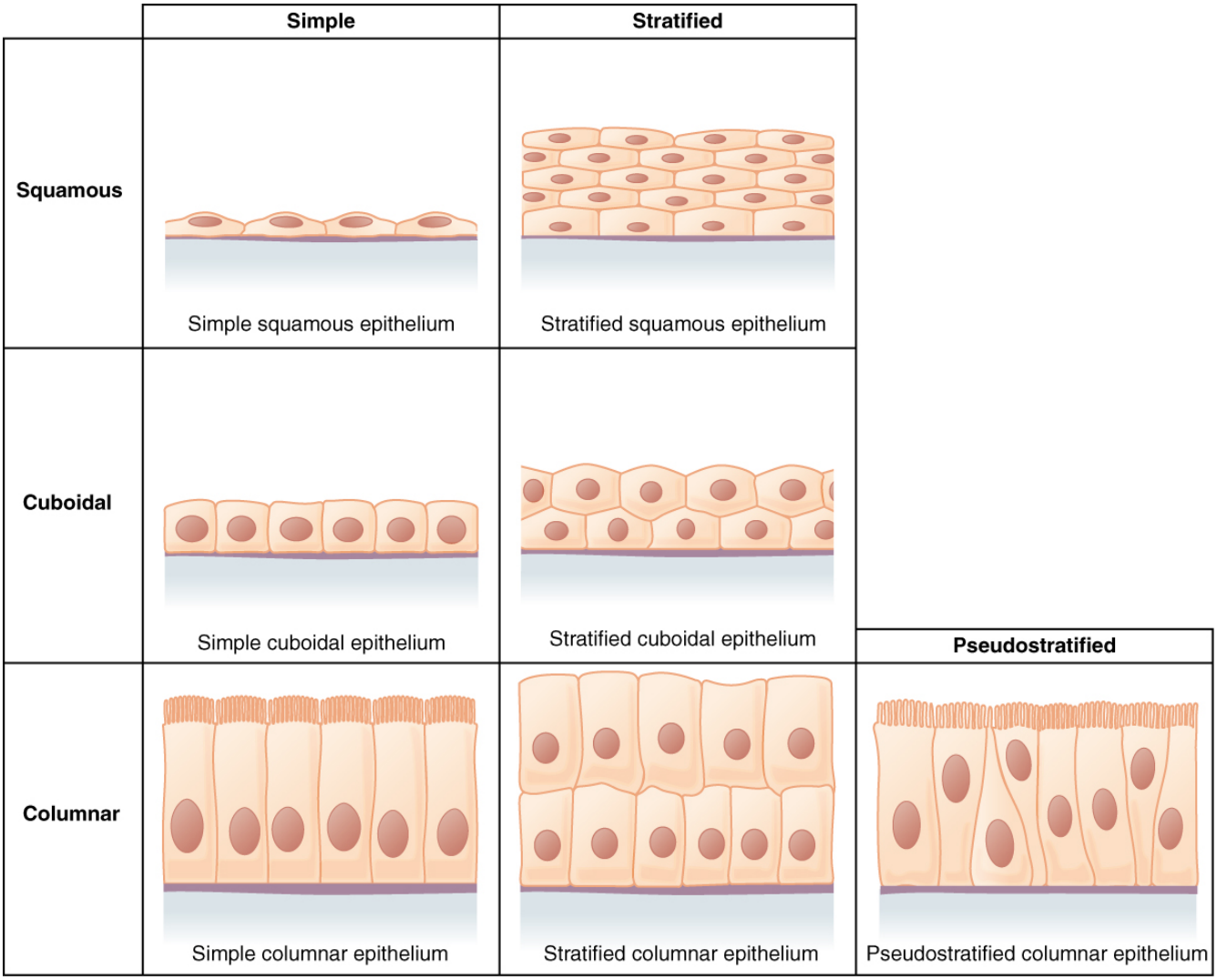
Types of Cell Junctions – The three basic types of cell-to-cell junctions are tight junctions, gap junctions, and anchoring junctions.

At one end of the spectrum is the tight junction, which separates the cells into apical and basal compartments. When two adjacent epithelial cells form a tight junction, there is no extracellular space between them and the movement of substances through the extracellular space between the cells is blocked. This enables the epithelia to act as selective barriers. An anchoring junction includes several types of cell junctions that help stabilize epithelial tissues. Anchoring junctions are common on the lateral and basal surfaces of cells where they provide strong and flexible connections. These junctions influence the shape and folding of the epithelial tissue.

In contrast with the tight and anchoring junctions, a gap junction forms an intercellular passageway between the membranes of adjacent cells to facilitate the movement of small molecules and ions between the cytoplasm of adjacent cells. These junctions allow electrical and metabolic coupling of adjacent cells, which coordinates function in large groups of cells.

Classification of Epithelial Tissues

Epithelial tissues are classified according to the shape of the cells and number of the cell layers formed. Cell shapes can be squamous (flattened and thin), cuboidal (boxy, as wide as it is tall), or columnar (rectangular, taller than it is wide). Similarly, the number of cell layers in the tissue can be one—where every cell rests on the basal lamina—which is a simple epithelium, or more than one, which is a stratified epithelium and only the basal layer of cells rests on the basal lamina. Pseudostratified (pseudo- = "false") describes tissue with a single layer of irregularly shaped cells that give the appearance of more than one layer. Transitional describes a form of specialized stratified epithelium in which the shape of the cells can vary.



Cells of Epithelial Tissue- Simple epithelial tissue is organized as a single layer of cells and stratified epithelial tissue is formed by several layers of cells.

Simple Epithelium

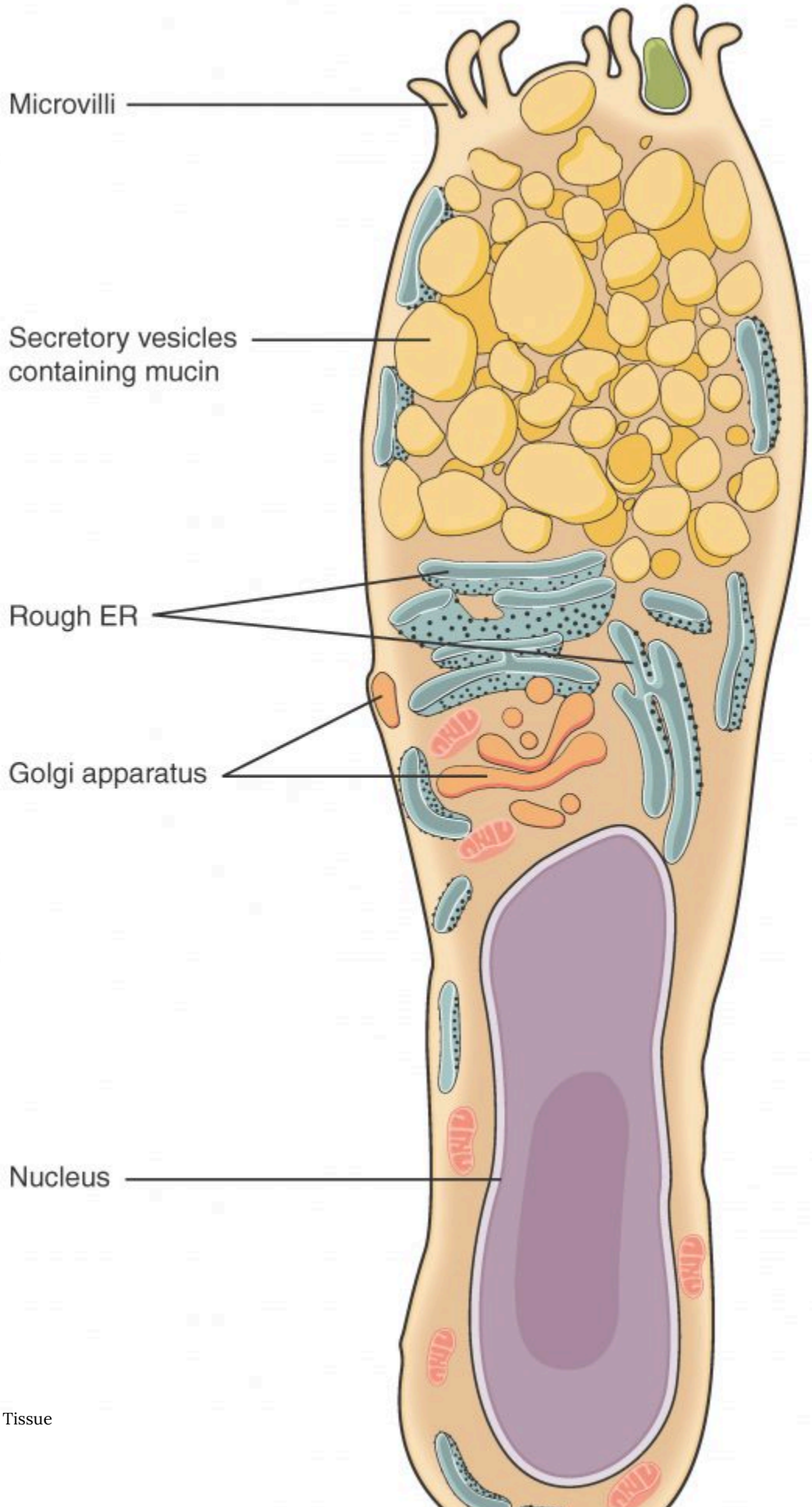
The shape of the cells in the single cell layer of simple epithelium reflects the functioning of those cells. The cells in simple squamous epithelium have the appearance of thin scales. Squamous cell nuclei tend to be flat, horizontal, and elliptical, mirroring the form of the cell. The endothelium is the epithelial tissue that lines vessels of the lymphatic and cardiovascular system, and it is made up of a single layer of squamous cells. Simple squamous epithelium, because of the thinness of the cell, is present where rapid passage of chemical compounds is observed. The alveoli of lungs where gases diffuse, segments of kidney tubules, and the lining of capillaries are also made of simple squamous epithelial tissue. The **mesothelium** is a **simple squamous epithelium** that forms the surface layer of the serous membrane that lines body cavities and internal organs. Its primary function is to provide a smooth and protective surface.

In **simple cuboidal epithelium**, the nucleus of the box-like cells appears round and is generally located near the center of the cell. These epithelia are active in the secretion and absorptions of molecules. Simple cuboidal epithelia are observed in the lining of the kidney tubules and in the ducts of glands.

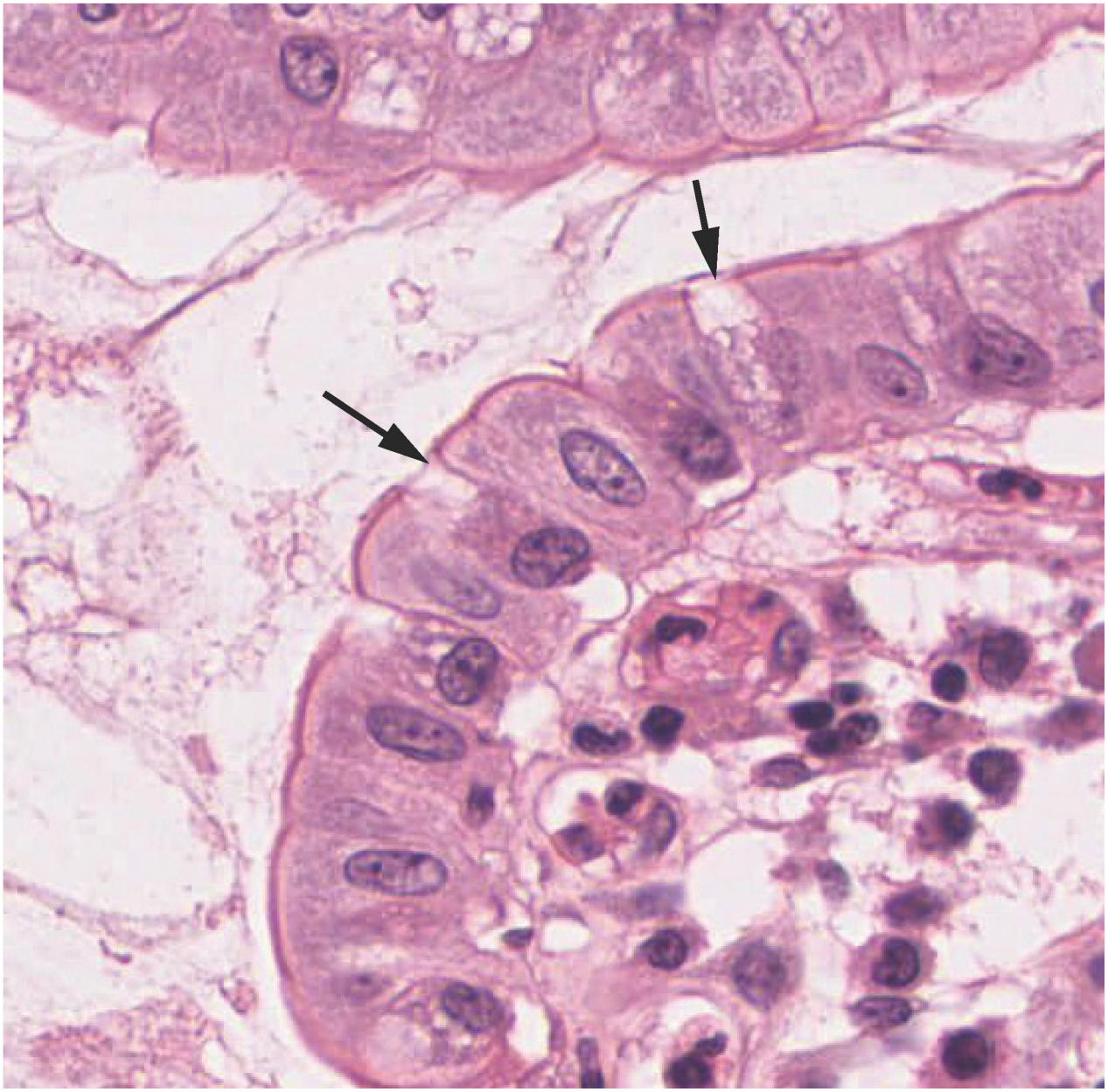
In **simple columnar epithelium**, the nucleus of the tall column-like cells tends to be elongated and located in the basal end of the cells. Like the cuboidal epithelia, this epithelium is active in the absorption and secretion of molecules. Simple columnar epithelium forms the lining of some sections of the digestive system and parts of the female reproductive tract. Ciliated columnar epithelium is composed of simple columnar epithelial cells with cilia on their apical surfaces. These epithelial cells are found in the lining of the fallopian tubes and parts of the respiratory system, where the beating of the cilia helps remove particulate matter.

Pseudostratified columnar epithelium is a type of epithelium that appears to be stratified but instead consists of a single layer of irregularly shaped and differently sized columnar cells. In pseudostratified epithelium, nuclei of neighboring cells appear at different levels rather than clustered in the basal end. The arrangement gives the appearance of stratification; but in fact all the cells are in contact with the basal lamina, although some do not reach the apical surface. Pseudostratified columnar epithelium is found in the respiratory tract, where some of these cells have cilia.

Both simple and pseudostratified columnar epithelia are heterogeneous epithelia because they include additional types of cells interspersed among the epithelial cells. For example, a **goblet cell** is a mucous-secreting unicellular “gland” interspersed between the columnar epithelial cells of mucous membranes.


Microvilli
Secretory vesicles containing mucin
Rough ER
Golgi apparatus
Nucleus

Goblet Cell – In the lining of the small intestine, columnar epithelium cells are interspersed with goblet cells.



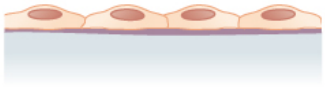
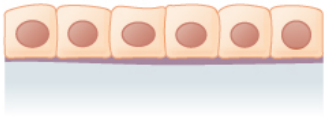
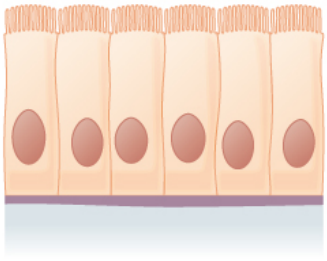
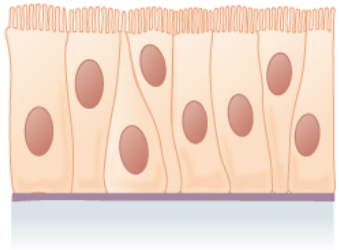
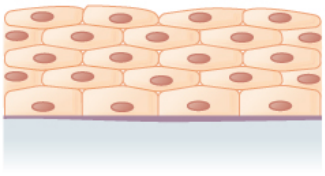
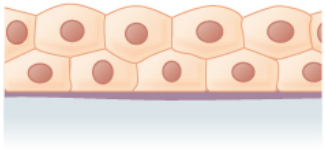
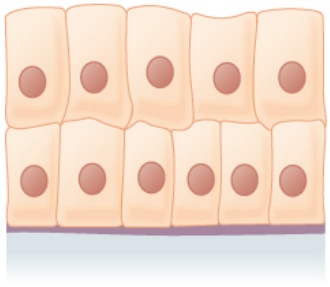
The arrows in this micrograph point to the mucous-secreting goblet cells. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

View the University of Michigan WebScope to explore the tissue sample in greater detail.

Stratified Epithelium

A stratified epithelium consists of several stacked layers of cells. This epithelium protects against physical and chemical wear and tear. The stratified epithelium is named by the shape of the most apical layer of cells, closest to the free space. Stratified squamous epithelium is the most common type of stratified epithelium in the human body. The apical cells are squamous, whereas the basal layer contains either columnar or cuboidal cells. The top layer may be covered with dead cells filled with keratin. Mammalian skin is an example of this dry, keratinized, stratified squamous epithelium. The lining of the mouth cavity is an example of an unkeratinized, stratified squamous epithelium. **Stratified cuboidal epithelium** and **stratified columnar epithelium** can also be found in certain glands and ducts, but are uncommon in the human body.

Another kind of stratified epithelium is **transitional epithelium**, so-called because of the gradual changes in the shapes of the apical cells as the bladder fills with urine. It is found only in the urinary system, specifically the ureters and urinary bladder. When the bladder is empty, this epithelium is convoluted and has cuboidal apical cells with convex, umbrella shaped, apical surfaces. As the bladder fills with urine, this epithelium loses its convolutions and the apical cells transition from cuboidal to squamous. It appears thicker and more multi-layered when the bladder is empty, and more stretched out and less stratified when the bladder is full and distended. The image below summarizes the different categories of epithelial cell tissue cells.

Cells	Location	Function
Simple squamous epithelium 	Air sacs of lungs and the lining of the heart, blood vessels, and lymphatic vessels	Allows materials to pass through by diffusion and filtration, and secretes lubricating substance
Simple cuboidal epithelium 	In ducts and secretory portions of small glands and in kidney tubules	Secretes and absorbs
Simple columnar epithelium 	Ciliated tissues are in bronchi, uterine tubes, and uterus; smooth (nonciliated tissues) are in the digestive tract, bladder	Absorbs; it also secretes mucous and enzymes
Pseudostratified columnar epithelium 	Ciliated tissue lines the trachea and much of the upper respiratory tract	Secretes mucus; ciliated tissue moves mucus
Stratified squamous epithelium 	Lines the esophagus, mouth, and vagina	Protects against abrasion
Stratified cuboidal epithelium 	Sweat glands, salivary glands, and the mammary glands	Protective tissue
Stratified columnar epithelium 	The male urethra and the ducts of some glands	Secretes and protects
Transitional epithelium 	Lines the bladder, uretha, and the ureters	Allows the urinary organs to expand and stretch

Glandular Epithelium

A gland is a structure made up of one or more cells modified to synthesize and secrete chemical substances. Most glands consist of groups of epithelial cells. A gland can be classified as an **endocrine gland**, a ductless gland that releases secretions directly into surrounding tissues and fluids (endo- = "inside"), or an **exocrine gland** whose secretions leave through a duct that opens directly, or indirectly, to the external environment (exo- = "outside").

Endocrine Glands

The secretions of endocrine glands are called hormones. Hormones are released into the interstitial fluid, diffused into the bloodstream, and delivered to targets, in other words, cells that have receptors to bind the hormones. The endocrine system is part of a major regulatory system coordinating the regulation and integration of body responses. A few examples of endocrine glands include the anterior pituitary, thymus, adrenal cortex, and gonads.

Exocrine Glands

Exocrine glands release their contents through a duct that leads to the epithelial surface. Mucous, sweat, saliva, and breast milk are all examples of secretions from exocrine glands. They are all discharged through tubular ducts. Secretions into the lumen of the gastrointestinal tract, technically outside of the body, are of the exocrine category.

Glandular Structure

Exocrine glands are classified as either unicellular or multicellular. The unicellular glands are scattered single cells, such as goblet cells, found in the mucous membranes of the small and large intestine. The multicellular exocrine glands known as **serous glands** develop from simple epithelium to form a secretory surface that secretes directly into an inner cavity. These glands line the internal cavities of the abdomen and chest and release their secretions directly into the cavities.

Section Review

In epithelial tissue, cells are closely packed with little or no extracellular matrix except for the **basal lamina** that separates the epithelium from underlying tissue. The main functions of epithelia are protection from the environment, coverage, secretion and excretion, absorption, and filtration. Cells are bound together by **tight junctions** that form an impermeable barrier. They can also be connected by **gap junctions**, which allow free exchange of soluble molecules between cells, and anchoring junctions, which attach cell to cell or cell to matrix. The different types of epithelial tissues

are characterized by their cellular shapes and arrangements: squamous, cuboidal, or columnar epithelia. Single cell layers form simple epithelia, whereas stacked cells form stratified epithelia. Very few capillaries penetrate these tissues.

Glands are secretory tissues and organs that are derived from epithelial tissues. Exocrine glands release their products through ducts. Endocrine glands secrete hormones directly into the interstitial fluid and blood stream.

Review Questions

1. Where in the body would one find non-keratinizing stratified squamous epithelium?

- The inside of the mouth, esophagus, vaginal canal, and anus
- Only on the skin on the sole of the foot
- Inside of the mouth only
- Alveolar walls in lungs

2. In observing epithelial cells under a microscope, the cells are arranged in a single layer and look tall and narrow, and the nucleus is located close to the basal side of the cell. The specimen is what type of epithelial tissue?

- Stratified
- Columnar
- Squamous
- Transitional

3. Which of the following is the epithelial tissue that lines the interior of blood vessels?

- Columnar
- Pseudostratified
- Simple squamous
- Transitional

4. Which type of epithelial tissue specializes in moving particles across its surface and is found in airways and lining of the oviduct?

- Transitional
- Stratified cilated columnar
- Pseudostratified ciliated columnar
- Stratified squamous

Answer Key

1. The inside of the mouth, esophagus, vaginal canal, and anus
2. Columnar
3. Simple squamous
4. Stratified ciliated columnar

Adaption

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Epithelial Tissue **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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Video Lessons on Histology

JENNIFER KONG; LYZ BOYD; AND JONATHAN BUSH

Learning Objectives

By the end of this section, you will be able to:

- Explain how hematoxylin & eosin staining works and which aspects of the cell it allows to be made visible microscopically.

Now that we know what to expect from epithelial tissue, we are ready to look at it microscopically.

Remember that tissue is normally clear, so we use stains to help distinguish its various components.

Hematoxylin and Eosin (H&E) Stain

H&E is the most commonly used stain and involves a sequential applications of two different dyes.

Hematoxylin is a blue basic dye and stains acidic elements in the tissue such as the nucleic acids (RNA and DNA). Nuclei of cells, therefore, appear as blue circles.

Eosin is a pink acidic dye and binds to basic molecules, which are mainly proteins. These are usually found in the cytosol of the cells and in the extracellular spaces. Collagen, an extra-cellular matrix protein, stains pink as do muscle cells.

Purple staining in an H&E slide indicates the presence of both acidic and basic components. The keratin layer in skin often stains purple due to the combination of pink-staining keratin and dark blue keratohyalin granules.

Video Demonstration of Looking at the Histology of Epithelial Tissue

How do we look at tissues like a histologist? This video demonstrates a histological description with H&E staining of thick skin.



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=903#h5p-44

Now let's listen to a histopathologist describe lung epithelial tissue using these skills.

Introduction to Histology Staining by Dr. Jonathan Bush, licensed under All Rights Reserved

Section Review

- Hematoxylin & Eosin (H&E) is the most common stain to visualize tissues.
  - Blue = DNA/RNA within nuclei (usually, one nuclei/cell)
  - Pink = protein (e.g. protein in the cytosol or other intracellular fluid)
  - White = nothing to stain (e.g. air) OR stain can't bind (e.g. fat)
- Nuclei are often the biggest structure within the cell, and may appear in either an oval or round shape.

Preface Summary

JENNIFER KONG

Key Takeaways

In this chapter you learned:

- The David Hardwick Pathology Learning Centre (DHPLC) is a free educational centre and resource for learning – both in person and virtually – about pathology from a gross anatomy and microscopic level.
- The DHPLC contains thousands of specimens from patients (with permission) taken during their health journey, for the purpose of health professional education.
- Specimens are prepared both at a gross anatomical (in plexiglass cases) and microscopic level (stained with dyes to make the cells visible) for viewing in person or virtually.
- Changes in tissue size, shape, colour, texture, and structure can give clues to the cause of the disease.

HEART FAILURE

Heart Failure Chapter Overview

JENNIFER KONG

Chapter Learning Objectives

By the end of this chapter, you will be able to:

- Define and differentiate left- versus right-sided heart failure.
- Identify structural and histological changes in the lungs and right- versus left-side of the heart, dependent on the type of heart failure.
- Explain why pulmonary edema is associated with left-sided heart failure.
- Briefly describe how interprofessional collaboration of health care professions work towards diagnosis of heart failure.

Heart failure, sometimes known as **congestive heart failure (CHF)**, occurs when your heart muscle can't pump well anymore. As a result, your heart is too weak or damaged to fill and pump efficiently. Heart failure can be subclassified with each classification having different causes and exhibit their own set of signs, symptoms, and diagnostic findings.

This chapter is subdivided into:

- Pre-test
- Normal heart anatomy, physiology & histology
- Types & causes of heart failure
- Pathophysiology of heart failure
  - Left sided heart failure with pulmonary complications
  - Right sided heart failure with liver complications
- Interview with health care professionals diagnosing/treating those with heart failure and its complications
  - Cardiac sonographer (Echocardiogram)
  - Medical Radiographer (Xray)
  - Medical Laboratory Science technologist (Microbiologist)
- Case study of a patient experiencing heart failure and their patient journey and interactions with health care professionals
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

ANS	Autonomic Nervous System
CCT	Certified Cardiographic Technician
CHF	Congestive Heart Failure
CPR	Cardiopulmonary Resuscitation
CRAT	Certified Rhythm Analysis Technician
FACC	Fellow of the American College of Cardiology
HDL	High-Density Lipoprotein
IVC	Inferior Vena Cava(e)
LAD	Left Anterior Descending Artery
LDL	Low-Density Lipoprotein
MI	Myocardial Infarction
RCCS	Registered Congenital Cardiac Sonographer
RCES	Registered Cardiac Electrophysiology Specialist
RCIS	Registered Cardiovascular Invasive Specialist
RCS	Registered Cardiac Sonographer
RPhS	Registered Phlebology Sonographer
RVS	Registered Vascular Specialist
STEMI	ST-Elevated MI

Pre-Test for Heart Failure

JENNIFER KONG

1. Finish the following sentence. If the left ventricle has a lower than normal ejection fraction, the result will be:

Select all that apply.

- Increased volume in the left ventricle (end systolic volume)
- Less blood delivered to the rest of the body
- Changes in height in an adult
- Pulmonary edema

2. Fill in the blanks.

_____ blood (visible as blue/purple colour) enters the _____ atrium from the superior and inferior _____. This blood passes through the _____ valve into the _____. Upon ventricular systole, this blood is ejected through the _____ valve into the pulmonary arteries which goes to the _____. The blood is now oxygenated and can be seen as it makes the blood the colour _____. Oxygenated blood returns to the heart via the _____, entering the _____ atrium and into the left ventricle via the _____ (or bicuspid) valve. During ventricular systole, the left ventricle contracts and pushes the blood through the _____ valve into the aorta which delivers the oxygenated blood to the heart via the _____ and the rest of the body.

Answer Key

1. Increased volume in the left ventricle (end systolic volume), less blood delivered to the rest of the body, pulmonary edema
2. Deoxygenated, right, vena cavae, tricuspid, right ventricle, pulmonary, lungs, red, pulmonary veins, left, mitral, aortic, coronary arteries

Heart Anatomy

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

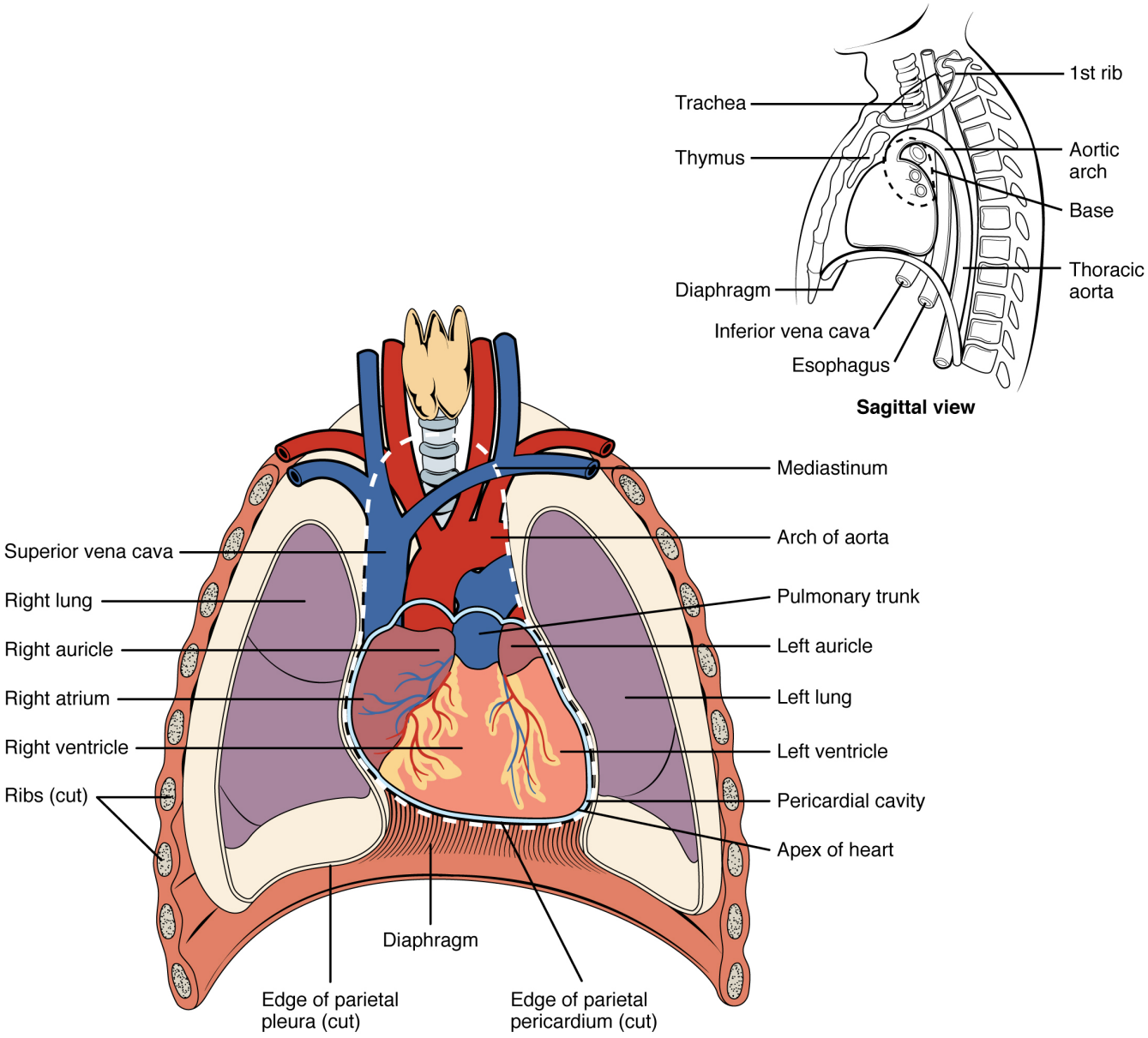
By the end of this section, you will be able to:

- Describe the location and position of the heart within the body cavity.
- Describe the internal and external anatomy of the heart.
- Identify the tissue layers of the heart.
- Relate the structure of the heart to its function as a pump.
- Compare systemic circulation to pulmonary circulation.
- Identify the veins and arteries of the coronary circulation system.
- Trace the pathway of oxygenated and deoxygenated blood thorough the chambers of the heart.

The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. The figure below shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane known as the **pericardium**, or **pericardial sac**, and sits in its own space called the **pericardial cavity**. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and **pulmonary trunk**, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in the figure below. The inferior tip of the heart, the apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the **cardiac notch**.



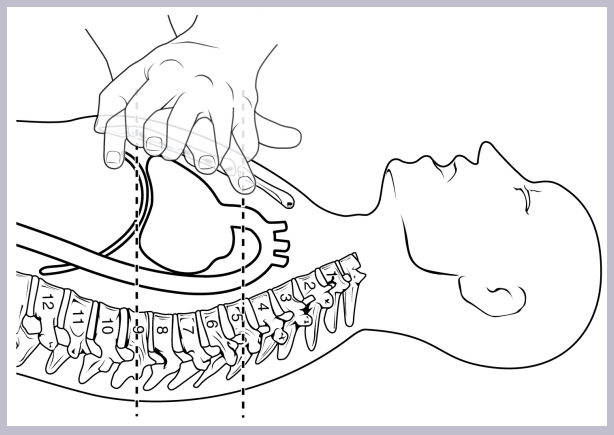
Heart Position in the Thoracic Cavity

Everyday Connection: CPR

CPR The position of the heart in the torso between the vertebrae and sternum for the position of the heart within the thorax) allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the line at T4 and T9, it is possible to manually compress the blood within

the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in "Staying Alive," recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, a version is available on www.youtube.com. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced healthcare professional. When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a consequence that may prove fatal for the patient. Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the American or Canadian Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.

CPR Technique



Position hands place on chest with reference to the heart

If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9. Visit the American Heart Association website or Canadian Red Cross website to help locate a course near your home in the United States or Canada. There are also many other national and regional heart associations that offer the same service, depending upon the location.

Shape and Size of the Heart

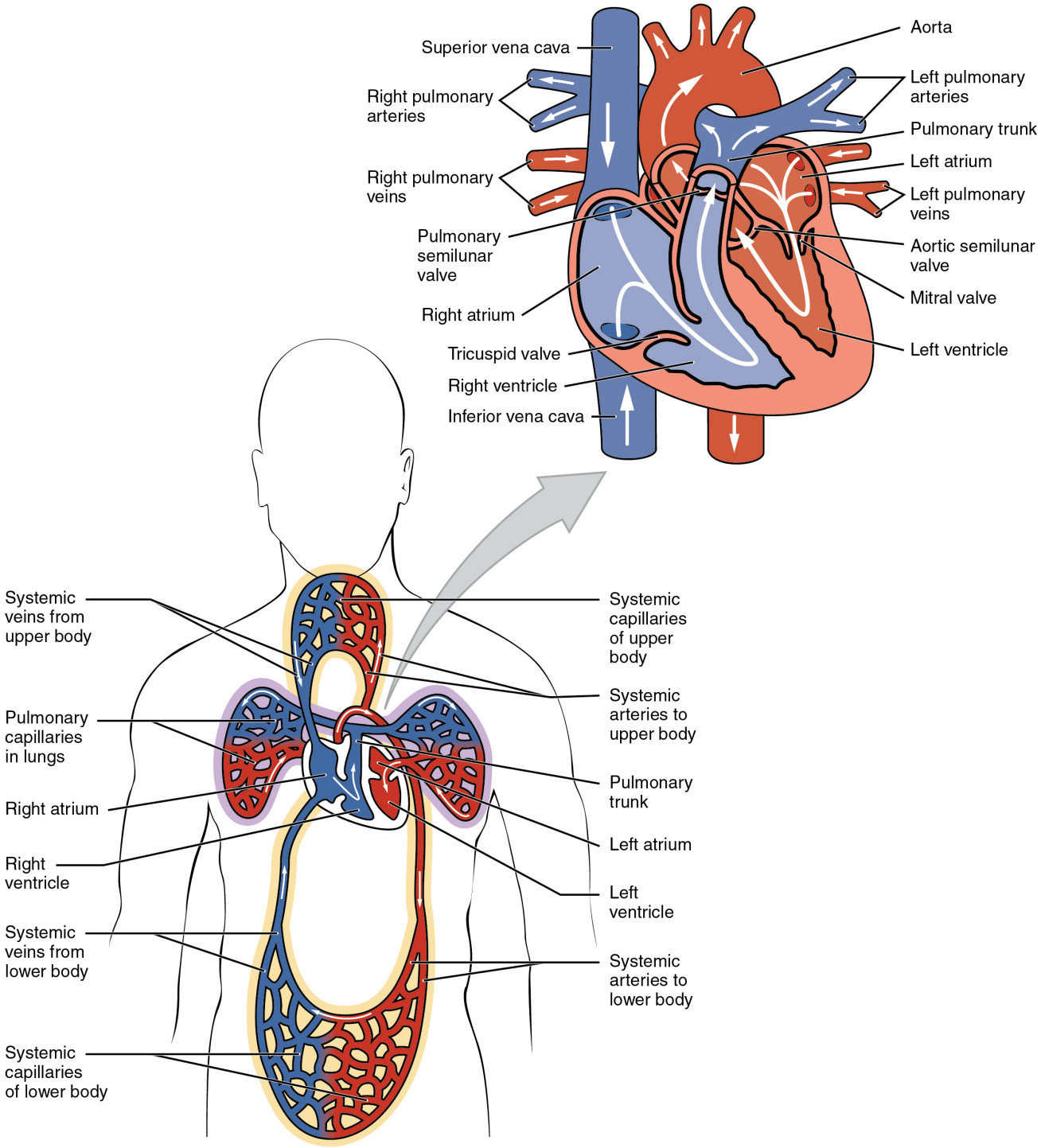
The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex. A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as **hypertrophic cardiomyopathy**. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one **atrium** and one **ventricle**. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.
There are two distinct but linked circuits in the human circulation called the pulmonary and **systemic circuits**. Although both circuits transport blood and everything it carries, we can initially view the circuits from the point of view of gases. The **pulmonary circuit** transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The systemic circuit transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

The right ventricle pumps deoxygenated blood into the pulmonary trunk, which leads toward the lungs and bifurcates into the left and right **pulmonary arteries**. These vessels in turn branch many times before reaching the **pulmonary capillaries**, where gas exchange occurs: Carbon dioxide exits the blood and oxygen enters. The pulmonary trunk arteries and their branches are the only arteries in the post-natal body that carry relatively deoxygenated blood. Highly oxygenated blood returning from the pulmonary capillaries in the lungs passes through a series of vessels that join together to form the **pulmonary veins**—the only post-natal veins in the body that carry highly oxygenated blood. The pulmonary veins conduct blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and on to the many branches of the systemic circuit. Eventually, these vessels will lead to the systemic capillaries, where exchange with the tissue fluid and cells of the body occurs. In this case, oxygen and nutrients exit the systemic capillaries to be used by the cells in their metabolic processes, and carbon dioxide and waste products will enter the blood.

The blood exiting the systemic capillaries is lower in oxygen concentration than when it entered. The capillaries will ultimately unite to form venules, joining to form ever-larger veins, eventually flowing into the two major systemic veins, the **superior vena cava** and the **inferior vena cava**, which return blood to the right atrium. The blood in the superior and inferior venae cavae flows into the right atrium, which pumps blood into the right ventricle. This process of blood circulation continues as long as the individual remains alive. Understanding the flow of blood through the pulmonary and systemic circuits is critical to all health professions.



Dual System of the Human Blood Circulation

Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon dioxide and

wastes in), blood returns to the right atrium and the cycle is repeated.

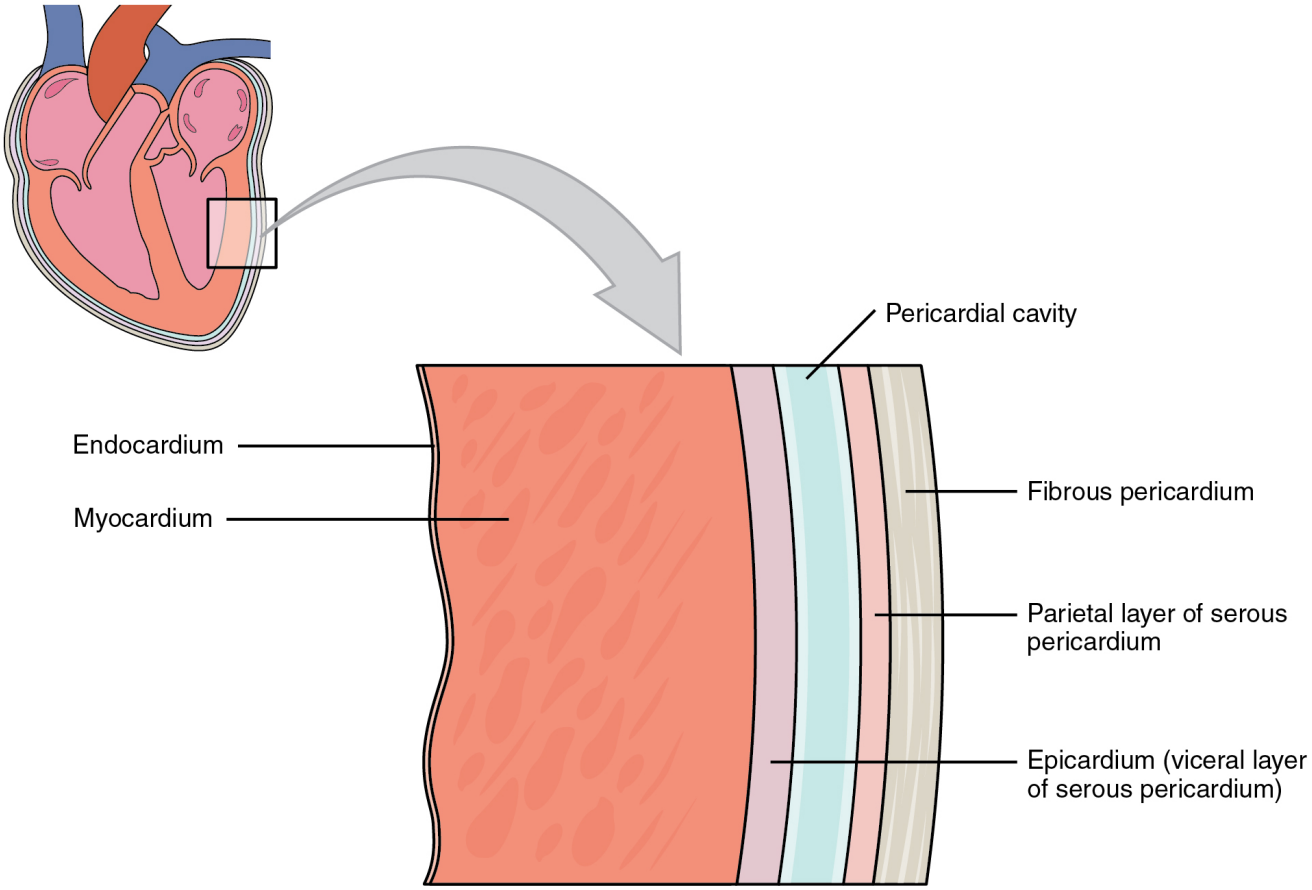
Membranes, Surface Features, and Layers

Our exploration of more in-depth heart structures begins by examining the membrane that surrounds the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.

Membranes

The membrane that directly surrounds the heart and defines the pericardial cavity is called the pericardium or pericardial sac. It also surrounds the "roots" of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as "around the heart," consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or **epicardium**, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a **mesothelium**, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts. The figure below illustrates the pericardial membrane and the layers of the heart.



Pericardial Membranes and Layers of the Heart Wall The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

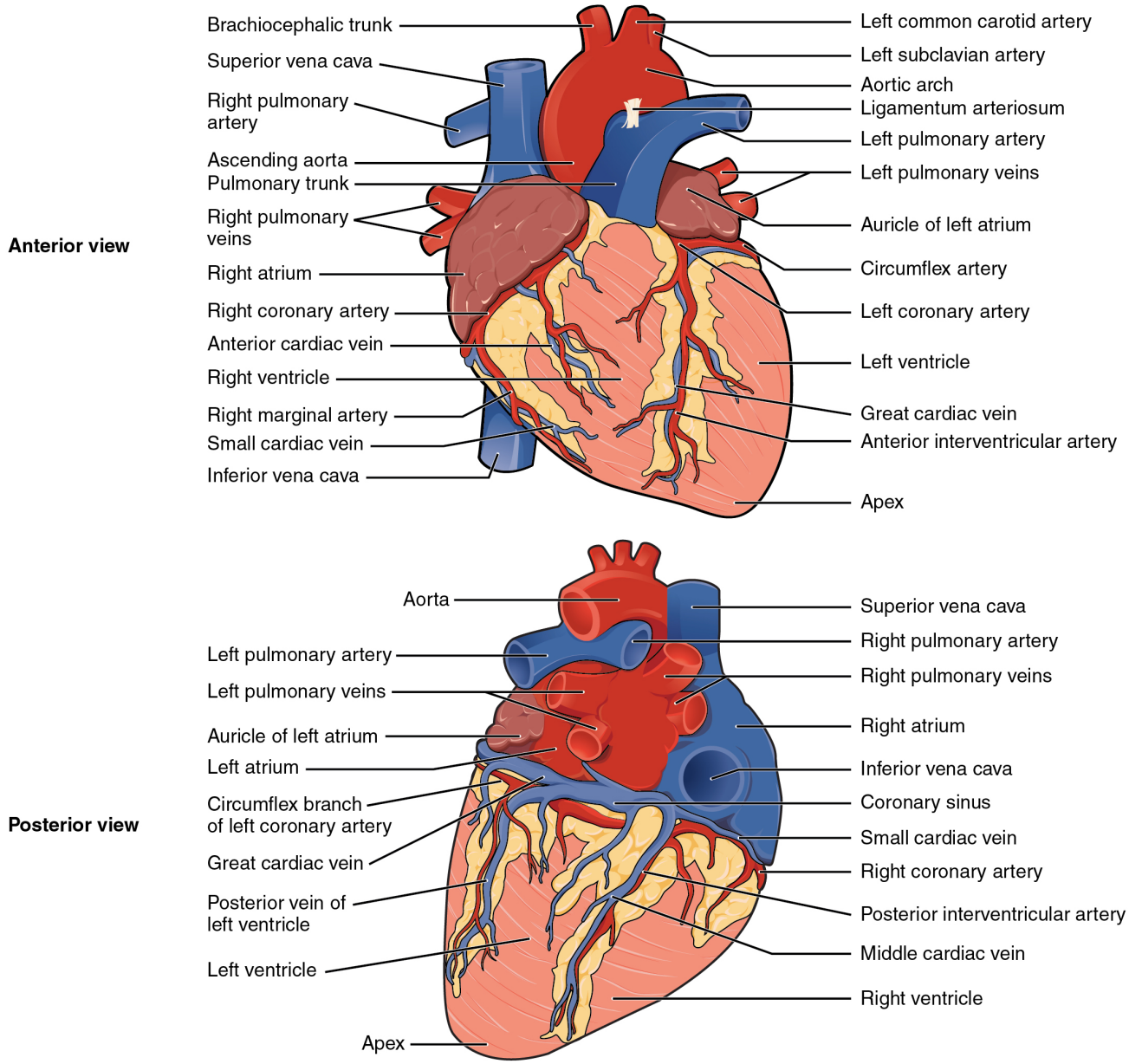
Disorders of the Heart

Cardiac Tamponade If excess fluid builds within the pericardial space, it can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates within the pericardial cavity. In order to fill with blood for the next contraction, the heart must relax. However, the excess fluid in the pericardial cavity puts pressure on the heart and prevents full relaxation, so the chambers within the heart contain slightly less blood as they begin each heart cycle. Over time, less and less blood is ejected from the heart. If the fluid builds up slowly, as in hypothyroidism, the pericardial cavity may be able to expand gradually to accommodate this extra volume. Some cases of fluid in excess of one liter within the pericardial cavity have been reported. Rapid accumulation of as little as 100 mL of fluid following trauma may trigger cardiac tamponade. Other common causes include myocardial rupture, pericarditis, cancer, or even cardiac surgery. Removal of this excess fluid requires insertion of drainage tubes into the pericardial cavity. Premature removal of these drainage tubes, for example, following cardiac surgery,

or clot formation within these tubes are causes of this condition. Untreated, cardiac tamponade can lead to death.

Surface Features of the Heart

Inside the pericardium, the surface features of the heart are visible, including the four chambers. There is a superficial leaf-like extension of the atria near the superior surface of the heart, one on each side, called an **auricle**—a name that means "ear like"—because its shape resembles the external ear of a human. Auricles are relatively thin-walled structures that can fill with blood and empty into the atria or upper chambers of the heart. You may also hear them referred to as atrial appendages. Also prominent is a series of fat-filled grooves, each of which is known as a **sulcus** (plural = sulci), along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci. The deep **coronary sulcus** is located between the atria and ventricles. Located between the left and right ventricles are two additional sulci that are not as deep as the coronary sulcus. The anterior interventricular sulcus is visible on the anterior surface of the heart, whereas the **posterior interventricular sulcus** is visible on the posterior surface of the heart. The figure below illustrates anterior and posterior views of the surface of the heart.



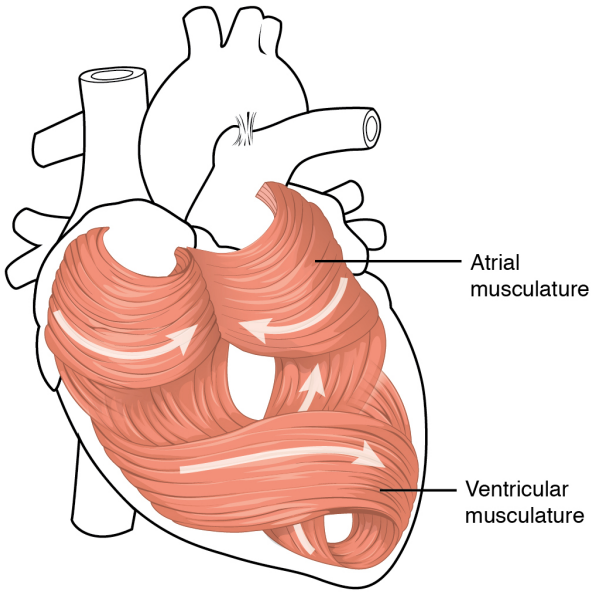
External Anatomy of the Heart Inside the pericardium, the surface features of the heart are visible.

Layers

The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the **myocardium**, and the **endocardium**. The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.

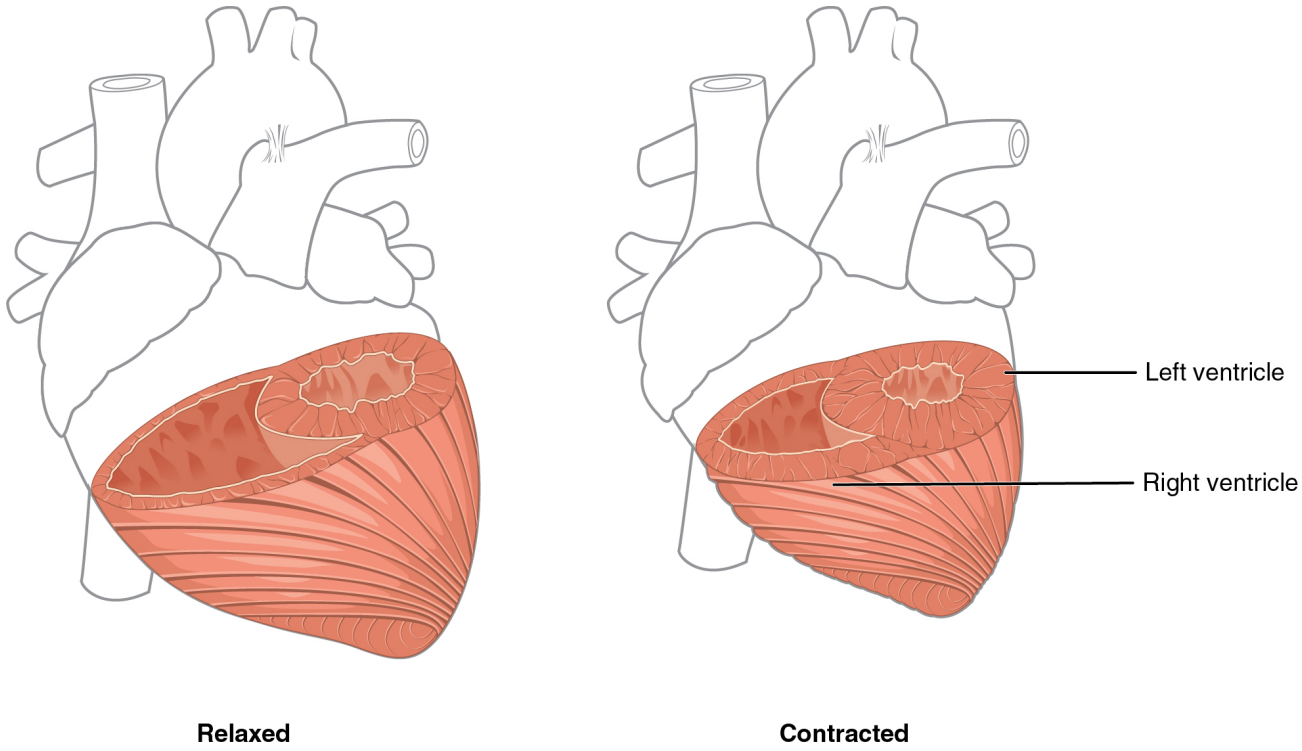
The middle and thickest layer is the myocardium, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure

8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. The image below illustrates the arrangement of muscle cells.



Heart Musculature The swirling pattern of cardiac muscle tissue contributes significantly to the heart's ability to pump blood effectively.

Although the ventricles on the right and left sides pump the same amount of blood per contraction, the muscle of the left ventricle is much thicker and better developed than that of the right ventricle. In order to overcome the high resistance required to pump blood into the long systemic circuit, the left ventricle must generate a great amount of pressure. The right ventricle does not need to generate as much pressure, since the pulmonary circuit is shorter and provides less resistance. The image below illustrates the differences in muscular thickness needed for each of the ventricles.



Differences in Ventricular Muscle Thickness

The myocardium in the left ventricle is significantly thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed and contracting states. Note the differences in the relative size of the lumens, the region inside each ventricle where the blood is contained.

The innermost layer of the heart wall, the endocardium, is joined to the myocardium with a thin layer of connective tissue. The endocardium lines the chambers where the blood circulates and covers the heart **valves**. It is made of simple squamous epithelium called **endothelium**, which is continuous with the endothelial lining of the blood vessels.

Once regarded as a simple lining layer, recent evidence indicates that the endothelium of the endocardium and the coronary capillaries may play active roles in regulating the contraction of the muscle within the myocardium. The endothelium may also regulate the growth patterns of the cardiac muscle cells throughout life, and the endothelins it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

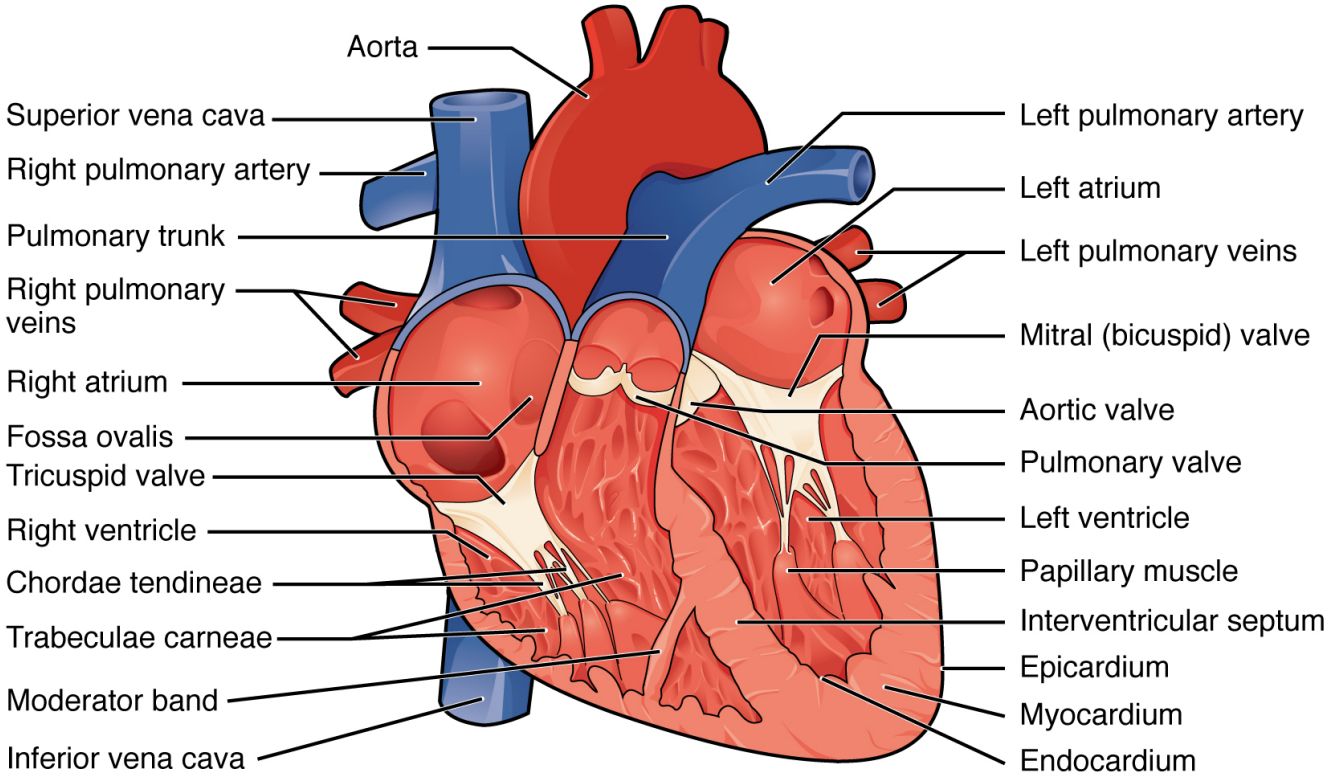
Internal Structure of the Heart

Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

The word **septum** is derived from the Latin for "something that encloses;" in this case, a septum (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the **interatrial septum**. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the **fossa ovalis**, a remnant of an opening in the fetal heart known as the **foramen ovale**. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the **septum primum** that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.
Between the two ventricles is a second septum known as the **interventricular septum**. Unlike the interatrial septum, the interventricular septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the **atrioventricular septum**. It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a valve, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as **atrioventricular valves**. The valves at the openings that lead to the pulmonary trunk and aorta are known generically as **semilunar valves**. The interventricular septum is visible in the image below. In this figure, the **atrioventricular septum** has been removed to better show the bicuspid and **tricuspid valves**; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the **atrioventricular septum**, the remaining tissue is heavily reinforced with dense connective tissue called the **cardiac skeleton**, or skeleton of the heart. It includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.



Anterior view

Internal Structures of the Heart This anterior view of the heart shows the four chambers, the major vessels and their early branches, as well as the valves. The presence of the pulmonary trunk and aorta covers the interatrial septum, and the atrioventricular septum is cut away to show the atrioventricular valves.

Disorders of the Heart: Heart Defects

Septal heart defects

One very common form of interatrial septum pathology is patent foramen ovale, which occurs when the septum primum does not close at birth, and the fossa ovalis is unable to fuse. The word patent is from the Latin root patens for "open." It may be benign or asymptomatic, perhaps never being diagnosed, or in extreme cases, it may require surgical repair to close the opening permanently. As much as 20–25 percent of the general population may have a patent foramen ovale, but fortunately, most have the benign, asymptomatic version. Patent foramen ovale is normally detected by auscultation of a heart murmur (an abnormal heart sound) and confirmed by imaging with an echocardiogram. Despite its prevalence in the general population, the causes of

patent ovale are unknown, and there are no known risk factors. In nonlife-threatening cases, it is better to monitor the condition than to risk heart surgery to repair and seal the opening.

Coarctation of the aorta is a congenital abnormal narrowing of the aorta that is normally located at the insertion of the ligamentum arteriosum, the remnant of the fetal shunt called the ductus arteriosus. If severe, this condition drastically restricts blood flow through the primary systemic artery, which is life threatening. In some individuals, the condition may be fairly benign and not detected until later in life. Detectable symptoms in an infant include difficulty breathing, poor appetite, trouble feeding, or failure to thrive. In older individuals, symptoms include dizziness, fainting, shortness of breath, chest pain, fatigue, headache, and nosebleeds. Treatment involves surgery to resect (remove) the affected region or angioplasty to open the abnormally narrow passageway. Studies have shown that the earlier the surgery is performed, the better the chance of survival.

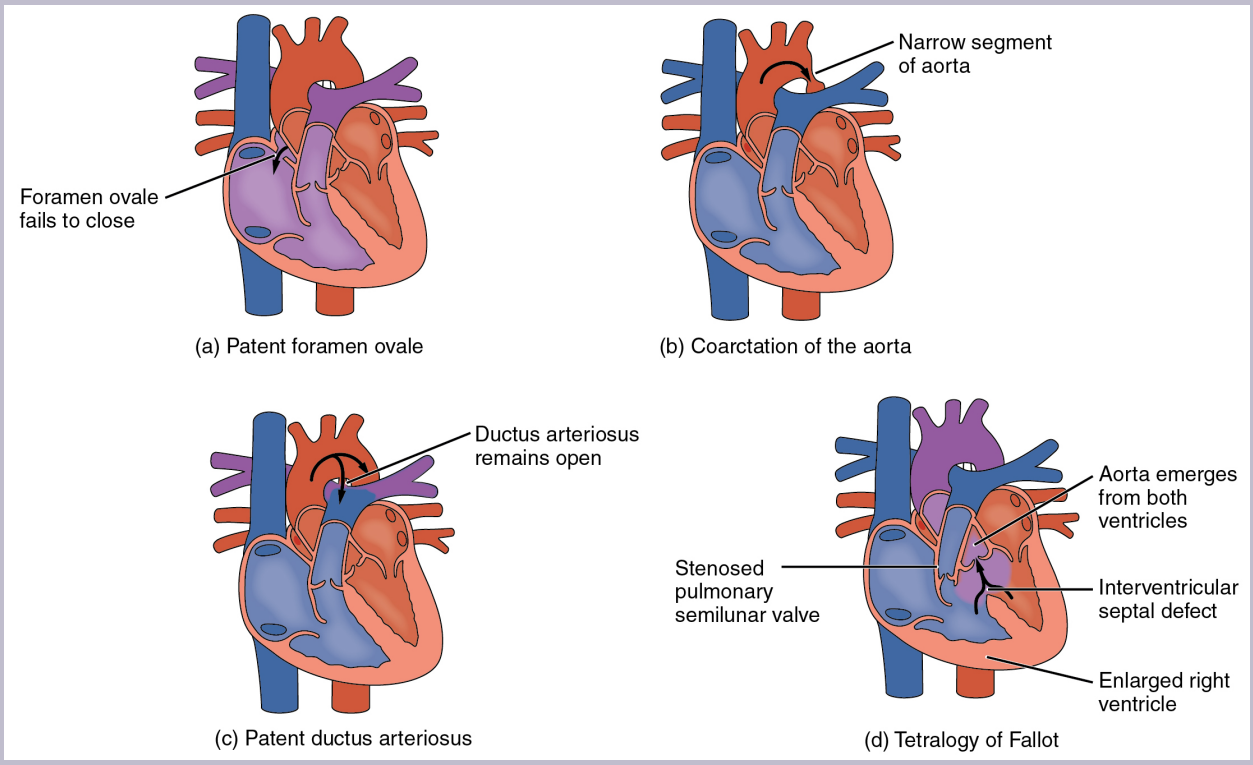
A patent ductus arteriosus is a congenital condition in which the ductus arteriosus fails to close. The condition may range from severe to benign. Failure of the ductus arteriosus to close results in blood flowing from the higher pressure aorta into the lower pressure pulmonary trunk. This additional fluid moving toward the lungs increases pulmonary pressure and makes respiration difficult. Symptoms include shortness of breath (dyspnea), tachycardia, enlarged heart, a widened pulse pressure, and poor weight gain in infants. Treatments include surgical closure (ligation), manual closure using platinum coils or specialized mesh inserted via the femoral artery or vein, or nonsteroidal anti-inflammatory drugs to block the synthesis of prostaglandin E2, which maintains the vessel in an open position. If untreated, the condition can result in congestive heart failure.

Septal defects are not uncommon in individuals and may be congenital or caused by various disease processes. Tetralogy of Fallot is a congenital condition that may also occur from exposure to unknown environmental factors; it occurs when there is an opening in the interventricular septum caused by blockage of the pulmonary trunk, normally at the pulmonary semilunar valve. This allows blood that is relatively low in oxygen from the right ventricle to flow into the left ventricle and mix with the blood that is relatively high in oxygen. Symptoms include a distinct heart murmur, low blood oxygen percent saturation, dyspnea or difficulty in breathing, polycythemia, broadening (clubbing) of the fingers and toes, and in children, difficulty in feeding or failure to grow and develop. It is the most common cause of cyanosis following birth. The term “tetralogy” is derived from the four components of the condition, although only three may be present in an individual patient: pulmonary infundibular stenosis (rigidity of the pulmonary valve), overriding aorta (the aorta is shifted above both ventricles), ventricular septal defect (opening), and right ventricular hypertrophy (enlargement of the right ventricle). Other heart defects may also accompany this condition, which is typically confirmed by echocardiography imaging. Tetralogy of Fallot occurs in approximately 400 out of one million live births. Normal treatment involves extensive surgical repair, including the use of stents to redirect blood flow and replacement of valves and patches to repair the septal defect, but the condition has a relatively high mortality. Survival rates are currently 75 percent during the first year of life; 60 percent by 4 years of age; 30 percent by 10 years; and 5 percent by 40 years.

In the case of severe septal defects, including both tetralogy of Fallot and patent foramen ovale, failure of the heart to develop properly can lead to a condition commonly known as a “blue baby.” Regardless of normal skin pigmentation, individuals with this condition have an insufficient supply of oxygenated blood, which leads to cyanosis, a blue or purple coloration of the skin, especially when active.

Septal defects are commonly first detected through auscultation, listening to the chest using a stethoscope. In this case, instead of hearing normal heart sounds attributed to the flow of blood and closing of heart valves, unusual heart sounds may be detected. This is often followed by medical imaging to confirm or rule out a diagnosis. In many cases, treatment may not be needed. Some common congenital heart defects are illustrated in below.

Congenital Heart Defects



(a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d) Tetralogy of Fallot includes an abnormal opening in the interventricular septum.

Right Atrium

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic circulation. The two major systemic veins, the superior and inferior venae cavae, and the large coronary vein called the **coronary sinus** that drains the heart myocardium empty into the right atrium. The superior vena cava drains blood from regions superior to the diaphragm: the head, neck, upper limbs, and the thoracic region. It empties into the superior and posterior portions of the right atrium. The inferior vena cava drains blood from areas inferior to the diaphragm: the lower limbs and abdominopelvic region of the body. It, too, empties into the posterior portion of the atria, but inferior to the opening of the superior vena cava. Immediately superior and slightly medial to the opening of the inferior vena cava on the posterior surface of the atrium is the opening of the coronary sinus. This thin-walled vessel drains most of the **coronary veins** that return systemic blood from the heart. The majority of the internal heart structures discussed in this and subsequent sections are illustrated in the internal structures of the heart image.

While the bulk of the internal surface of the right atrium is smooth, the depression of the fossa ovalis is medial, and the anterior surface demonstrates prominent ridges of muscle called the **pectinate muscles**. The right auricle also has pectinate muscles. The left atrium does not have pectinate muscles except in the auricle.

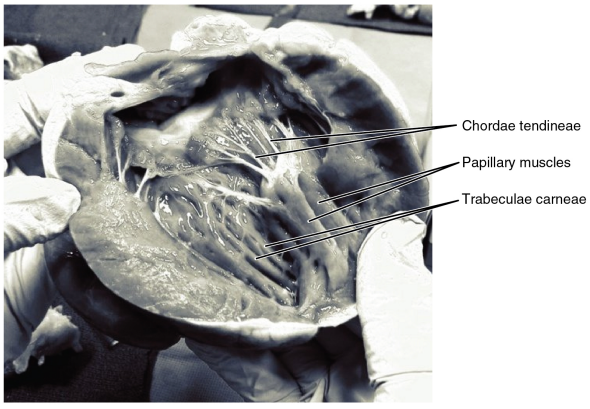
The atria receive venous blood on a nearly continuous basis, preventing venous flow from stopping while the ventricles are contracting. While most ventricular filling occurs while the atria are relaxed, they do demonstrate a contractile phase and actively pump blood into the ventricles just prior to ventricular contraction. The opening between the atrium and ventricle is guarded by the tricuspid valve.

Right Ventricle

The right ventricle receives blood from the right atrium through the tricuspid valve. Each flap of the valve is attached to strong strands of connective tissue, the **chordae tendineae**, literally "tendinous cords," or sometimes more poetically referred to as "heart strings." There are several chordae tendineae associated with each of the flaps. They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the flaps to a **papillary muscle** that extends from the inferior ventricular surface. There are three papillary muscles in the right ventricle, called the anterior, posterior, and septal muscles, which correspond to the three sections of the valves.

When the myocardium of the ventricle contracts, pressure within the ventricular chamber rises. Blood, like any fluid, flows from higher pressure to lower pressure areas, in this case, toward the pulmonary trunk and the atrium. To prevent any potential backflow, the papillary muscles also contract, generating tension on the chordae tendineae. This prevents the flaps of the valves from being forced into the atria and regurgitation of the blood back into the atria during ventricular contraction. Image below shows papillary muscles and chordae tendineae attached to the tricuspid valve.

Chordae Tendineae and Papillary Muscles



In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae. (credit: modification of work by "PV KS"/flickr.com)

The walls of the ventricle are lined with **trabeculae carneae**, ridges of cardiac muscle covered by endocardium. In addition to these muscular ridges, a band of cardiac muscle, also covered by endocardium, known as the **moderator band** The image above reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It

arises from the inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

Left Atrium

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the **mitral valve**.

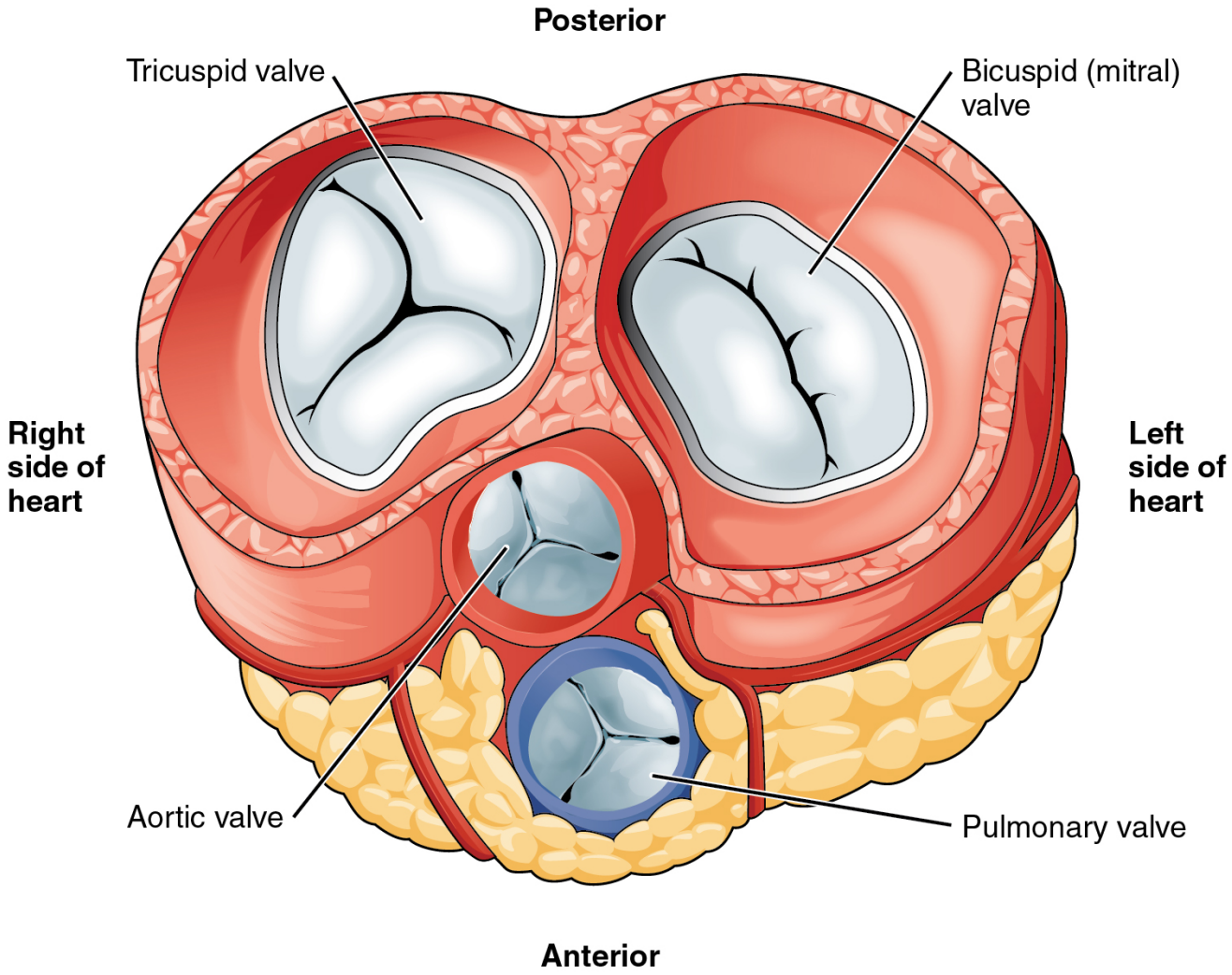
Left Ventricle

Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right. Like the right ventricle, the left also has trabeculae carneae, but there is no moderator band. The mitral valve is connected to papillary muscles via chordae tendineae. There are two papillary muscles on the left—the anterior and posterior—as opposed to three on the right.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

Heart Valve Structure and Function

A transverse section through the heart slightly above the level of the **atrioventricular septum** reveals all four heart valves along the same plane. The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the **right atrioventricular valve**, or tricuspid valve. It typically consists of three flaps, or leaflets, made of endocardium reinforced with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves.



Heart Valves – With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

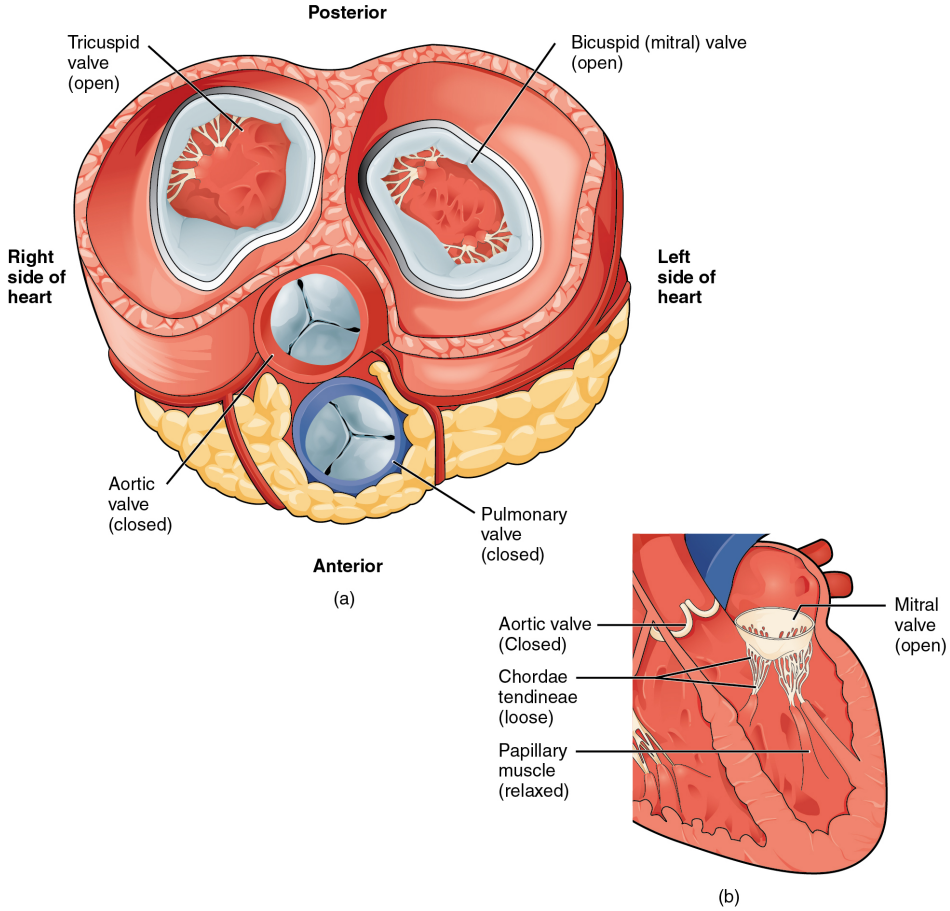
Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or the **pulmonary valve**; it is also known as the pulmonic valve or the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes, the pressure differential causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close and producing an audible sound. Unlike the **atrioventricular valves**, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

Located at the opening between the left atrium and left ventricle is the mitral valve, also called the **bicuspid valve** or the **left atrioventricular valve**. Structurally, this valve consists of two cusps, known as the anterior medial cusp and the posterior medial cusp, compared to the three cusps of the tricuspid valve. In a clinical setting, the valve is referred to as the mitral valve, rather than the bicuspid valve. The two cusps of the mitral valve are attached by chordae tendineae to two papillary muscles that project from the wall of the ventricle.

At the base of the aorta is the aortic semilunar valve, or the **aortic valve**, which prevents backflow from the aorta. It

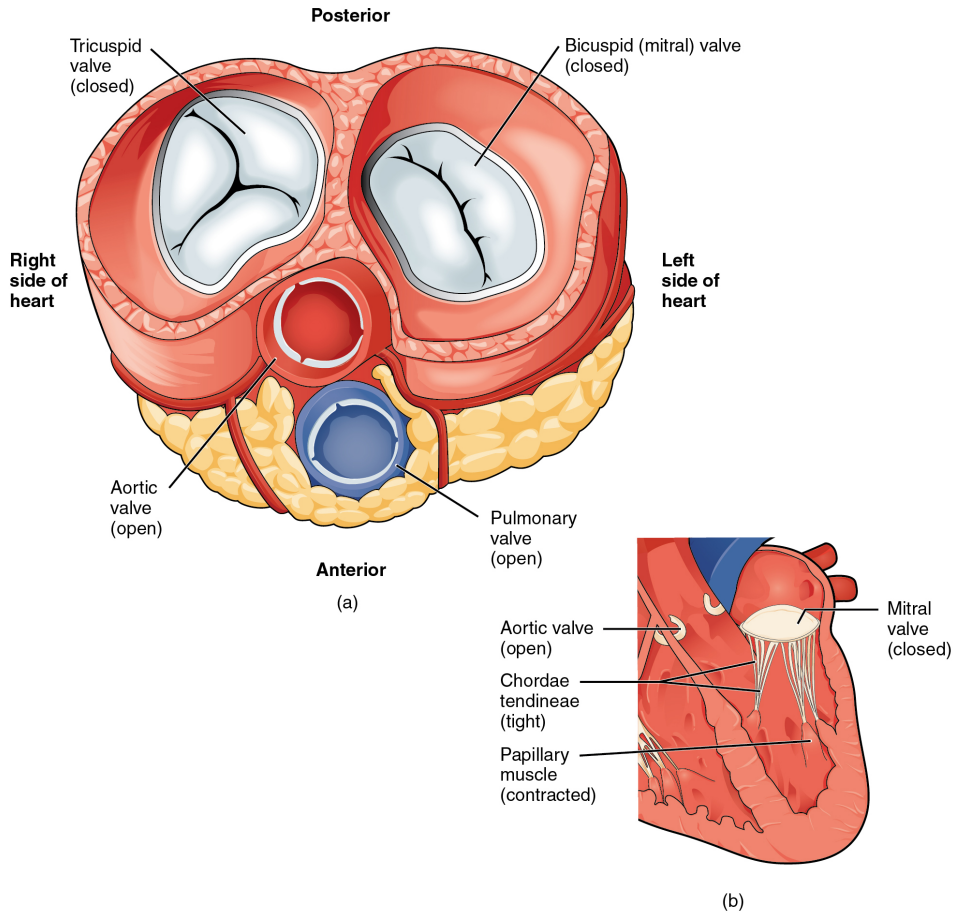
normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

In the image below, the two **atrioventricular valves** are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and when the atria contract to pump blood into the ventricles. Although only the left side of the heart is illustrated, the process is virtually identical on the right.



Blood Flow from the Left Atrium to the Left Ventricle (a) A transverse section through the heart illustrates the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the mitral valve is open, it allows blood to move from the left atrium to the left ventricle. The aortic semilunar valve is closed to prevent backflow of blood from the aorta to the left ventricle.

The image below shows the **atrioventricular valves** closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two **atrioventricular valves** prevents blood from being forced back into the atria. This stage can be seen from a frontal view in below.



Blood Flow from the Left Ventricle into the Great Vessels (a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.

When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the papillary muscles are also relaxed and the tension on the chordae tendineae is slight. However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae, helping to hold the cusps of the **atrioventricular valves** in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the **atrioventricular valves**. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

Visit Diagnosis of Heart Failure to hear from a cardiac sonographer and observe an echocardiogram of

actual heart valves opening and closing. Although much of the heart isn't visible from this video loop such that the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Examples: Disorders of the Heart Valves

When heart valves do not function properly, they are often described as incompetent and result in valvular heart disease, which can range from benign to lethal. Some of these conditions are congenital, that is, the individual was born with the defect, whereas others may be attributed to disease processes or trauma. Some malfunctions are treated with medications, others require surgery, and still others may be mild enough that the condition is merely monitored since treatment might trigger more serious consequences. Valvular disorders are often caused by carditis, or inflammation of the heart. One common trigger for this inflammation is rheumatic fever, or scarlet fever, an autoimmune response to the presence of a bacterium, *Streptococcus pyogenes*, normally a disease of childhood.

While any of the heart valves may be involved in valve disorders, mitral regurgitation is the most common, detected in approximately 2 percent of the population, and the pulmonary semilunar valve is the least frequently involved. When a valve malfunctions, the flow of blood to a region will often be disrupted. The resulting inadequate flow of blood to this region will be described in general terms as an insufficiency. The specific type of insufficiency is named for the valve involved: aortic insufficiency, mitral insufficiency, tricuspid insufficiency, or pulmonary insufficiency.

If one of the cusps of the valve is forced backward by the force of the blood, the condition is referred to as a prolapsed valve. Prolapse may occur if the chordae tendineae are damaged or broken, causing the closure mechanism to fail. The failure of the valve to close properly disrupts the normal one-way flow of blood and results in regurgitation, when the blood flows backward from its normal path. Using a stethoscope, the disruption to the normal flow of blood produces a heart murmur.

Stenosis is a condition in which the heart valves become rigid and may calcify over time. The loss of flexibility of the valve interferes with normal function and may cause the heart to work harder to propel blood through the valve, which eventually weakens the heart. Aortic stenosis affects approximately 2 percent of the population over 65 years of age, and the percentage increases to approximately 4 percent in individuals over 85 years. Occasionally, one or more of the chordae tendineae will tear or the papillary muscle itself may die as a component of a myocardial infarction (heart attack). In this case, the patient's condition will deteriorate dramatically and rapidly, and immediate surgical intervention may be required.

Auscultation, or listening to a patient's heart sounds, is one of the most useful diagnostic tools, since it is proven, safe, and inexpensive. The term auscultation is derived from the Latin for "to listen," and the technique has been used for diagnostic purposes as far back as the ancient Egyptians. Valve and septal disorders will trigger abnormal heart sounds. If a valvular disorder is detected or suspected, a test called an echocardiogram, or simply an "echo," may be ordered. Echocardiograms are sonograms of the heart and can help in the diagnosis of valve disorders as well as a wide variety of heart pathologies.

Career Connection

Cardiologists are medical doctors that specialize in the diagnosis and treatment of diseases of the heart. After completing 4 years of medical school, cardiologists complete a three-year residency in internal medicine followed by an additional three or more years in cardiology. Following this 10-year period of medical training and clinical experience, they qualify for a rigorous two-day examination administered by the Board of Internal Medicine that tests their academic training and clinical abilities, including diagnostics and treatment. After successful completion of this examination, a physician becomes a board-certified cardiologist. Some board-certified cardiologists may be invited to become a Fellow of the American College of Cardiology (FACC). This professional recognition is awarded to outstanding physicians based upon merit, including outstanding credentials, achievements, and community contributions to cardiovascular medicine.

Visit the American College of Cardiology to learn more about cardiologists.

Cardiovascular Technologist/Technicians are trained professionals who perform a variety of imaging techniques, such as sonograms or echocardiograms, used by physicians to diagnose and treat diseases of the heart. Nearly all of these positions require an associate degree, and these technicians earn a median salary of $70,000 as of May 2020, according to the U.S. Bureau of Labor Statistics. Growth within the field is fast, projected at 29 percent from 2010 to 2020.

There is a considerable overlap and complementary skills between cardiac technicians and vascular technicians, and so the term cardiovascular technician is often used. Special certifications within the field require documenting appropriate experience and completing additional and often expensive certification examinations. These subspecialties include Certified Rhythm Analysis Technician (CRAT), Certified Cardiographic Technician (CCT), Registered Congenital Cardiac Sonographer (RCCS), Registered Cardiac Electrophysiology Specialist (RCES), Registered Cardiovascular Invasive Specialist (RCIS), Registered Cardiac Sonographer (RCS), Registered Vascular Specialist (RVS), and Registered Phlebology Sonographer (RPhS).

Visit this site for more information on cardiovascular technologists/technicians.

Coronary Circulation

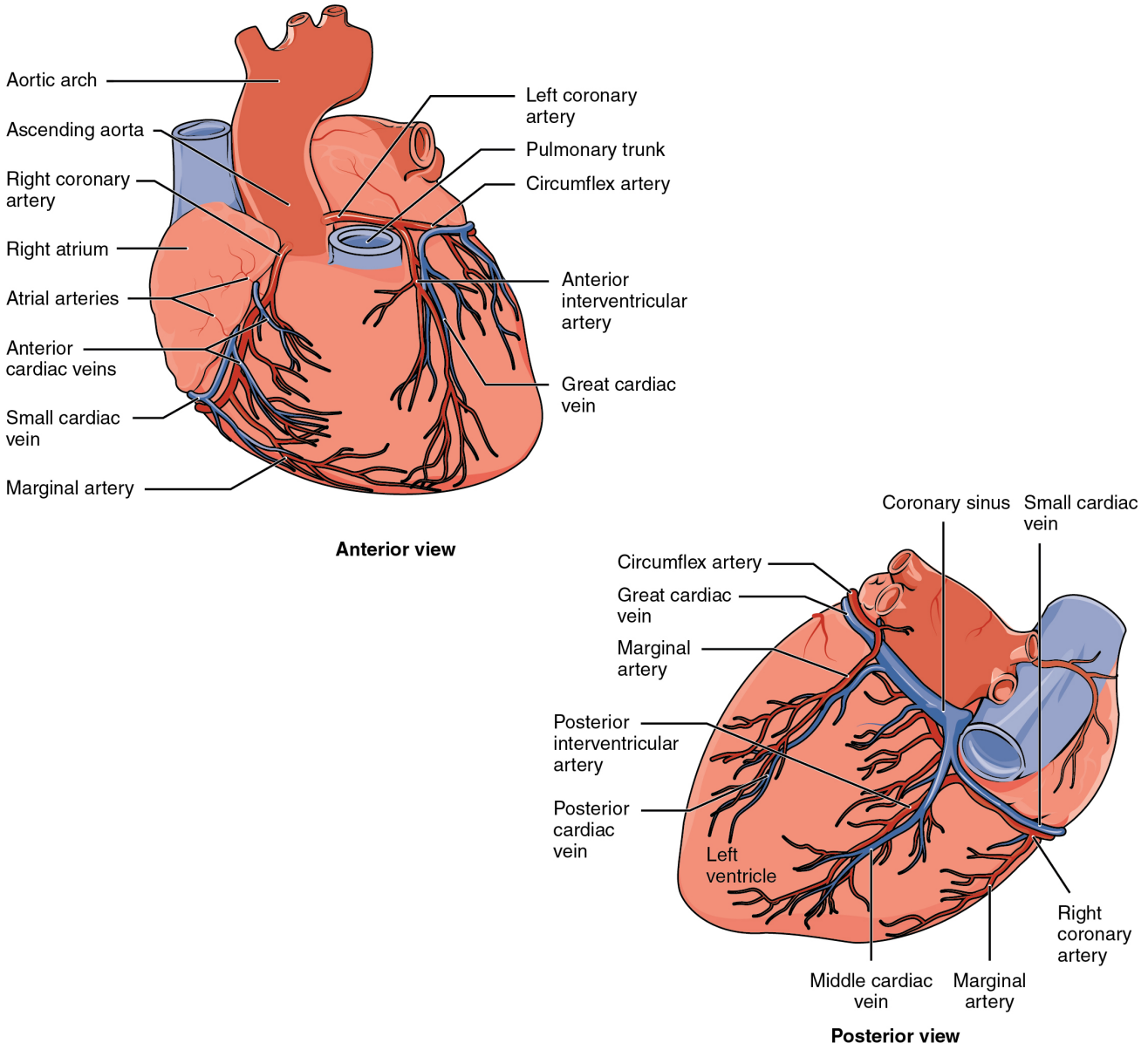
You will recall that the heart is a remarkable pump composed largely of cardiac muscle cells that are incredibly active throughout life. Like all other cells, a **cardiomyocyte** requires a reliable supply of oxygen and nutrients, and a way to remove wastes, so it needs a dedicated, complex, and extensive coronary circulation. And because of the critical and nearly ceaseless activity of the heart throughout life, this need for a blood supply is even greater than for a typical cell. However, coronary circulation is not continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

Coronary Arteries

Coronary arteries supply blood to the myocardium and other components of the heart. The first portion of the aorta after it arises from the left ventricle gives rise to the coronary arteries. There are three dilations in the wall of the aorta just superior to the aortic semilunar valve. Two of these, the left posterior aortic sinus and anterior aortic sinus, give rise to the left and right coronary arteries, respectively. The third sinus, the right posterior aortic sinus, typically does not give rise to a vessel. Coronary vessel branches that remain on the surface of the artery and follow the sulci are called **epicardial coronary arteries**.

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The **circumflex artery** arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery. The larger **anterior interventricular artery**, also known as the left anterior descending artery (LAD), is the second major branch arising from the left coronary artery. It follows the **anterior interventricular sulcus** around the pulmonary trunk. Along the way it gives rise to numerous smaller branches that interconnect with the branches of the **posterior interventricular artery**, forming anastomoses. An **anastomosis** is an area where vessels unite to form interconnections that normally allow blood to circulate to a region even if there may be partial blockage in another branch. The anastomoses in the heart are very small. Therefore, this ability is somewhat restricted in the heart so a coronary artery blockage often results in death of the cells (myocardial infarction) supplied by the particular vessel.

The right coronary artery proceeds along the coronary sulcus and distributes blood to the right atrium, portions of both ventricles, and the heart conduction system. Normally, one or more **marginal arteries** arise from the right coronary artery inferior to the right atrium. The marginal arteries supply blood to the superficial portions of the right ventricle. On the posterior surface of the heart, the right coronary artery gives rise to the posterior interventricular artery, also known as the posterior descending artery. It runs along the posterior portion of the interventricular sulcus toward the apex of the heart, giving rise to branches that supply the interventricular septum and portions of both ventricles. The image below presents views of the coronary circulation from both the anterior and posterior views.



Coronary Circulation The anterior view of the heart shows the prominent coronary surface vessels. The posterior view of the heart shows the prominent coronary surface vessels.

Diseases of the Heart: Myocardial Infarction (MI)

Myocardial infarction (MI) is the formal term for what is commonly referred to as a heart attack. It normally results from a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart, resulting in death of the cardiac muscle cells. An MI often occurs when a coronary artery is blocked by the buildup of

atherosclerotic plaque consisting of lipids, cholesterol and fatty acids, and white blood cells, primarily macrophages. It can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels. The resulting blockage restricts the flow of blood and oxygen to the myocardium and causes death of the tissue. MIs may be triggered by excessive exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel. In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms.

An MI can be confirmed by examining the patient's ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells.

Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future.

MIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as "bad" cholesterol), low levels of high-density lipoprotein (HDL, or "good" cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

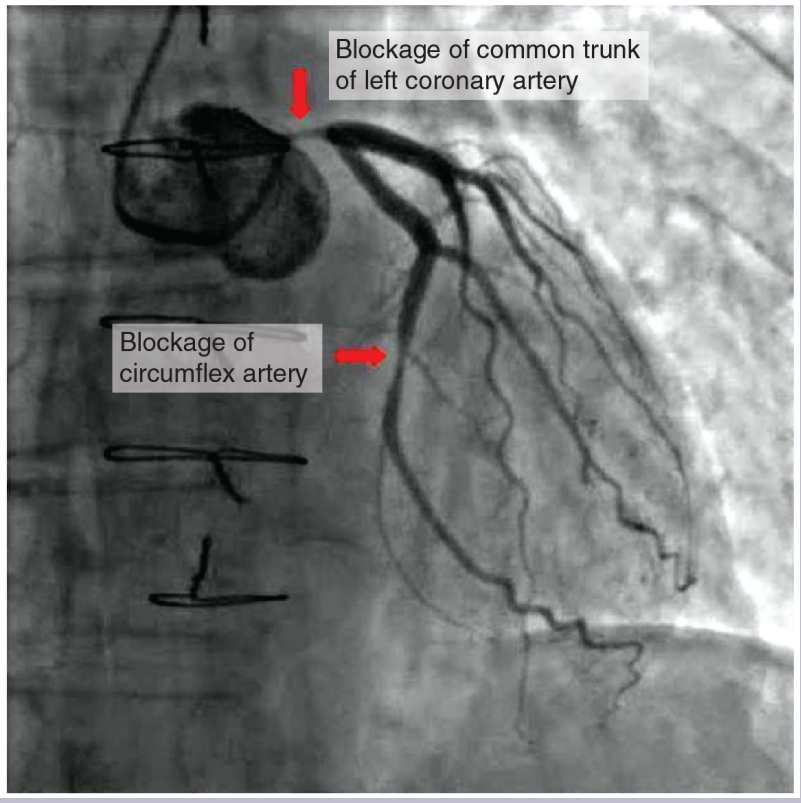
Coronary Veins

Coronary veins drain the heart and generally parallel the large surface arteries. The **great cardiac vein** can be seen initially on the surface of the heart following the interventricular sulcus, but it eventually flows along the coronary sulcus into the coronary sinus on the posterior surface. The great cardiac vein initially parallels the **anterior interventricular artery** and drains the areas supplied by this vessel. It receives several major branches, including the posterior cardiac vein, the **middle cardiac vein**, and the **small cardiac vein**. The **posterior cardiac vein** parallels and

drains the areas supplied by the marginal artery branch of the circumflex artery. The middle cardiac vein parallels and drains the areas supplied by the posterior interventricular artery. The small cardiac vein parallels the right coronary artery and drains the blood from the posterior surfaces of the right atrium and ventricle. The coronary sinus is a large, thin-walled vein on the posterior surface of the heart lying within the atrioventricular sulcus and emptying directly into the right atrium. The **anterior cardiac veins** parallel the small cardiac arteries and drain the anterior surface of the right ventricle. Unlike these other cardiac veins, it bypasses the coronary sinus and drains directly into the right atrium.

Diseases of the Heart: Coronary Artery Disease

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque—a fatty material including cholesterol, connective tissue, white blood cells, and some smooth muscle cells—within the walls of the arteries obstructs the flow of blood and decreases the flexibility or compliance of the vessels. This condition is called atherosclerosis, a hardening of the arteries that involves the accumulation of plaque. As the coronary blood vessels become occluded, the flow of blood to the tissues will be restricted, a condition called ischemia that causes the cells to receive insufficient amounts of oxygen, called hypoxia. The image below shows the blockage of coronary arteries highlighted by the injection of dye. Some individuals with coronary artery disease report pain radiating from the chest called angina pectoris, but others remain asymptomatic. If untreated, coronary artery disease can lead to MI or a heart attack.



Atherosclerotic Coronary Arteries In this coronary angiogram (X-ray), the dye makes visible two occluded coronary arteries. Such blockages can lead to decreased blood flow (ischemia) and insufficient oxygen (hypoxia) delivered to the cardiac tissues. If uncorrected, this can lead to cardiac muscle death (myocardial infarction).

The disease progresses slowly and often begins in children and can be seen as fatty "streaks" in the vessels. It then gradually progresses throughout life. Well-documented risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia or high circulating levels of lipids in the blood. Treatments may include medication, changes to diet and exercise, angioplasty with a balloon catheter, insertion of a stent, or coronary bypass procedure.

Angioplasty is a procedure in which the occlusion is mechanically widened with a balloon. A specialized catheter with an expandable tip is inserted into a superficial vessel, normally in the leg, and then directed to the site of the occlusion. At this point, the balloon is inflated to compress the plaque material and to open the vessel to increase blood flow. Then, the balloon is deflated and retracted. A stent consisting of a specialized mesh is typically inserted at the site of occlusion to reinforce the weakened and damaged walls. Stent insertions have been routine in cardiology for more than 40 years.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine

regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

Section Review

The heart resides within the pericardial sac and is located in the mediastinal space within the thoracic cavity. The pericardial sac consists of two fused layers: an outer fibrous capsule and an inner parietal pericardium lined with a serous membrane. Between the pericardial sac and the heart is the pericardial cavity, which is filled with lubricating serous fluid. The walls of the heart are composed of an outer epicardium, a thick myocardium, and an inner lining layer of endocardium. The human heart consists of a pair of atria, which receive blood and pump it into a pair of ventricles, which pump blood into the vessels. The right atrium receives systemic blood relatively low in oxygen and pumps it into the right ventricle, which pumps it into the pulmonary circuit. Exchange of oxygen and carbon dioxide occurs in the lungs, and blood high in oxygen returns to the left atrium, which pumps blood into the left ventricle, which in turn pumps blood into the aorta and the remainder of the systemic circuit. The septa are the partitions that separate the chambers of the heart. They include the interatrial septum, the interventricular septum, and the **atrioventricular septum**. Two of these openings are guarded by the **atrioventricular valves**, the right tricuspid valve and the left mitral valve, which prevent the backflow of blood. Each is attached to chordae tendineae that extend to the papillary muscles, which are extensions of the myocardium, to prevent the valves from being blown back into the atria. The pulmonary valve is located at the base of the pulmonary trunk, and the left semilunar valve is located at the base of the aorta. The right and left coronary arteries are the first to branch off the aorta and arise from two of the three sinuses located near the base of the aorta and are generally located in the sulci. Cardiac veins parallel the small cardiac arteries and generally drain into the coronary sinus.

Interactive Link Questions

Visit this echocardiogram of heart valves to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been "removed" from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the **atrioventricular valves** (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

The pressure gradient between the atria and the ventricles is much greater than that between the ventricles and the pulmonary trunk and aorta. Without the presence of the chordae tendineae and papillary muscles, the valves would be blown back (prolapsed) into the atria and blood would regurgitate.

Review Questions

1. Which of the following is *not* important in preventing backflow of blood?

- Chordae tendinae
- Papillary muscles

- AV valves
- Endocardium

2. Which valve separates the left atrium from the left ventricle?

- Mitral (bicuspid)
- Tricuspid
- Pulmonary
- Aortic

3. Which of the following lists the valves in the order through which the blood flows from the vena cava through the heart?

- Tricuspid, pulmonary semilunar, bicuspid, aortic semilunar
- Mitral, pulmonary semilunar, bicuspid, aortic semilunar
- Aortic semilunar, pulmonary semilunar, tricuspid, bicuspid
- Bicuspid, aortic semilunar, tricuspid, pulmonary semilunar

4. Which chamber initially receives blood from the systemic circuit?

- Left artrium
- Left ventricle
- Right atrium
- Right ventricle

5. Fill in the blank.

The _____ layer secretes chemicals that help to regulate ionic environments and strength of contraction and serve as powerful vasoconstrictors.

6. Fill in the blank.

The myocardium would be the thickest in the _____.

7. In which septum is it normal to find openings in the adult? Select all that apply.

- Interatrial septum
- Interventricular septum
- Atrioventricular septum

8. Describe how the valves keep the blood moving in one direction.

9. Why is the pressure in the pulmonary circulation lower than in the systemic circulation?

Answer Key

1. Endocardium
2. Mitral (bicuspid)
3. Tricuspid, pulmonary semilunar, bicuspid, aortic semilunar
4. Right atrium
5. Endocardium/endocardial
6. Left ventricle
7. Atrioventricular septum
8. When the ventricles contract and pressure begins to rise in the ventricles, there is an initial tendency for blood to flow back (regurgitate) to the atria. However, the papillary muscles also contract, placing tension on the chordae tendineae and holding the atrioventricular valves (tricuspid and mitral) in place to prevent the valves from prolapsing and being forced back into the atria. The semilunar valves (pulmonary and aortic) lack chordae tendineae and papillary muscles, but do not face the same pressure gradients as do the atrioventricular valves. As the ventricles relax and pressure drops within the ventricles, there is a tendency for the blood to flow backward. However, the valves, consisting of reinforced endothelium and connective tissue, fill with blood and seal off the opening preventing the return of blood.
9. The pulmonary circuit consists of blood flowing to and from the lungs, whereas the systemic circuit carries blood to and from the entire body. The systemic circuit is far more extensive, consisting of far more vessels and offers much greater resistance to the flow of blood, so the heart must generate a higher pressure to overcome this resistance. This can be seen in the thickness of the myocardium in the ventricles.

Adaption

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Cardiac Muscle Tissue

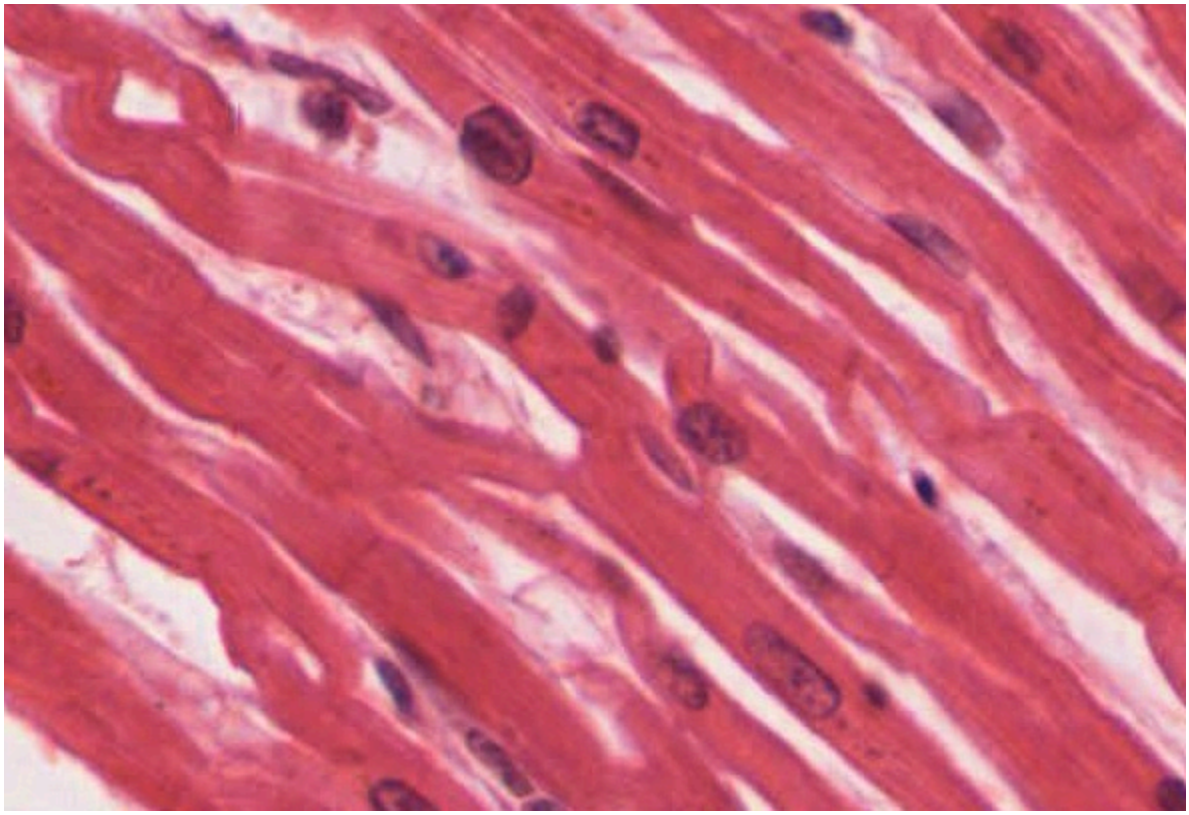
J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe intercalated discs and gap junctions.
- Describe a desmosome.

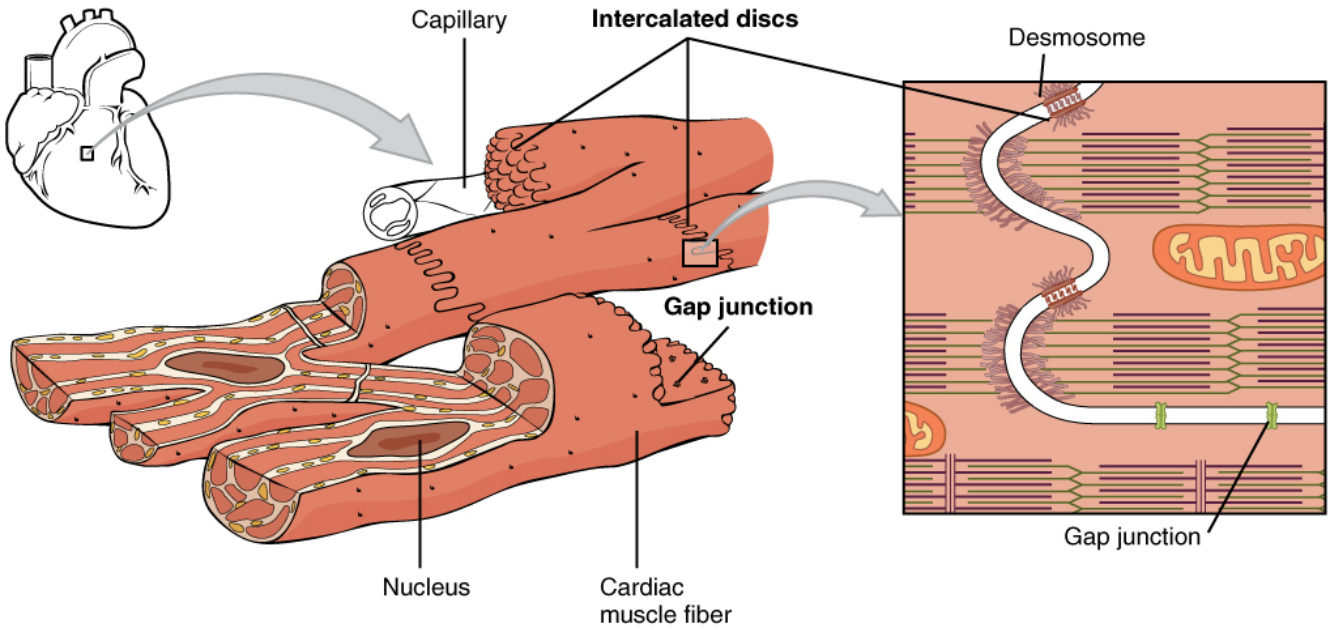
Cardiac muscle tissue is only found in the heart. Highly coordinated contractions of cardiac muscle pump blood into the vessels of the circulatory system. Similar to skeletal muscle, cardiac muscle is striated and organized into sarcomeres, possessing the same banding organization as skeletal muscle. However, cardiac muscle fibers are shorter than skeletal muscle fibers and usually contain only one nucleus, which is located in the central region of the cell. Cardiac muscle fibers also possess many mitochondria and myoglobin, as ATP is produced primarily through aerobic metabolism. Cardiac muscle fibers cells also are extensively branched and are connected to one another at their ends by **intercalated discs**. An intercalated disc allows the cardiac muscle cells to contract in a wave-like pattern so that the heart can work as a pump.



Cardiac Muscle Tissue LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

View the University of Michigan WebScope to explore the tissue sample in greater detail.

Intercalated discs are part of the sarcolemma and contain two structures important in cardiac muscle contraction: gap junctions and **desmosomes**. A gap junction forms channels between adjacent cardiac muscle fibers that allow the depolarizing current produced by cations to flow from one cardiac muscle cell to the next. This joining is called electric coupling, and in cardiac muscle it allows the quick transmission of action potentials and the coordinated contraction of the entire heart. This network of electrically connected cardiac muscle cells creates a functional unit of contraction called a syncytium. The remainder of the intercalated disc is composed of desmosomes. A desmosome is a cell structure that anchors the ends of cardiac muscle fibers together so the cells do not pull apart during the stress of individual fibers contracting.



Intercalated discs are part of the cardiac muscle sarcolemma and they contain gap junctions and desmosomes.

Contractions of the heart (heartbeats) are controlled by specialized cardiac muscle cells called pacemaker cells that directly control heart rate. Although cardiac muscle cannot be consciously controlled, the pacemaker cells respond to signals from the autonomic nervous system (ANS) to speed up or slow down the heart rate. The pacemaker cells can also respond to various hormones that modulate heart rate to control blood pressure.

The wave of contraction that allows the heart to work as a unit, called a functional syncytium, begins with the pacemaker cells. This group of cells is self-excitable and able to depolarize to threshold and fire action potentials on their own, a feature called **autorhythmicity**; they do this at set intervals which determine heart rate. Because they are connected with gap junctions to surrounding muscle fibers and the specialized fibers of the heart's conduction system, the pacemaker cells are able to transfer the depolarization to the other cardiac muscle fibers in a manner that allows the heart to contract in a coordinated manner.

Another feature of cardiac muscle is its relatively long action potentials in its fibers, having a sustained depolarization "plateau." The plateau is produced by Ca^{++} entry though voltage-gated calcium channels in the sarcolemma of cardiac muscle fibers. This sustained depolarization (and Ca^{++} entry) provides for a longer contraction than is produced by an action potential in skeletal muscle. Unlike skeletal muscle, a large percentage of the Ca^{++} that initiates contraction in cardiac muscles comes from outside the cell rather than from the SR.

Critical Thinking Exercise

Answer these questions for yourself:

- Consider the function of cardiac muscle cells

- How do the shape, structure, arrangement, size, and number of these cells support their function?
- Speculate on the level of cellular change that can affect these cells and their function.

Section Review

Cardiac muscle is striated muscle that is found exclusively in the heart. Cardiac muscle fibers are branched, contain a single nucleus, and are joined to one another by intercalated discs. These discs contain gap junctions for depolarization between cells and desmosomes to hold the fibers together when the heart contracts. Contraction in each cardiac muscle fiber is triggered by Ca^{++} ions in a similar manner as skeletal muscle, but here the Ca^{++} ions come from sarcoplasmic reticulum (SR) and through voltage-gated calcium channels in the sarcolemma. Pacemaker cells stimulate the spontaneous contraction of cardiac muscle as a functional unit, called a syncytium.

Review Questions

1. Finish the following sentence. Cardiac muscles differ from skeletal muscles in that they:

- Are striated
- Utilize aerobic metabolism
- Contain myofibrils
- Contain intercalated discs

2. Finish the following sentence. If cardiac muscle cells were prevented from undergoing aerobic metabolism, they ultimately would:

- Undergo glycolysis
- Synthesize ATP
- Stop contracting
- Start contracting

3. What would be the drawback of cardiac contractions being the same duration as skeletal muscle contractions?

4. How are cardiac muscle cells similar to and different from skeletal muscle cells?

Answer Key

1. Contain intercalated discs

2. Stop contracting
3. An action potential could reach a cardiac muscle cell before it has entered the relaxation phase, resulting in the sustained contractions of tetanus. If this happened, the heart would not beat regularly.
4. Cardiac and skeletal muscle cells both contain ordered myofibrils and are striated. Cardiac muscle cells are branched and contain intercalated discs, which skeletal muscles do not have.

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Video Lessons of Normal Heart Function, Anatomy, and Histology

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Identify the main chambers and great vessels of the normal heart.
- Describe the path blood normally takes from when it enters the right atrium to when it leaves the aorta.
- Demonstrate knowledge of histology by identifying normal myofibrils on a tissue stained with H&E.

Normal Cardiac Cycle – Interactive Video

This video is awaiting licensing approval and will be available shortly. Normal Heart Structure and Function by Jennifer Kong, licensed under All Rights Reserved

Normal Cardiac Anatomy

Of course, looking at the heart in a multicolour textbook image is very different than identifying structures in a real heart. The next video demonstrates a frontal section of the normal heart (i.e. heart is sliced into front & back). Thus, both the right and left heart structures are visible at the same time.

This video is awaiting licensing approval and will be available shortly. Normal Frontal Section of Heart by Jennifer Kong, licensed under All Rights Reserved

Normal Cardiac Histology

Before viewing this video, recall your knowledge of H&E staining of tissue preparations from “How are specimens obtained and prepared.” Key points to remember are:

- Protein-rich areas will stain pink/purple. The stronger the stain in the cytoplasm, the more protein is present.
- Nuclei will stain purplish blue. The bigger the nuclei, the more nuclear activity is present (e.g. protein synthesis).
- Cells that fulfill a single function will create tissues with little variety in cell appearance.

Critical Thinking and Histology Exercises

Answer these questions for yourself before viewing the next video:

- Consider the function of the heart wall – especially the ventricles.
    1. What is the purpose of the ventricular tissue? Will there be a need for more than one type of cell type?
    2. Will a cardiomyocyte (ie the typical cell in the ventricle) have a large nucleus? A small nucleus? Why or why not?
    3. Will a cardiomyocyte have a large or small cytoplasm? What would be "filling up" that cytoplasm?
    4. Would there be much space between cardiomyocytes? HINT: think about the near-instantaneous communication between cardiomyocytes during electrical conduction.
- Why would the wall to the atria be thinner than the ventricular wall?
- If the slice of heart tissue cut through a coronary artery, nestled between the atrium and ventricle, what shape would it be?



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Histology of Normal Heart Tissue by Jonathan Bush, licensed under All Rights Reserved

Section Review

- Deoxygenated blood (visible as blue/purple colour) enters the right atrium from the superior and inferior vena cavae. This blood passes through the tricsupid valve into the right ventricle. Upon ventricular systole, this blood is ejected through the pulmonary valve into the pulmonary arteries which goes to the lungs. The blood is now oxygenated and can be seen as it makes the blood the colour red. Oxygenated blood returns to the heart via the pulmonary veins, entering the left atrium and into the left ventricle via the mitral (or bicuspid) valve. During ventricular systole, the left ventricle contracts and pushes the blood through the aortic valve into the aorta which

delivers the oxygenated blood to the heart via the coronary arteries and the rest of the body.

- The left ventricular wall is thicker than the right because more pumping force is needed to reach the rest of the body (compared to the lungs which is the destination of the right ventricle). Similarly, the atrial walls are thinner than the ventricular walls because their pumping force just needs to reach the respective neighbouring ventricle.
- Ventricular tissue is predominantly made of cardiomyocytes which allow for contraction. These myocytes have large protein-filled cytoplasms which are comprised of contractile units (i.e. the proteins actin, myosin, troponin, and tropomyosin).
- Once mature, cardiomyocytes tend to have small nuclei as they do very little protein synthesis and are not replicating.
- Because the contractile cardiomycoytes need near-instantaneous communication between cells, cardiomyocytes are joined by gap junctions with no appreciable space between cells.

Review Questions

1. Fill in the missing words

Blue _____ blood enters the _____ atria and ventricle during diastolic filling. Atrial systole occurs, completely filling the ventricles and ends with the closing of the _____ valve in the right heart. At the start of ventricular systole, pressure builds up in the right ventricle, exerting pressure on both the atrioventricular _____ valve and the semilunar _____ valve. The atrioventricular valve can not open in response to this pressure due to the strong _____ which are holding the valve leaflets closed. Thus, the right ventricle produces enough pressure to open the _____valve thus ejecting the blood to the lungs. At the lungs, the blood becomes oxygenated becoming _____ in colour. This oxygenated blood returns to the left atrium via the "pulmonary veins". During diastolic filling, the _____ valve is open as the left atria and ventricles fill. During ventricular systole, the _____ valve can't open due to the strong _____ holding it closed. As such, the _____valve is opened during ventricular systole, thus allowing oxygenated blood to be ejected to the rest of the body.**2. Cardiac cells have large nuclei and little cytoplasm because of the intense amount of protein synthesis that is involved.**

- True
- False

3. Which is the correct statement? The walls of the right ventricle are thicker than those of the right atria

- The right ventricle wall is thicker than that of the left ventricle
- The aortic valve separates the right atria and ventricle
- The tricuspid valve separates the left atria and ventricle

Answer Key

1. Blue **deoxygenated** blood enters the **right** atria and ventricle during diastolic filling. Atrial systole occurs, completely filling the ventricles and ends with the closing of the **tricuspid** valve in the right heart. At the start of ventricular systole, pressure builds up in the right ventricle, exerting pressure on both the atrioventricular **tricuspid** valve and the semilunar **pulmonary** valve. The atrioventricular valve can not open in response to this pressure due to the strong **chordae tendinae** which are holding the valve leaflets closed. Thus, the right ventricle produces enough pressure to open the **pulmonary** valve thus ejecting the blood to the lungs. At the lungs, the blood becomes oxygenated becoming **red** in colour. This oxygenated blood returns to the left atrium via the "pulmonary veins". During diastolic filling, the **mitral/bicuspid** valve is open as the left atria and ventricles fill. During ventricular systole, the "**mitral/bicuspid"** valve can't open due to the strong **chordae tendinae** holding it closed. As such, the **aortic** valve is opened during ventricular systole, thus allowing oxygenated blood to be ejected to the rest of the body.
2. False
3. The walls of the right ventricle are thicker than those of the right atria

Left-Sided Heart Failure: From Cellular to Clinical

JENNIFER KONG AND HELEN DYCK

Learning Objectives

By the end of this section, you will be able to:

- Define ejection fraction.
- Describe the pathophysiology and histopathology of left-sided heart failure.
- List common signs and symptoms of left-sided heart failure.
- Explain the development and histological appearance of pulmonary edema due to left sided heart failure.
- Correlate the signs and symptoms listed on a patient chart/card with your understanding of the pathophysiology of left-sided heart failure.

Pathogenesis of Left-Sided Heart Failure

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What is Ejection Fraction? Is Ejection Fraction Always Compromised during Heart Failure?

Ejection fraction is the percentage of blood ejected into the aorta after the left ventricle contracts. Normally, only 50-75% of the LV volume is ejected into the aorta with each beat: this volume being sufficient to feed both the heart itself and the rest of the body. However, the impaired pumping ability of Left-sided heart failure may (or may not) affect ejection fraction. How can you tell? It depends on whether the changes in the heart structure are predominantly affecting heart pumping (systole) or resting/filling (diastole).

Transverse Plane of Heart Specimens

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This video is awaiting licensing approval and will be available shortly. Transverse Plane of normal vs. hypertrophic heart by Jennifer Kong, licensed under All rights reserved

Anatomy of Left-Sided Heart Failure (Concentric Hypertrophy) – DHPLC Specimen: B0611

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Critical Thinking and Histopathology Exercises

Now that you have viewed the gross specimen of concentric hypertrophy, consider the following questions. Record your answers for yourself before viewing the next video on the "Histopathology of Heart Failure."

- Recall the histology of the H&E stained normal heart. How much sarcoplasm (pink) was there in comparison to nuclei (purple)?
- Thinking about the pathophysiology of concentric hypertrophy, what would you expect to see in the cardiomyocyte? Will there be a change in sarcoplasm and/or nuclear size?
- Cardiac remodelling is common in hypertrophy and heart failure – particularly the increased presence of collagen. What would these non-contractile cells and proteins look like histologically?

Histopathology of Left-Sided Heart Failure

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Histopathology of Left-sided Heart Failure by Jonathan Bush, licensed under All rights reserved

Pulmonary Consequences of Left-Sided Heart Failure

Because the left ventricle can not eject sufficient blood into the aorta, there will be leftover blood in the left ventricle. This results in blood backing up from the left ventricle into the left atrium and then the lungs. Because the lungs have many, many pulmonary vessels which are in close contact with alveoli, there are many pulmonary consequences. This will manifest in problems with breathing and oxygenation.

Pathophysiology of Pulmonary Consequences of Left-Sided Heart Failure

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Histopathology of Pulmonary Edema Due to Left-Sided Heart Failure

With excess blood filling the pulmonary vasculature, there is increase pressure in the pulmonary vessels. This will cause two immediate effects:

1. Increased pulmonary blood pressure (pulmonary hypertension) can 'push' fluid out of the pulmonary capillaries.
2. Alveoli fill with fluid from the blood in the pulmonary capillaries causing more complications:
    - a barrier to gas exchange between the airways and pulmonary capillaries. –> decreased oxygenation of blood and retention of CO2.

These effects result in pulmonary edema – or "excess fluid in the lungs." The fluid in the lungs are very similar to plasma in the blood – thus it is fluid filled with protein and nutrients.

One can see this fluid at the gross anatomy level and histologically:

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Histopathology of Pulmonary Edema Due to Left-sided Heart Failure by Jonathan Bush, licensed under All rights reserved

Pathology of Pulmonary Edema Due to Left-Sided Heart Failure

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Signs and Symptoms of Left-Sided Heart Failure

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Further complications of pulmonary edema will lead to issues with oxygenation of blood and infection since the nutrient-rich fluid in alveoli becomes a very good environment for the growth of pathogens – thus causing pneumonia.

Summary Exercises

Consolidate your knowledge of left sided heart failure by creating a mind map or diagram of the pathophysiology of left-sided heart failure. Consider including these concepts to help you deepen your understanding

- Chronically high afterload (e.g. stiff aortic valve that is hard to open)

- Increased sarcoplasm (pink) and larger nuclei
- Reduced ejection fraction
- Increase LV wall thickness

Section Review

- Left sided heart failure occurs when the left ventricle can't pump as much blood out to the rest of the body. It can be due to poor pumping abilities (i.e. reduced ejection fraction) or reduced ventricular filling due to heart remodelling to non-compliant tissue (i.e. ejection fraction is normal). The former can be termed as systolic heart failure and the latter as diastolic heart failure. Regardless of the type, the patient will have signs of symptoms of insufficient blood flow – manifested as weakness & fatigue since muscles can't get sufficient oxygen nor nutrients.
- To adapt to changes in resistance and/or pumping, the left ventricle will remodel. The left ventricle can remodel to include more collagen protein that is more stiff, thus making the remodelled ventricle to be less elastic. To increase pumping force, the cardiomyocytes of the left ventricle can increase its size, filling it with more contractile protein units. This requires more nuclear activity to the demand for more synthesis of new contractile proteins.
- Because a reduced volume of blood is ejected out of the left ventricle, there is a back-up of blood into the left atrium which has a small fixed volume. Hence, the blood will continue to back up into the lungs causing pulmonary vessels to be overfilled with blood causing increased blood pressure (pulmonary hypertension).
- Pulmonary hypertension of the pulmonary capillaries will cause leakage of protein-rich plasma-like fluid out of the blood into the alveolar air space causing pulmonary edema. The presence of alveolar fluid can be heard as "crackles" during **auscultation**.
- The fluid in the alveoli will cause a barrier in gas exchange at the alveolar level, causing poor blood oxygenation (visibly evident with cyanosis) and dyspnea. Pulmonary edema is also an environment which pathogens are likely to grow, leading to lung infections (pneumonia).

Review Questions

1. Left-sided heart failure can be subclassified as systolic vs diastolic failure.

- True
- False

2. Fill in the blanks.

Concentric hypertrophy in left-sided heart failure will manifest as a _____ than normal heart with _____ walls in the left ventricle. As a result, there will be _____ blood filling the left ventricle during diastole. Initially, the contraction of the ventricle is preserved, thus this type of left heart failure is classified as a _____ failure. As the heart continues to stiffen and get thicker, the left ventricle will not be able to contract as well, leading to a _____ failure as well.

3. Complete the following statement. In left-sided concentric hypertrophy, the cells will:

- thicken in circumference
- increase in length
- increase in number (hyperplasia)
- increase their mitotic rate

4. In concentric hypertrophy, why are the nuclei larger but farther spaced apart?

- Each cardiomyocyte is longer, thus nuclei are spaced farther apart in all directions
- Each cardiomyocyte is actively undergoing mitosis and cytokinesis, thus the increased nuclear size and spacing
- Each cardiomyocyte is actively doing protein synthesis to create more contractile components, thus thickening each cell: this explains the spacing apart
- Each cardiomyocyte is undergoing pre-cancerous changes, causing a variation of cell shapes and sizes, thus the spacing apart.

Answer Key

1. True
2. Concentric hypertrophy in left-sided heart failure will manifest as a **larger-than-normal** heart with **thick** walls in the left ventricle. As a result, there will be **less** blood filling the left ventricle during diastole. Initially, the contraction of the ventricle is preserved, thus this type of left heart failure is classified as a **diastolic** failure. As the heart continues to stiffen and get thicker, the left ventricle will not be able to contract as well, leading to a **systolic** failure as well.
3. Thicken in circumference
4. Each cardiomyocyte are actively doing protein synthesis to create more contractile components, thus thickening each cell: this explains the spacing apart
5. The left heart can not pump all of its blood out during heart failure, there is less diastolic filling between the cycles. Thus, the left atria can never empty fully which means the blood in the pulmonary veins don't fully empty. This blood backs up to the pulmonary capillaries and hence, the alveolar space. Because there is increase pressure in the capillaries, the protein-rich plasma and some red blood cells can leak out of the capillaries and into the alveolar space.

Types and Causes of Heart Failure

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Define heart failure and hypertrophy.
- Differentiate between the heart failure types: right- vs left-sided heart failure.
- Explain the common causes of heart failure.
- Differentiate between concentric vs eccentric hypertrophy.

What is Heart Failure?

Heart failure is when your heart muscle can not contract strongly enough to eject all of its blood to its destination. As a result, the heart can't deliver the blood needed for the body to function well AND a redistribution (i.e. backup) of blood due to the poor pumping. As a result, heart failure will have signs and symptoms in both the cardiovascular and non-cardiac systems.

Types of Heart Failure

The type of heart failure depends on the location of the poor pumping. If the right ventricle is too weak in pumping, this is called "right sided heart failure." If the left ventricle has poor pumping abilities, this is called "left-sided heart failure."

Left sided heart failure can be subdivided into two subtypes:

- systolic failure (a.k.a. heart failure with reduced ejection fraction)
- diastolic failure (a.k.a. heart failure with preserved ejection fraction)

We will discuss these subtypes in more depth in the next chapter.

Conditions that Lead to Heart Failure

Heart failure is a result of injury to the heart and/or the heart can't keep up with what the body needs due to a variety of reasons. Regardless of which type of heart failure, heart failure is commonly caused by:

- Asking the heart to work abnormally hard for too long due to some kind of increased resistance downstream of the ventricle (i.e. **afterload**):
    - Valvular disease, chronic high blood pressure, severe lung disease
- The heart muscle is directly hurt by:
    - Not enough oxygen or nutrients to feed the heart muscle during pumping (e.g. decrease blood flow to coronary arteries due to coronary artery disease)
    - Increased workload for remaining undamaged heart tissue (e.g. previous myocardial infarction causing loss of viable heart tissue)
    - Aging
    - Damage due to infection or inflammation
    - Certain medications and illicit drugs
- Heart is not 'made well' (i.e. abnormal structure) thus can't contract and fill efficiently. Examples of abnormal structure are:
    - Congenital (i.e. since birth) heart defect of muscles and/or valves,
    - Defects in heart's electrical system causing arrhythmias – resulting in heart beating too fast, slow, or irregular.

Concentric versus Eccentric Hypertrophy

What is Hypertrophy?

Hearts, like any muscle, get bigger and thicker when it has a lot of resistance/workload to frequently push against. It's like lifting hand weights to increase the size of the bicep. The cells in heart tissue get individually larger – not more numerous. This enlargement of muscle cells – whether it's cardiac or skeletal muscle – is known as **hypertrophy**. The muscle cell hypertrophies because it is adding more contractile proteins to enable greater contractile strength. Going back to the bicep example – the larger bicep is because each individual bicep muscle cell undergoes hypertrophy even though it has not changed in muscle cell number.

Thus, the walls of muscle hypertrophy when there is chronically a lot of resistance/workload. That means each cardiomyocyte is undergoing hypertrophy, rather than dividing into more cells (**hyperplasia**), as cardiomyocytes can't undergo cell division.

During hypertrophy, cells of the heart wall can:

a) Become bigger in circumference. These plumper cardiomyocytes make the heart wall grow thicker from the outside in, resulting in the heart becoming heavier. The larger in circumference the cells get, the harder it is for oxygen and nutrients to diffuse inside the cell, which will eventually cause metabolic problems. This is the basis of concentric hypertrophy

or

b) Become longer in length and more narrow in circumference. These narrower cardiomyocytes are 'stretched out' because the heart wall is undergoing more tension with over-filling with blood volume. To adapt to this stretching, the heart remodels by replacing contracting cardiomyocytes with non-contractile cardiac cells. As a result, the heart wall get thinner with weaker contractile strength. This is the basis of eccentric hypertrophy.

c) Remodel (i.e. change their cellular make up in tissue). When the cardiomyocytes do not get enough oxygen and/

or nutrients (e.g. heart attack, extreme hypertrophy) or receive increased inflammatory signals (e.g. inflammation, infection), the cardiomyocytes will die. As a result, the cardiomyocytes are then replaced with connective tissue – principally collagen – which is NOT contractile. The heart tissue becomes less contractile, making it harder to empty the chamber. In addition, the collagen- filled heart wall becomes stiffer and not as stretchy to fill easily.

Concentric Hypertrophy

Concentric hypertrophy occurs when the left ventricular wall is remodelling due to a chronically increased resistance to push against. The LV wall gets thicker (due to plumper cardiomyocytes) resulting in the space within the ventricle (i.e. lumen) shrinking. This shrinkage of lumen means less volume of blood available to fill during diastole. At first, ejection fraction is preserved despite less diastolic filling, thus giving rise to the alternate terms of "**diastolic heart failure** " or "heart failure with preserved ejection fraction." Because ejection fraction is preserved, the body is getting sufficient supply of blood and thus there would be few signs/symptoms.

However, as the wall gets thicker, it becomes stiffer and not as "stretchy" to fill easily. Eventually, there will be a point where the diastolic filling volume will not be enough to maintain sufficient ejection fraction, regardless of how well the LV wall can pump. This is when signs and symptoms will begin to be noticed.

Eccentric Hypertrophy

When the heart chambers get overloaded with volume, the cells of the heart wall will compensate by becoming thinner & longer. This overfilling will cause the heart to remodel into a larger lumen with thinner walls and less contractile strength. If this eccentric hypertrophy occurs in the ventricle, this would be **systolic failure** or "heart failure with reduced ejection fraction" as the volume to pump is sufficient but the pumping ability is too weak. Unfortunately, as ejection fraction is reduced, there will be even more fluid left in the chamber – thus complicating the already chronic volume overload.

Section Review

- You can have both concentric and eccentric cardiomyopathy if the heart has to deal with both increased pressure and increased volume.
- Both systolic and diastolic failure have the same end result: the heart can't pump enough blood out to feed the body.

Review Questions

1. Concentric hypertrophy will have a larger lumen size for filling and is thus associated with systolic failure.

- True
- False

2. Put the types of left-sided heart failure in the correct column.

caused by increased resistance (afterload)	diastolic filling is reduced
caused by overfilling of the heart	contraction during systole is weaker
eccentric hypertrophy	concentric hypertrophy

Abnormally Thick Ventricular Walls	Abnormally Thin Ventricular Walls

3. Choose the correct statement.

- Heart failure occurs when the heart cannot pump out sufficient blood with each ejection.
- Heart failure involves enlargement of the heart walls, due to hyperplasia.
- Heart failure is caused by chronically circulating reduced blood volume.
- Heart failure is mainly divided into those with preserved vs reduced ejection fraction.

Answer Key

1. False
2.

Abnormally Thick Ventricular Walls	Abnormally Thin Ventricular Walls
concentric hypertrophy diastolic filling is reduced caused by increased resistance (afterload)	caused by overfilling of the heart Contraction during systole is weaker eccentric hypertrophy

3. Heart failure occurs when the heart cannot pump out sufficient blood with each ejection.

Right-Sided Heart Failure - From Cellular to Clinical

JENNIFER KONG AND HELEN DYCK

Learning Objectives

By the end of this section, you will be able to:

- Describe the pathophysiology of right-sided heart failure.
- Relate histological findings of Cor Pulmonale with the pathogenesis of right-sided heart failure.
- Explain how right-sided heart failure can lead to congestion of liver.
- List common signs and symptoms associated with right-sided heart failure.

Pathogenesis of Right-Sided Heart Failure

Right sided heart failure is a cardiac condition when the right ventricle can't pump strong enough to eject blood into the pulmonary vessels. Similar to left-sided heart failure, the right heart might have problems with damage to the right ventricle wall (e.g. cardiomyopathy, previous heart attack in right heart) itself or the right heart wasn't made quite right resulting in inadequate pumping (e.g. valvular issues, congenital heart defect on right side). However, the more common cause of right-sided heart failure is a significant increase in resistance/afterload in the lungs, a condition known as pulmonary hypertension. The resulting alterations in the right heart, due to pulmonary hypertension, is known as **cor pulmonale**.

What is Pulmonary Hypertension?

Normally, pulmonary vessels have very low blood pressure – due to the fact that the right heart doesn't have to push the blood very far to get to the pulmonary vessels and pulmonary vessels are larger and more distensible.

1. Pulmonary hypertension can be caused fluid overload in the pulmonary vasculature. This fluid overload in vasculature can be a result of multiple conditions originating outside of the lungs – including the back up of blood seen in left-sided heart failure.
2. Pulmonary hypertension can be caused by very strong vasoconstriction across the entire lungs – a phenomenon seen in alveoli that are globally poorly ventilated. This occurs in patients with severe pulmonary diseases (see the Emphysema chapter)

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Pathology of Right-Sided Heart Failure (DHPLC #B0606 from the Boyd Collection)

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Abdominal Consequences of Right-Sided Heart Failure: "Nutmeg Liver"

Right sided heart failure causes back up of blood into both the superior & inferior vena cavae (IVC). These vessels will, in turn, lead to back up of blood to their tributaries. The portal vein is a major tributary of the IVC: a backup here will result in liver which is congested with blood causing damage to the liver tissue.

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Signs and Symptoms of Right-Sided Heart Failure

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Critical Thinking Exercises

Consolidate your knowledge by creating a mind map or drawing of the pathophysiology of right-sided heart failure. Include the following words (in no particular order):

- swollen legs and feet
- pulmonary hypertension
- ejection fraction
- right ventricle
- concentric & eccentric hypertrophy

Section Review

- Right sided heart failure is caused by insufficient blood leaving the right ventricle during systole, thus causing a back up of blood into the right atrium and vena cavae.
- If the cause of the insufficient pumping is due to pulmonary hypertension, the right ventricle remodels try to pump better, causing the cardiomyocytes to enlarge with more contractile proteins and resulting in right ventricular thickening (Cor Pulmonale).
- As insufficient blood is leaving the right ventricle, blood backs up into the right atrium and then the superior and inferior vena cavae. This excess blood will cause an overfilling of the veins which feed into the vena cavae.
- Overloaded superior vena cava will cause a back up of blood in the neck veins which is observable to health care providers.
- Overloaded inferior vena cava will lead to a back up of blood in the abdominal veins and beyond, particularly the portal vein resulting in an enlargement of the liver, congested with blood.
- Because the right ventricle can't pump sufficient blood through the lungs, there is insufficient blood entering the left heart. Thus, signs of poor blood flow to the rest of the body (i.e. fatigue, weakness).
- Right-sided heart failure can be a consequence of the pulmonary hypertension caused by left-sided heart failure, but not in all cases.

Review Questions

1. Fill in the missing words Right-sided heart failure occurs when the right ventricle can not pump all of its blood out during _____ . This can be due to either a weakened right ventricle or due to excess _____ in the lungs. In the former case, previous damage to the right ventricular wall will result in a weaker _____ (e.g.prior myocyardial infarct). In the latter case, the right ventricle can not overcome the abnormally high pressures in the _____. If the alveoli are experiencing potent vessel constriction, this causes pulmonary _____- a source of afterload for the right heart. Pulmonary _____ occurs when there is poor oxygenation in parts of the lung causing pulmonary vessel constriction. In the case of severe pulmonary disease like emphysema, the poorly ventilated airways cause poor oxygenation in _____leading to pulmonary vessel constriction. In pulmonary edema as with left-sided heart failure, the proteinaceous fluid forms a barrier for _____ of gases resulting in poor oxygenation and potent vasoconstriction of pulmonary vessels.

2. Finish the following statement. In right-sided heart failure, blood backs up to the:

- lungs
- left-heart
- vena cavae
- aorta

3. Cor pulmonale is right-sided heart remodeling in response to pulmonary hypertension.

- True
- False

1. Right-sided heart failure occurs when the right ventricle can not pump all of its blood out during **systole**. This can be due to either a weakened right ventricle or due to excess **resistance/afterload** in the lungs. In the former case, previous damage to the right ventricular wall will result in a weaker **contraction/systole** (e.g. prior myocyardial infarct). In the latter case, the right ventricle can not overcome the abnormally high pressures in the **lung/alveoli**. If the alveoli are experiencing potent vessel constriction, this causes pulmonary **hypertension** – a source of afterload for the right heart. Pulmonary **hypertension** occurs when there is poor oxygenation in parts of the lung causing pulmonary vessel constriction. In the case of severe pulmonary disease like emphysema, the poorly ventilated airways cause poor oxygenation in **alveoli** leading to pulmonary vessel constriction. In pulmonary edema as with left-sided heart failure, the proteinaceous fluid forms a barrier for **diffusion/exchange** of gases resulting in poor oxygenation and potent vasoconstriction of pulmonary vessels.
2. vena cavae
3. True

Diagnosis of Heart Failure

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Briefly describe what cardiac ultrasound is and how it is used in the diagnosis of heart failure.

Cardiac Ultrasound (Echocardiography)

Listen to Heather Bourke, a cardiac sonographer, introduce her field of diagnostic medical sonography (ultrasound). She shows real echocardiography clips while speaking about what a patient can expect during echocardiography and the role of sonography in diagnosis of diseases.



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Cardiac Ultrasound by Heather Bourke & Jennifer Kong, licensed under All rights reserved

Section Review

- Health care professionals work collaboratively in the diagnosis and management of heart failure and complications.
- Cardiac ultrasound (echocardiography) shows the real time pumping of the heart, thus helping to measure ventricular wall movement and ejection fraction.

Review Questions

1. Complete the following statement. Echocardiography is a(n):

- ultrasound method that uses sound waves to measure the motion of heart walls, determine speed of blood flow,

and can calculate the volume within chambers
- method of imaging that takes still 3D images using magnetism
- method of measuring heart electrical activity during systole and diastole
- method using radiation to measure how well the heart is receiving nutrients and oxygen via the coronary vessels

2. In all of BC, there are more than 500 echocardiograms performed each day.

- True
- False

Answer Key

1. ultrasound method that uses sound waves to measure the motion of heart walls, determine speed of blood flow, and can calculate the volume within chambers
2. True

Clinical Side of Heart Failure

JENNIFER KONG

Want more practice with the clinical side of heart failure? Or to read what it's like for a patient to have heart failure? See these additional Open Education resources:

A Patient's Journey Through the Health Care System

Meet fictional patient Meryl Smith in the Appendices: Case Study for Heart Failure where we follow her journey from a cardiac event and hospital admission, as she meets many health care professionals working together on her diagnosis and care.

Select Clinical Skills Used by Health Care Providers

To learn about the skills of assessing a patient with signs and symptoms of heart failure, please read chapter 2 "Patient Assessment" from the Open Education resource Clinical procedures for safer patient care by Doyle & McCutcheon.

Heart Failure Chapter Summary and Credits

JENNIFER KONG

Chapter Summary

Heart failure is a condition when the heart can't pump strongly enough to supply the body with oxygenated blood. There are many causes of heart failure which can be loosely organized as too much resistance/workload, direct damage to heart tissue, or abnormal heart structure.

Heart failure can be identified based on the site of the problematic pumping: left- vs right-sided heart failure. To compensate for the cause of the heart failure, the heart remodels and hypertrophies. The manner of hypertrophy (concentric vs eccentric) allows the heart to contract better but this is not sustainable. Histologically, remodeling is evident (i.e. cardiomyocytes get too plump to be nourished; contracting tissue gets replaced with stiffer and/or non contractile collagen tissue) and provide clues to the poor pumping. Thus, based on the manner of hypertrophy, left sided heart failure can be further subdivided into diastolic (or preserved ejection fraction) or systolic (or reduced ejection fraction) heart failure.

Left sided heart failure involves weak pumping of the left ventricle. This results in poor blood delivery to all parts of the body manifesting overall body weakness and fatigue. The blood that can't be ejected out of the left ventricle, due to the poor pumping, will back up into the lung vasculature thus causing pulmonary consequences such as pulmonary edema. Due to the nature of excess fluid in alveoli, pulmonary edema may cause problems with oxygenation of blood and infection (pneumonia).

Right sided heart failure involves weak pumping of the right ventricle. Histologically, the right heart remodels to address both increased resistance and fluid overload, most often due to a pulmonary problem such as pulmonary hypertension. This remodeling is known as cor pulmonale. Insufficient pumping of the right ventricle results in poor blood delivery to the left heart: thus symptoms of right-sided overlap with those of left-sided. The blood that can't get into the lungs cause a back up of blood into the right atrium and then into the superior & inferior vena cavae. This manifests as engorgement of the veins which are tributaries to the vena cavae: for SVC that would be engorged neck & subclavian veins. For IVC, that would be engorged abdominal veins manifesting in impaired venous drainage of both internal organs (e.g. liver) and external structures (e.g. legs & feet). Often – but not always – right sided heart failure develops from a pulmonary cause (i.e. high resistance) to its weak pumping. Thus, pulmonary symptoms might also be present. Right-sided heart failure can develop due to the pulmonary congestion seen in left-sided, but it not always the case.

Diagnosis of heart failure is done through a multidisciplinary team of allied health professionals. Cardiac ultrasound (echocardiogram) shows real-time anatomy and function of the heart. Cardiac ultrasound allows for measurements of heart structures (e.g. aortic valve opening) and determine pumping abilities (i.e. ejection fraction, wall kinetics) and extent of remodelling (e.g. wall thickness). Medical radiography technologists take X-rays of the chest thus allowing for a visualization of both heart size and lung structure. X-rays are good at determining the extent of pulmonary vessel engorgement and alveolar fluid as they create a radio-opacity (i.e. white/gray on X-ray) in a normally radio-luscent (i.e. black on X-ray) lung.

Pulmonary edema often can cause infection and pneumonia. Again, X-rays are useful in diagnosing pneumonia. However, medical laboratory technologists (microbiologists) can determine the pathogen causing the pneumonia and the antimicrobial agent which can be used to treat the infection (e.g. antibiotic).

Key Takeaways

- Heart failure is poor pumping – the site of the problem determining if it is left- vs right-sided heart failure.
- In response to the cause of heart failure, the heart will remodel (hypertrophy) to try to preserve pumping abilities. However, this is unsustainable. Eventually, there will be insufficient blood going to the body AND signs of blood backing up into structures upstream- thus causing further complications.
- Left sided heart failure will have signs of poor oxygenation to the whole body and lung symptoms such as pulmonary edema.
- Right sided heart failure will have signs of poor oxygenation to the whole body AND back up of blood in the tributaries of the vena cavae.
- Cardiac ultrasound gives a real time assessment of heart structure and function.
- Chest Xray gives a visualization of the size of the heart and the degree of fluid in lungs.
- Microbiologist can identify the pathogen that is causing pneumonia and suggest an antimicrobial as a treatment.

Credits

Author: Dr. Jennifer Kong (BCIT & UBC)

Gross anatomy video: Helen Dyck (UBC)

Histopathology video: Dr. Jonathan Bush (UBC, BC Children's Hospital)

Cardiac Sonographer: Heather Bourke (Diagnostic Sonography, BCIT)

Video producer: Ian Whittlesey (BCIT)

Post-Test for Heart Failure

JENNIFER KONG

1. After 30+ years with an aortic valve that is difficult to open, this 65-year-old woman is showing signs of left-sided heart failure that has progressed to right side. Select all of the signs and symptoms she might be experiencing.

- Pulmonary edema
- Veins in neck are very full and distended
- Overall weakness and low tolerance to activity
- Swollen legs and feet
- Difficulty breathing with increased respiratory rate
- Strong pulses with warm, flushed skin

2. Right sided heart failure will have pulmonary (lungs) symptoms.

- True
- False

3. Fill in the blanks.

Concentric hypertrophy occurs when there is high _____, causing the myocytes to get larger and fatter. Eccentric hypertrophy occurs when there is high _____ causing the myocytes to become longer and thinner.

Answer Key

1. Pulmonary edema, veins in neck are very full and distended, overall weakness and low tolerance to activity, swollen legs and feet, difficulty breathing with increased respiratory rate
2. True
3. Afterload/resistance, volume

METASTATIC CANCER - MELANOMA

Melanoma Chapter Overview

JENNIFER KONG

Chapter Learning Objectives

By the end of this chapter, you will be able to:

- Describe the normal role of melanocytes in skin.
- Explain how damage to DNA can cause cancerous changes in genes – particularly proto-oncogenes and tumour suppressors.
- Examine a histological preparation of skin and identify common histological features in cancerous cells and the basement membrane.
- Briefly describe how metastasis can develop and likely sites of metastasis.
- Explain how collaboration between health care professionals work towards diagnosis and management of melanoma.
- Recall measures to lower one's risk for developing melanoma.

Skin cancers are THE most common types of cancers. Thankfully, most types of skin cancers do not result in death. However, melanoma is one type of skin cancer that can be lethal if not detected and treated early enough. This chapter will first discuss normal epithelial tissue and skin anatomy and histology, followed by a brief introduction to how cancer can develop in a cell. To introduce melanoma, author Lyz Boyd will guide you from the point of view the reader who sees a funny looking mole to the naked eye. Lyz will introduce the histopathology of melanoma and metastasis.

Watch this Open Education video for a quick introduction to melanoma.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=506#h5p-4

How Likely Are You to Get Skin Cancer? by New York Magazine, licensed under CC-BY 4.0

This chapter is subdivided into:

- Pre-test
- Normal skin anatomy & histology
- Introduction to cell differentiation and cancer
- Pathophysiology of melanoma
- Progression of melanoma: metastasis
- Interview with medical Laboratory Science technologist about biopsy of possible melanoma

- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

ACTH	Adrenocorticotropic Hormone
BMI	Body Mass Index
CDK	Cyclin-Dependent Kinase
G1	Gap 1 Phase
G2	Gap 2 Phase
hESCs	Human Embryonic Stem Cells
iPSCs	Induced Pluripotent Stem Cells
MSH	Melanocyte-Stimulating Hormone
S phase	Synthesis Phase
UV	Ultraviolet

Acknowledgement

This chapter was predominantly composed by medical student Lyz Boyd as part of her Yr 1 FLEX project with UBC Undergraduate Medical Program.

Pre-Test for Metastatic Melanoma

JENNIFER KONG

Normal skin anatomy & histology

1. This protects skin cells from the damaging UV rays.

- Melanocytes
- Keratin
- Sweat produced by sweat glands
- Hair
- Blood vessels

2. The junction between the hypodermis and underlying muscle is the basement membrane of the epidermis (skin).

- True
- False

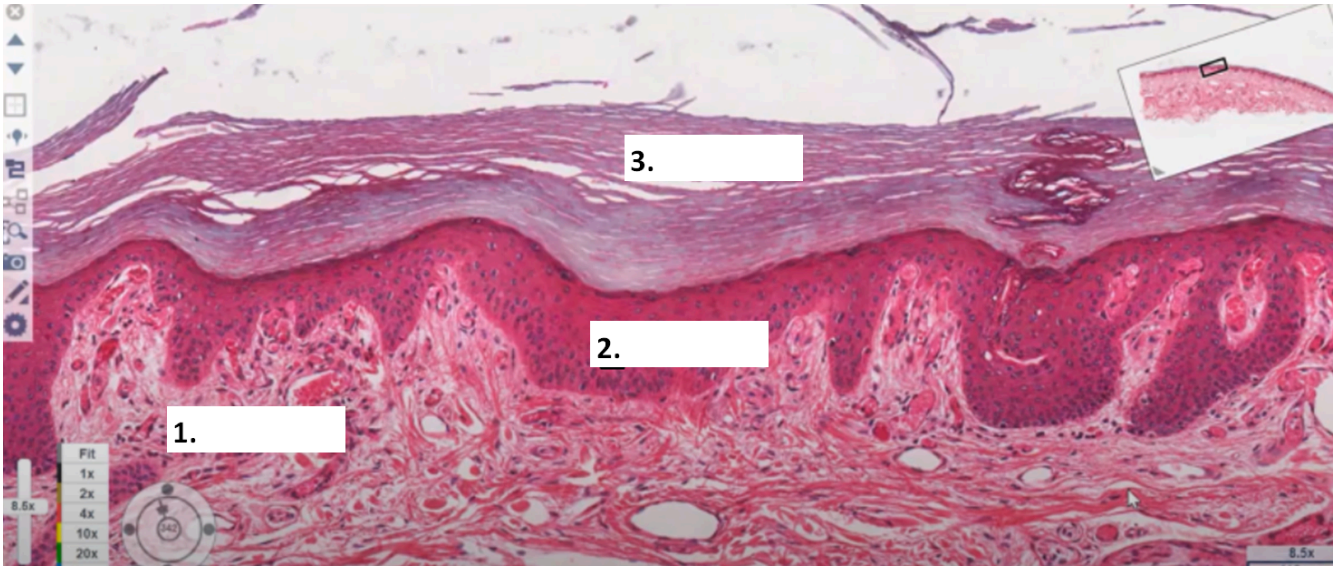
3. Fill in the blanks with the following words:

melanocytes, keratin, epidermis, melanin cells, hypodermis, cells, dead living keratinocyte, dermis

The skin is divided into the very thin, outermost _____, the slightly thicker _____ and the fatty _____. The predominant cell in the epidermis is the _____ which is responsible for making the tough protective protein _____. The outermost layer is made entirely out of _____. To protect the _____, _____ make the protein _____ which act as a pigment to 'shade' the UV rays of sun.

4. Place the following terms on the histology diagram:

epidermis (dead layer), epidermis (alive layer), dermis.



5. Fill in the blank.

A 3mm mole on the arm has an increased number of _____ compared to the surrounding skin. This is evident due to the mole's increased pigmentation which vary from brown to black.

Metastatic melanoma

1. Damage to DNA leading to melanoma occurs after the age of 50 years old.

- True
- False

2. Finish the following sentence. Cancer is uncontrolled growth of cells due to:

Select all that apply.

- A loss of function of the genes responsible for tumour suppression
- A loss of function of the genes responsible for cell division
- An increase in function of the genes responsible for tumour suppression
- An increase of function of the genes responsible for cell division

3. Finish the following sentence. A likely site for metastasis from a melanoma that originates in the skin is:

- Liver
- Nails
- Heart
- Tongue
- Hair

Answer Key

Normal Skin Anatomy & Histology

1. Melanocytes

2. False

3. Epidermis, dermis, hypodermis, keratinocyte, keratin, dead cells, living cells, melanocytes, melanin

4. 1. Dermis, 2. Epidermis (alive layer), 3. Epidermis (dead layer)

5. Melanocytes

Metastatic Melanoma

1. False
2. A loss of function of the genes responsible for tumour suppression, an increase of function of the genes responsible for cell division
3. Liver

Media Attributions

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Layers of the Skin

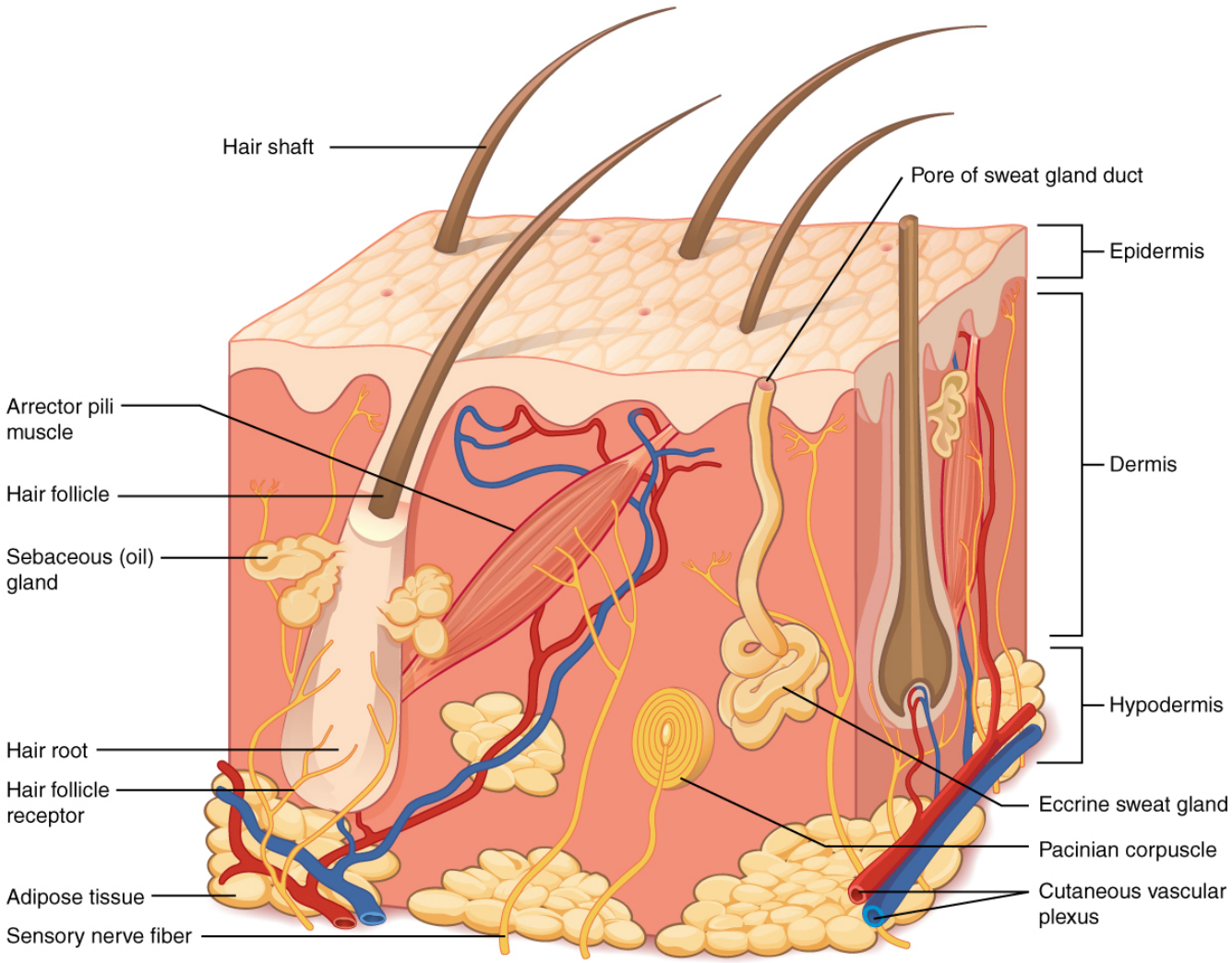
J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Identify the components of the integumentary system.
- Describe the layers of the skin and the functions of each layer.
- Identify and describe the **hypodermis** and deep fascia.
- Describe the role of keratinocytes and their life cycle.
- Describe the role of melanocytes in skin pigmentation.

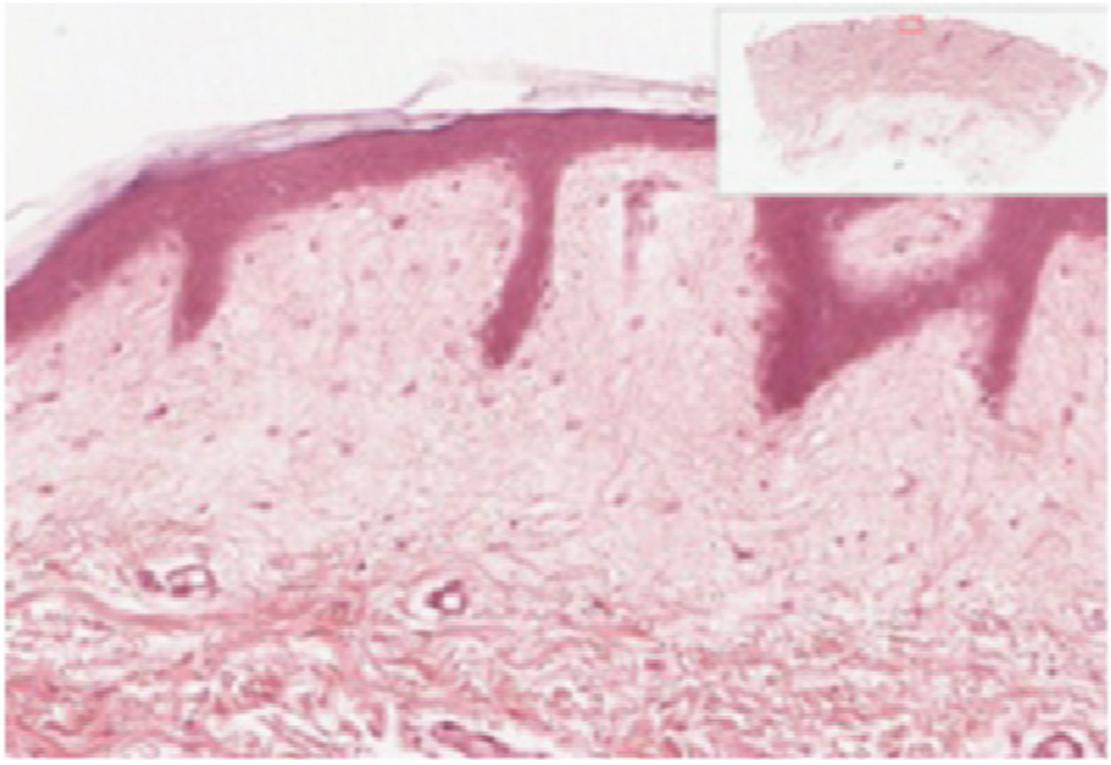
Although you may not typically think of the skin as an organ, it is in fact made of tissues that work together as a single structure to perform unique and critical functions. The skin and its accessory structures make up the integumentary system, which provides the body with overall protection. The skin is made of multiple layers of cells and tissues, which are held to underlying structures by connective tissue. The deeper layer of skin is well vascularized (has numerous blood vessels). It also has numerous sensory, and autonomic and sympathetic nerve fibers ensuring communication to and from the brain.



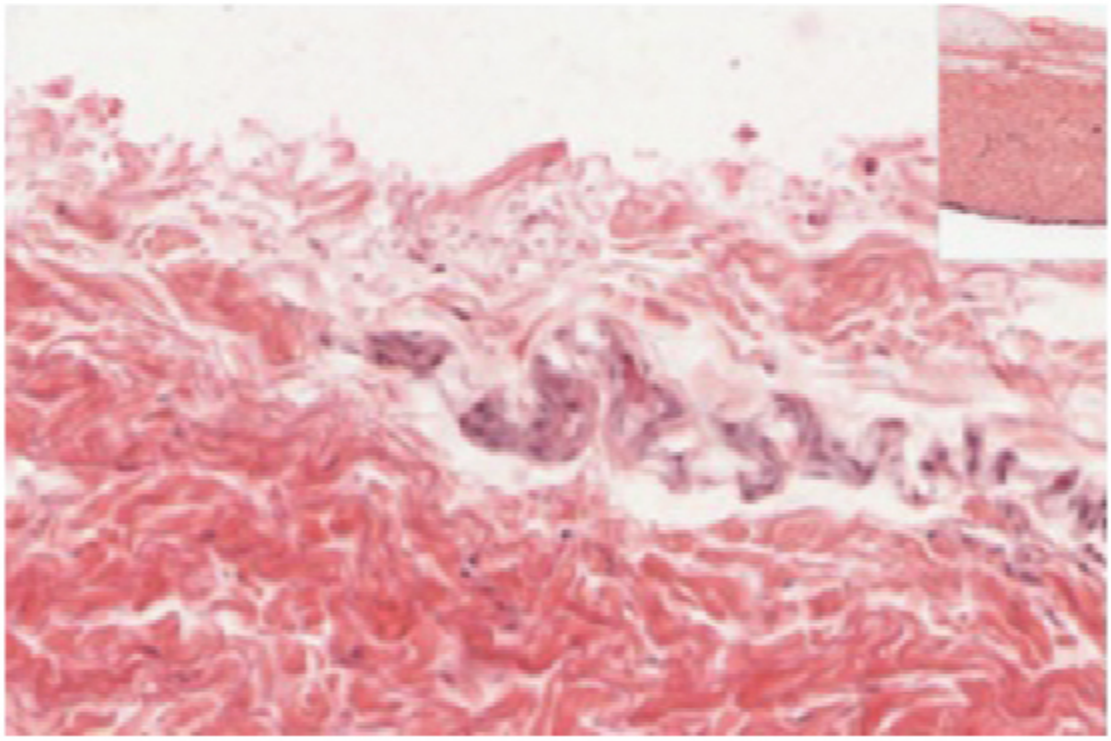
Layers of Skin The skin is composed of two main layers: the epidermis, made of closely packed epithelial cells, and the dermis, made of dense, irregular connective tissue that houses blood vessels, hair follicles, sweat glands, and other structures. Beneath the dermis lies the hypodermis, which is composed mainly of loose connective and fatty tissues.

The Epidermis

The epidermis is composed of keratinized, stratified squamous epithelium. It is made of four or five layers of epithelial cells, depending on its location in the body. It does not have any blood vessels within it (i.e., it is avascular). Skin that has four layers of cells is referred to as "thin skin." From deep to superficial, these layers are the **stratum basale**, **stratum spinosum**, **stratum granulosum**, and **stratum corneum**. Most of the skin can be classified as thin skin. "Thick skin" is found only on the palms of the hands and the soles of the feet. It has a fifth layer, called the **stratum lucidum**, located between the stratum corneum and the stratum granulosum.



(a)

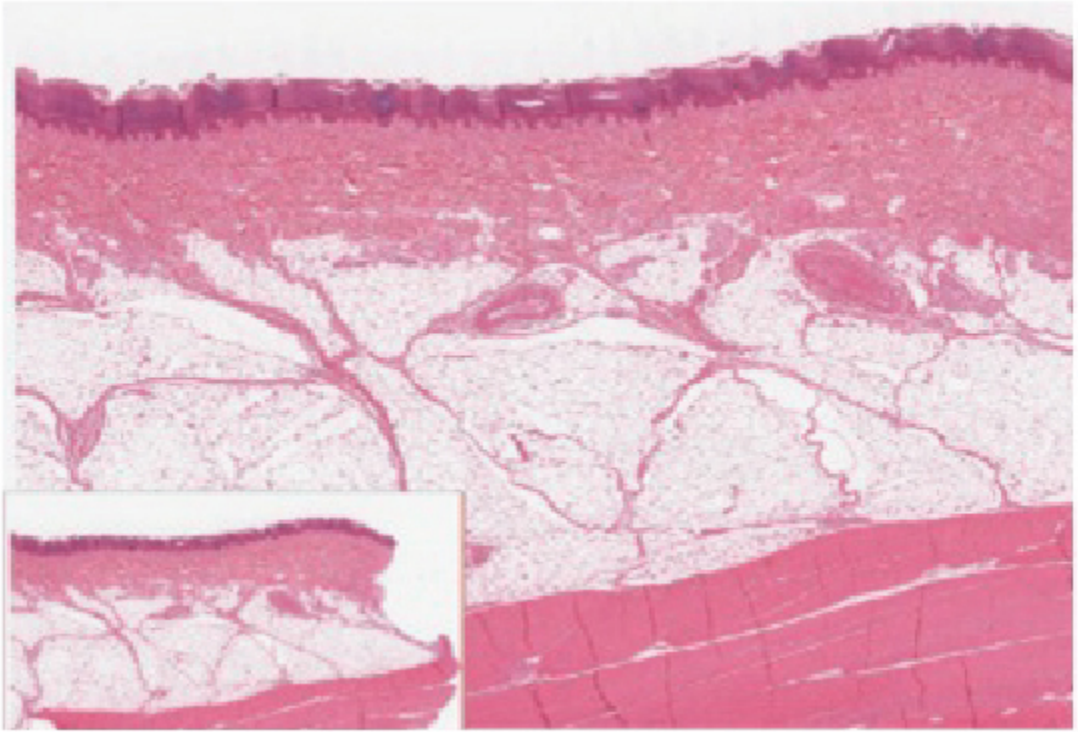


(b)

Thin Skin versus Thick Skin These slides show cross-sections of the epidermis and dermis of (a) thin and (b) thick skin. Note the significant difference in the thickness of the epithelial layer of the thick skin. From top, LM × 40, LM ×

40. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The cells in all of the layers except the stratum basale are called **keratinocytes**. A keratinocyte is a cell that manufactures and stores the protein **keratin**. Keratin is an intracellular fibrous protein that gives hair, nails, and skin their hardness and water-resistant properties. The keratinocytes in the stratum corneum are dead and regularly slough away, being replaced by cells from the deeper layers.

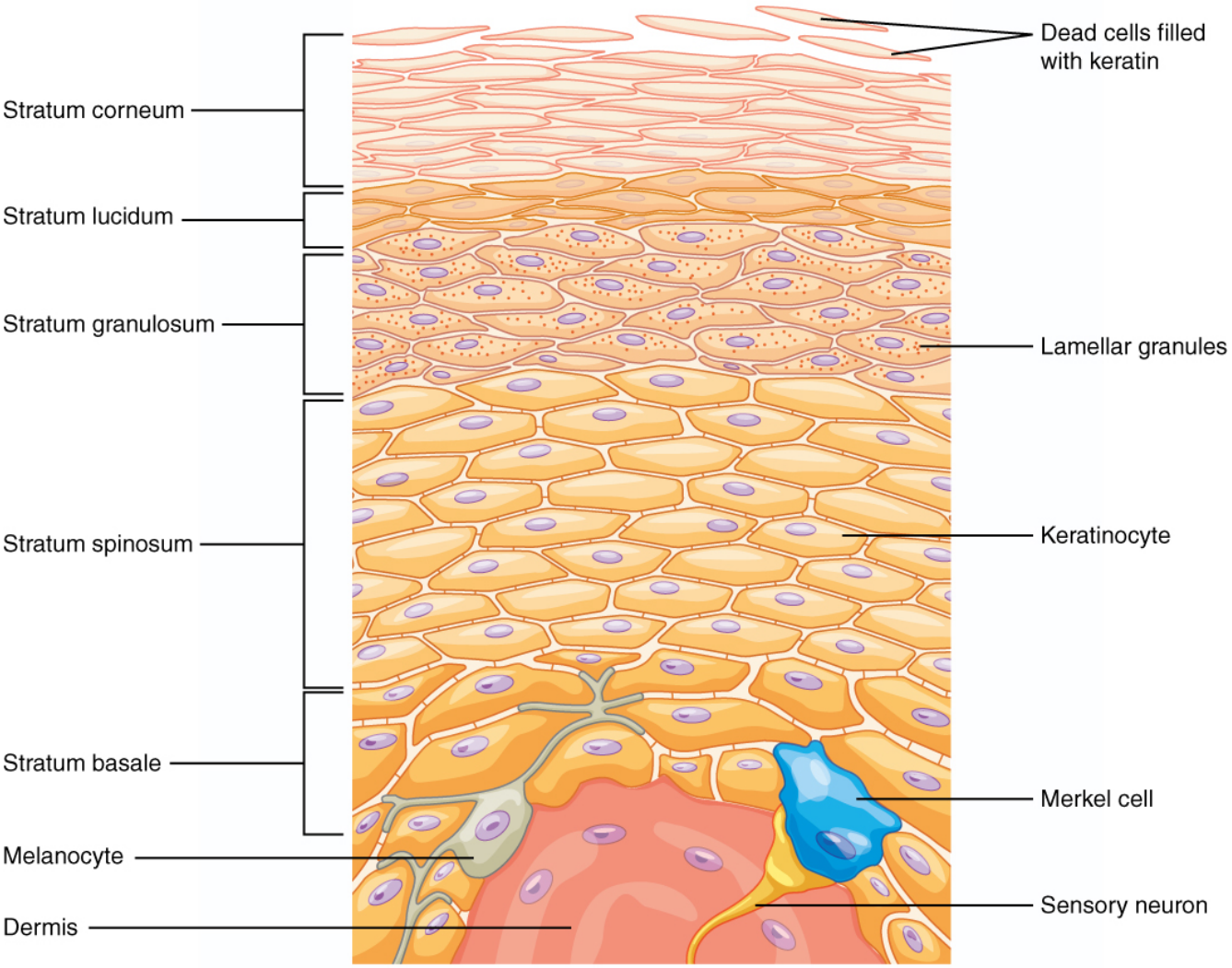


Epidermis The epidermis is epithelium composed of multiple layers of cells. The basal layer consists of cuboidal cells, whereas the outer layers are squamous, keratinized cells, so the whole epithelium is often described as being keratinized stratified squamous epithelium. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

View the University of Michigan WebScope to explore the tissue sample in greater detail. If you zoom on the cells at the outermost layer of this section of skin, what do you notice about the cells?

Stratum Basale

The stratum basale(also called the stratum germinativum) is the deepest epidermal layer and attaches the epidermis to the basal lamina, below which lie the layers of the **dermis**. The cells in the stratum basale bond to the dermis via intertwining collagen fibers, referred to as the basement membrane. A finger-like projection, or fold, known as the **dermal papilla (plural = dermal papillae)** is found in the superficial portion of the dermis. Dermal papillae increase the strength of the connection between the epidermis and dermis; the greater the folding, the stronger the connections made.



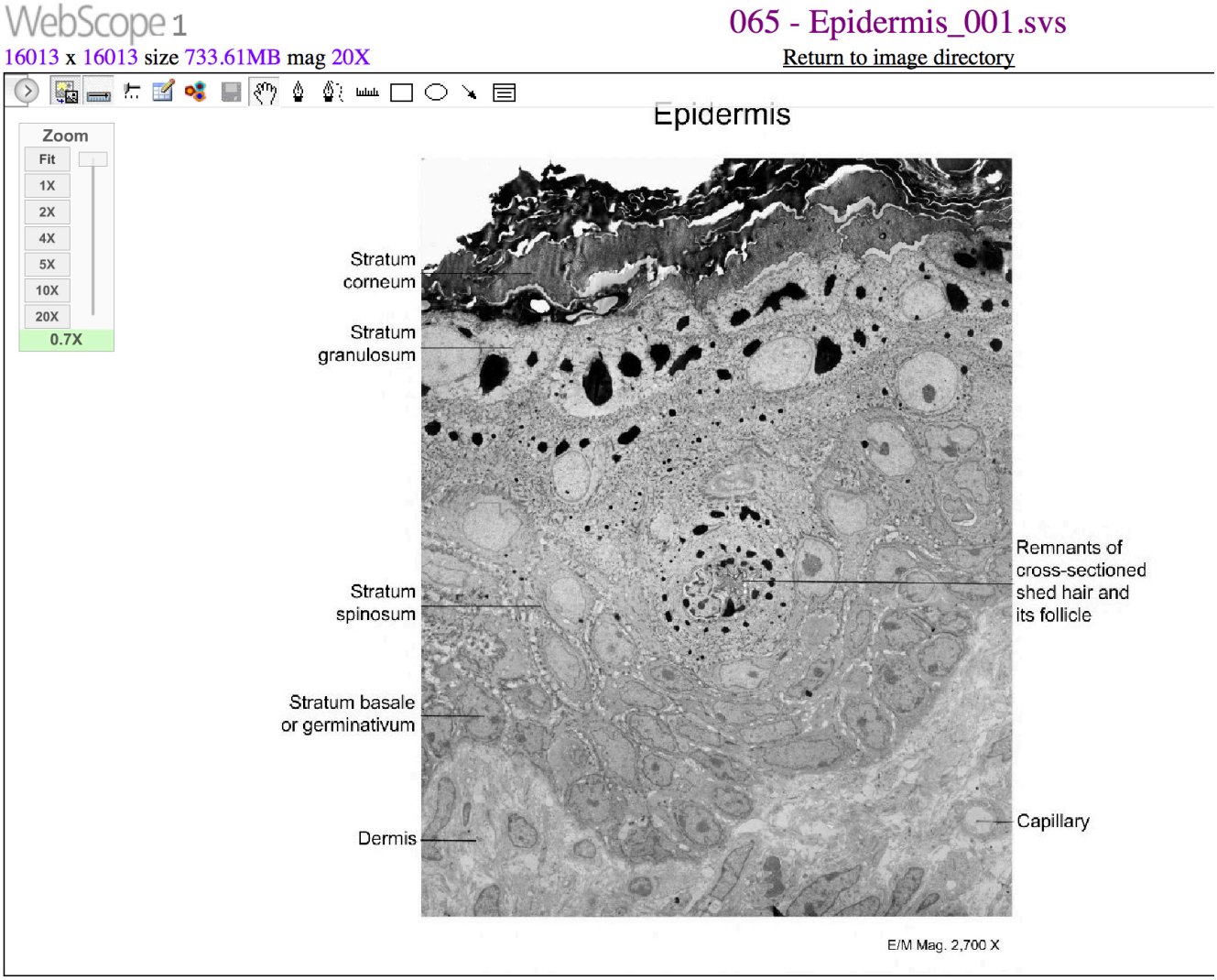
Layers of the Epidermis The epidermis of thick skin has five layers: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum.

The stratum basale is a single layer of cells primarily made of **basal cells**. A basal cell is a cuboidal-shaped stem cell that is a precursor of the keratinocytes of the epidermis. All of the keratinocytes are produced from this single layer of cells, which are constantly going through mitosis to produce new cells. As new cells are formed, the existing cells are pushed superficially away from the stratum basale. Two other cell types are found dispersed among the basal cells in the stratum basale. The first is a **Merkel cell**, which functions as a receptor and is responsible for stimulating sensory nerves that the brain perceives as touch. These cells are especially abundant on the surfaces of the hands and feet. The second is a **melanocyte**, a cell that produces the pigment **melanin**. Melanin gives hair and skin its color, and also helps protect the living cells of the epidermis from ultraviolet (UV) radiation damage.

In a growing fetus, fingerprints form where the cells of the stratum basale meet the papillae of the underlying dermal layer (**papillary layer**), resulting in the formation of the ridges on your fingers that you recognize as fingerprints. Fingerprints are unique to each individual and are used for forensic analyses because the patterns do not change with the growth and aging processes.

Stratum Spinosum

As the name suggests, the stratum spinosum is spiny in appearance due to the protruding cell processes that join the cells via a structure called a **desmosome**. The desmosomes interlock with each other and strengthen the bond between the cells. It is interesting to note that the "spiny" nature of this layer is an artifact of the staining process. Unstained epidermis samples do not exhibit this characteristic appearance. The stratum spinosum is composed of eight to 10 layers of keratinocytes, formed as a result of cell division in the stratum basale. Interspersed among the keratinocytes of this layer is a type of dendritic cell called the **Langerhans cell**, which functions as a macrophage by engulfing bacteria, foreign particles, and damaged cells that occur in this layer.



Cells of the Epidermis The cells in the different layers of the epidermis originate from basal cells located in the stratum basale, yet the cells of each layer are distinctively different. EM × 2700. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

View the University of Michigan WebScope to explore the tissue sample in greater detail. If you zoom on the cells at the outermost layer of this section of skin, what do you notice about the cells?

The keratinocytes in the stratum spinosum begin the synthesis of keratin and release a water-repelling glycolipid that

helps prevent water loss from the body, making the skin relatively waterproof. As new keratinocytes are produced atop the stratum basale, the keratinocytes of the stratum spinosum are pushed into the stratum granulosum.

Stratum Granulosum

The stratum granulosum has a grainy appearance due to further changes to the keratinocytes as they are pushed from the stratum spinosum. The cells (three to five layers deep) become flatter, their cell membranes thicken, and they generate large amounts of the proteins keratin, which is fibrous, and keratohyalin, which accumulates as lamellar granules within the cells. These two proteins make up the bulk of the keratinocyte mass in the stratum granulosum and give the layer its grainy appearance. The nuclei and other cell organelles disintegrate as the cells die, leaving behind the keratin, keratohyalin, and cell membranes that will form the stratum lucidum, the stratum corneum, and the accessory structures of hair and nails.

Stratum Lucidum

The stratum lucidum is a smooth, seemingly translucent layer of the **epidermis** located just above the stratum granulosum and below the stratum corneum. This thin layer of cells is found only in the thick skin of the palms, soles, and digits. The keratinocytes that compose the stratum lucidum are dead and flattened. These cells are densely packed with **eleiden**, a clear protein rich in lipids, derived from keratohyalin, which gives these cells their transparent (i.e., lucid) appearance and provides a barrier to water.

Stratum Corneum

The stratum corneum is the most superficial layer of the epidermis and is the layer exposed to the outside environment. The increased keratinization (also called cornification) of the cells in this layer gives it its name. There are usually 15 to 30 layers of cells in the stratum corneum. This dry, dead layer helps prevent the penetration of microbes and the dehydration of underlying tissues, and provides a mechanical protection against abrasion for the more delicate, underlying layers. Cells in this layer are shed periodically and are replaced by cells pushed up from the stratum granulosum (or stratum lucidum in the case of the palms and soles of feet). The entire layer is replaced during a period of about 4 weeks. Cosmetic procedures, such as microdermabrasion, help remove some of the dry, upper layer and aim to keep the skin looking “fresh” and healthy.

Dermis

The dermis might be considered the “core” of the **integumentary system** (derma- = “skin”), as distinct from the epidermis (epi- = “upon” or “over”) and hypodermis (hypo- = “below”). It contains blood and lymph vessels, nerves, and other structures, such as hair follicles and sweat glands. The dermis is made of two layers of connective tissue that compose an interconnected mesh of elastin and collagenous fibers, produced by fibroblasts.



Layers of the Dermis This stained slide shows the two components of the dermis—the papillary layer and the reticular layer. Both are made of connective tissue with fibers of collagen extending from one to the other, making the border between the two somewhat indistinct. The dermal papillae extending into the epidermis belong to the papillary layer, whereas the dense collagen fiber bundles below belong to the reticular layer. LM × 10. (credit: modification of work by "kilbad"/Wikimedia Commons)

Papillary Layer

The papillary layer is made of loose, areolar connective tissue, which means the collagen and **elastin fibers** of this layer form a loose mesh. This superficial layer of the dermis projects into the stratum basale of the epidermis to form finger-

like dermal papillae. Within the papillary layer are fibroblasts, a small number of fat cells (adipocytes), and an abundance of small blood vessels. In addition, the papillary layer contains phagocytes, defensive cells that help fight bacteria or other infections that have breached the skin. This layer also contains lymphatic capillaries, nerve fibers, and touch receptors called the Meissner corpuscles.

Reticular Layer

Underlying the papillary layer is the much thicker **reticular layer**, composed of dense, irregular connective tissue. This layer is well vascularized and has a rich sensory and sympathetic nerve supply. The reticular layer appears reticulated (net-like) due to a tight meshwork of fibers. Elastin fibers provide some elasticity to the skin, enabling movement. Collagen fibers provide structure and tensile strength, with strands of collagen extending into both the papillary layer and the hypodermis. In addition, collagen binds water to keep the skin hydrated. Collagen injections and Retin-A creams help restore skin turgor by either introducing collagen externally or stimulating blood flow and repair of the dermis, respectively.

Hypodermis

The hypodermis (also called the subcutaneous layer or superficial fascia) is a layer directly below the dermis and serves to connect the skin to the underlying fascia (fibrous tissue) of the bones and muscles. It is not strictly a part of the skin, although the border between the hypodermis and dermis can be difficult to distinguish. The hypodermis consists of well-vascularized, loose, areolar connective tissue and adipose tissue, which functions as a mode of fat storage and provides insulation and cushioning for the integument.

Everyday Connection

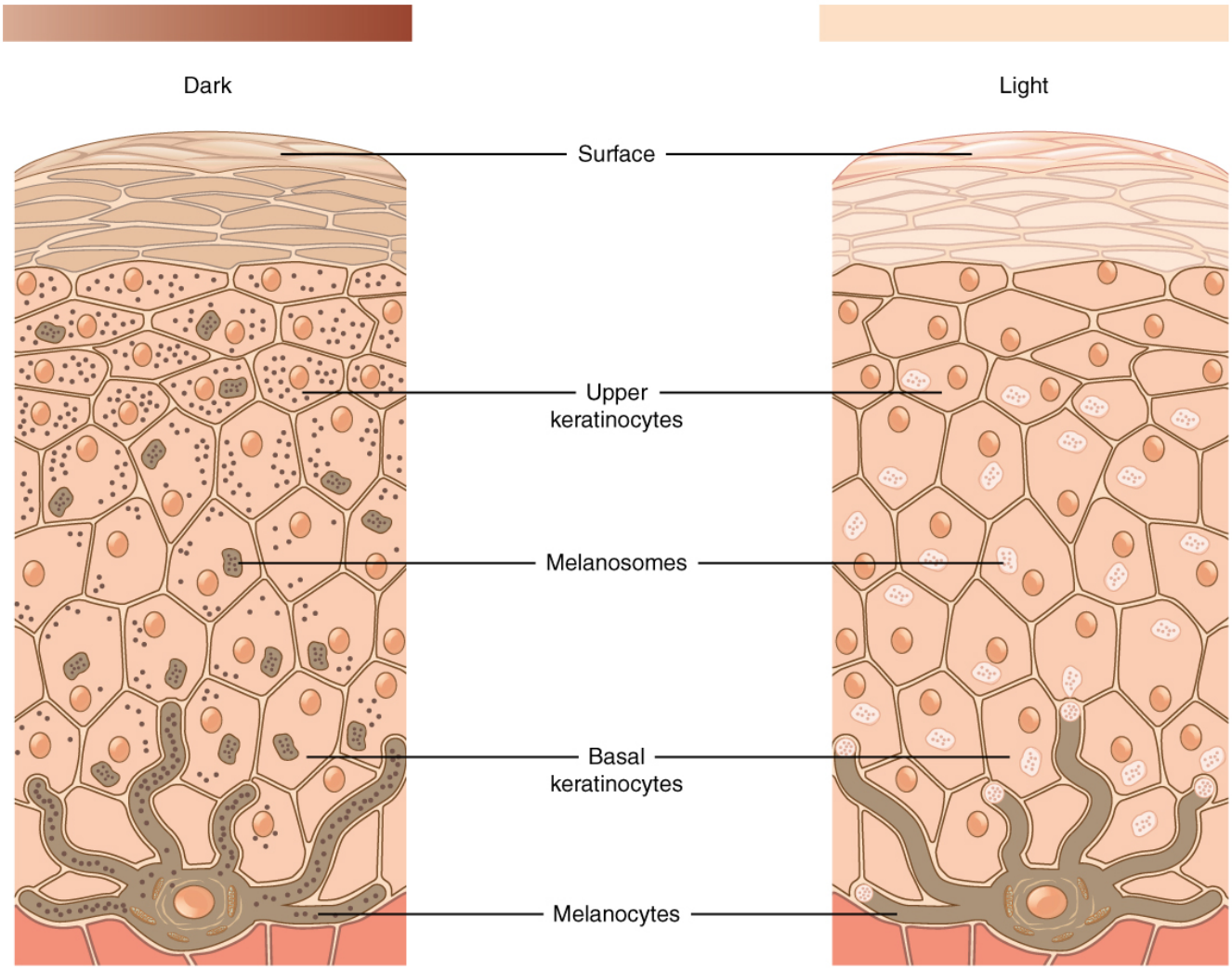
Lipid Storage The hypodermis is home to most of the fat that concerns people when they are trying to keep their weight under control. Adipose tissue present in the hypodermis consists of fat-storing cells called adipocytes. This stored fat can serve as an energy reserve, insulate the body to prevent heat loss, and act as a cushion to protect underlying structures from trauma.
Where the fat is deposited and accumulates within the hypodermis depends on hormones (testosterone, estrogen, insulin, glucagon, leptin, and others), as well as genetic factors. Fat distribution changes as our bodies mature and age. Men tend to accumulate fat in different areas (neck, arms, lower back, and abdomen) than do women (breasts, hips, thighs, and buttocks). The body mass index (BMI) is often used as a measure of fat, although this measure is, in fact, derived from a mathematical formula that compares body weight (mass) to height. Therefore, its accuracy as a health indicator can be called into question in individuals who are extremely physically fit.

In many animals, there is a pattern of storing excess calories as fat to be used in times when food is not readily available. In much of the developed world, insufficient exercise coupled with the ready availability

and consumption of high-calorie foods have resulted in unwanted accumulations of adipose tissue in many people. Although periodic accumulation of excess fat may have provided an evolutionary advantage to our ancestors, who experienced unpredictable bouts of famine, it is now becoming chronic and considered a major health threat. Recent studies indicate that a distressing percentage of our population is overweight and/or clinically obese. Not only is this a problem for the individuals affected, but it also has a severe impact on our healthcare system. Changes in lifestyle, specifically in diet and exercise, are the best ways to control body fat accumulation, especially when it reaches levels that increase the risk of heart disease and diabetes.

Pigmentation

The color of skin is influenced by a number of pigments, including melanin, carotene, and hemoglobin. Recall that melanin is produced by cells called melanocytes, which are found scattered throughout the stratum basale of the epidermis. The melanin is transferred into the keratinocytes via a cellular vesicle called a **melanosome**.

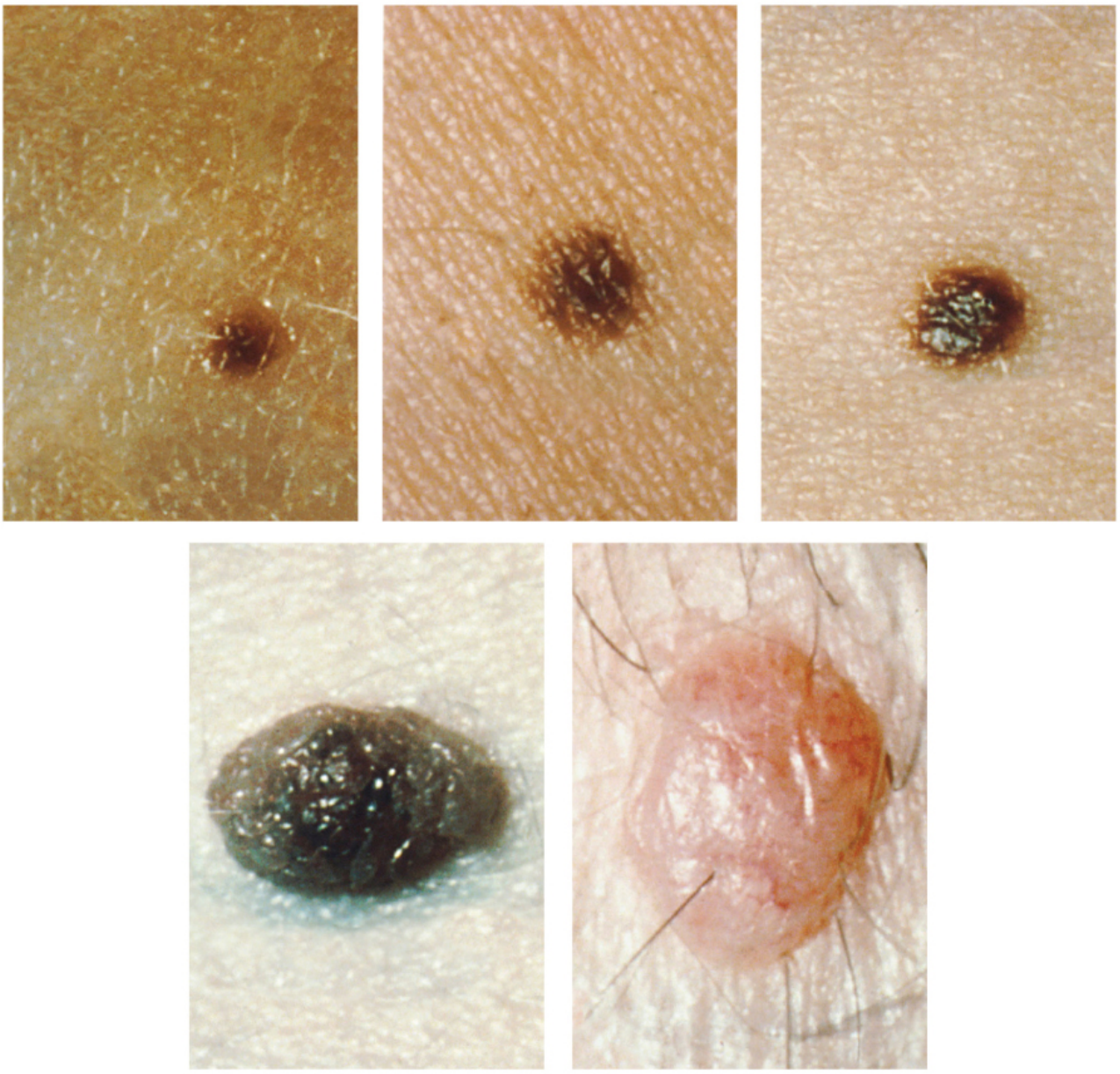


Skin Pigmentation The relative coloration of the skin depends of the amount of melanin produced by melanocytes in the stratum basale and taken up by keratinocytes.

Melanin occurs in two primary forms. Eumelanin exists as black and brown, whereas pheomelanin provides a red color. Dark-skinned individuals produce more melanin than those with pale skin. Exposure to the UV rays of the sun or a tanning salon causes melanin to be manufactured and built up in keratinocytes, as sun exposure stimulates keratinocytes to secrete chemicals that stimulate melanocytes. The accumulation of melanin in keratinocytes results in the darkening of the skin, or a tan. This increased melanin accumulation protects the DNA of epidermal cells from UV ray damage and the breakdown of folic acid, a nutrient necessary for our health and well-being. In contrast, too much melanin can interfere with the production of vitamin D, an important nutrient involved in calcium absorption. Thus, the amount of melanin present in our skin is dependent on a balance between available sunlight and folic acid destruction, and protection from UV radiation and vitamin D production.

It requires about 10 days after initial sun exposure for melanin synthesis to peak, which is why pale-skinned individuals tend to suffer sunburns of the epidermis initially. Dark-skinned individuals can also get sunburns, but are more protected than are pale-skinned individuals. Melanosomes are temporary structures that are eventually destroyed by fusion with lysosomes; this fact, along with melanin-filled keratinocytes in the stratum corneum sloughing off, makes tanning impermanent.

Too much sun exposure can eventually lead to wrinkling due to the destruction of the cellular structure of the skin, and in severe cases, can cause sufficient DNA damage to result in skin cancer. When there is an irregular accumulation of melanocytes in the skin, freckles appear. Moles are larger masses of melanocytes, and although most are benign, they should be monitored for changes that might indicate the presence of cancer.



Moles range from benign accumulations of melanocytes to melanomas. These structures populate the landscape of our skin. (credit: the National Cancer Institute)

Disorders of the Integumentary System

The first thing a clinician sees is the skin, and so the examination of the skin should be part of any thorough physical examination. Most skin disorders are relatively benign, but a few, including melanomas, can be fatal if untreated. A couple of the more noticeable disorders, **albinism** and **vitiligo**, affect the appearance of the skin

and its accessory organs. Although neither is fatal, it would be hard to claim that they are benign, at least to the individuals so afflicted. Albinism is a genetic disorder that affects (completely or partially) the coloring of skin, hair, and eyes. The defect is primarily due to the inability of melanocytes to produce melanin. Individuals with albinism tend to appear white or very pale due to the lack of melanin in their skin and hair. Recall that melanin helps protect the skin from the harmful effects of UV radiation. Individuals with albinism tend to need more protection from UV radiation, as they are more prone to sunburns and skin cancer. They also tend to be more sensitive to light and have vision problems due to the lack of pigmentation on the retinal wall. Treatment of this disorder usually involves addressing the symptoms, such as limiting UV light exposure to the skin and eyes. In vitiligo, the melanocytes in certain areas lose their ability to produce melanin, possibly due to an autoimmune reaction. This leads to a loss of color in patches. Neither albinism nor vitiligo directly affects the lifespan of an individual.

Vitiligo

Individuals with vitiligo experience depigmentation that results in lighter colored patches of skin. The condition is especially noticeable on darker skin.



Patient with vitiligo (credit: Klaus D. Peter)

Other changes in the appearance of skin coloration can be indicative of diseases associated with other body systems. Liver disease or liver cancer can cause the accumulation of bile and the yellow pigment bilirubin, leading to the skin appearing yellow or jaundiced (*jaune* is the French word for "yellow"). Tumours of the pituitary gland can result in the secretion of large amounts of melanocyte-stimulating hormone (MSH), which results in a darkening of the skin. Similarly, Addison's disease can stimulate the release of excess amounts of adrenocorticotropic hormone (ACTH), which can give the skin a deep bronze color. A sudden drop in oxygenation can affect skin color, causing the skin to initially turn ashen (white). With a prolonged reduction in oxygen levels, dark red deoxyhemoglobin becomes dominant in the blood, making the skin appear blue, a condition referred to as cyanosis (*kyanos* is the Greek word for "blue"). This happens when the oxygen supply is restricted, as when someone is experiencing difficulty in breathing because of asthma or a heart attack. However, in these cases the effect on skin color has nothing do with the skin's pigmentation.

This ABC video follows the story of a pair of fraternal African-American twins, one of whom is albino. Watch this video to learn about the challenges these children and their family face. Which ethnicities do you think are exempt from the possibility of albinism?

Section Review

The skin is composed of two major layers: a superficial epidermis and a deeper dermis. The epidermis consists of several layers beginning with the innermost (deepest) stratum basale (germinatum), followed by the stratum spinosum, stratum granulosum, stratum lucidum (when present), and ending with the outermost layer, the stratum corneum. The topmost layer, the stratum corneum, consists of dead cells that shed periodically and is progressively replaced by cells formed from the basal layer. The stratum basale also contains melanocytes, cells that produce melanin, the pigment primarily responsible for giving skin its color. Melanin is transferred to keratinocytes in the stratum spinosum to protect cells from UV rays.

The dermis connects the epidermis to the hypodermis, and provides strength and elasticity due to the presence of collagen and elastin fibers. It has only two layers: the papillary layer with papillae that extend into the epidermis and the lower, reticular layer composed of loose connective tissue. The hypodermis, deep to the dermis of skin, is the connective tissue that connects the dermis to underlying structures; it also harbors adipose tissue for fat storage and protection.

Interactive Link Questions

1. The skin consists of two layers and a closely associated layer. View this animation to learn more about layers of the skin. What are the basic functions of each of these layers?
2. This ABC video follows the story of a pair of fraternal African-American twins, one of whom is albino. Watch this video on albinism to learn about the challenges these children and their family face. Which ethnicities do you think are exempt from the possibility of albinism?

Review Questions

1. Finish the following sentence. Langerhans cells are commonly found in the:

- Stratum spinosum
- Stratum corneum
- Stratum granulosum
- Stratum basale

2. Finish the following sentence. The papillary and reticular layers of the dermis are composed mainly of:

- Melanocytes
- Keratinocytes
- Connective tissue
- Adipose tissue

3. Collagen lends _ _ _ _ _ to the skin.

- Elasticity
- Structure and strength
- Colour
- UV protection

4. What determines the colour of skin, and what is the process that darkens skin when it is exposed to UV light?

Answer Key

1. Stratum spinosum
2. Connective tissue
3. Structure and strength
4. The pigment melanin, produced by melanocytes, is primarily responsible for skin color. Melanin comes in different shades of brown and black. Individuals with darker skin have darker, more abundant melanin, whereas fair-skinned individuals have a lighter shade of skin and less melanin. Exposure to UV irradiation stimulates the melanocytes to produce and secrete more melanin.

Adaption

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Video Lessons on Normal Anatomy and Histology of Skin

LYZ BOYD; HELEN DYCK; AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- List the three layers of skin and the cells that occupy each layer.
- Identify the three layers of skin and cells which are protein rich vs. poor or alive vs. dead based on H&E staining.

Skin, like all tissues, is made out of multiple cells attached together to serve a common function. Thus, there can be a variety of different cells residing within the same tissue.

One Minute Video of Normal Skin Anatomy

Skin is divided into 3 major layers: the **epidermis**, **dermis**, and **hypodermis**. This chapter will focus predominantly in the epidermal layer as this is where **melanocytes** reside.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=508#h5p-43

1 Minute Video of Normal Skin Anatomy by Lyz Boyd, licensed under All Rights Reserved

Normal Skin Histology

Presented by Lyz Boyd using a histology slide of H&E stained normal skin (**DHPLC *e-slide*: PATH 304-004**)

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=508#h5p-9

1 Minute Video of Normal Skin Histology by Lyz Boyd, licensed under All Rights Reserved

Section Review

- The skin has three layers: the epidermis, dermis & hypodermis (subcutaneous).
- The epidermis is the most exposed layer, comprised mostly of keratinocytes and a minor amount of melanocytes. Keratinocytes are filled with the tough protein keratin, which helps the epidermis be durable. The most exposed layer of the epidermis are layers of dead, keratin-filled keratinocytes histologically evident by its lack of nuclei and strong staining for protein.
- Melanocytes reside in the epidermis on the regenerative layer (i.e. stratum basale). Melanocytes continually produce the protein pigment melanin which provides a physical barrier near the nuclei of living keratinocytes, thus protecting the DNA from UV damage. When the keratinocytes die at the most-exposed layer, the melanin pigment has already degraded as there is no longer any need to protect living nuclei. Thus, the most exposed layer of the skin lacks pigment.
- The thicker dermal & epidermal layers contain large vessels and nerves which help supply the epidermis with nutrients and sensation.

Review Questions

1. The papillary layer of the dermis is most closely associated with which layer of the epidermis?

- Stratum corneum
- Stratum granulosum
- Stratum basale
- Stratum spinosum

2. Which of the following is *not* a function of the hypodermis?

- Protects underlying organs
- Helps maintain body temperature
- Source of blood vessels in the epidermis
- A site for long-term storage

3. Cells of the epidermis derive from stem cells of the stratum basale. Describe how the cells change as they become integrated into the different layers of the epidermis.

Answer Key

1. Stratum basale
2. Source of blood vessels in the epidermis
3. As the cells move into the stratum spinosum, they begin the synthesis of keratin and extend cell processes, desmosomes, which link the cells. As the stratum basale continues to produce new cells, the keratinocytes of the stratum spinosum are pushed into the stratum granulosum. The cells become flatter, their cell membranes thicken, and they generate large amounts of the proteins keratin and keratohyalin. The nuclei and other cell organelles disintegrate as the cells die, leaving behind the keratin, keratohyalin, and cell membranes that form the stratum lucidum and the stratum corneum. The keratinocytes in these layers are mostly dead and flattened. Cells in the stratum corneum are periodically shed.

Overview of Cancer

HELEN DYCK AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Briefly describe how a normal cell becomes cancerous.
- Explain the rationale behind naming cancers.

What Exactly is Cancer?

"Cancer" is a term which still causes shock and fear when you hear it as a diagnosis. But what exactly is cancer?

Cancer is actually a group of diseases which have in common a loss of regulation of cell division, cell death, and cell migration. This loss of regulation usually arises because of damage to the DNA and so cancer, like genetically inherited diseases, can be though of as a disease of the DNA. In the case of cancer, the damage happens to genes which regulate either cell division (starting or stopping), DNA repair, cell maturation (differentiation) or cell death. Therefore, the cells with this damage can either divide endlessly or live a lot longer than their normal counterparts. This increased number of cells with uncontrolled growth is known as a **tumour**. They also like to migrate to nutrient rich organs. This is known as metastasis. Metastatic tumours behave like the original cancer cells, just in a new location. For example when osteosarcoma (a type of bone cancer) cells migrate to the lung they still behave as osteosarcoma cells not as a type of lung cancer, and respond to the same type of treatment as the original osteosarcoma.

Cancers are grouped by the organ in which they arise (for example: skin cancer). They are further differentiated by the type of cell in which the uncontrolled growth is happening or the type of behaviour they exhibit. In the skin cancers these are squamous cell, basal cell (both which arise from the squamous epithelium in the dermis) and melanoma (which arises from melanocytes). Each of these types of skin cancer behave quite differently and have a different **prognosis** from each other. As more research is done, more differences are being found even within the traditional classification, which are reflected in differing responses to various treatments.

Because cancers are primarily diseases involving damage to particular genes involved in cell division you can encounter the same damage in different types of cancer. For example, you can have the same genetic damage in breast, ovarian and colon cancers involving the BRCA1 and BRCA2 genes. These types of cancers that have the same underlying genetic change can be said to be much more closely related than types of breast cancer with or without the BRCA1 & 2 gene involvement.

What Controls Normal Cell Division?

To understand what cancer really is, we need to first look at what makes cells enter cell division and what stops cell division if an error is found. The following chapters describe the process that cells undergo during replication and during cell differentiation. As you work through the next two chapters, think about what points of cell cycle control are important for normal function.

Critical Thinking Exercise to do before the next chapter on Cell Division

- Regenerative ability and its impact on the risk of developing cancer in that tissue.
- If there is DNA damage to the genes encoding cyclin B (mitotic metaphase (M) checkpoint) resulting in an overproduction of cyclin B, will the cell be pro- or anti-mitotic?
- Is it possible for red blood cells, which do not undergo mitosis, to develop into a cancer?

Section Summary

- Cancer occurs when damage happens to genes which regulate either cell division (starting or stopping), DNA repair, cell maturation (differentiation), or cell death. As a result, cells with this damage experience uncontrolled growth.
- Terminology of cancer is based first on the organ which the cancer arises and then sub-classified based on the original cell which the cancerous DNA damage has occurred.
- Commonality of cancers are based on the similar gene which is damaged and not based on the organ from which it arose.

Review Questions

1. Fill in the blanks.A _____ is the increase in uncontrolled growth of cells. _____ occurs when tumors move to another location in the body and are known as _____ tumors.

Answer Key

Normal Skin Anatomy & Histology

1. Tumor/tumour, metastasis, metastatic

Cell Growth and Division

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the stages of the cell cycle.
- Discuss how the cell cycle is regulated.
- Describe the implications of losing control over the cell cycle.
- Describe the stages of mitosis and cytokinesis, in order.

So far in this chapter, you have read numerous times of the importance and prevalence of cell division. While there are a few cells in the body that do not undergo cell division (such as gametes, red blood cells, most neurons, and some muscle cells), most **somatic cells** divide regularly. A somatic cell is a general term for a body cell, and all human cells, except for the cells that produce eggs and sperm (which are referred to as germ cells), are somatic cells. Somatic cells contain *two* copies of each of their chromosomes (one copy received from each parent). A **homologous** pair of chromosomes is the two copies of a single chromosome found in each somatic cell. The human is a **diploid** organism, having 23 homologous pairs of chromosomes in each of the somatic cells. The condition of having pairs of chromosomes is known as diploidy.

Cells in the body replace themselves over the lifetime of a person. For example, the cells lining the gastrointestinal tract must be frequently replaced when constantly "worn off" by the movement of food through the gut. But what triggers a cell to divide, and how does it prepare for and complete cell division? The **cell cycle** is the sequence of events in the life of the cell from the moment it is created at the end of a previous cycle of cell division until it then divides itself, generating two new cells.

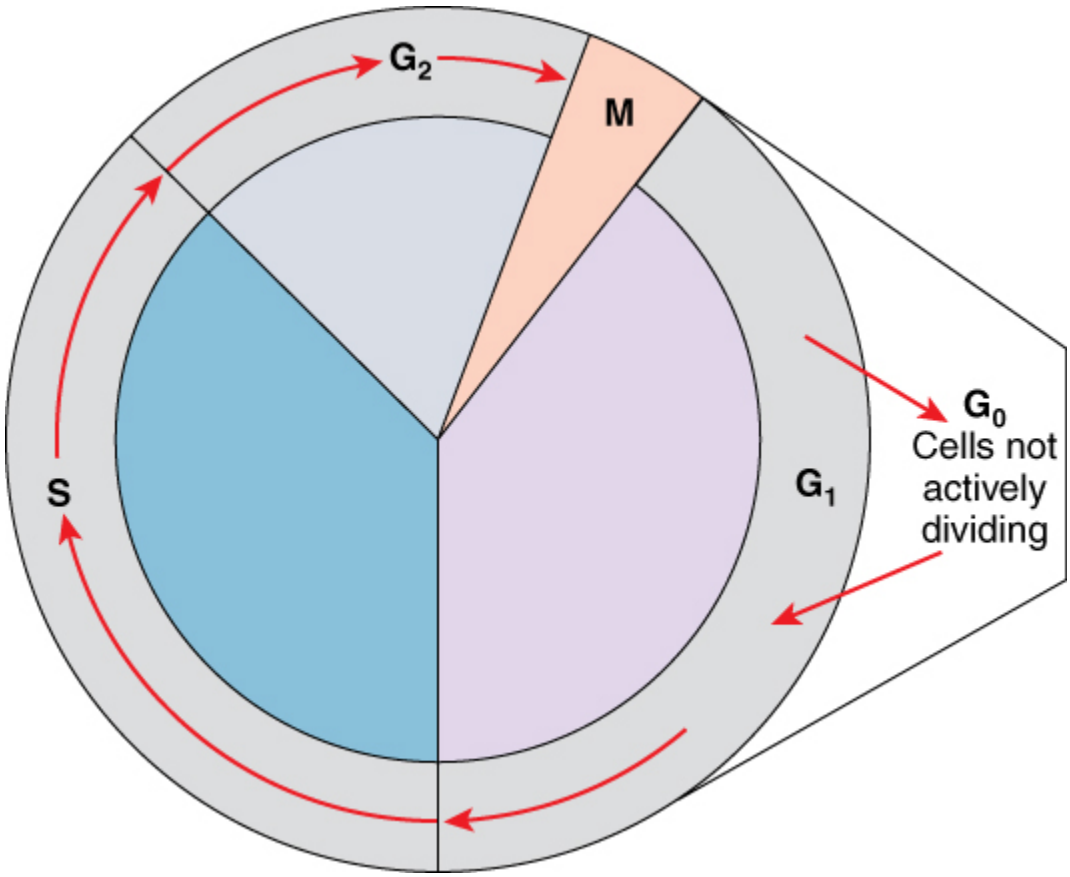
The Cell Cycle

One "turn" or cycle of the cell cycle consists of two general phases: **interphase**, followed by **mitosis** and **cytokinesis**. Interphase is the period of the cell cycle during which the cell is not dividing. The majority of cells are in interphase most of the time. Mitosis is the division of genetic material, during which the cell nucleus breaks down and two new, fully functional, nuclei are formed. Cytokinesis divides the cytoplasm into two distinctive cells.

Interphase

A cell grows and carries out all normal metabolic functions and processes in a period called G_1. **G_1 phase** (gap 1 phase) is

the first gap, or growth phase in the cell cycle. For cells that will divide again, G_1 is followed by replication of the DNA, during the S phase. The S phase (synthesis phase) is period during which a cell replicates its DNA.



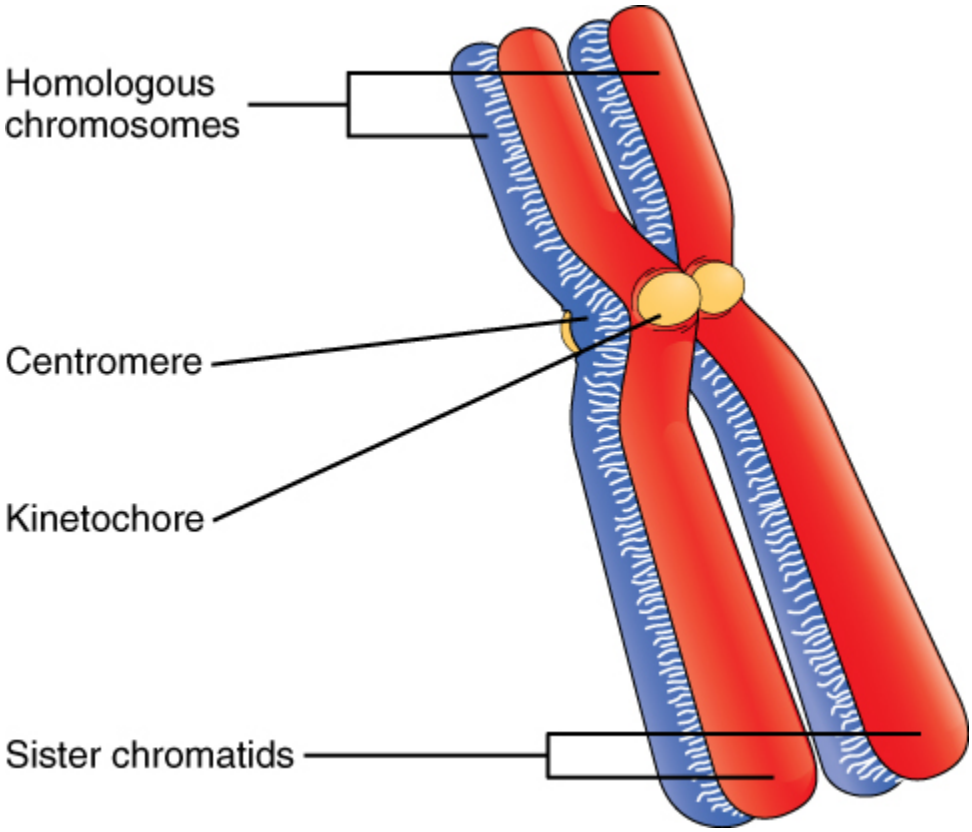
Cell Cycle – *The two major phases of the cell cycle include mitosis (cell division), and interphase, when the cell grows and performs all of its normal functions. Interphase is further subdivided into G1, S, and G2 phases.*

After the synthesis phase, the cell proceeds through the **G_2 phase**. The G_2 phase is a second gap phase, during which the cell continues to grow and makes the necessary preparations for mitosis. Between G_1, S, and G_2 phases, cells will vary the most in their duration of the G1 phase. It is here that a cell might spend a couple of hours, or many days. The **S phase** typically lasts between 8-10 hours and the G_2 phase approximately 5 hours. In contrast to these phases, the **G_0 phase** is a resting phase of the cell cycle. Cells that have temporarily stopped dividing and are resting (a common condition) and cells that have permanently ceased dividing (like nerve cells) are said to be in G_0.

The Structure of Chromosomes

Billions of cells in the human body divide every day. During the synthesis phase (S, for DNA synthesis) of interphase, the amount of DNA within the cell precisely doubles. Therefore, after DNA replication but before cell division, each cell actually contains *two* copies of each chromosome. Each copy of the chromosome is referred to as a **sister chromatid** and is physically bound to the other copy. The **centromere** is the structure that attaches one sister chromatid to another. Because a human cell has 46 chromosomes, during this phase, there are 92 chromatids (46 × 2) in the cell. Make sure

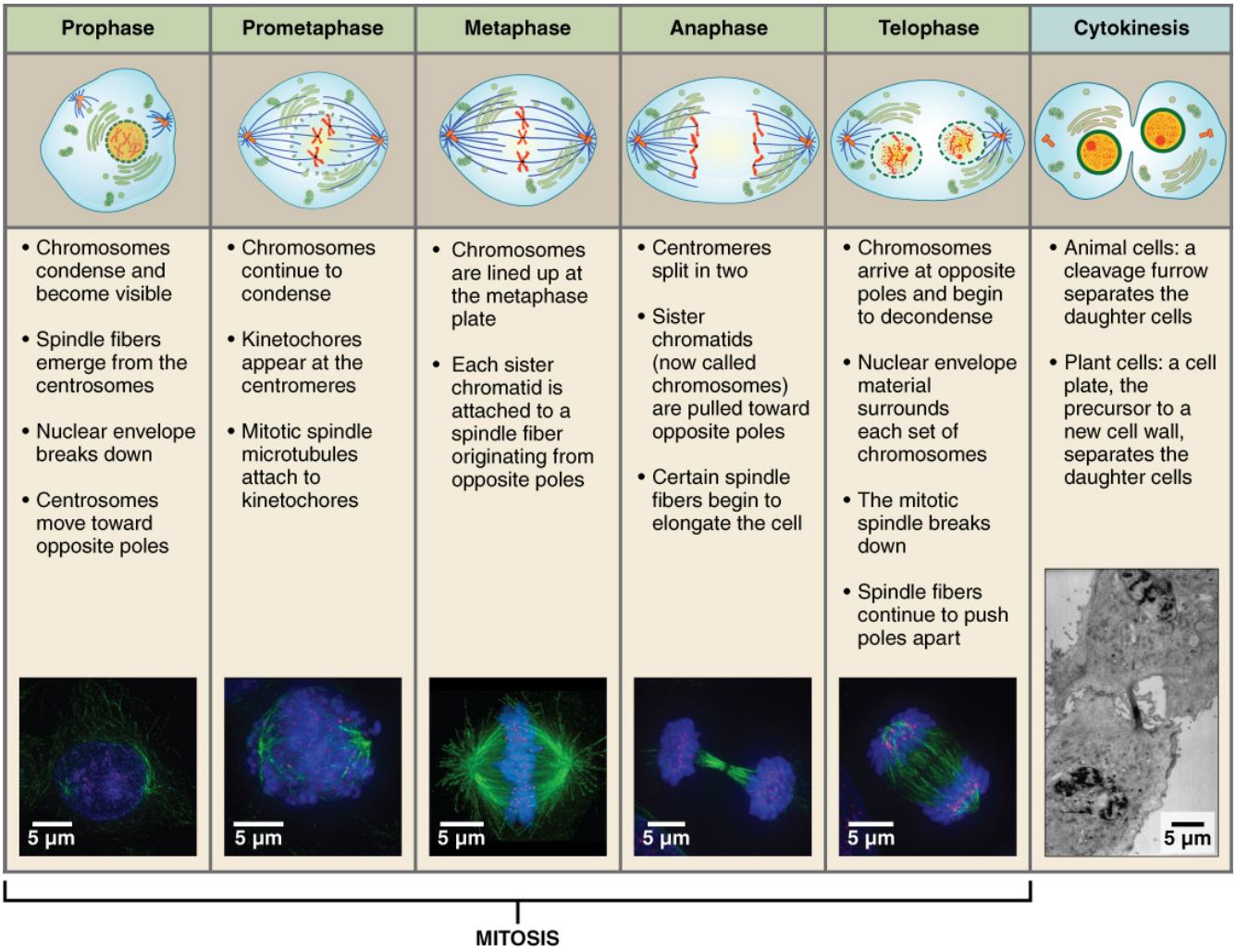
not to confuse the concept of a pair of chromatids (one chromosome and its exact copy attached during mitosis) and a homologous pair of chromosomes (two paired chromosomes which were inherited separately, one from each parent).



A *Homologous Pair of Chromosomes with their Attached Sister Chromatids* – *The red and blue colors correspond to a homologous pair of chromosomes. Each member of the pair was separately inherited from one parent. Each chromosome in the homologous pair is also bound to an identical sister chromatid, which is produced by DNA replication, and results in the familiar "X" shape.*

Mitosis and Cytokinesis

The **mitotic phase** of the cell typically takes between 1 and 2 hours. During this phase, a cell undergoes two major processes. First, it completes mitosis, during which the contents of the nucleus are equitably pulled apart and distributed between its two halves. Cytokinesis then occurs, dividing the cytoplasm and cell body into two new cells. Mitosis is divided into four major stages that take place after interphase and in the following order: **prophase**, metaphase, **anaphase**, and **telophase**. The process is then followed by cytokinesis.



Cell Division: Mitosis Followed by Cytokinesis – *The stages of cell division oversee the separation of identical genetic material into two new nuclei, followed by the division of the cytoplasm.*

Prophase is the first phase of mitosis, during which the loosely packed chromatin coils and condenses into visible chromosomes. During prophase, each chromosome becomes visible with its identical partner attached, forming the familiar X-shape of sister chromatids. The nucleolus disappears early during this phase, and the nuclear envelope also disintegrates.

A major occurrence during prophase concerns a very important structure that contains the origin site for microtubule growth. Recall the cellular structures called centrioles that serve as origin points from which microtubules extend. These tiny structures also play a very important role during mitosis. A **centrosome** is a pair of centrioles together. The cell contains two centrosomes side-by-side, which begin to move apart during prophase. As the centrosomes migrate to two different sides of the cell, microtubules begin to extend from each like long fingers from two hands extending toward each other. The mitotic spindle is the structure composed of the centrosomes and their emerging microtubules. Near the end of prophase there is an invasion of the nuclear area by microtubules from the mitotic spindle. The nuclear membrane has disintegrated, and the microtubules attach themselves to the centromeres that adjoin pairs of sister chromatids. The **kinetochore** is a protein structure on the centromere that is the point of attachment between the mitotic spindle and the sister chromatids. This stage is referred to as late prophase or "prometaphase" to indicate the transition between prophase and **metaphase**.

Metaphase is the second stage of mitosis. During this stage, the sister chromatids, with their attached microtubules, line up along a linear plane in the middle of the cell. A **metaphase plate** forms between the centrosomes that are now located at either end of the cell. The metaphase plate is the name for the plane through the center of the spindle on which the sister chromatids are positioned. The microtubules are now poised to pull apart the sister chromatids and bring one from each pair to each side of the cell.

Anaphase is the third stage of mitosis. Anaphase takes place over a few minutes, when the pairs of sister chromatids are separated from one another, forming individual chromosomes once again. These chromosomes are pulled to opposite ends of the cell by their kinetochores, as the microtubules shorten. Each end of the cell receives one partner from each pair of sister chromatids, ensuring that the two new daughter cells will contain identical genetic material.

Telophase is the final stage of mitosis. Telophase is characterized by the formation of two new daughter nuclei at either end of the dividing cell. These newly formed nuclei surround the genetic material, which uncoils such that the chromosomes return to loosely packed chromatin. Nucleoli also reappear within the new nuclei, and the mitotic spindle breaks apart, each new cell receiving its own complement of DNA, organelles, membranes, and centrioles. At this point, the cell is already beginning to split in half as cytokinesis begins.

The **cleavage furrow** is a contractile band made up of microfilaments that forms around the midline of the cell during cytokinesis. (Recall that microfilaments consist of actin.) This contractile band squeezes the two cells apart until they finally separate. Two new cells are now formed. One of these cells (the "stem cell") enters its own cell cycle; able to grow and divide again at some future time. The other cell transforms into the functional cell of the tissue, typically replacing an "old" cell there.

Imagine a cell that completed mitosis but never underwent cytokinesis. In some cases, a cell may divide its genetic material and grow in size, but fail to undergo cytokinesis. This results in larger cells with more than one nucleus. Usually this is an unwanted aberration and can be a sign of cancerous cells.

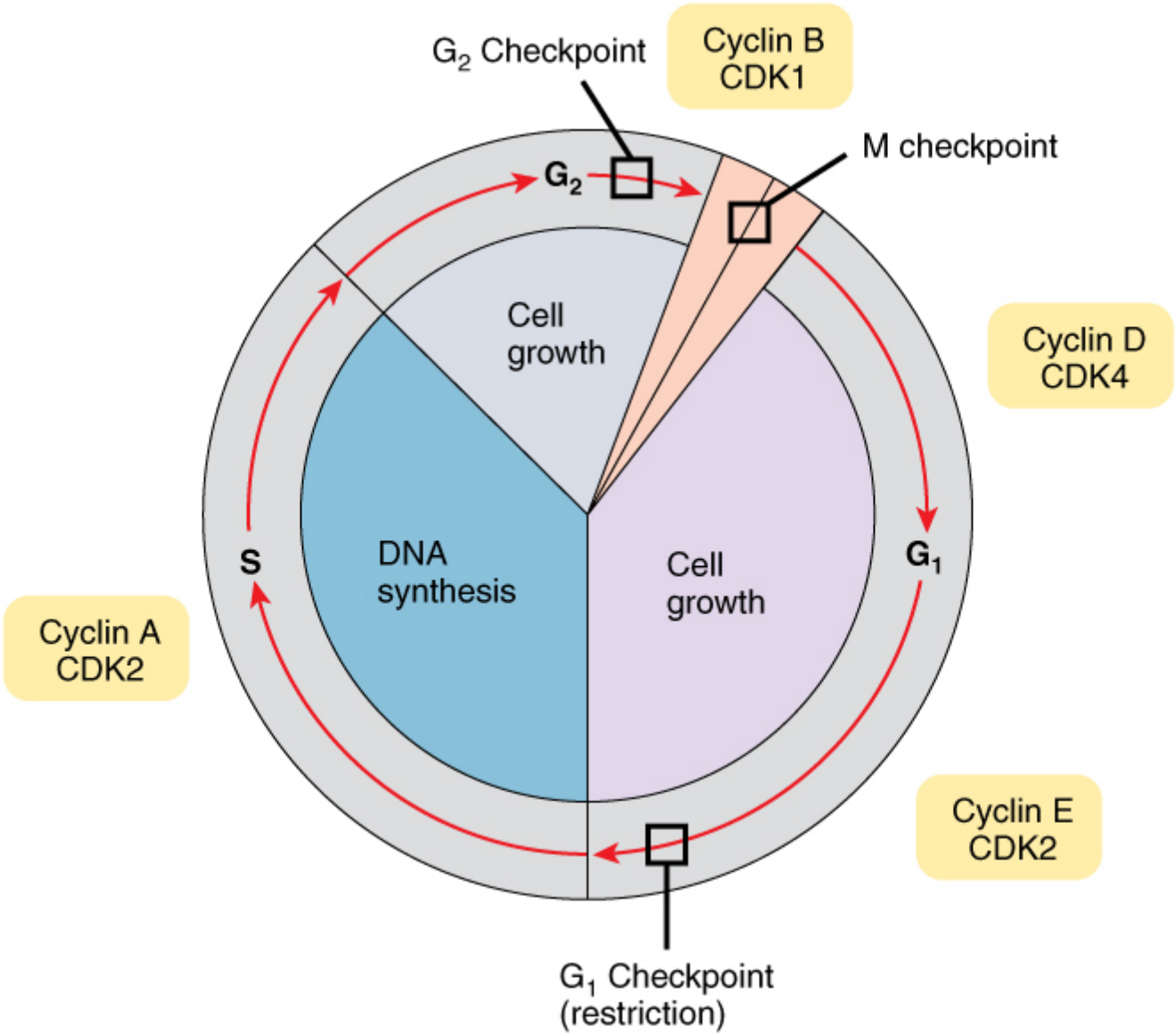
Cell Cycle Control

A very elaborate and precise system of regulation controls direct the way cells proceed from one phase to the next in the cell cycle and begin mitosis. The control system involves molecules within the cell as well as external triggers. These internal and external control triggers provide "stop" and "advance" signals for the cell. Precise regulation of the cell cycle is critical for maintaining the health of an organism, and loss of cell cycle control can lead to cancer.

Mechanisms of Cell Cycle Control

As the cell proceeds through its cycle, each phase involves certain processes that must be completed before the cell should advance to the next phase. A **checkpoint** is a point in the cell cycle at which the cycle can be signaled to move forward or stopped. At each of these checkpoints, different varieties of molecules provide the stop or go signals, depending on certain conditions within the cell. A **cyclin** is one of the primary classes of cell cycle control molecules. A **cyclin-dependent kinase** (CDK) is one of a group of molecules that work together with cyclins to determine progression past cell checkpoints. By interacting with many additional molecules, these triggers push the cell cycle forward unless prevented from doing so by "stop" signals, if for some reason the cell is not ready. At the G_1 checkpoint, the cell must be ready for DNA synthesis to occur. At the G_2 checkpoint the cell must be fully prepared for mitosis. Even during mitosis, a crucial stop and go checkpoint in metaphase ensures that the cell is fully prepared to complete cell division.

The metaphase checkpoint ensures that all sister chromatids are properly attached to their respective microtubules and lined up at the metaphase plate before the signal is given to separate them during anaphase.



Control of the Cell Cycle – *Cells proceed through the cell cycle under the control of a variety of molecules, such as cyclins and cyclin-dependent kinases. These control molecules determine whether or not the cell is prepared to move into the following stage.*

The Cell Cycle Out of Control: Implications

Most people understand that cancer or tumours are caused by abnormal cells that multiply continuously. If the abnormal cells continue to divide unstopped, they can damage the tissues around them, spread to other parts of the body, and eventually result in death. In healthy cells, the tight regulation mechanisms of the cell cycle prevent this from happening, while failures of cell cycle control can cause unwanted and excessive cell division. Failures of control may be caused by inherited genetic abnormalities that compromise the function of certain "stop" and "go" signals. Environmental insult

that damages DNA can also cause dysfunction in those signals. Often, a combination of both genetic predisposition and environmental factors lead to cancer.

The process of a cell escaping its normal control system and becoming cancerous may actually happen throughout the body quite frequently. Fortunately, certain cells of the immune system are capable of recognizing cells that have become cancerous and destroying them. However, in certain cases the cancerous cells remain undetected and continue to proliferate. If the resulting tumour does not pose a threat to surrounding tissues, it is said to be benign and can usually be easily removed. If capable of damage, the tumour is considered malignant and the patient is diagnosed with cancer.

Homeostatic Imbalances

Cancer Arises from Homeostatic Imbalances Cancer is an extremely complex condition, capable of arising from a wide variety of genetic and environmental causes. Typically, mutations or aberrations in a cell's DNA that compromise normal cell cycle control systems lead to cancerous tumours. Cell cycle control is an example of a homeostatic mechanism that maintains proper cell function and health. While progressing through the phases of the cell cycle, a large variety of intracellular molecules provide stop and go signals to regulate movement forward to the next phase. These signals are maintained in an intricate balance so that the cell only proceeds to the next phase when it is ready. This homeostatic control of the cell cycle can be thought of like a car's cruise control. Cruise control will continually apply just the right amount of acceleration to maintain a desired speed, unless the driver hits the brakes, in which case the car will slow down. Similarly, the cell includes molecular messengers, such as cyclins, that push the cell forward in its cycle.

In addition to cyclins, a class of proteins that are encoded by genes called proto-oncogenes provide important signals that regulate the cell cycle and move it forward. Examples of proto-oncogene products include cell-surface receptors for growth factors, or cell-signaling molecules, two classes of molecules that can promote DNA replication and cell division. In contrast, a second class of genes known as tumour suppressor genes sends stop signals during a cell cycle. For example, certain protein products of tumour suppressor genes signal potential problems with the DNA and thus stop the cell from dividing, while other proteins signal the cell to die if it is damaged beyond repair. Some tumour suppressor proteins also signal a sufficient surrounding cellular density, which indicates that the cell need not presently divide. The latter function is uniquely important in preventing tumour growth: normal cells exhibit a phenomenon called "contact inhibition;" thus, extensive cellular contact with neighboring cells causes a signal that stops further cell division.

These two contrasting classes of genes, proto-oncogenes and tumour suppressor genes, are like the accelerator and brake pedal of the cell's own "cruise control system," respectively. Under normal conditions, these stop and go signals are maintained in a homeostatic balance. Generally speaking, there are two ways that the cell's cruise control can lose control: a malfunctioning (overactive) accelerator, or a malfunctioning (underactive) brake. When compromised through a mutation, or otherwise altered, proto-oncogenes can be converted to oncogenes, which produce oncoproteins that push a cell forward in its cycle and stimulate cell division even when it is undesirable to do so. For example, a cell that should be programmed to self-destruct (a process called apoptosis) due to extensive DNA damage might instead be triggered to proliferate by an oncoprotein. On the other hand, a dysfunctional tumour suppressor gene may fail to provide the cell with a necessary stop signal, also resulting in unwanted cell division and proliferation.

A delicate homeostatic balance between the many proto-oncogenes and tumour suppressor genes delicately controls the cell cycle and ensures that only healthy cells replicate. Therefore, a disruption of this homeostatic balance can cause aberrant cell division and cancerous growths.

Visit this link to learn about mitosis. Mitosis results in two identical diploid cells. What structures forms during

prophase?

Section Review

The life of cell consists of stages that make up the cell cycle. After a cell is born, it passes through an interphase before it is ready to replicate itself and produce daughter cells. This interphase includes two gap phases (G_1 and G_2), as well as an S phase, during which its DNA is replicated in preparation for cell division. The cell cycle is under precise regulation by chemical messengers both inside and outside the cell that provide "stop" and "go" signals for movement from one phase to the next. Failures of these signals can result in cells that continue to divide uncontrollably, which can lead to cancer.

Once a cell has completed interphase and is ready for cell division, it proceeds through four separate stages of mitosis (prophase, metaphase, anaphase, and telophase). Telophase is followed by the division of the cytoplasm (cytokinesis), which generates two daughter cells. This process takes place in all normally dividing cells of the body except for the germ cells that produce eggs and sperm.

Review Questions

1. There are many time checkpoints during a cell's lifecycle that permit growth. Identify which checkpoints occur during the respective phase of the lifecycle below. As well, physical cellular products known as cyclins and CDKs accumluate during these checkpoints. Please organize the respective cyclin/CDK into the respective lifecycle below.

Cyclin D	Cyclin E
CDK 2	CDK 4
Cyclin B	Cyclin G
G2 Checkpoint	CDK 1
G1 Checkpoint	M Checkpoint
S Checkpoint	Cyclin A

Checkpoint(s) during G1 Phase	Checkpoint and CDKs in G1 Phase
Checkpoint during S Phase	**Cyclins & CDK in S Phase**
Checkpoint during G2 Phase	**Cyclin & CDK in G2 Phase**
Checkpoint during Mitosis	**Cyclin and CDK in Mitosis**

2. There are 4 major checkpoints in the cell cycle

- True
- False

3. Fill in the blanks with the following words:

benign, malignant

A _____ tumor often does not damage surrounding tissues and can be removed easily. On the other hand, a _____ tumor can damage surrounding tissue and is more difficult to remove.

4. Which class of genes encode proteins that promote the progression of the cell cycle and therefore promote cell growth?

- Proto-oncogenes
- Tumor suppressor genes
- None of the above

Answer Key

1.

Checkpoint(s) during G1 Phase	Checkpoint and CDKs in G1 Phase
G1 Checkpoint	Cyclin D CKD 4 Cyclin E CDK 2
Checkpoint during S Phase	**Cyclins & CDK in S Phase**
	Cyclin A CDK 2
Checkpoint during G2 Phase	**Cyclin & CDK in G2 Phase**
G2 Checkpoint	Cyclin B CDK 1
Checkpoint during Mitosis	**Cyclin and CDK in Mitosis**
M Checkpoint	

2. False
3. Benign, malignant
4. Proto-oncogenes

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Cellular Differentiation

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Discuss how the generalized cells of a developing embryo or the stem cells of an adult organism become differentiated into specialized cells.
- Distinguish between the categories of stem cells.

How does a complex organism such as a human develop from a single cell—a fertilized egg—into the vast array of cell types such as nerve cells, muscle cells, and epithelial cells that characterize the adult? Throughout development and adulthood, the process of cellular differentiation leads cells to assume their final morphology and physiology. Differentiation is the process by which unspecialized cells become specialized to carry out distinct functions.

Stem Cells

A **stem cell** is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate.

The first embryonic cells that arise from the division of the zygote are the ultimate stem cells; these stems cells are described as **totipotent** because they have the potential to differentiate into any of the cells needed to enable an organism to grow and develop.

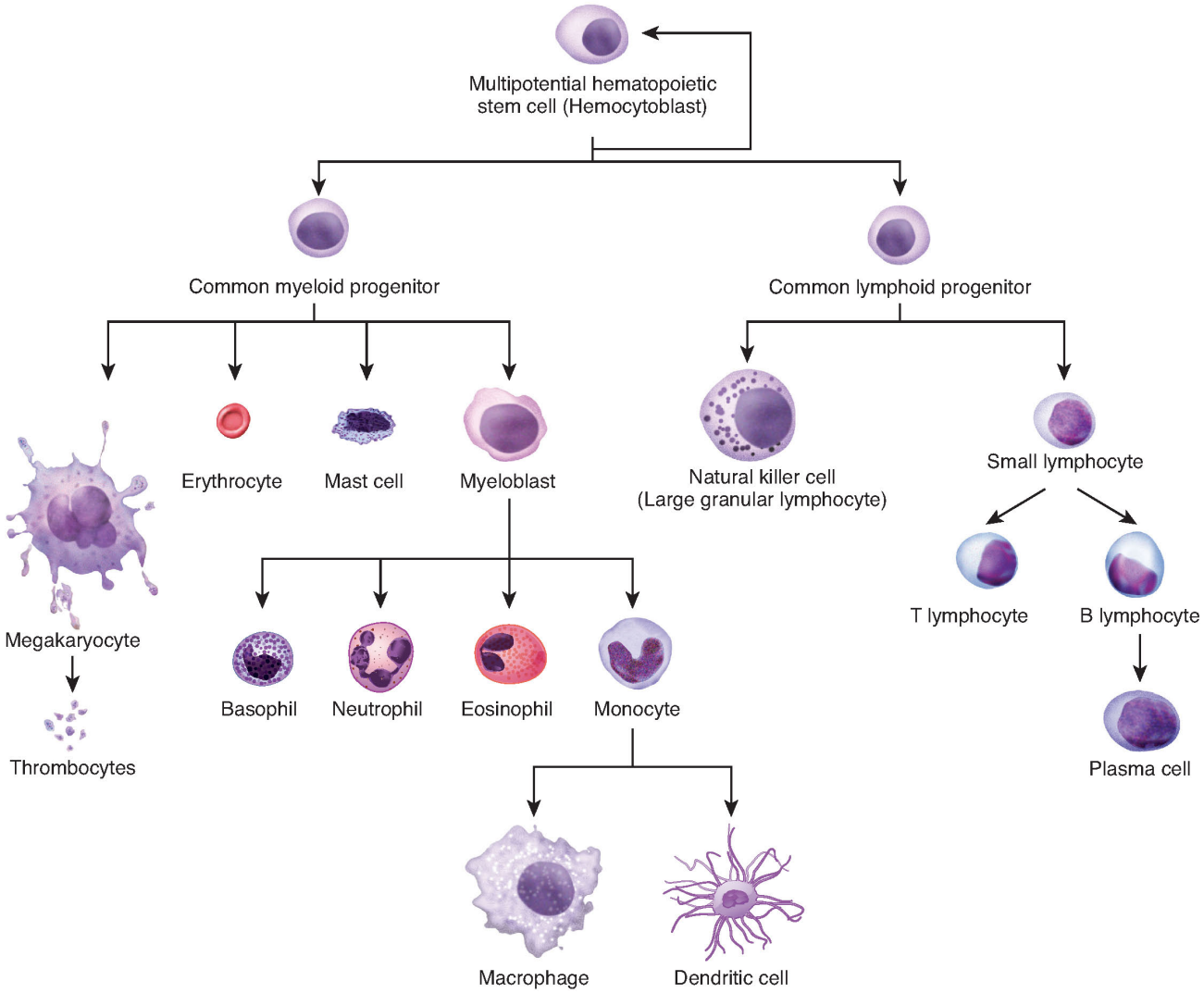
The embryonic cells that develop from totipotent stem cells and are precursors to the fundamental tissue layers of the embryo are classified as pluripotent. A pluripotent stem cell is one that has the potential to differentiate into any type of human tissue but cannot support the full development of an organism. These cells then become slightly more specialized, and are referred to as **multipotent** cells.

A multipotent stem cell has the potential to differentiate into different types of cells within a given cell lineage or small number of lineages, such as a red blood cell or white blood cell.

Finally, multipotent cells can become further specialized **oligopotent** cells. An oligopotent stem cell is limited to becoming one of a few different cell types. In contrast, a **unipotent** cell is fully specialized and can only reproduce to generate more of its own specific cell type.

Stem cells are unique in that they can also continually divide and regenerate new stem cells instead of further specializing. There are different stem cells present at different stages of a human's life. They include the embryonic stem

cells of the embryo, fetal stem cells of the fetus, and adult stem cells in the adult. One type of adult stem cell is the epithelial stem cell, which gives rise to the keratinocytes in the multiple layers of epithelial cells in the epidermis of skin. Adult bone marrow has three distinct types of stem cells: hematopoietic stem cells, which give rise to red blood cells, white blood cells, and platelets; endothelial stem cells, which give rise to the endothelial cell types that line blood and lymph vessels; and mesenchymal stem cells, which give rise to the different types of muscle cells.



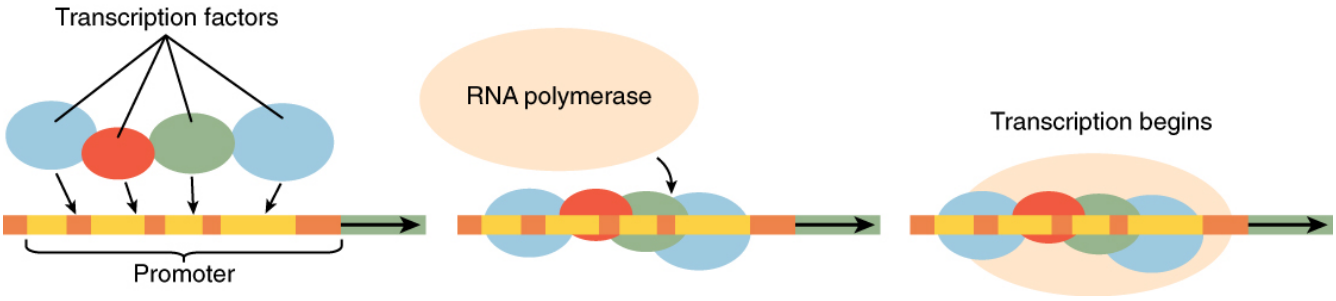
Hematopoiesis – *The process of hematopoiesis involves the differentiation of multipotent cells into blood and immune cells. The multipotent hematopoietic stem cells give rise to many different cell types, including the cells of the immune system and red blood cells.*

Differentiation

When a cell differentiates (becomes more specialized), it may undertake major changes in its size, shape, metabolic activity, and overall function. Because all cells in the body, beginning with the fertilized egg, contain the same DNA, how do the different cell types come to be so different? The answer is analogous to a movie script. The different actors in a movie all read from the same script, however, they are each only reading their own part of the script. Similarly, all cells

contain the same full complement of DNA, but each type of cell only "reads" the portions of DNA that are relevant to its own function. In biology, this is referred to as the unique genetic expression of each cell.

In order for a cell to differentiate into its specialized form and function, it need only manipulate those genes (and thus those proteins) that will be expressed, and not those that will remain silent. The primary mechanism by which genes are turned "on" or "off" is through **transcription factors**. A transcription factor is one of a class of proteins that bind to specific genes on the DNA molecule and either promote or inhibit their transcription.



Transcription Factors Regulate Gene Expression – *While each body cell contains the organism's entire genome, different cells regulate gene expression with the use of various transcription factors. Transcription factors are proteins that affect the binding of RNA polymerase to a particular gene on the DNA molecule.*

Everyday Connection: Stem Cell Research

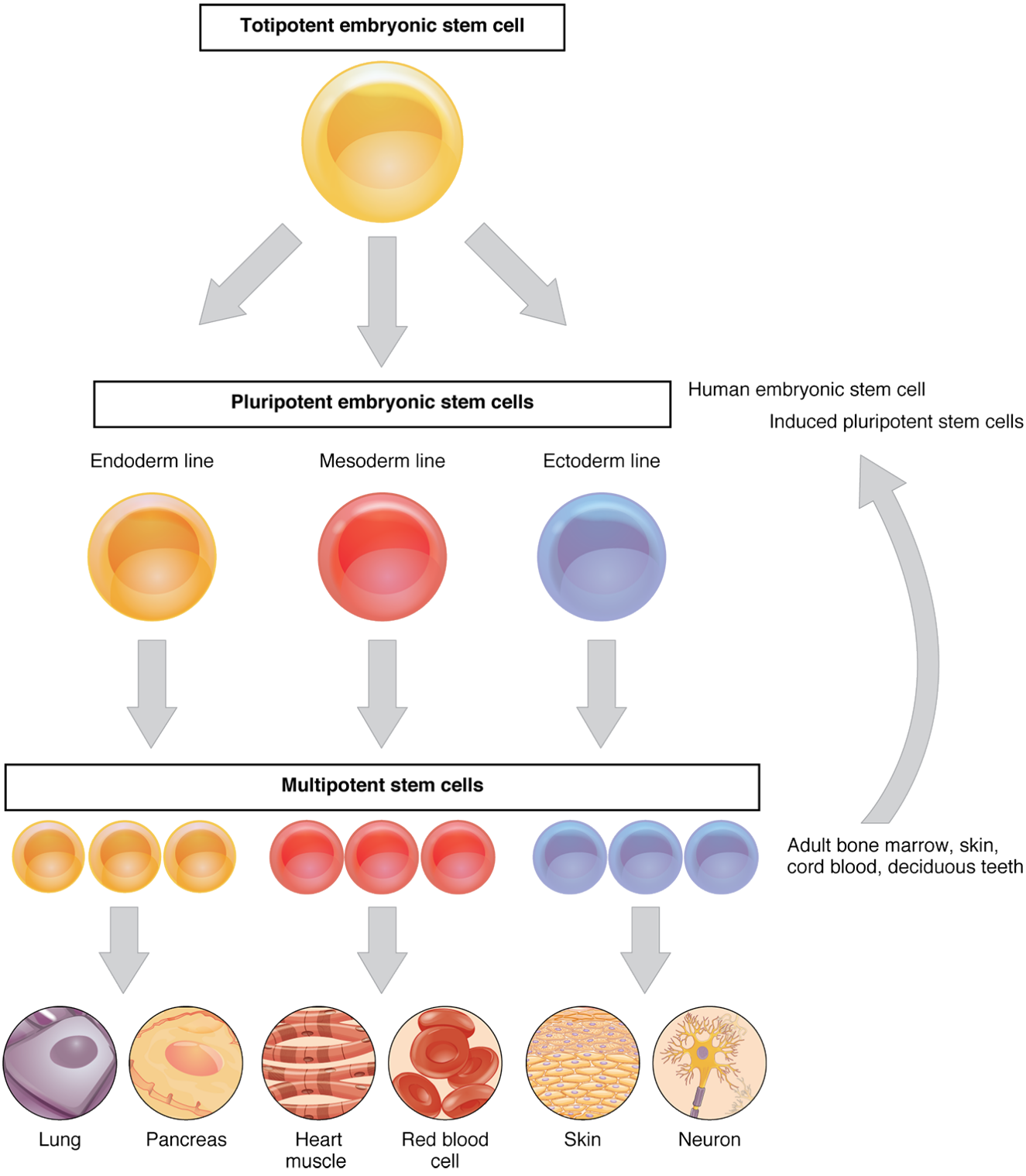
Stem cell research aims to find ways to use stem cells to regenerate and repair cellular damage. Over time, most adult cells undergo the wear and tear of aging and lose their ability to divide and repair themselves. Stem cells do not display a particular morphology or function. Adult stem cells, which exist as a small subset of cells in most tissues, keep dividing and can differentiate into a number of specialized cells generally formed by that tissue. These cells enable the body to renew and repair body tissues.

The mechanisms that induce a non-differentiated cell to become a specialized cell are poorly understood. In a laboratory setting, it is possible to induce stem cells to differentiate into specialized cells by changing the physical and chemical conditions of growth. Several sources of stem cells are used experimentally and are classified according to their origin and potential for differentiation. Human embryonic stem cells (hESCs) are extracted from embryos and are **pluripotent**. The adult stem cells that are present in many organs and differentiated tissues, such as bone marrow and skin, are multipotent, being limited in differentiation to the types of cells found in those tissues. The stem cells isolated from umbilical cord blood are also multipotent, as are cells from deciduous teeth (baby teeth). Researchers have recently developed induced pluripotent stem cells (iPSCs) from mouse and human adult stem cells. These cells are genetically reprogrammed multipotent adult cells that function like embryonic stem cells; they are capable of generating cells characteristic of all three germ layers.

Because of their capacity to divide and differentiate into specialized cells, stem cells offer a potential treatment for diseases such as diabetes and heart disease. Cell-based therapy refers to treatment in which stem cells induced to differentiate in a growth dish are injected into a patient to repair damaged or destroyed cells or

tissues. Many obstacles must be overcome for the application of cell-based therapy. Although embryonic stem cells have a nearly unlimited range of differentiation potential, they are seen as foreign by the patient's immune system and may trigger rejection. Also, the destruction of embryos to isolate embryonic stem cells raises considerable ethical and legal questions.

n contrast, adult stem cells isolated from a patient are not seen as foreign by the body, but they have a limited range of differentiation. Some individuals bank the cord blood or deciduous teeth of their child, storing away those sources of stem cells for future use, should their child need it. Induced pluripotent stem cells are considered a promising advance in the field because using them avoids the legal, ethical, and immunological pitfalls of embryonic stem cells.



Stem Cells – *The capacity of stem cells to differentiate into specialized cells make them potentially valuable in therapeutic applications designed to replace damaged cells of different body tissues.*

Section Review

One of the major areas of research in biology is that of how cells specialize to assume their unique structures and functions, since all cells essentially originate from a single fertilized egg. Cell differentiation is the process of cells becoming specialized as they body develops. A stem cell is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate. While all somatic cells contain the exact same genome, different cell types only express some of those genes at any given time. These differences in gene expression ultimately dictate a cell's unique morphological and physiological characteristics. The primary mechanism that determines which genes will be expressed and which ones will not is through the use of different transcription factor proteins, which bind to DNA and promote or hinder the transcription of different genes. Through the action of these transcription factors, cells specialize into one of hundreds of different cell types in the human body.

Review Questions

1. Match the term with its definition.

Totipotent	Further differentiates into one of a few cell types
Pluripotent	Able to differentiate to cell types with a lineage
Multipotent	Only able to reproduce its own specific type of cells
Oligopotent	Able to differentiate to any cell type and can support full development of an organism (includes embryonic lineages)
Unipotent	Able to differentiate to any cell type but can't support full development of an organism (excludes embryonic images)

2. Fill in the blank.

- Mesenchymal stem cells are able to differentiate into different cell types such as myocytes (muscle cells) and adipocytes (fat cells). They are considered _____ stem cells.

3. Which of the following statements is false? Select all that apply.

- Differentiated cells contain only the DNA that they express
- Differentiated cells contain DNA that they do not express
- Differentiated cells contain the same DNA as undifferentiated cells
- Pluripotent cells contain more DNA than unipotent cells

Answer Key

1. **Totipotent**: Able to differentiate to any cell type and can support full development of an organism (includes embryonic lineages)
   Pulripotent: Able to differentiate to any cell type but can't support full development of an organism (excludes embryonic images)
   Multipotent:Able to differentiate to cell types with a lineage
   Oligopotent:Further differentiates into one of a few cell types
   Unipotent:Only able to reproduce its own specific type of cells
2. Multipotent
3. Differentiated cells contain only the DNA that they express, pluripotent cells contain more DNA than unipotent cells

Adaption

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Cellular differentiation **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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Cancer and the Cell Cycle

MARY ANN CLARK; JUNG CHOI; AND MATTHEW DOUGLAS

Learning Objectives

By the end of this section, you will be able to do the following:

- Describe how cancer is caused by uncontrolled cell growth.
- Understand how proto-oncogenes are normal cell genes that, when mutated, become oncogenes.
- Describe how tumour suppressors function.
- Explain how mutant tumour suppressors cause cancer.

Cancer comprises many different diseases caused by a common mechanism: uncontrolled cell growth. Despite the redundancy and overlapping levels of cell-cycle control, errors do occur. One of the critical processes monitored by the cell-cycle checkpoint surveillance mechanism is the proper replication of DNA during the S phase. Even when all of the cell-cycle controls are fully functional, a small percentage of replication errors (mutations) will be passed on to the daughter cells. If changes to the DNA nucleotide sequence occur within a coding portion of a gene and are not corrected, a gene mutation results. All cancers start when a gene mutation gives rise to a faulty protein that plays a key role in cell reproduction.

The change in the cell that results from the malformed protein may be minor: perhaps a slight delay in the binding of Cdk to cyclin or an Rb protein that detaches from its target DNA while still phosphorylated. Even minor mistakes, however, may allow subsequent mistakes to occur more readily. Over and over, small uncorrected errors are passed from the parent cell to the daughter cells and amplified as each generation produces more non-functional proteins from uncorrected DNA damage. Eventually, the pace of the cell cycle speeds up as the effectiveness of the control and repair mechanisms decreases. Uncontrolled growth of the mutated cells outpaces the growth of normal cells in the area, and a tumour ("-oma") can result.

Proto-oncogenes

The genes that code for the positive cell-cycle regulators are called **proto-oncogenes**. Proto-oncogenes are normal genes that, when mutated in certain ways, become **oncogenes**—genes that cause a cell to become cancerous. Consider what might happen to the cell cycle in a cell with a recently acquired oncogene. In most instances, the alteration of the DNA sequence will result in a less functional (or non-functional) protein. The result is detrimental to the cell and will likely prevent the cell from completing the cell cycle; however, the organism is not harmed because the mutation will not be carried forward. If a cell cannot reproduce, the mutation is not propagated and the damage is minimal. Occasionally, however, a gene mutation causes a change that increases the activity of a positive regulator. For example, a mutation

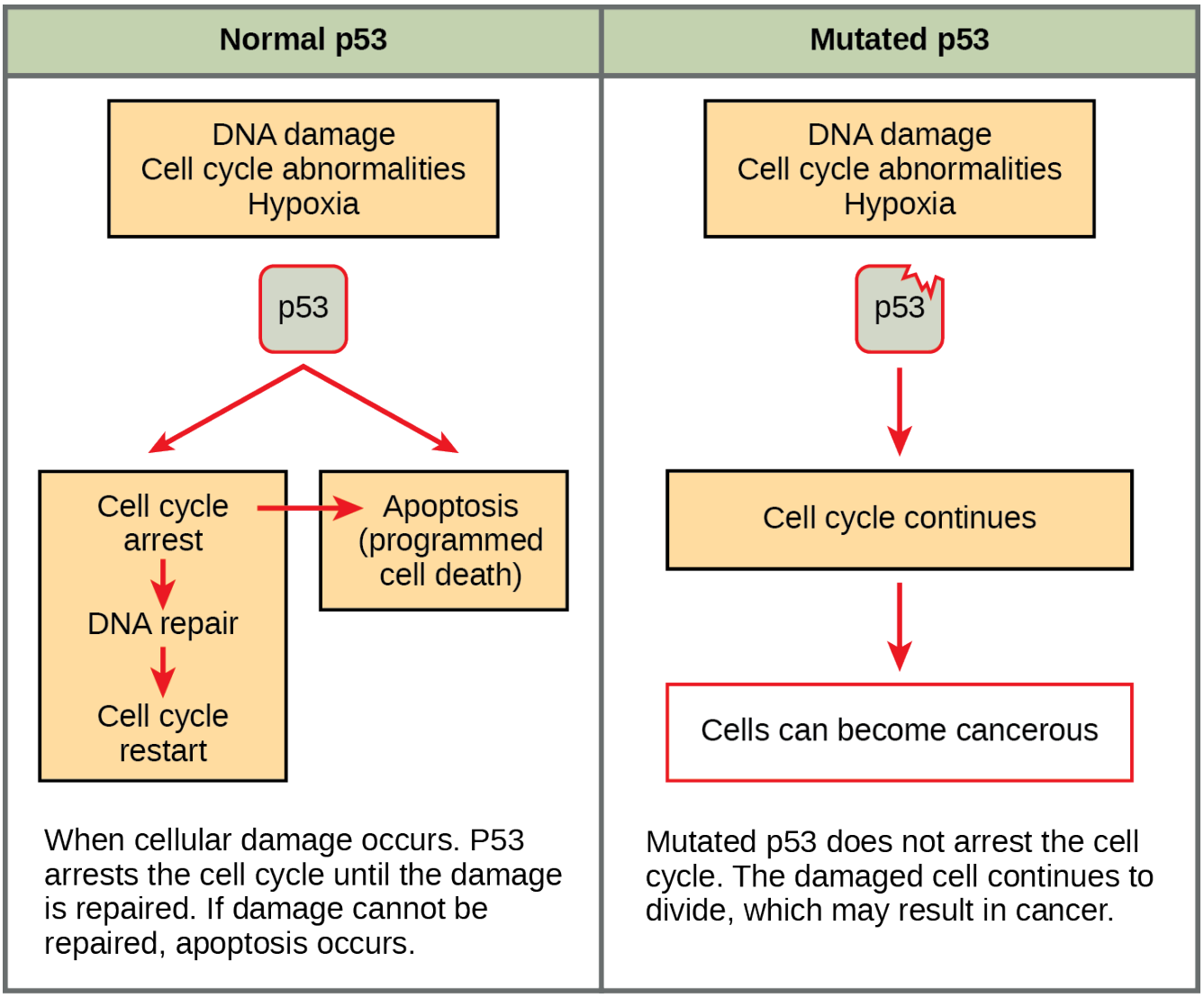
that allows Cdk to be activated without being partnered with cyclin could push the cell cycle past a checkpoint before all of the required conditions are met. If the resulting daughter cells are too damaged to undergo further cell divisions, the mutation would not be propagated and no harm would come to the organism. However, if the atypical daughter cells are able to undergo further cell divisions, subsequent generations of cells may accumulate even more mutations, some possibly in additional genes that regulate the cell cycle.

The Cdk gene in the above example is only one of many genes that are considered proto-oncogenes. In addition to the cell-cycle regulatory proteins, any protein that influences the cycle can be altered in such a way as to override cell-cycle checkpoints. An oncogene is any gene that, when altered, leads to an increase in the rate of cell-cycle progression.

Tumour Suppressor Genes

Like proto-oncogenes, many of the negative cell-cycle regulatory proteins were discovered in cells that had become cancerous. **Tumour suppressor** genes are segments of DNA that code for negative regulator proteins, the type of regulators that, when activated, can prevent the cell from undergoing uncontrolled division. The collective function of the best-understood tumour suppressor gene proteins, Rb, p53, and p21, is to put up a roadblock to cell-cycle progression until certain events are completed. A cell that carries a mutated form of a negative regulator might not be able to halt the cell cycle if there is a problem. Tumour suppressors are similar to brakes in a vehicle: Malfunctioning brakes can contribute to a car crash!

Mutated p53 genes have been identified in more than 50 percent of all human tumour cells. This discovery is not surprising in light of the multiple roles that the p53 protein plays at the G_1 checkpoint. A cell with a faulty p53 may fail to detect errors present in the genomic DNA. Even if a partially functional p53 does identify the mutations, it may no longer be able to signal the necessary DNA repair enzymes. Either way, damaged DNA will remain uncorrected. At this point, a functional p53 will deem the cell unsalvageable and trigger programmed cell death (apoptosis). The damaged version of p53 found in cancer cells, however, cannot trigger apoptosis.
The role of normal p53 is to monitor DNA and the supply of oxygen (hypoxia is a condition of reduced oxygen supply). If damage is detected, p53 triggers repair mechanisms. If repairs are unsuccessful, p53 signals apoptosis. A cell with an abnormal p53 protein cannot repair damaged DNA and thus cannot signal apoptosis.



Cells with abnormal p53 can become cancerous. (credit: modification of work by Thierry Soussi)

The loss of p53 function has other repercussions for the cell cycle. Mutated p53 might lose its ability to trigger p21 production. Without adequate levels of p21, there is no effective block on Cdk activation. Essentially, without a fully functional p53, the G_1 checkpoint is severely compromised and the cell proceeds directly from G_1 to S regardless of internal and external conditions. At the completion of this shortened cell cycle, two daughter cells are produced that have inherited the mutated p53 gene. Given the non-optimal conditions under which the parent cell reproduced, it is likely that the daughter cells will have acquired other mutations in addition to the faulty tumour-suppressor gene. Cells such as these daughter cells quickly accumulate both oncogenes and non-functional tumour-suppressor genes. Again, the result is tumour growth.

Watch an animation of how cancer results from errors in the cell cycle.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://pressbooks.bccampus.ca/pathology/?p=994#oembed-1

Section Summary

Cancer is the result of unchecked cell division caused by a breakdown of the mechanisms that regulate the cell cycle. The loss of control begins with a change in the DNA sequence of a gene that codes for one of the regulatory molecules. Faulty instructions lead to a protein that does not function as it should. Any disruption of the monitoring system can allow other mistakes to be passed on to the daughter cells. Each successive cell division will give rise to daughter cells with even more accumulated damage. Eventually, all checkpoints become nonfunctional, and rapidly reproducing cells crowd out normal cells, resulting in a tumour or leukemia (blood cancer).

Review Questions

1. Human papillomavirus can cause cervical cancer. The virus encodes E6, a protein that binds p53. Based on this fact and what you know about p53, what effect do you think E6 binding has on p53 activity?

- E6 activates p53
- E6 inactivaes p53
- E6 mutates p53
- E6 binding marks p53 for degradation

2. Fill in the blank.
_____ are changes to the order of nucleotides in a segment of DNA that codes for a protein.

3. Fill in the blank.

A gene that codes for a positive cell-cycle regulator is called a(n) _____.

4. A mutated gene that codes for an altered version of Cdk that is active in the absence of cyclin is a(n):

- Kinase inhibitor
- Tumour suppressor gene
- Proto-oncogene
- Oncogene

5. Which molecule is a Cdk inhibitor that is controlled by p53?

- Cyclin
- p21
- Anti-kinase
- Rb

6. List the regulatory mechanisms that might be lost in a cell producing faulty p53.

7. p53 can trigger apoptosis if certain cell-cycle events fail. How does this regulatory outcome benefit a multicellular organism?

8. Explain the difference between a proto-oncogene and a tumor-suppressor gene.

9. Fill in the blanks. Outline the steps that lead to a cell becoming cancerous.

If one of the genes that produces regulator proteins becomes mutated, _____. This increases the chance of more mutations will be _____. As a result, subsequent generations of cells _____. The cell cycle can speed up as a result of _____. The cells can lose the ability to _____ and eventually become "immortalized."

10. What is a consequence of uncontrolled cell growth?

11. Oncogenes are normal genes that become cancerous proto-oncogenes when they are mutated.

- True
- False

12. Which instance(s) would likely cause the cell cycle to be upregulated?

- Mutation that causes decreased expression of tumor suppressor genes
- Mutation that causes decreased expression of proto-oncogenes
- Mutation that causes decreased expression of oncogenes

13. Choose from the words in square brackets to complete the sentence. Imagine a cell with mutated proto-oncogenes. When would this cell be considered cancerous?

This cell would be considered cancerous when the mutated proto-oncogenes cause **[increased / decreased / unchanged]** rates of cell-cycle progression (becoming oncogenes). The daughter cells would **[stop / continue]** dividing without regulation.

Answer Key

1. E6 binding marks p53 for degradation
2. Gene mutations/DNA mutations/mutations
3. Proto-oncogene
4. Oncogene
5. p21
6. Monitoring of the quality of the genomic DNA, recruiting of repair enzymes, and the triggering of apoptosis
7. If a cell has damaged DNA, the likelihood of producing faulty proteins is higher. The daughter cells of

such a damaged parent cell would also produce faulty proteins that might eventually become cancerous. If p53 recognizes this damage and triggers the cell to self-destruct, the damaged DNA is degraded and recycled. No further harm comes to the organism. Another healthy cell is triggered to divide instead.

8. A proto-oncogene is a segment of DNA that codes for one of the positive cell cycle regulators. If that gene becomes mutated so that it produces a hyperactivated protein product, it is considered an oncogene. A tumor suppressor gene is a segment of DNA that codes for one of the negative cell cycle regulators. If that gene becomes mutated so that the protein product becomes less active, the cell cycle will run unchecked. A single oncogene can initiate abnormal cell divisions; however, tumor suppressors lose their effectiveness only when both copies of the gene are damaged.
9. Mutated gene produces a malformed (possibly non-functional) cell-cycle regulator, left unrepaired in the cell, sustain more damage to DNA, the loss of functional checkpoint proteins, self-destruct
10. Cancer
11. False
12. Mutation that causes decreased expression of tumor suppressor genes
13. Increased, continue

Adaption

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Cancer and the cell cycle **in** Biology 2e by Rice University (OpenStax) is licensed under a Creative Commons Attribution 4.0 International License

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General Introduction to the Cellular Development of Cancer and Metastasis

LYZ BOYD; HELEN DYCK; AND JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Explain the roles of proto-oncogenes and tumour suppression genes in the development of cancer.
- List common features of cancerous tissue.

Cancer doesn't arise from just any DNA damage. We are exposed to many insults in our environment, food, water, and activities and our DNA can be easily damaged. As well, there are naturally occurring errors that occur during DNA replication. So why doesn't all of this DNA damage lead to cancer right away? The answer is – it depends on which gene the DNA damage is located.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=518#h5p-45

Overview of Genetic Basis of Cancer by Lyz Boyd, licensed under CC-BY-NC

Metastasis

Metastasis is when the cancerous growth spreads beyond its original site. With the exception of cancers of blood tissue, most tumours begin in their local site, but is still confined to its **basement membrane**. By staying within this localized site, the tumour can tap into blood supply to feed its growth. However, when the tumour's growth disrupt and then invade the basement membrane, the tumour now has access to even more blood and lymphatic vessels. Similarly cancerous cells that aren't attached well to each other can now detach and join the lymphatic or the blood flow. These traveling cancerous cells will eventually enter the systemic blood circulation, allowing it to reach every organ and tissue in the body. The cells that enter the lymphatic vessels encounter the lymph nodes on their way to the blood circulation and will often colonize the lymph nodes making lymph node involvement a handy marker for how far the cancer has spread.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=518#h5p-46

Metastasis by Lyz Boyd, licensed under CC-BY-NC

The site of metastasis depends upon the following factors:

- Type of cancer: currently, certain cancers tend to metastasize to a specific organ. The mechanism has not yet been elucidated.
- An organ's blood supply: the liver, lungs, & brain are highly vascularized with tiny vessels which allow for slow blood flow, thus allowing a cancerous cell to leave the blood and attach to its new metastatic site.
- Geographic location: neighbouring structures are frequently invaded by groups of traveling cells or cells that have been rubbed off on to neighbouring structures, (e.g. peritoneal metastasis of ovarian cancer).
- The local biochemical environment of the target organ interacting with selective metastatic cancer cells. This is known as "seed and soil" hypothesis of why cells stick to particular place.

Section Review

Cancer is uncontrolled growth in tissue. This uncontrolled growth begins with damage to the DNA, particularly in areas that have genes that encode for pro-growth (proto-oncogene) and/or tumour suppression. Some common features of cancerous tissue – regardless of the tissue are:

- Rapid replication of cells. May look like disorganized growth and invading surrounding structures (e.g. basement membrane).
- Large nuclei of various sizes to represent the high nuclear activity and different levels of differentiation and replication.
- Tissue and organs with cancerous changes usually have loss of function due to loss of differentiation. In rarer cases, there may be a gain of function (i.e. produces an unusual product).
- Their rapid growth often compress surrounding structures thus affecting their function.
- Cancerous growth has a high demand for nutrients and blood flow due to it's uncontrolled cell division & growth. The more tumours, the more demand.
- Metastasis is the primary cause of death from cancer because it compromises the functions of the target organ.

Review Questions

1. Which of the following are the factors that influence metastasis? Select all that apply.

- The cancer type
- The organ's blood supply

- The location of the cancer
- The biochemical environment

2. All of the following are common features of cancerous cells: rapid replication, large nuclei, rapid growth, high nutrient demand.

- True
- False

Answer Key

1. The cancer type, the organ's blood supply, the location of the, the biochemical environment
2. True

Pathophysiology of Melanoma

LYZ BOYD; HELEN DYCK; AND JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Describe how melanoma on the skin would appear upon visual inspection.
- Briefly explain histologically how melanoma originating in the skin can spread via metastasis.

Melanoma is a type of cancer arising from damage to the DNA in melanocytes – most commonly in the skin. As such, there is uncontrolled growth (and function) of melanocytes. Initially, the melanocytes, which normally reside near the basement membrane, will grow towards the skin surface (**pagetoid** spread) – thus keeping the basement membrane in tact. To the naked eye, melanoma will look like a dark, irregular looking mole (see later section on early detection), which indicates the increased amount of melanocytes and/or melanin. However, eventually, the tumour will grow past the basement membrane and invade the dermal layer (papillary layer). Once into the papillary layer of the dermis there are no barriers to moving into the deeper layers of the dermis. The reticular dermal layer contains larger blood and lymphatics vessels – sites where melanoma cells can can enter and spread via metastasis.

When melanoma spreads to distant organs, the cancer, with all of its properties, continue their growth and production of melanin. Signs and symptoms of melanoma will be more recognizable as the growth of the tumour may compress delicate structures (e.g. brain, pulmonary airways and vessels) and/or the presence of melanin is visibly noticed or found to interfere with the organ's function (e.g. brain, kidney).

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Progression of Melanoma by Lyz Boyd, licensed under CC-BY-NC

Section Review

- Melanoma appears as an abnormal collection of melanocytes which is visibly noted by a localized darkening of skin (i.e. abnormal mole) of abnormal size, shape, and variety of colours – all of which is indicative of the uncontrolled growth and localized spread of melanocytes.

- If the uncontrolled growth of melanocytes break through the basement membrane of the epidermis, these abnormal melanocytes can be in close proximity to blood and lymphatic vessels that reside in the dermis & hypodermis. Upon entering these vessels, melanoma can spread (metastasize) to distant organs.

Review Questions

1. Finish the following sentence. Melanocytes normally reside in the:

- Hypodermis
- Dermis
- Stratum corneum
- Basement membrane

2. Fill in the blanks.

As melanocytes develop cancerous change, the rate of melanocyte reproduction increases with melanocytes migrating to the most exposed layer of the skin, the stratum _____. To the naked eye, this could appear as an abnormal skin colouring with moles looking _____ or variable in colour.

3. What is the consequence if the rapid growth of melanocytes breaks through the basement membrane? What is below the basement membrane?

Answer Key

1. Basement membrane
2. Corneum, darker
3. Cancerous melanoyctes will break through the basement membrane, entering the dermal layer which has blood vessels and lymphatics. Cancerous melanocytes will enter the lymphatics and thus leave the original site. This is metastasis.

Histopathology of Melanoma

LYZ BOYD AND JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Identify common histopathological features of melanoma.
- Determine whether the cancer is contained vs invading based on the basement membrane.

Before viewing these next videos on the histopathology of melanoma, please recall that:

- Cancerous changes are seen histologically by nuclear changes.
- Whether cancer is contained (i.e. localized) or invading depends on whether it has crossed the basement membrane.
- Metastasis can be determined if the primary cancer is found in distant structures. Metastasis can't be diagnosed from the original site.

Critical Thinking & Histopathology Exercises

Answer the following questions for yourself before viewing the following videos.

- Melanocytes are few in number compared to keratinocytes. What would melanoma look like on low power magnification?
- Recall the cellular basis of cancer and what is happening at the DNA level. How would that look in nuclei stained with H&E?
- Cancer is known for uncontrolled growth. What would you expect to be the size of the cell undergoing cancerous changes? What would make that cell be bigger? smaller?
- Cancerous tissues are known to be at different levels of differentiation. What would that look like when looking at thousands of cells on low magnification vs dozens of cells on high power magnification?
- Whether a cancer spreads depends on whether it invades the basement membrane. What would that look like in low power magnification?

Histopathology of Melanoma- Smaller Magnification

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=295#h5p-47

Malignant Melanoma (Low Power) – DHPLC eslide PATH 425-249 by Lyz Boyd, licensed under All rights reserved

Histopathology of Melanoma – Greater Magnification

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Malignant Melanoma (High Power) – DHPLC eslide: PATH 425-249 by Lyz Boyd, licensed under All rights reserved

Section Review

- Melanoma is identifiable by an abnormal number and collection of melanocytes compared to its normal distribution among keratinocytes.
- Common cancerous changes in melanocytes include:
  - Nuclei of different sizes with very little cytosol.
  - Cells in different sizes and stages of differentiation and cellular division.
- Melanoma is considered invasive if the abnormal growth of melanocytes has breached the basement membrane separating the epidermis and the dermis. Should these abnormal melanocytes be in close proximity to the blood vessels and lymphatics of the dermis & hypodermis, metastasis can occur.

Review Questions

1. What can cause an area of increased keratinization?

- Increased blood flow to the area
- Inflammation due to something irritating the skin (e.g. frequent abrasion)
- Increased exposure to temperature (eg. sunshine)
- Increased movement in the area (eg. moving an arm up/down)

- Inflammation due to something irritating the skin (e.g. frequent abrasion)

2. Where should melanocytes sit?

- Basement membrane
- Stratum corneum
- Stratum lucidim
- Stratum granulosum
- Stratum spinosum
- Dermis
- Hypodermis

3. The size of nuclei shrinks as the cell matures.

- True
- False

Answer Key

1. Inflammation due to something irritating the skin (e.g. frequent abrasion)
2. Basement membrane
3. True

Gross Anatomy of Metastatic Melanoma

LYZ BOYD AND JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Name common sites of metastasis.
- Upon visual inspection, identify key features of metastatic melanoma in organs.

Melanoma frequently metastasizes to the liver, lungs, and brain. However, metastases can also occur in other organs. The DHPLC collection is fortunate to have specimens (from various patients) of melanoma metastases in the liver, brain, lungs, kidneys and the heart. Regardless of the metastatic site, the melanoma will look similar to that seen in the primary site (i.e. skin). In essence, metastases will look like moles in these organs which normally would NOT have any melanocytes present.

This video is awaiting licensing approval and will be available shortly. ***DHPLC Specimen: M0935*** Metastatic Melanoma in Liver and ***DHPLC Specimen: A0901C*** Lung by Lyz Boyd, licensed under All rights reserved

This video is awaiting licensing approval and will be available shortly. ***DHPLC Specimen: P0932*** Metastatic Melanoma in Brain and ***DHPLC Specimen: B0901*** Heart by Lyz Boyd, licensed under All rights reserved

Melanoma can metastasize to other, less common, sites. The following images are from different patients, all with metastatic melanoma.

Recall that there are melanocytes in the uvea of the eye. Although less common, melanoma can arise within the eye and metastasize to any of the pre-mentioned locations.

Section Review

- Common sites of metastasis are liver, lungs, and brain.
- Metastasis can occur to other organs, provided that they have blood or lymphatic flow. These abnormal melanocytes will grow in this new location, regardless of whether melanocytes were previously present. Thus melanoma will visually appear similar to those of the original site, but now in a distant organ: dark, irregularly

shaped and sized moles of varying colours.
- Melanoma can also arise from tissues which also have melanocytes – the eye being an example of a less common origin of melanoma.

Review Questions

1. Which of the following organs is NOT a common site for metastases?

- Brain
- Liver
- Bone marrow
- Skin

2. Why can melanoma develop in the eye?

- There are melanocytes present in the eye which can get damaged and develop cancerous changes.
- The eye is highly vascularized with slow blood flow – an ideal location for metastatic cells to colonize.
- The eye has lots of lymphatic flow and mestatic melanoma tends to travel in the lymph.
- The eye is physically close to where primary melanoma cancers develop: on the upper face.

3. Fill in the blanks.

You are a surgeon, doing a surgery on the liver biliary tree trying to discover why the patient is experiencing jaundice and liver dysfunction. During the surgery, you find a lesion that you suspect is metastatic melanoma. This is because the lesion is _____ in colour with lots of blood vessels present. You take a biopsy of this lesion and send it to a pathologist for examination. The pathologist notices the presence of _____ in both the liver lobules and biliary tract. With these results, medical imaging is arranged to look for metastases in the _____ and ask if there are any neurological symptoms.

Answer Key

1. Skin
2. There are melanocytes present in the eye which can get damaged and develop cancerous changes.
3. Black, melanocytes, brain

Signs and Symptoms of Metastatic Melanoma

LYZ BOYD AND JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Outline the ABCDEs of self skin checks during early detection of melanoma on the skin.
- Briefly explain the pathophysiology behind signs and symptoms of metastatic melanoma.

Melanoma can occur on any part of the skin (or eyes!) – with the more likely spots to develop in areas of sun exposure. Because melanoma is localized to the skin, it is difficult to notice symptoms other than visual changes to skin.

What can melanoma on the skin look like? Well, that's part of early detection.



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Early Detection of Melanoma by Lyz Boyd, licensed under CC BY NC

Other than visually assessing moles, it is difficult to observe signs and symptoms of metastatic melanoma until it has spread to other organs, thus impairing those organs' functions. In the DHPLC, there is a large collection of melanoma metastatic sites with patient information outlining their signs and symptoms.

Organ with Melanoma Metastasis	Normal Function of Organ	Sign/Symptom of Metastatic melanoma
Lungs	Ventilation and gas exchange	Shortness of breath, poor oxygenation of blood, generalized fatigue
Liver	Nutrient storage, detoxification, synthesis of blood proteins, delays venous blood return to heart from abdominal & leg veins.	Enlarged liver, **ascites**, weight loss with increased abdominal girth
Brain	Controls EVERYTHING – both voluntary & involuntary functions of the body	Seizures, difficulties with coordinated movements
Intestines	Digestion and absorption of nutrients and elimination of wastes	Indigestion, possible intestinal obstruction if metastasis grows large enough
Eye*	Vision	Impaired vision with areas of blind spots in the affected eye
Heart	Pumping blood	Heart function was preserved despite several melanoma metastases
Kidneys	Filter wastes out of blood to produce urine	Dark brown/black urine
* This patient actually had melanoma start in his eye. There are many melanocytes in the retina of the eye to help absorb the light entering.		

Figure 4.20 – CLINICAL MANIFESTATIONS OF METASTATIC MELANOMA

Section Review

- Identifying melanoma is through regular self skin checks, looking changes in skin moles using the ABCDE mnemonic: asymmetry, border, colour, diameter, and evolving changes in mole appearance.
- Metastatic melanoma can not be seen visibly (as the metastatic sites are not visible), so signs and symptoms are associated with compression of surrounding structures, thus causing a dysfunction in the organ. Alternatively, the production of melanin may be noticed as its presence may impair normal organ function (e.g. vision, urine production).

Review Questions

1. Fill in the blanks with the following words: black urine, seizures, blindness, ascites, dyspnea

_____ are a sign of metastases in the brain.
_____ are a sign of metastases in the kidney
_____ is often felt when there are metastases in the lungs
_____ is experienced when there is a lesion in the eyes.
_____ is a sign of liver dysfunction, possibly caused by a metastases in the liver.

2. What are the ABCDEs of mole screening?

A is for _____

B is for _____

C is for _____

D is for _____

E is for _____

Answer Key

1. Seizures, black urine, dyspnea, blindness, ascites
2. Asymmetry, border, colour, diameter, evolving

Diagnosis and Treatment of Metastatic Melanoma

LYZ BOYD AND JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Explain how melanoma is diagnosed by histological examination of a tissue biopsy.
- Describe how interprofessional collaboration between health care professionals aid in the diagnosis and treatment of metastatic melanoma.
- Outline key prevention measures that one can take to reduce their risk of developing melanoma.

Diagnosis

Diagnosis of melanoma is through histological examination. What does this look like?

Often, melanoma starts as a irregular looking mole on the skin. That mole, with a little bit of surrounding 'normal' tissue is cut out (ie **biopsy**) by a health care professional. This biopsy is taking the entire mole including the epidermal and dermal layer of the skin. The biopsied mole is cut into very thin slices and mounted onto a glass slide and stained with H&E. All of this work is performed by a medical laboratory technologist with a histology specialization. After a preliminary glance of the stained slide of the biopsied mole, the technologist then sends the slide to a histopathologist for diagnosis, using some of the skills and terms Lyz had demonstrated in the previous chapter.

Treatment

Treatment of melanoma, as well as most cancers, can be grouped as:

- Chemo- and radiotherapy: both of these strategies aim to kill rapidly dividing cells whether by:
    - Chemotherapy uses chemicals which slow down or inhibit cell division. Usually, chemotherapy is absorbed in the entire body, so cell division in normal healthy cells will also be affected.
    - Radiotherapy uses radiation to kill rapidly growing tumour cells. Usually, radiotherapy is localized to the site of the cancerous growth. However, some normal tissue – especially skin – will be affected by radiation if it happens to be in the path of the radiation beam. An important issue for radiotherapy is that certain organs have different 'tolerance' for radiation exposure.
- Surgical excision: remove the cancerous tissue and some surrounding tissue.

- Requires biopsy of surrounding structures and lymph nodes to assess for possibility of nearby metastases as a hint to possible further spread.
- Surgical excision of metastases will not cure the cancer – but it can relieve signs & symptoms caused by the metastasis.

Medical Laboratory Sciences (Anatomic Pathology) in Surgical Treatment of Cancer

Listen to Marion Regan, a medical laboratory technologist, speak about how technologists are giving instantaneous histological specimens to surgeons while the surgeon is excising cancerous tissues.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=550#h5p-54

Histological Preparation of Biopsy Tissue During Surgery by Marion Regan & Jennifer Kong, licensed under CC BY NC

- Immunotherapy: allow the body's immune system to recognize abnormal cancer cells and remove them.
  - This is in the early stages of implementation.
- Targeted therapy: inhibit the genes (or their protein products) which were damaged – thus stopping the uncontrollable cell division.
  - This is in the early stages of research and implementation.

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Treatment of Melanoma by Lyz Boyd, licensed under CC BY NC

Prevention

What's unique about melanoma, compared to many cancers, is that one can lower one's risk by by limiting exposure of the skin & eyes to the sun. Continuous monitoring of the skin – especially moles – may allow for early detection and, hence, early treatment. Patient survival rates increase when cancers are detected early.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=550#h5p-53

Prevention of Melanoma by Lyz Boyd, licensed under – CC BY NC

Section Review

- Whether it is a biopsy of a suspicious mole or surgical excision of a tumour, a medical laboratory technologist will histologically prepare and stain the tissue, allowing for visual examination of key features of cancerous changes and whether the basement membrane is intact.
- Depending on the level of invasion of spread, melanoma can be treated by surgical excision of the tumour, localized treatment with radiotherapy, or systemic treatment with chemo- or immunotherapy.
- Prevention measures of modifiable risk factors (e.g. limiting sun damage to skin) can reduce the risk of developing melanoma. However, non-modifiable risk factors (e.g. age, genetics, skin tone) can not be changed; thus, there is always a risk.

Review Questions

1. Upon discovering an abnormal mole, a patient will be fast tracked for radiotherapy.

- True
- False

2. How do you prevent melanoma? Fill in the blanks with the following words:

clothing, staying indoors, sunscreen, age

Several lifestyle changes can be implemented to lower one's chance of melanoma. This is different than non-modifiable risks such as _____ which can't be changed with any lifestyle choice. Prevention of damaging exposure to the sun is best done by _____ during the sunniest times of the day. When going out into the sun, one is encouraged to wear _____ as reapplication isn't required, as seen with applying _____.

Answer Key

1. False
2. Age, staying indoors, clothing, sunscreen

Melanoma Chapter Summary and Credits

JENNIFER KONG

Chapter Summary

Key Takeaways

- Melanoma is a type of cancer which involves uncontrolled growth of melanocytes.
- Cancerous changes occur when there is DNA damage in melanocytes that results in a dysfunction of anti-tumour and/or pro-growth genes.
- Melanocytes grow rapidly in a disorganized fashion, and have different levels of differentiation and cell sizes. Melanocytes can make a lot of melanin, thus providing visual clues to tumour development.
- When cancerous melanocytes invade the basement membrane and circulate in either the blood or lymph, this is metastatic melanoma. The brain, liver, and lungs are common – but not the only – sites of metastases.
- The most effective treatment to melanoma is for recognition of melanoma at an early stage recognition. The mnemonic ABCDE will help you identify suspicious moles that can develop into melanoma.
- PREVENTION is the most effective treatment to melanoma. So recall your sun safety tips!
- Health care professional team work together to help diagnose and treat metastatic melanoma.

Credits

Authors: Lyz Boyd (UBC Medical student), Helen Dyck (UBC) & Dr. Jennifer Kong (BCIT & UBC)

Gross anatomy & histology videos: Lyz Boyd (UBC medical student)

Medical Laboratory Technology interview: Marion Regan (BCIT – School of Health Sciences)

Videoproduction & editing: Dr. Jennifer Kong (BCIT & UBC) and Yimei Qin (UBC undergraduate student)

Editing: Eva Su (UBC Undergraduate student)

Post-Test for Metastatic Melanoma

JENNIFER KONG

1. Melanoma can occur in any person, regardless of age, skin tone, and sun exposure.

- True
- False

2. Metastatic melanoma is lethal.

- True
- False

3. Where can melanoma begin?

- Eyes
- Skeletal muscle
- Brain
- Heart

4. Where are common sites of metastases? Select all that apply.

- Lungs
- Bone marrow
- Heart
- Liver
- Fat
- Brain
- Nails

5. Fill in the blanks with the following words:

Older adults, tumour suppressor genes, DNA damage, young adults

Melanoma can occur when there is a perfect combination of _____ to _____. Melanoma commonly appears in _____ because of years of accumulated errors in important genes. However, the original damage to DNA occurred when they were _____.

6. Melanoma that starts in the skin can metastasize to distant sites by:

Select all that apply.

- Blood flow
- Lymphatic flow
- Exhalation
- Rubbing skin with the melanoma site

7. Refer to Figure 4.6. What do you notice about the cells at the outermost layer (S. corneum) of this section of skin?

8. Refer to Figure 4.6. What is distinctive about the cells of the stratum spinosum?



Figure 4.6

9. Where is the basement membrane?

- Between the S. corneum and S. Basale
- At the bottom of the reticular layer of the dermis
- At the junction between the S. basale and papillary layer of the dermis
- At the junction between the papillary and reticular layer of the dermis

Answer Key

1. True
2. True
3. Eyes
4. Lungs, bone marrow, liver, brain
5. DNA damage, tumour suppressor genes, older adults, young adults
6. Blood flow, lymphatic flow
7. These cells do not have nuclei, so you can deduce that they are dead. They appear to be sloughing off.
8. These cells have dehydrated and collapsed, thus giving them their spinay appearance.
9. At the junction between the S. basale and papillary layer of the dermis

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EMPHYSEMA

Emphysema Chapter Overview

JENNIFER KONG

Chapter Learning Objectives

At the end of this chapter, you will be able to:

- Describe the pathophysiology of emphysema as a consequence of chronic injury and inflammation.
- Identify key histological features associated with emphysema.
- Outline expected clinical changes in a patient in response to remodelling, loss of alveolar tissue & lung elasticity.

This chapter is about emphysema, a condition that is under the umbrella term of chronic obstructive pulmonary disease (**COPD**). Emphysema is chronic condition of continuous lung injury and inflammation which will progressively worsen with no known cure. Thus, it takes many health care providers working collaboratively to manage an emphysema patient during the exacerbations and progression of their disease.

This chapter is subdivided into:

- Pre-test
- Normal lung anatomy and histology
- Normal physiology of breathing
- Inflammation and Tissue remodeling
- Pathophysiology and histopathology of emphysema
- Interview with health care professionals diagnosing/treating those with emphysema and its complications
    - Medical Radiographer (Computerized tomography)
    - Nurse
- Case study of a patient experiencing exacerbation with COPD and her patient journey and interactions with health care professionals
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

AAT	Alpha-1-Antitrypsin
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CT	Computed Tomography
DRG	Dorsal Respiratory Group
ERV	Expiratory Reserve Volume
FRC	Functional Residual Capacity
HRVC	Human Rhinovirus C
IC	Inspiratory Capacity
IFN- γ	Interferon-γ
IL-1	Interleukin-1
IRV	Inspiratory Reserve Volume
LPS	Lipopolysaccharide
P_{alv}	Intra-alveolar Pressure
P_{atm}	Atmospheric Pressure
PGE_2	Prostaglandin E2
P_{ip}	Intrapleural Pressure
PRG	Pontine Respiratory Group
PRRs	Pattern Recognition Receptor
RV	Residual Volume
TLC	Total Lung Capacity
TNF	Tumour Necrosis Factor
TV	Tidal Volume
VC	Vital Capacity
VRG	Ventral Respiratory Group

Pre-Test for Emphysema

JENNIFER KONG

Normal Lung Pre-Test

1. Where does gas exchange (i.e. respiration) occur? Select all that apply.

- Trachea
- Bronchi & bronchioles
- Alveoli
- Surfactant

2. Lungs are smaller outside of the chest due to the elastin in the lung retracting.

- True
- False

3. Fill in the blanks with the following words:

pulmonary capillaries, carbon dioxide, pulmonary veins, oxygenated blood, deoxygenated, pulmonary arteries, oxygen

_____ blood leaves the right ventricle and enters the _____ which then branch into smaller and smaller vessels. The _____ surround alveoli and allow for near instantaneous gas exchange with the alveolar gases: _____ leaves the alveoli going into the blood and _____ leaves the blood and into the alveoli. _____ leave the lungs and enter _____ and enter the left atrium.

Emphysema Pre-Test

1. Inhalation is an active process (i.e. takes energy) whereas exhalation is a passive process thanks to the elastic nature of lung tissue.

- True
- False

2. Fill in the blanks with the following phrases:

alpha-1-antitrypsin will deactivate the enzymes released by white blood cells, only the foreign particles are destroyed by white blood cells, inflammatory damage to normal healthy tissue, recruiting white blood cells to ingest the foreign particle

When tissue is infected or injured, the inflammation process occurs. Using cigarette smoking as an example, the lungs will first react to inhaled smoke by _____. To prevent normal healthy tissue from being injured _____. As a result _____. If there is either too frequent injury or insufficient alpha-1-antitrypsin, the result is _____.

3. Finish the following sentence. In emphysema, it takes energy to exhale because:

- Loss of elastin in lung tissue causes airways to collapse during exhalation
- Gain of collagen in lung tissue causing airways to be always open
- Loss of muscle in the diaphragm due to inflammation of lung tissue
- Increase in alpha 1 antitrypsin blocks airways causing an obstruction during exhalation

Answer Key

Normal Lung Pre-Test

1. Alveoli

2. True

3. Deoxygenated, pulmonary arteries, pulmonary capillaries, oxygen, carbon dioxide, oxygenated blood,pulmonary veins

Emphysema Pre-Test

1. True

2. Recruiting white blood cells to ingest the foreign particle, alpha-1-antitrypsin will deactivate the enzymes released by white blood cells, only the foreign particles are destroyed by white blood cells,inflammatory damage to normal healthy tissue

3. Loss of elastin in lung tissue causes airways to collapse during exhalation

Organs and Structures of the Respiratory System

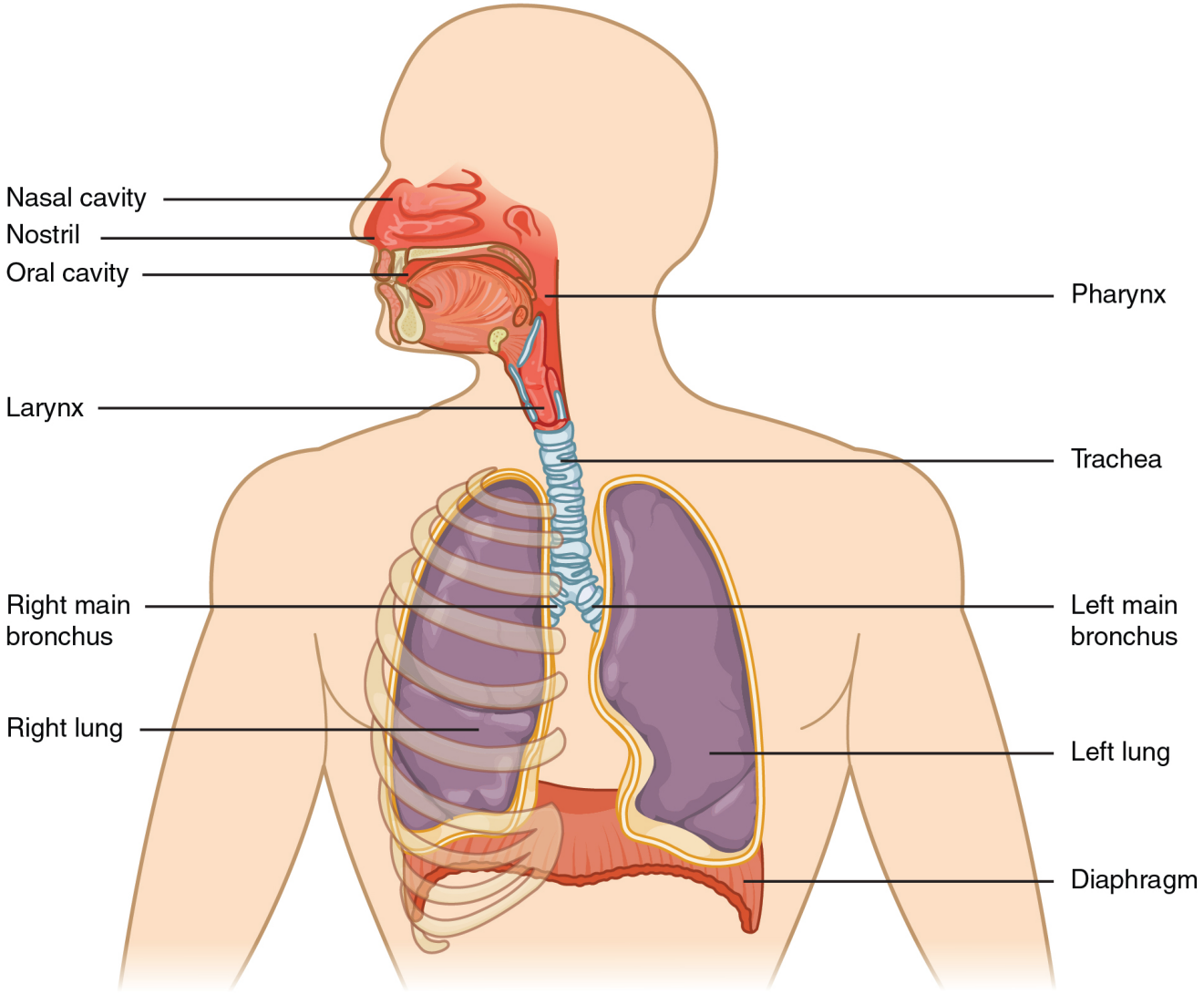
J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- List the structures that make up the respiratory system.
- Describe how the respiratory system processes oxygen and CO_2.
- Compare and contrast the functions of upper respiratory tract with the lower respiratory tract.

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing.



Major Respiratory Structures The major respiratory structures span the nasal cavity to the diaphragm.

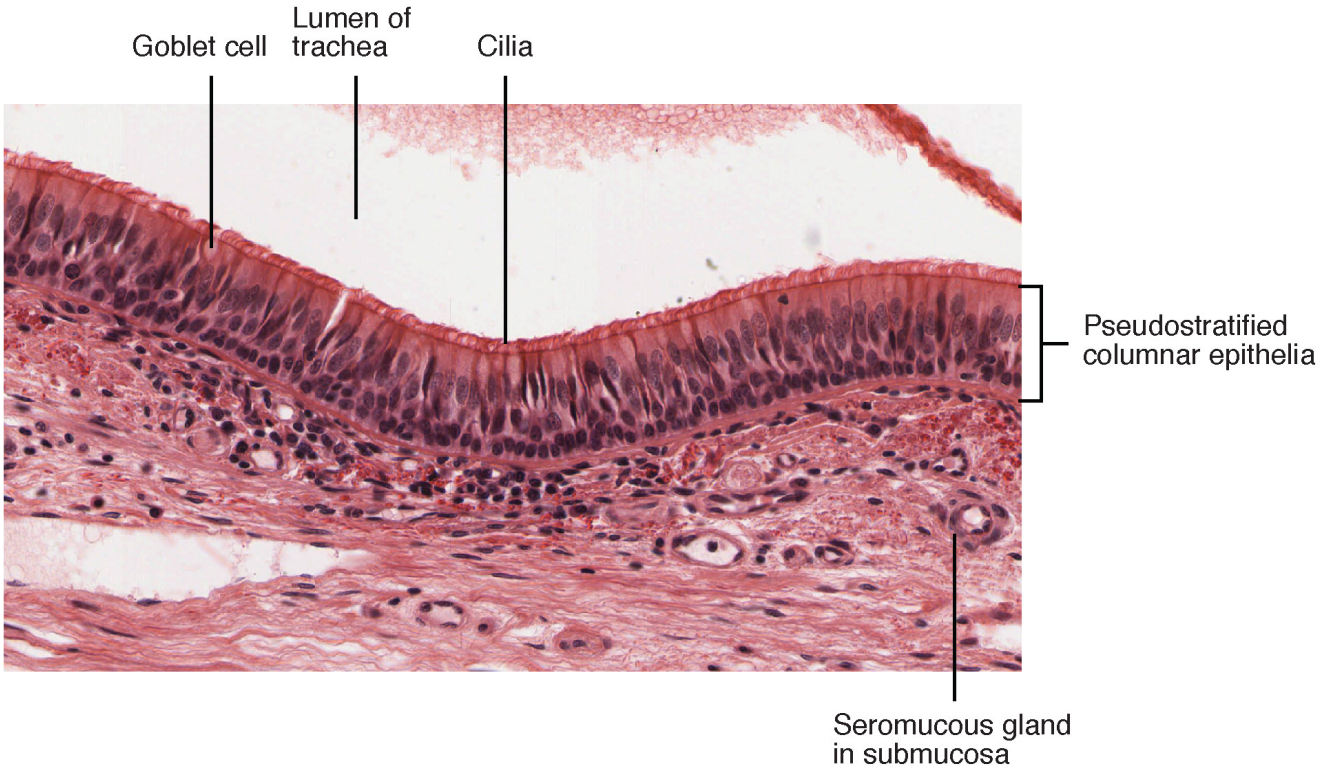
Functionally, the respiratory system can be divided into a **conducting zone** and a **respiratory zone**. The conducting zone of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the respiratory zone.

Conducting Zone

The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone perform other functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

Aspects of the upper respiratory tract are lined by**respiratory epithelium** composed of pseudostratified ciliated

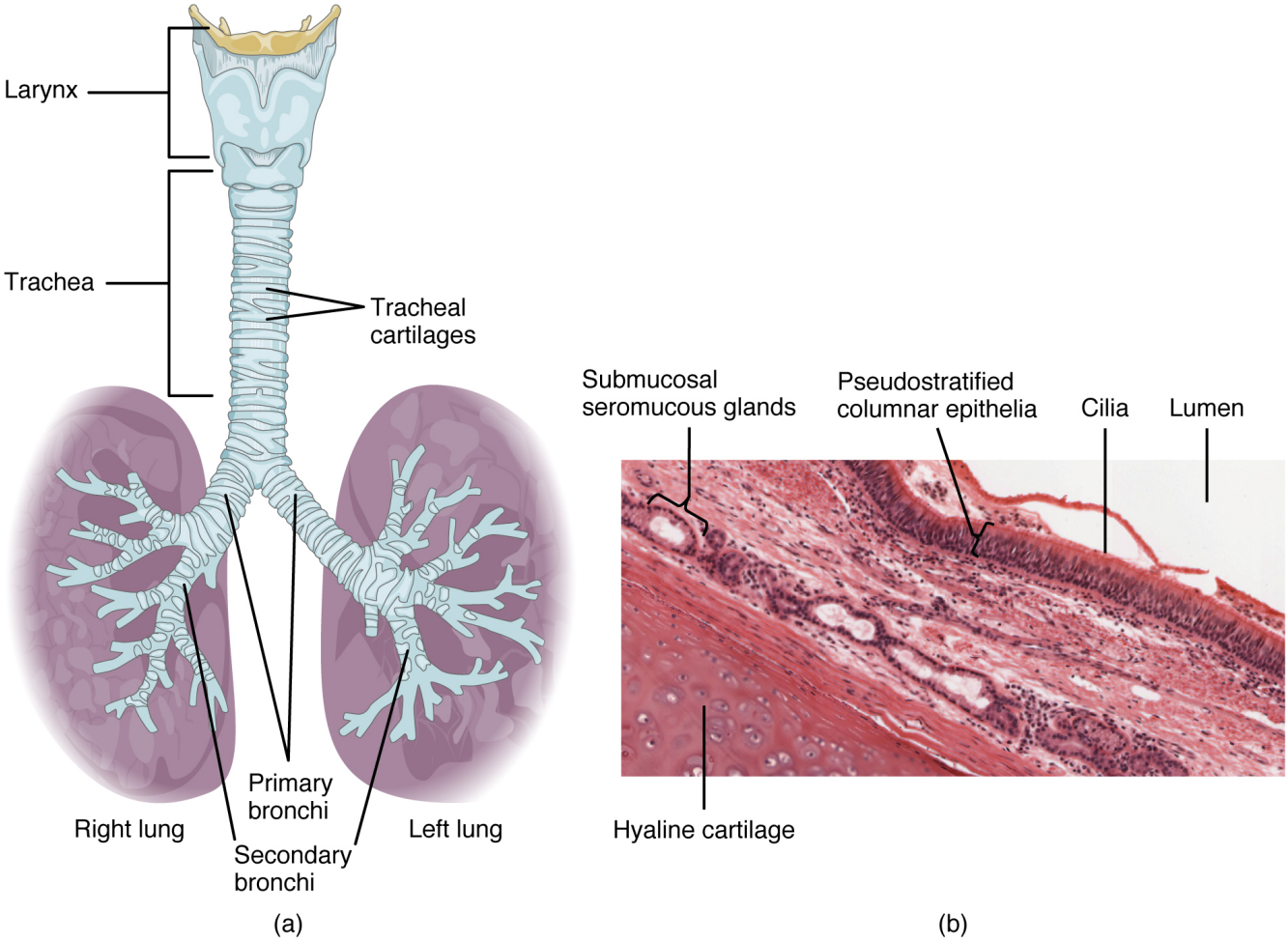
columnar epithelium. The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.



Pseudostratified Ciliated Columnar Epithelium – *Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM × 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

View the University of Michigan WebScope to explore the tissue sample in greater detail.

The **trachea** (windpipe) extends from the **larynx** toward the lungs. The trachea is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The **trachealis muscle** and elastic connective tissue together form the **fibroelastic membrane**, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.



Trachea *(a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM × 1220. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

Bronchial Tree

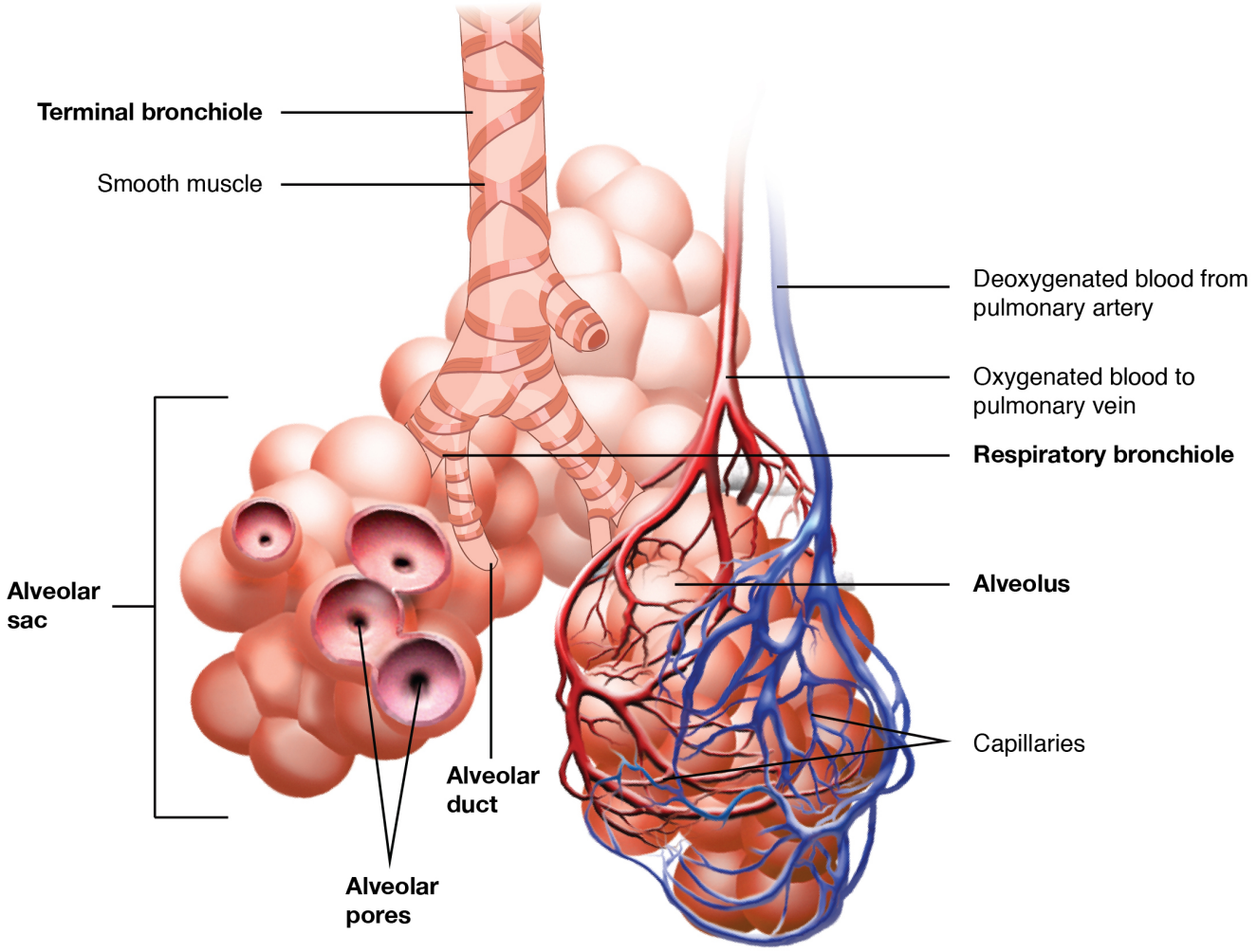
The trachea branches into the right and left primary bronchi at the carina. These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells. The carina is a raised structure that contains specialized nervous tissue that induces violent coughing if a foreign body, such as food, is present. Rings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The bronchi continue to branch into bronchial a tree. A **bronchial tree** (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens.

A bronchiole branches from the tertiary bronchi. **Bronchioles**, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles, which lead to the structures of gas exchange. There are more than 1000

terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. The respiratory zone begins where the terminal bronchioles join a **respiratory bronchiole**, the smallest type of bronchiole, which then leads to an **alveolar duct**, opening into a cluster of alveoli.



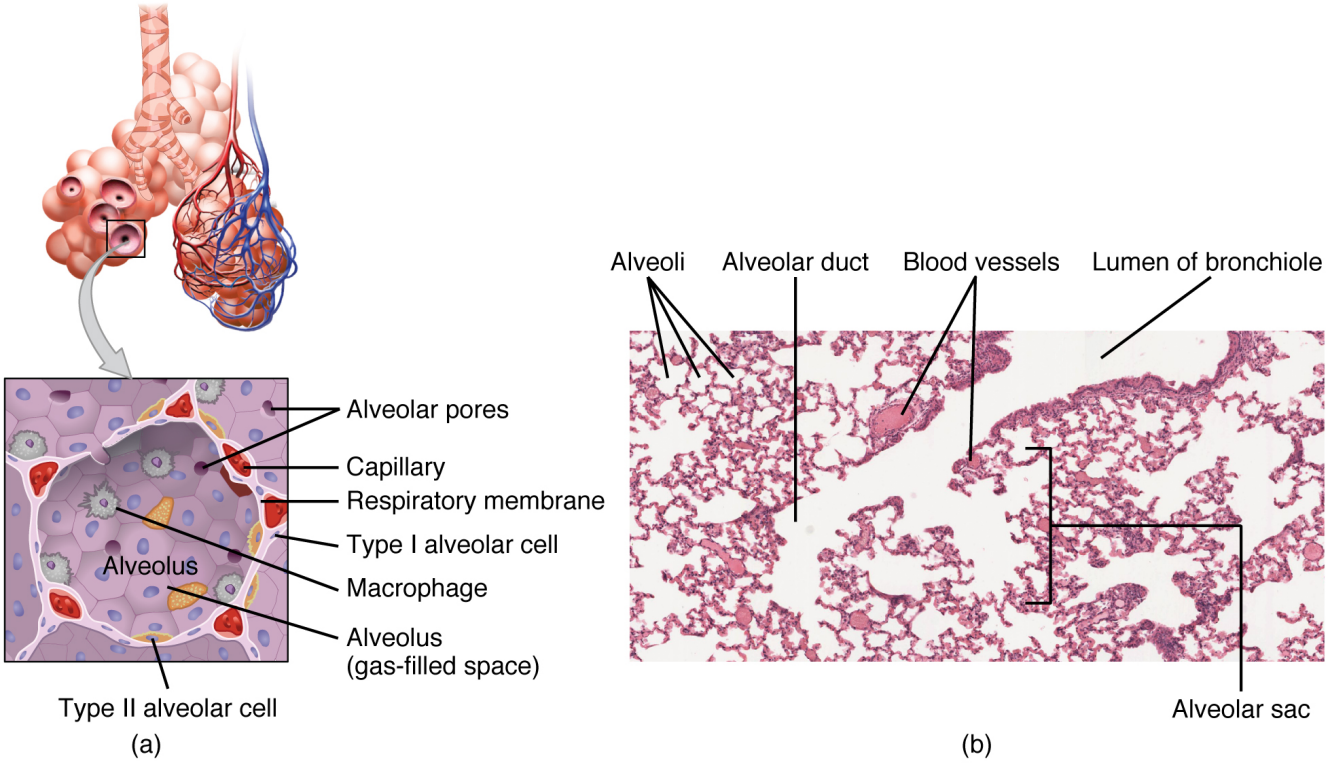
Respiratory Zone – *Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.*

Alveoli

An alveolar duct is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An **alveolus** is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An **alveolar sac** is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately

200 μm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by **alveolar pores**, which help maintain equal air pressure throughout the alveoli and lung.



Structures of the Respiratory Zone *(a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

The alveolar wall consists of three major cell types: **type I alveolar cells**, **type II alveolar cells**, and **alveolar macrophages**. A type I alveolar cell is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. A type II alveolar cell is interspersed among the type I cells and secretes **pulmonary surfactant**, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli. Roaming around the alveolar wall is the alveolar macrophage, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a **respiratory membrane** that is approximately 0.5 μm (micrometers) thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO_2 to be released into the air of the alveoli.

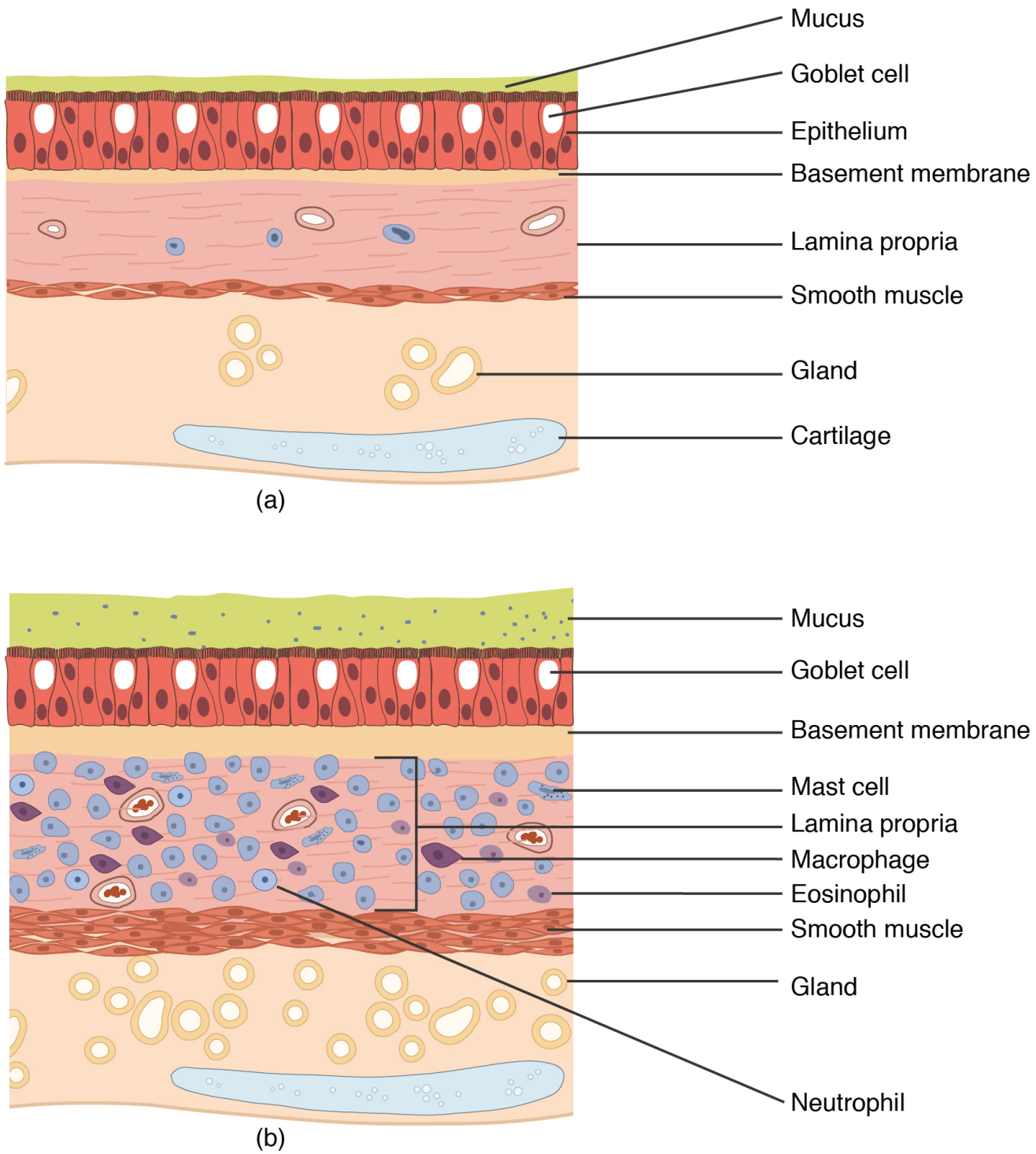
Diseases of the Respiratory System: Asthma

Asthma is common condition that affects the lungs in both adults and children. Approximately 8.2 percent of adults (18.7

million) and 9.4 percent of children (7 million) in the United States suffer from asthma. In addition, asthma is the most frequent cause of hospitalization in children.

Asthma is a chronic disease characterized by inflammation and edema of the airway, and bronchospasms (that is, constriction of the bronchioles), which can inhibit air from entering the lungs. In addition, excessive mucus secretion can occur, which further contributes to airway occlusion. Cells of the immune system, such as eosinophils and mononuclear cells, may also be involved in infiltrating the walls of the bronchi and bronchioles.

Bronchospasms occur periodically and lead to an "asthma attack." An attack may be triggered by environmental factors such as dust, pollen, pet hair, or dander, changes in the weather, mold, tobacco smoke, and respiratory infections, or by exercise and stress.



Normal and Bronchial Asthma Tissues *(a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.*

Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the condition, frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-

term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that are used to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer.

In many cases, the underlying cause of the condition is unknown. However, recent research has demonstrated that certain viruses, such as human rhinovirus C (HRVC), and the bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are contracted in infancy or early childhood, may contribute to the development of many cases of asthma.

Visit this video on how airway size is involved in asthma to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Section Review

The respiratory system is responsible for obtaining oxygen and getting rid of carbon dioxide, and aiding in speech production and in sensing odors. From a functional perspective, the respiratory system can be divided into two major areas: the conducting zone and the respiratory zone. The conducting zone consists of all of the structures that provide passageways for air to travel into and out of the lungs: the nasal cavity, **pharynx,** trachea, bronchi, and most bronchioles. The nasal passages contain the conchae and **meatuses** that expand the surface area of the cavity, which helps to warm and humidify incoming air, while removing debris and pathogens. The pharynx is composed of three major sections: the **nasopharynx**, which is continuous with the nasal cavity; the **oropharynx**, which borders the nasopharynx and the oral cavity; and the **laryngopharynx**, which borders the oropharynx, trachea, and esophagus. The respiratory zone includes the structures of the lung that are directly involved in gas exchange: the terminal bronchioles and alveoli.

The lining of the conducting zone is composed mostly of pseudostratified ciliated columnar epithelium with goblet cells. The mucus traps pathogens and debris, whereas beating cilia move the mucus superiorly toward the throat, where it is swallowed. As the bronchioles become smaller and smaller, and nearer the alveoli, the epithelium thins and is simple squamous epithelium in the alveoli. The endothelium of the surrounding capillaries, together with the alveolar epithelium, forms the respiratory membrane. This is a blood-air barrier through which gas exchange occurs by simple diffusion.

Review Questions

1. Which of the following anatomical structures is *not* part of the conducting zone?

- Pharynx
- Nasal cavity
- Alveoli
- Bronchi

2. Which of the following are structural features of the trachea? Select all that apply.

- C-shaped cartilage
- Smooth muscle fibres
- Cilia

- None of the above

3. What is the role of alveolar macrophages?

- To secrete antimicrobial proteins
- To remove pathogens and debris
- To facilitate gas exchange
- To secrete pulmonary surfactant

4. Compare and contrast the conducting and respiratory zone.

Answer Key

1. Alveoli
2. C-shaped cartilage
3. To remove pathogens and debris
4. The conducting zone includes the organs and structures that are not directly involved in gas exchange, but perform other duties such as providing a passageway for air, trapping and removing debris and pathogens, and warming and humidifying incoming air. Such structures include the nasal cavity, pharynx, larynx, trachea, and most of the bronchial tree. The respiratory zone includes all the organs and structures that are directly involved in gas exchange, including the respiratory bronchioles, alveolar ducts, and alveoli.

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Adaption

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The Process of Breathing

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the mechanisms that drive breathing.
- Discuss how pressure, volume, and resistance are related.
- List the steps involved in pulmonary ventilation.
- Discuss the physical factors related to breathing.
- Discuss the meaning of respiratory volume and capacities.
- Define respiratory rate.
- Outline the mechanisms behind the control of breathing.
- Describe the respiratory centers of the medulla oblongata.
- Describe the respiratory centers of the pons.
- Discuss factors that can influence the respiratory rate.

Pulmonary ventilationis the act of breathing, which can be described as the movement of air into and out of the lungs. The major mechanisms that drive pulmonary ventilation are atmospheric pressure (P_{atm}); the air pressure within the alveoli, called **intra-alveolar pressure** (P_{alv}); and the pressure within the pleural cavity, called **intrapleural pressure** (P_{ip}).

Mechanisms of Breathing

The intra-alveolar and intrapleural pressures are dependent on certain physical features of the lung. However, the ability to breathe—to have air enter the lungs during **inspiration** and air leave the lungs during **expiration** is dependent on the air pressure of the atmosphere and the air pressure within the lungs.

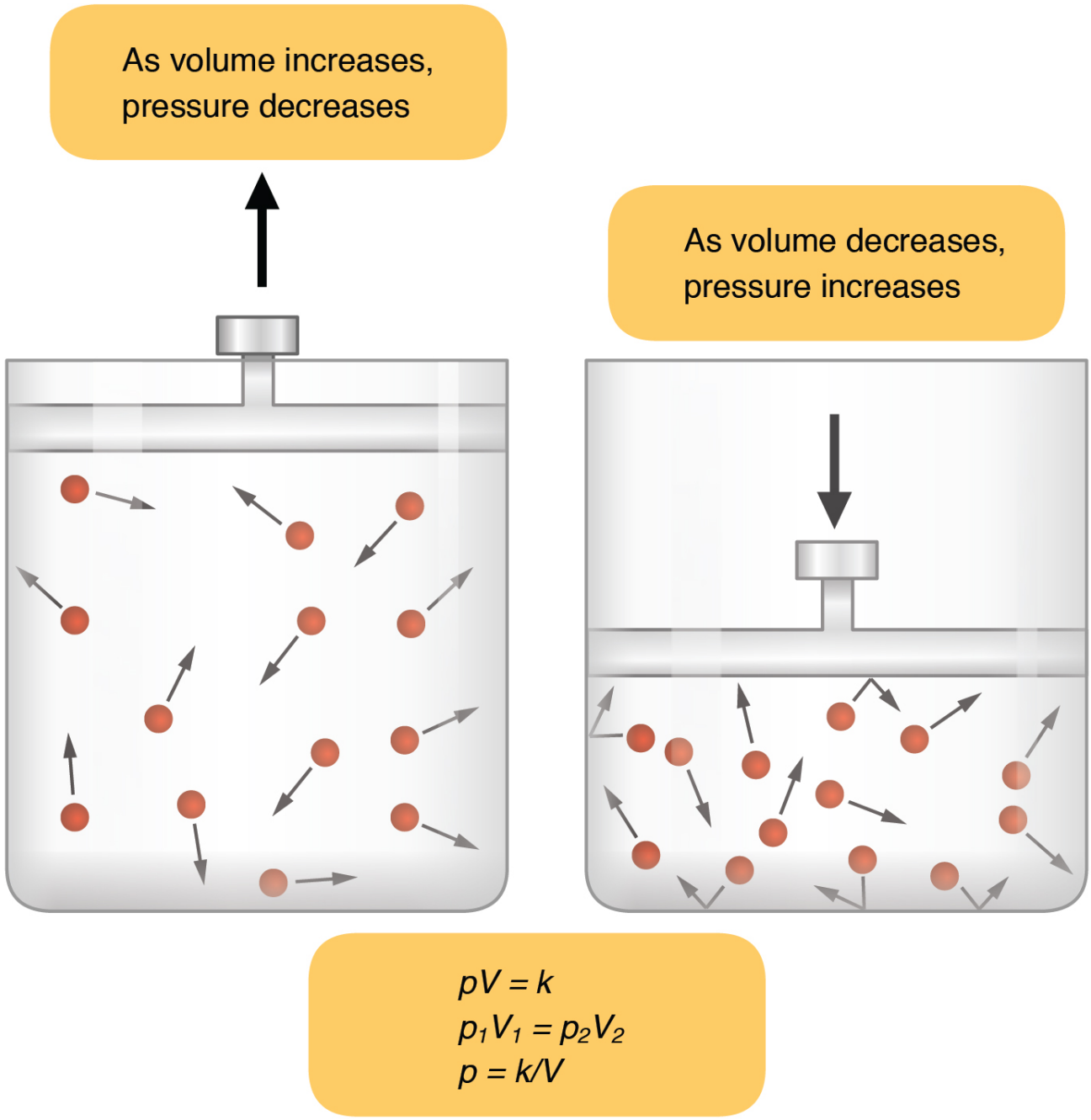
Pressure Relationships

Inspiration (or inhalation) and expiration (or exhalation) are dependent on the differences in pressure between the atmosphere and the lungs. In a gas, pressure is a force created by the movement of gas molecules that are confined. For example, a certain number of gas molecules in a two-liter container has more room than the same number of gas molecules in a one-liter container. In this case, the force exerted by the movement of the gas molecules against the walls of the two-liter container is lower than the force exerted by the gas molecules in the one-liter container. Therefore, the pressure is lower in the two-liter container and higher in the one-liter container. At a constant temperature, changing

the volume occupied by the gas changes the pressure, as does changing the number of gas molecules. **Boyle's law** describes the relationship between volume and pressure in a gas at a constant temperature. Boyle discovered that the pressure of a gas is inversely proportional to its volume: If volume increases, pressure decreases. Likewise, if volume decreases, pressure increases. Pressure and volume are inversely related ($P = k/V$). Therefore, the pressure in the one-liter container (one-half the volume of the two-liter container) would be twice the pressure in the two-liter container. Boyle's law is expressed by the following formula:

$$P_1V_1 = P_2V_2$$

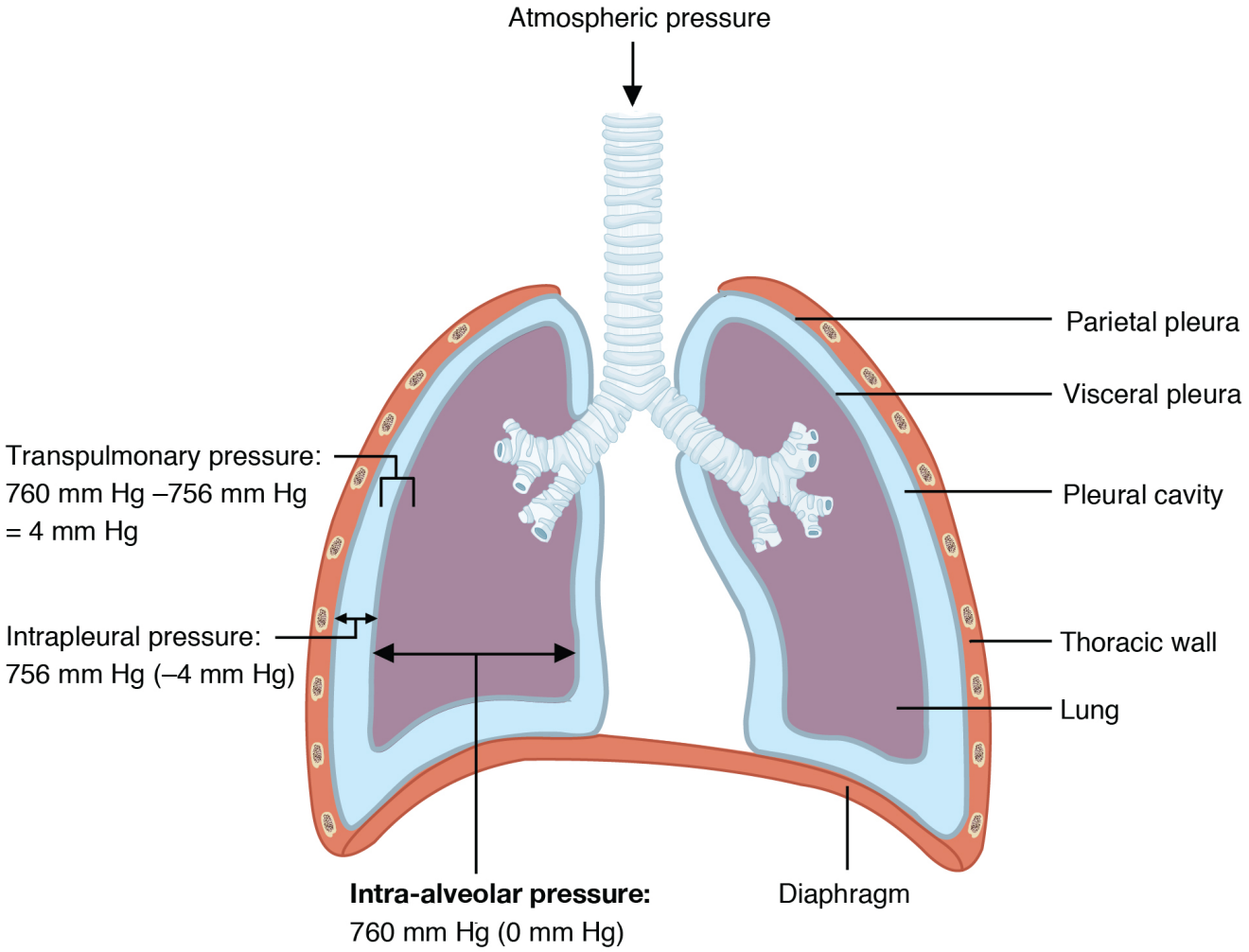
In this formula, P_1 represents the initial pressure and V_1 represents the initial volume, whereas the final pressure and volume are represented by P_2 and V_2, respectively. If the two- and one-liter containers were connected by a tube and the volume of one of the containers were changed, then the gases would move from higher pressure (lower volume) to lower pressure (higher volume).



Boyle's Law In a gas, pressure increases as volume decreases.

Pulmonary ventilation is dependent on three types of pressure: atmospheric, intra-alveolar, and intrapleural. Atmospheric pressure is the **amount of force** that is exerted by gases in the air surrounding any given surface, such as the body. Atmospheric pressure can be expressed in terms of the unit atmosphere, abbreviated atm, or in millimeters of mercury (mm Hg). One atm is equal to 760 mm Hg, which is the atmospheric pressure at sea level. Typically, for respiration, other pressure values are discussed in relation to atmospheric pressure. Therefore, negative pressure is pressure lower than the atmospheric pressure, whereas positive pressure is pressure that it is greater than the atmospheric pressure. A pressure that is equal to the atmospheric pressure is expressed as zero.

Intra-alveolar pressure (intrapulmonary pressure) is the pressure of the air within the alveoli, which changes during the different phases of breathing. Because the alveoli are connected to the atmosphere via the tubing of the airways (similar to the two- and one-liter containers in the example above), the intrapulmonary pressure of the alveoli always equalizes with the atmospheric pressure.



Intrapulmonary and Intrapleural Pressure Relationships – *Intra-alveolar pressure changes during the different phases of the cycle. It equalizes at 760 mm Hg but does not remain at 760 mm Hg.*

Intrapleural pressure is the pressure of the air within the pleural cavity, between the visceral and parietal pleurae. Similar to intra-alveolar pressure, intrapleural pressure also changes during the different phases of breathing. However, due to certain characteristics of the lungs, the intrapleural pressure is always lower than, or negative to, the intra-alveolar pressure (and therefore also to atmospheric pressure). Although it fluctuates during inspiration and expiration, intrapleural pressure remains approximately –4 mm Hg throughout the breathing cycle.

Competing forces within the thorax cause the formation of the negative intrapleural pressure. One of these forces relates to the elasticity of the lungs themselves—elastic tissue pulls the lungs inward, away from the thoracic wall. Surface tension of alveolar fluid, which is mostly water, also creates an inward pull of the lung tissue. This inward tension from the lungs is countered by opposing forces from the pleural fluid and thoracic wall. Surface tension within the pleural cavity pulls the lungs outward. Too much or too little pleural fluid would hinder the creation of the negative intrapleural pressure; therefore, the level must be closely monitored by the mesothelial cells and drained

by the lymphatic system. Since the parietal pleura is attached to the thoracic wall, the natural elasticity of the chest wall opposes the inward pull of the lungs. Ultimately, the outward pull is slightly greater than the inward pull, creating the −4 mm Hg intrapleural pressure relative to the intra-alveolar pressure. **Transpulmonary pressure** is the difference between the intrapleural and intra-alveolar pressures, and it determines the size of the lungs. A higher transpulmonary pressure corresponds to a larger lung.

Physical Factors Affecting Ventilation

In addition to the differences in pressures, breathing is also dependent upon the contraction and relaxation of muscle fibers of both the diaphragm and thorax. The lungs themselves are passive during breathing, meaning they are not involved in creating the movement that helps inspiration and expiration. This is because of the adhesive nature of the pleural fluid, which allows the lungs to be pulled outward when the thoracic wall moves during inspiration. The recoil of the thoracic wall during expiration causes compression of the lungs. Contraction and relaxation of the diaphragm and intercostals muscles (found between the ribs) cause most of the pressure changes that result in inspiration and expiration. These muscle movements and subsequent pressure changes cause air to either rush in or be forced out of the lungs.

Other characteristics of the lungs influence the effort that must be expended to ventilate. Resistance is a force that slows motion, in this case, the flow of gases. The size of the airway is the primary factor affecting resistance. A small tubular diameter forces air through a smaller space, causing more collisions of air molecules with the walls of the airways. The following formula helps to describe the relationship between airway resistance and pressure changes:

$$F = \Delta P / R$$

As noted earlier, there is surface tension within the alveoli caused by water present in the lining of the alveoli. This surface tension tends to inhibit expansion of the alveoli. However, pulmonary surfactant secreted by type II alveolar cells mixes with that water and helps reduce this surface tension. Without pulmonary surfactant, the alveoli would collapse during expiration.

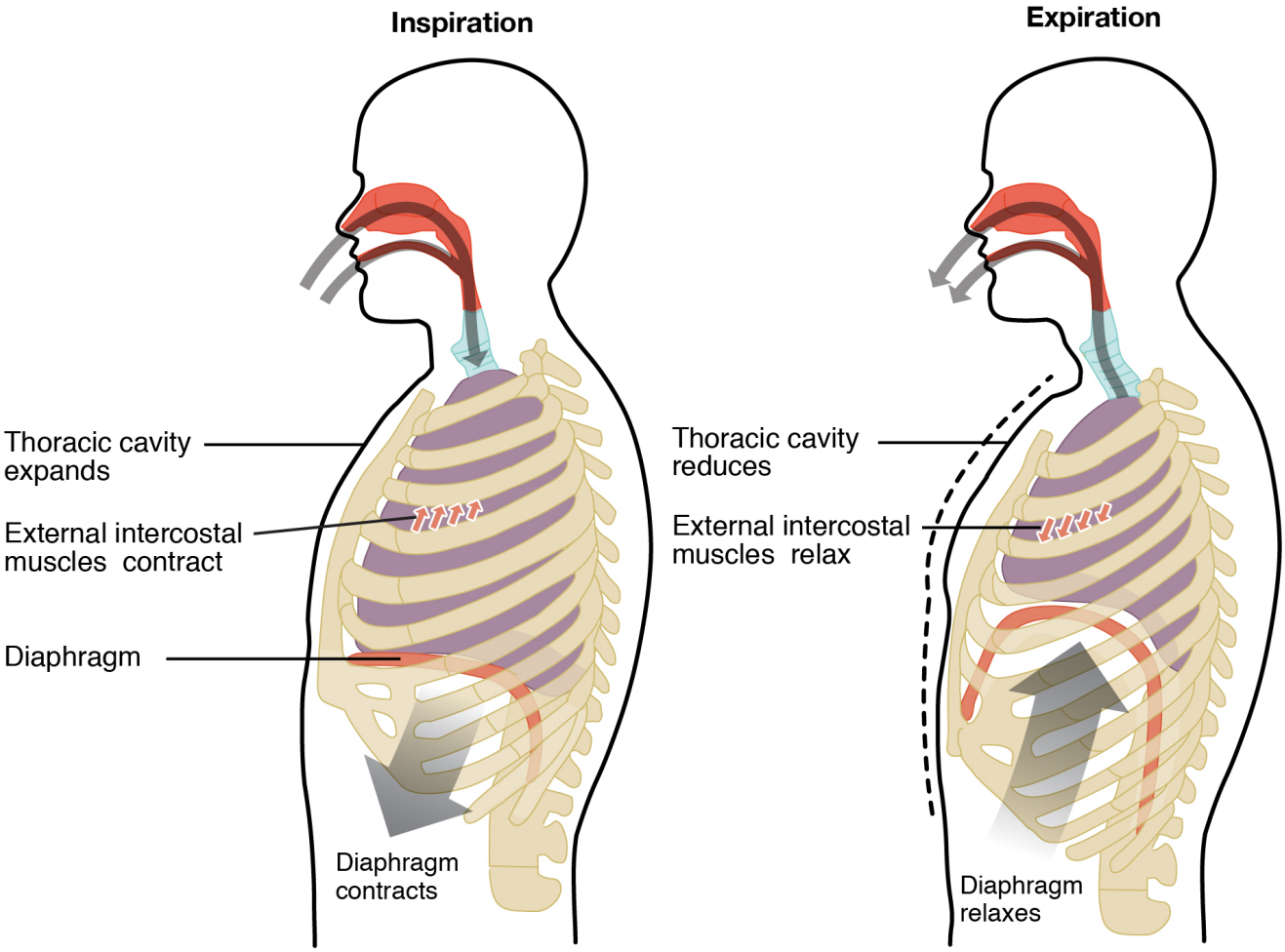
Thoracic wall compliance is the ability of the thoracic wall to stretch while under pressure. This can also affect the effort expended in the process of breathing. In order for inspiration to occur, the thoracic cavity must expand. The expansion of the thoracic cavity directly influences the capacity of the lungs to expand. If the tissues of the thoracic wall are not very compliant, it will be difficult to expand the thorax to increase the size of the lungs.

Pulmonary Ventilation

The difference in pressures drives pulmonary ventilation because air flows down a pressure gradient, that is, air flows from an area of higher pressure to an area of lower pressure. Air flows into the lungs largely due to a difference in pressure; atmospheric pressure is greater than intra-alveolar pressure, and intra-alveolar pressure is greater than intrapleural pressure. Air flows out of the lungs during expiration based on the same principle; pressure within the lungs becomes greater than the atmospheric pressure.

Pulmonary ventilation comprises two major steps: inspiration and expiration. Inspiration is the process that causes air to enter the lungs, and expiration is the process that causes air to leave the lungs. A **respiratory cycle** is one sequence of inspiration and expiration. In general, two muscle groups are used during normal inspiration: the diaphragm and the external intercostal muscles. Additional muscles can be used if a bigger breath is required. When the diaphragm

contracts, it moves inferiorly toward the abdominal cavity, creating a larger thoracic cavity and more space for the lungs. Contraction of the external intercostal muscles moves the ribs upward and outward, causing the rib cage to expand, which increases the volume of the thoracic cavity. Due to the adhesive force of the pleural fluid, the expansion of the thoracic cavity forces the lungs to stretch and expand as well. This increase in volume leads to a decrease in intra-alveolar pressure, creating a pressure lower than atmospheric pressure. As a result, a pressure gradient is created that drives air into the lungs.



Inspiration and Expiration – *Inspiration and expiration occur due to the expansion and contraction of the thoracic cavity, respectively*

The process of normal expiration is passive, meaning that energy is not required to push air out of the lungs. Instead, the elasticity of the lung tissue causes the lung to recoil, as the diaphragm and intercostal muscles relax following inspiration. In turn, the thoracic cavity and lungs decrease in volume, causing an increase in intrapulmonary pressure. The intrapulmonary pressure rises above atmospheric pressure, creating a pressure gradient that causes air to leave the lungs.

There are different types, or modes, of breathing that require a slightly different process to allow inspiration and expiration.**Quiet breathing**, also known as eupnea, is a mode of breathing that occurs at rest and does not require the cognitive thought of the individual. During quiet breathing, the diaphragm and external intercostals must contract.

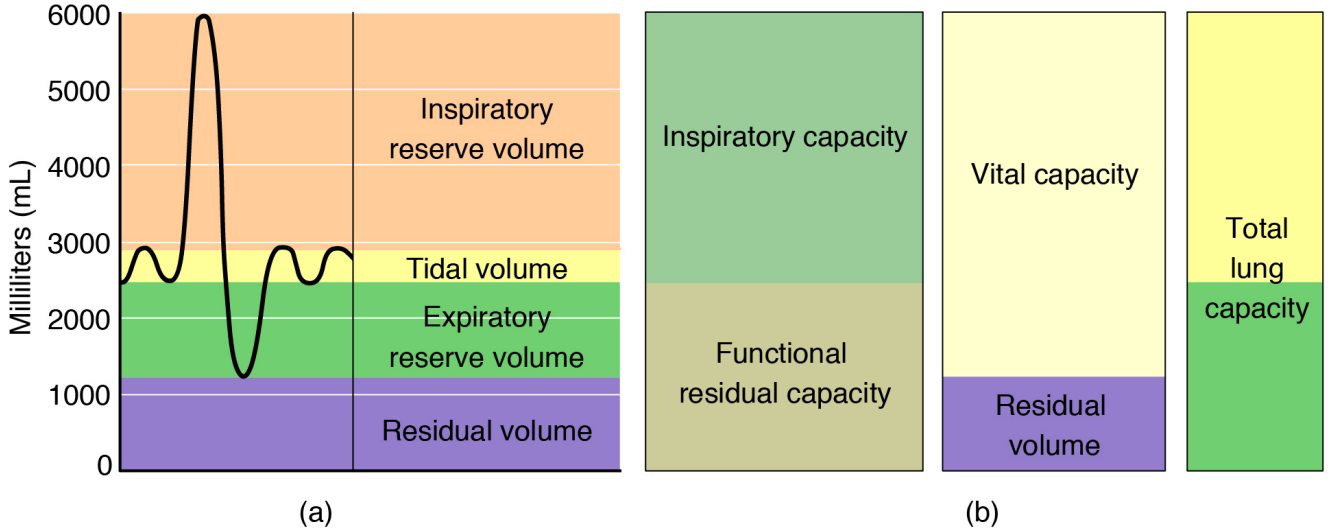
A deep breath, called diaphragmatic breathing, requires the diaphragm to contract. As the diaphragm relaxes, air

passively leaves the lungs. A shallow breath, called costal breathing, requires contraction of the intercostal muscles. As the intercostal muscles relax, air passively leaves the lungs.

In contrast,**forced breathing**, also known as hyperpnea, is a mode of breathing that can occur during exercise or actions that require the active manipulation of breathing, such as singing. During forced breathing, inspiration and expiration both occur due to muscle contractions. In addition to the contraction of the diaphragm and intercostal muscles, other accessory muscles must also contract. During forced inspiration, muscles of the neck, including the scalenes, contract and lift the thoracic wall, increasing lung volume. During forced expiration, accessory muscles of the abdomen, including the obliques, contract, forcing abdominal organs upward against the diaphragm. This helps to push the diaphragm further into the thorax, pushing more air out. In addition, accessory muscles (primarily the internal intercostals) help to compress the rib cage, which also reduces the volume of the thoracic cavity.

Respiratory Volumes and Capacities

Respiratory volume is the term used for various volumes of air moved by or associated with the lungs at a given point in the respiratory cycle. There are four major types of respiratory volumes: tidal, residual, inspiratory reserve, and expiratory reserve. <**Tidal volume (TV)** is the amount of air that normally enters the lungs during quiet breathing, which is about 500 milliliters. **Expiratory reserve volume** (ERV) is the amount of air you can forcefully exhale past a normal tidal expiration, up to 1200 milliliters for men. **Inspiratory reserve volume (IRV)** is produced by a deep inhalation, past a tidal inspiration. This is the extra volume that can be brought into the lungs during a forced inspiration. **Residual volume (RV)** is the air left in the lungs if you exhale as much air as possible. The residual volume makes breathing easier by preventing the alveoli from collapsing. Respiratory volume is dependent on a variety of factors, and measuring the different types of respiratory volumes can provide important clues about a person's respiratory health.



Respiratory Volumes and Capacities – *These two graphs show (a) respiratory volumes and (b) the combination of volumes that results in respiratory capacity.*

Pulmonary function test	Instrument	Measures	Function
Spirometry	Spirometer	Forced vital capacity (FVC)	Volume of air that is exhaled after maximum inhalation
		Forced expiratory volume (FEV)	Volume of air exhaled during one forced breath
		Forced expiratory flow, 25–75 percent	Air flow in the middle of exhalation
		Peak expiratory flow (PEF)	Rate of exhalation
		Maximum voluntary ventilation (MVV)	Volume of air that can be inspired and expired in 1 minute
		Slow vital capacity (SVC)	Volume of air that can be slowly exhaled after inhaling past the tidal volume
		Total lung capacity (TLC)	Volume of air in the lungs after maximum inhalation
		Functional residual capacity (FRC)	Volume of air left in the lungs after normal expiration
		Residual volume (RV)	Volume of air in the lungs after maximum exhalation
		Total lung capacity (TLC)	Maximum volume of air that the lungs can hold
		Expiratory reserve volume (ERV)	The volume of air that can be exhaled beyond normal exhalation
Gas diffusion	Blood gas analyzer	Arterial blood gases	Concentration of oxygen and carbon dioxide in the blood

Pulmonary Function Testing

Respiratory capacity is the combination of two or more selected volumes, which further describes the amount of air in the lungs during a given time. For example,**total lung capacity (TLC)** is the sum of all of the lung volumes (TV, ERV, IRV, and RV), which represents the total amount of air a person can hold in the lungs after a forceful inhalation. TLC is about 6000 mL air for men, and about 4200 mL for women.**Vital capacity (VC)** is the amount of air a person can move into or out of his or her lungs, and is the sum of all of the volumes except residual volume (TV, ERV, and IRV), which is between 4000 and 5000 milliliters. **Inspiratory capacity (IC)**is the maximum amount of air that can be inhaled past a normal tidal expiration, is the sum of the tidal volume and inspiratory reserve volume. On the other hand, the **functional residual capacity (FRC)** is the amount of air that remains in the lung after a normal tidal expiration; it is the sum of expiratory reserve volume and residual volume.

Watch this video to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

In addition to the air that creates respiratory volumes, the respiratory system also contains **anatomical dead space**, which is air that is present in the airway that never reaches the alveoli and therefore never participates in gas exchange. **Alveolar dead space** involves air found within alveoli that are unable to function, such as those affected by disease or abnormal blood flow. **Total dead space** is the anatomical dead space and alveolar dead space together, and represents all of the air in the respiratory system that is not being used in the gas exchange process.

Respiratory Rate and Control of Ventilation

Breathing usually occurs without thought, although at times you can consciously control it, such as when you swim under water, sing a song, or blow bubbles. The **respiratory rate** is the total number of breaths, or respiratory cycles, that occur each minute. Respiratory rate can be an important indicator of disease, as the rate may increase or decrease during an illness or in a disease condition. The respiratory rate is controlled by the respiratory center located within the medulla oblongata in the brain, which responds primarily to changes in carbon dioxide, oxygen, and pH levels in the blood.

The normal respiratory rate of a child decreases from birth to adolescence. A child under 1 year of age has a normal respiratory rate between 30 and 60 breaths per minute, but by the time a child is about 10 years old, the normal rate is closer to 18 to 30. By adolescence, the normal respiratory rate is similar to that of adults, 12 to 18 breaths per minute.

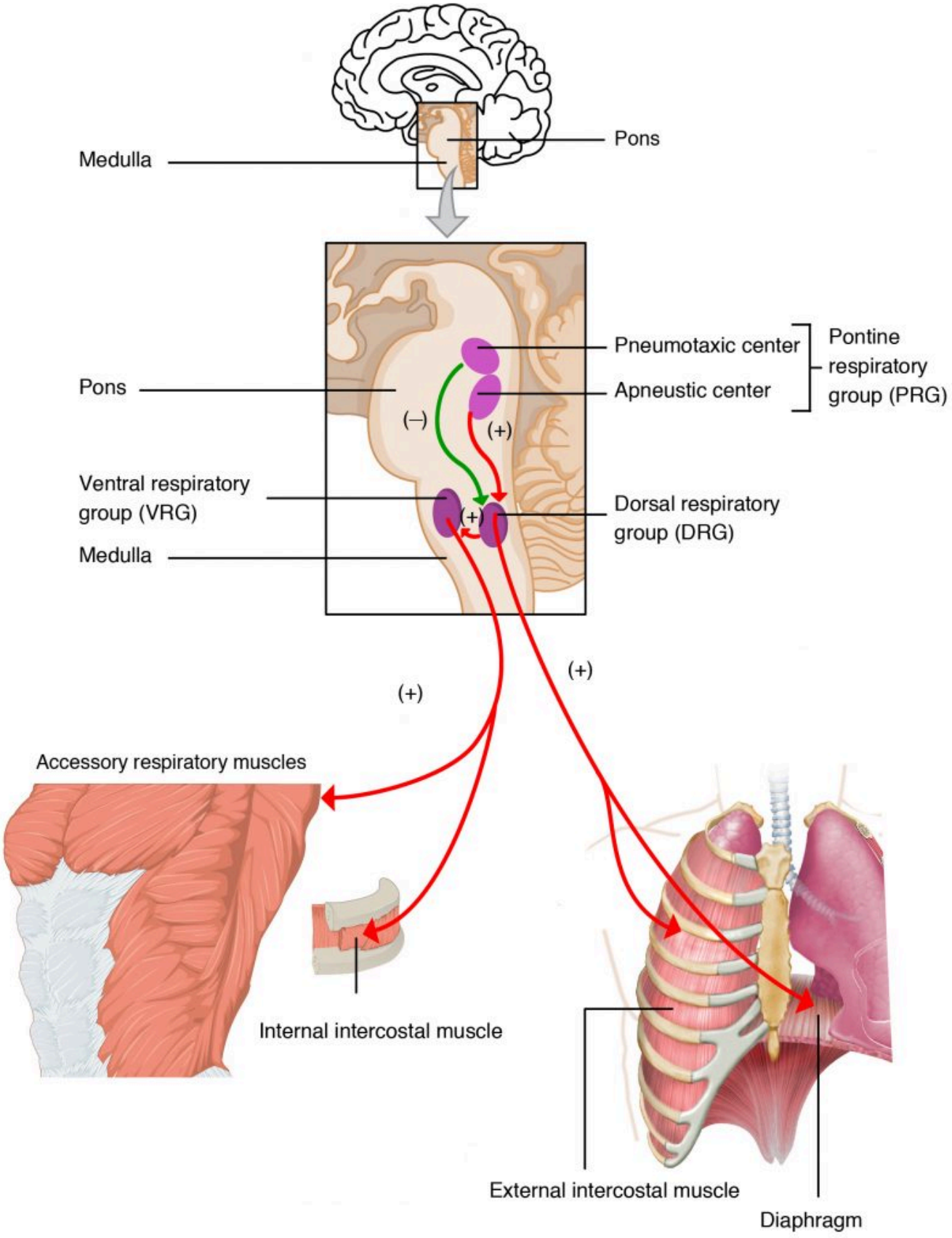
Ventilation Control Centers

The control of ventilation is a complex interplay of multiple regions in the brain that signal the muscles used in pulmonary ventilation to contract. The result is typically a rhythmic, consistent ventilation rate that provides the body with sufficient amounts of oxygen, while adequately removing carbon dioxide.

Summary of Ventilation Regulation

System component	Function
Medullary respiratory renter	Sets the basic rhythm of breathing
Ventral respiratory group (VRG)	Generates the breathing rhythm and integrates data coming into the medulla
Dorsal respiratory group (DRG)	Integrates input from the stretch receptors and the chemoreceptors in the periphery
Pontine respiratory group (PRG)	Influences and modifies the medulla oblongata's functions
Aortic body	Monitors blood PCO_2, PO_2, and pH
Carotid body	Monitors blood PCO_2, PO_2, and pH
Hypothalamus	Monitors emotional state and body temperature
Cortical areas of the brain	Control voluntary breathing
Proprioceptors	Send impulses regarding joint and muscle movements
Pulmonary irritant reflexes	Protect the respiratory zones of the system from foreign material
Inflation reflex	Protects the lungs from over-inflating

Neurons that innervate the muscles of the respiratory system are responsible for controlling and regulating pulmonary ventilation. The major brain centers involved in pulmonary ventilation are the medulla oblongata and the pontine respiratory group.



Respiratory Centers of the Brain

The medulla oblongata contains the **dorsal respiratory group** (DRG) and the **ventral respiratory group (VRG)**. The DRG is involved in maintaining a constant breathing rhythm by stimulating the diaphragm and intercostal muscles to contract, resulting in inspiration. When activity in the DRG ceases, it no longer stimulates the diaphragm and intercostals to contract, allowing them to relax, resulting in expiration. The VRG is involved in forced breathing, as the neurons in the VRG stimulate the accessory muscles involved in forced breathing to contract, resulting in forced inspiration. The VRG also stimulates the accessory muscles involved in forced expiration to contract.

The second respiratory center of the brain is located within the pons, called the pontine respiratory group, and consists of the apneustic and **pneumotaxic centers**. The **apneustic center** is a double cluster of neuronal cell bodies that stimulate neurons in the DRG, controlling the depth of inspiration, particularly for deep breathing. The pneumotaxic center is a network of neurons that inhibits the activity of neurons in the DRG, allowing relaxation after inspiration, and thus controlling the overall rate.

Factors That Affect the Rate and Depth of Respiration

The respiratory rate and the depth of inspiration are regulated by the medulla oblongata and pons; however, these regions of the brain do so in response to systemic stimuli. It is a dose-response, negative-feedback relationship in which the greater the stimulus, the greater the response. Thus, increasing stimuli results in forced breathing. Multiple systemic factors are involved in stimulating the brain to produce pulmonary ventilation.

The major factor that stimulates the medulla oblongata and pons to produce respiration is surprisingly not oxygen concentration, but rather the concentration of carbon dioxide in the blood. As you recall, carbon dioxide is a waste product of cellular respiration and can be toxic. Concentrations of chemicals are sensed by chemoreceptors. A **central chemoreceptor**is one of the specialized receptors that are located in the brain and brainstem, whereas a**peripheral chemoreceptor** is one of the specialized receptors located in the carotid arteries and aortic arch. Concentration changes in certain substances, such as carbon dioxide or hydrogen ions, stimulate these receptors, which in turn signal the respiration centers of the brain. In the case of carbon dioxide, as the concentration of CO_2 in the blood increases, it readily diffuses across the blood-brain barrier, where it collects in the extracellular fluid. As will be explained in more detail later, increased carbon dioxide levels lead to increased levels of hydrogen ions, decreasing pH. The increase in hydrogen ions in the brain triggers the central chemoreceptors to stimulate the respiratory centers to initiate contraction of the diaphragm and intercostal muscles. As a result, the rate and depth of respiration increase, allowing more carbon dioxide to be expelled, which brings more air into and out of the lungs promoting a reduction in the blood levels of carbon dioxide, and therefore hydrogen ions, in the blood. In contrast, low levels of carbon dioxide in the blood cause low levels of hydrogen ions in the brain, leading to a decrease in the rate and depth of pulmonary ventilation, producing shallow, slow breathing.

Another factor involved in influencing the respiratory activity of the brain is systemic arterial concentrations of hydrogen ions. Increasing carbon dioxide levels can lead to increased H^+ levels, as mentioned above, as well as other metabolic activities, such as lactic acid accumulation after strenuous exercise. Peripheral chemoreceptors of the aortic arch and carotid arteries sense arterial levels of hydrogen ions. When peripheral chemoreceptors sense decreasing, or more acidic, pH levels, they stimulate an increase in ventilation to remove carbon dioxide from the blood at a quicker rate. Removal of carbon dioxide from the blood helps to reduce hydrogen ions, thus increasing systemic pH.

Blood levels of oxygen are also important in influencing respiratory rate. The peripheral chemoreceptors are responsible for sensing large changes in blood oxygen levels. If blood oxygen levels become quite low—about 60 mm Hg or less—then peripheral chemoreceptors stimulate an increase in respiratory activity. The chemoreceptors are only able to sense dissolved oxygen molecules, not the oxygen that is bound to hemoglobin. As you recall, the majority of oxygen is bound

by hemoglobin; when dissolved levels of oxygen drop, hemoglobin releases oxygen. Therefore, a large drop in oxygen levels is required to stimulate the chemoreceptors of the aortic arch and carotid arteries.

The hypothalamus and other brain regions associated with the limbic system also play roles in influencing the regulation of breathing by interacting with the respiratory centers. The hypothalamus and other regions associated with the limbic system are involved in regulating respiration in response to emotions, pain, and temperature. For example, an increase in body temperature causes an increase in respiratory rate. Feeling excited or the fight-or-flight response will also result in an increase in respiratory rate.

Disorders of the Respiratory System: Sleep Apnea

Sleep apnea is a chronic disorder that can occur in children or adults, and is characterized by the cessation of breathing during sleep. These episodes may last for several seconds or several minutes, and may differ in the frequency with which they are experienced. Sleep apnea leads to poor sleep, which is reflected in the symptoms of fatigue, evening napping, irritability, memory problems, and morning headaches. In addition, many individuals with sleep apnea experience a dry throat in the morning after waking from sleep, which may be due to excessive snoring.There are two types of sleep apnea: obstructive sleep apnea and central sleep apnea. Obstructive sleep apnea is caused by an obstruction of the airway during sleep, which can occur at different points in the airway, depending on the underlying cause of the obstruction. For example, the tongue and throat muscles of some individuals with obstructive sleep apnea may relax excessively, causing the muscles to push into the airway. Another example is obesity, which is a known risk factor for sleep apnea, as excess adipose tissue in the neck region can push the soft tissues towards the lumen of the airway, causing the trachea to narrow.In central sleep apnea, the respiratory centers of the brain do not respond properly to rising carbon dioxide levels and therefore do not stimulate the contraction of the diaphragm and intercostal muscles regularly. As a result, inspiration does not occur and breathing stops for a short period. In some cases, the cause of central sleep apnea is unknown. However, some medical conditions, such as stroke and congestive heart failure, may cause damage to the pons or medulla oblongata. In addition, some pharmacologic agents, such as morphine, can affect the respiratory centers, causing a decrease in the respiratory rate. The symptoms of central sleep apnea are similar to those of obstructive sleep apnea.A diagnosis of sleep apnea is usually done during a sleep study, where the patient is monitored in a sleep laboratory for several nights. The patient's blood oxygen levels, heart rate, respiratory rate, and blood pressure are monitored, as are brain activity and the volume of air that is inhaled and exhaled. Treatment of sleep apnea commonly includes the use of a device called a continuous positive airway pressure (CPAP) machine during sleep. The CPAP machine has a mask that covers the nose, or the nose and mouth, and forces air into the airway at regular intervals. This pressurized air can help to gently force the airway to remain open, allowing more normal ventilation to occur. Other treatments include lifestyle changes to decrease weight, eliminate alcohol and other sleep apnea–promoting drugs, and changes in sleep position. In addition to these treatments, patients with central sleep apnea may need supplemental oxygen during sleep.Watch this video about lung volumes and spirometry Spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.Patients with respiratory ailments (such as asthma, emphysema, COPD, etc.) have issues with airway resistance and/or lung compliance. Both of these factors can interfere with the patient's ability to move air effectively. A spirometry test can determine how much air the patient can move into and out of the lungs. If the air volumes are low, this can indicate that the patient has a respiratory disease or that the treatment regimen may need to be adjusted. If the numbers are normal, the patient does not have a significant respiratory disease or the treatment regimen is working as expected.

Section Review

Pulmonary ventilation is the process of breathing, which is driven by pressure differences between the lungs and the atmosphere. Atmospheric pressure is the force exerted by gases present in the atmosphere. The force exerted by gases within the alveoli is called intra-alveolar (intrapulmonary) pressure, whereas the force exerted by gases in the pleural cavity is called intrapleural pressure. Typically, intrapleural pressure is lower, or negative to, intra-alveolar pressure. The difference in pressure between intrapleural and intra-alveolar pressures is called transpulmonary pressure. In addition, intra-alveolar pressure will equalize with the atmospheric pressure. Pressure is determined by the volume of the space occupied by a gas and is influenced by resistance. Air flows when a pressure gradient is created, from a space of higher pressure to a space of lower pressure. Boyle's law describes the relationship between volume and pressure. A gas is at lower pressure in a larger volume because the gas molecules have more space to in which to move. The same quantity of gas in a smaller volume results in gas molecules crowding together, producing increased pressure.Resistance is created by inelastic surfaces, as well as the diameter of the airways. Resistance reduces the flow of gases. The surface tension of the alveoli also influences pressure, as it opposes the expansion of the alveoli. However, pulmonary surfactant helps to reduce the surface tension so that the alveoli do not collapse during expiration. The ability of the lungs to stretch, called lung compliance, also plays a role in gas flow. The more the lungs can stretch, the greater the potential volume of the lungs. The greater the volume of the lungs, the lower the air pressure within the lungs.Pulmonary ventilation consists of the process of inspiration (or inhalation), where air enters the lungs, and expiration (or exhalation), where air leaves the lungs. During inspiration, the diaphragm and external intercostal muscles contract, causing the rib cage to expand and move outward, and expanding the thoracic cavity and lung volume. This creates a lower pressure within the lung than that of the atmosphere, causing air to be drawn into the lungs. During expiration, the diaphragm and intercostals relax, causing the thorax and lungs to recoil. The air pressure within the lungs increases to above the pressure of the atmosphere, causing air to be forced out of the lungs. However, during forced exhalation, the internal intercostals and abdominal muscles may be involved in forcing air out of the lungs.

Respiratory volume describes the amount of air in a given space within the lungs, or which can be moved by the lung, and is dependent on a variety of factors. Tidal volume refers to the amount of air that enters the lungs during quiet breathing, whereas inspiratory reserve volume is the amount of air that enters the lungs when a person inhales past the tidal volume. Expiratory reserve volume is the extra amount of air that can leave with forceful expiration, following tidal expiration. Residual volume is the amount of air that is left in the lungs after expelling the expiratory reserve volume. Respiratory capacity is the combination of two or more volumes. Anatomical dead space refers to the air within the respiratory structures that never participates in gas exchange, because it does not reach functional alveoli. Respiratory rate is the number of breaths taken per minute, which may change during certain diseases or conditions.

Both respiratory rate and depth are controlled by the respiratory centers of the brain, which are stimulated by factors such as chemical and pH changes in the blood. These changes are sensed by central chemoreceptors, which are located in the brain, and peripheral chemoreceptors, which are located in the aortic arch and carotid arteries. A rise in carbon dioxide or a decline in oxygen levels in the blood stimulates an increase in respiratory rate and depth.

Review Questions

1. Which of the following processes does atmospheric pressure play a role in?

- Pulmonary ventilation
- Production of pulmonary surfactant
- Resistance

- Surface tension

2. Fill in the blank.A decrease in volume leads to a(n) _____ in pressure.**3. Gas flow decreases as _____ increases.**

- Resistance
- Pressure
- Airway diameter
- Friction

4. Contraction of the external intercostal muscles causes which of the following to occur?

- The diaphragm moves downward
- The rib cage is compressed
- The thoracic cavity volume decreases
- The ribs and sternum move upward

5. Which of the following prevents the alveoli from collapsing?

- Residual volume
- Tidal volume
- Expiratory reserve volume
- Inspiratory reserve volume

6. Fill in the blanks. Describe what is meant by the term "lung compliance." How does it play a role in breathing?Lung compliance is _____. Lung compliance plays a role in _____.**7. What is respiratory rate and how is it controlled? What is a normal respiratory rate?8. Fill in the blanks with the following words:**Quiet breathing occurs at rest and without active thought. During quiet breathing, the diaphragm and external intercostal muscles work at different extents, depending on the situation. For inspiration, the diaphragm _____, causing the diaphragm to _____, thus helping to _____ the thoracic cavity. The external intercostal muscles contract, causing the rib cage to expand resulting in the rib cage and sternum to _____ also expanding the thoracic cavity. Expansion of the thoracic cavity also causes the lungs to expand, due to the adhesiveness of the _____. As a result, the pressure within the lungs _____ that of the atmosphere, causing air to rush into the lungs. In contrast, expiration is a passive process. As the diaphragm and intercostal muscles relax, the lungs and thoracic tissues _____, and the volume of the lungs _____. This causes the pressure within the lungs to _____ that of the atmosphere, causing air to leave the lungs.

Answer Key

1. Pulmonary ventilation
2. Increase
3. Resistance
4. The ribs and sternum move upward
5. Residual volume

6. The ability of lung tissue to stretch under pressure, which is determined in part by the surface tension of the alveoli and the ability of the connective tissue to stretch, determining how much the lungs can change in volume, which in turn helps to determine pressure and air movement
7. Respiratory rate is the number of breaths taken per minute. Respiratory rate is controlled by the respiratory center, located in the medulla oblongata. Conscious thought can alter the normal respiratory rate through control by skeletal muscle, although one cannot consciously stop the rate altogether. A typical resting respiratory rate is about 14 breaths per minute.
8. Contracts, flatten and drop towards the abdominal cavity, expand, move outward, pleural fluid, drops below, recoil, decreases, increases above

Adaption

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Video Lessons on Normal Anatomy and Histology of Lungs

JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- List differences in lung tissue between being in the body vs. preserved and mounted for presentation.
- Identify bronchioles and alveoli by gross anatomy and microscopically, being aware of the limitations of visualization.

Normal Lung: Gross Anatomy

Lungs are normally encased in the thoracic (chest) cavity, within pleural membranes, under negative pressure (a vacuum). Thus, when we remove lungs to put in a specimen case, the lungs will appear more shrunken than its size when in the chest, thanks to the high amount of elastin within the lung. The high elastin content allows the lungs to 'snap' back into a smaller volume: this is akin to an elastic band which, when relaxed, snaps back to a smaller size. Due to this elasticity, exhalation is a passive process – i.e. no muscle contraction is necessary as all of the work is done by the elastin snapping back and squeezing the air.

Knowing that lungs will be smaller than in the chest, let's look at the gross anatomy of the internal lung.

This video is awaiting licensing approval and will be available shortly. ***DHPLC specimen*: A0001** Gross Anatomy of Normal Lung with Blood by Jennifer Kong, licensed under All Rights Reserved

When the blood is washed out, it is easier to see the lung's structure from a gross perspective. The obvious visible holes are the large to medium size airways (bronchioles).

Critical Thinking Exercises

Looking at the gross anatomy of lung, what are the black specks?

Every breath one takes in their lifetime, we inhale pathogens, irritants, and debris. The lung's defenses (e.g. ciliated epithelia, mucous, coughing, alveolar macrophages, etc.) can trap & remove them physically or immunologically. However, one does inhale irritants which the lung's defenses can't remove. As such, what can't be removed stays within the lungs for one's entire life. These black specks can be from everyday environmental pollution, forest fire smoke, inhaled occupational dust, etc. Thus, over the years, a certain amount (albeit small) of lung tissue will not be able to ventilate due to these accumulated foreign debris plugging up the airways.

To visualize the 'holes' better, lungs can be prepared using the Gough technique: a thin section of the lung lobe is dried flat, thus allowing for both visual and tactile examination. Even though this preparation still won't allow us to view the microscopic alveoli, this method does allow for the homogeneity of the lung tissue and the size of intact small airways.

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Histology of Normal Lung Tissue

Recall that the bulk of the lung's volumes are alveoli – thus giving the lungs an incredible amount of surface area for gas exchange. Thus, when viewing lung tissue at lower power magnification, the majority of the tissue seen are alveoli of similar shape and size, thus giving a **homogenous** pattern. Large spaces are bronchioles, with the amount of cartilage visible (stains purple with H&E) indicating the proximal airways to the primary bronchi and the amount of smooth muscle indicating the distal airways, closer to the alveoli. Although H&E stain protein in general, it cannot differentiate between protein types (e.g. elastin vs collagen). However, normal lungs have a relatively large amount of elastin.

Let's listen to histopathologist Dr. Jonathan Bush examine normal lung tissue, stained with H&E, at low- and high-power magnification.



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Section Review

- Lungs are highly vascularized (via pulmonary blood vessels) and in the body, fully expanded, because of the negative pressure within the chest cavity. However, during preservation and mounting, the lungs have the blood either washed out or react with preservatives giving it a grey colour. Similarly, the lungs are smaller and collapsed in the presentation case as they are no longer under negative pressure.
- Large airways such as bronchi and bronchioles are visible to the naked eye. Microscopic examination on high power allows for visualization of alveoli and pulmonary blood vessels.
- Alveoli are identifiable by a large air space, surrounded by a very thin wall, one cell thick, with blood vessels in close proximity.

Review Questions

1. You can visualize alveoli with the naked eye.

- True
- False

2. What statement describes bronchi and bronchioles best?

- As bronchi branch into increasingly smaller bronchioles, there is an increase in both cartilage and surface area
- As the bronchioles branch into bronchi, the amount of smooth muscle increases and the amount of cartilage decreases
- The walls of the bronchioles are very thin – only one cell thick – and surrounded by capillaries
- As bronchi branch into increasingly smaller bronchioles, there is a decrease in cartilage

3. Which statement is correct?

- Lungs are very elastic and mostly filled with air – akin to a balloon
- Lungs are very red and dense – akin to muscle
- Lungs are very heavy and dense due to all of the blood vessels
- Lungs are inelastic and red – akin to skin

Answer Key

1. False
2. As bronchi branch into increasingly smaller bronchioles, there is a decrease in cartilage
3. Lungs are very elastic and mostly filled with air – akin to a balloon

General Introduction to Tissue Injury, Inflammation, and Remodelling

JENNIFER KONG

Emphysema is a disease in which frequent, and chronic injury to the lungs causes inflammation and remodelling. Thus, to understand emphysema, the next chapter explains what inflammation is and how it leads to remodeling of tissue.

Key Takeaways

Inflammation is a normal response any kind of damage/infection/death of cells or tissues. Inflammation first has to limit loss of blood and block entry of pathogens into the wound (i.e. – hemostasis, clotting mechanism), clean up damaged tissue and destroy pathogens within the wound (i.e. neutrophils, extravasation, diapedesis, chemokine trail etc.), prepare wound site for new, but temporary, connective tissue (i.e. fibroblasts), and then replace temporary tissue with original tissue (if possible).

- The hallmark signs of inflammation is red (if visible), heat, swelling, and pain. These signs indicate the increased blood flow to the wound as part of the acute inflammatory process recruiting more leukocytes using chemical mediators. Leukocytes will track the pathogen and eliminate them, thus sterilizing the injury or infection, making the site ready for wound healing.
- Chemical mediators may also stimulate an inflammatory response distant from the site of injury, a systemic inflammatory response. Fever is an example of a systemic inflammatory response. Fever is intended to increase body temperature such that it kills the pathogens introduced with the wound.
- Assuming the healing process is not interrupted, the injury site will undergo an acute inflammatory process which completes within a week.
- An inflammatory process becomes chronic when the damage to tissue is frequent and/or the tissue does not have a chance to heal properly before being injured again.

Review Questions

1. An inflammatory response can occur without a pathogen (e.g. bacteria, virus)

- True
- False

2. Match each symptom to the correct category:

Fever, Swelling, Red (Erythema), Pain, Hot skin, Malaise

Signs of Localized Inflammation:

Signs of Systemic Inflammation:

Answer Key

1. True
2. **Signs of Localized Inflammation:** Swelling, Hot Skin, Pain, Red (Erythema)
   Signs of Systemic Inflammation: Fever, Malaise

Inflammation and Fever

NINA PARKER; MARK SCHNEEGURT; ANH-HUE THI TU; PHILIP LISTER; AND BRIAN M. FORSTER

Learning Objectives

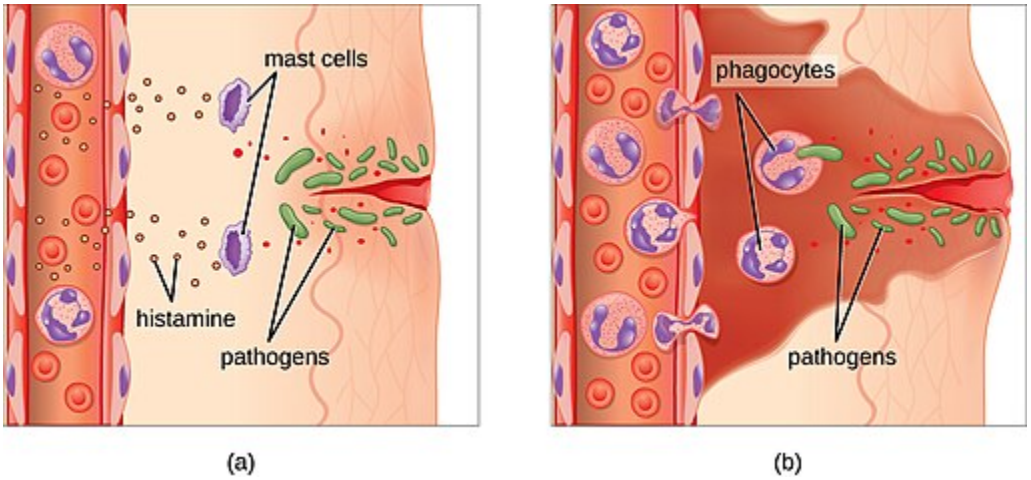
At the end of this section, you will be able to:

- Identify the signs of inflammation and fever and explain why they occur.
- Explain the advantages and risks posed by inflammatory responses.

The inflammatory response, or **inflammation**, is triggered by a cascade of chemical mediators and cellular responses that may occur when cells are damaged and stressed or when pathogens successfully breach the physical barriers of the innate immune system. Although inflammation is typically associated with negative consequences of injury or disease, it is a necessary process insofar as it allows for recruitment of the cellular defenses needed to eliminate pathogens, remove damaged and dead cells, and initiate repair mechanisms. Excessive inflammation, however, can result in local tissue damage and, in severe cases, may even become deadly.

Acute Inflammation

An early, if not immediate, response to tissue injury is **acute inflammation**. Immediately following an injury, vasoconstriction of blood vessels will occur to minimize blood loss. The amount of **vasoconstriction** is related to the amount of vascular injury, but it is usually brief. Vasoconstriction is followed by **vasodilation** and increased vascular permeability, as a direct result of the release of histamine from resident mast cells. Increased blood flow and vascular permeability can dilute toxins and bacterial products at the site of injury or infection. They also contribute to the five observable signs associated with the inflammatory response: **erythema** (redness), **edema**, heat, pain, and altered function. Vasodilation and increased vascular permeability are also associated with an influx of phagocytes at the site of injury and/or infection. This can enhance the inflammatory response because phagocytes may release proinflammatory chemicals when they are activated by cellular distress signals released from damaged cells, by **PAMPs** , or by **opsonins** on the surface of pathogens. Activation of the complement system can further enhance the inflammatory response through the production of the anaphylatoxin C5a. The image below illustrates a typical case of acute inflammation at the site of a skin wound.

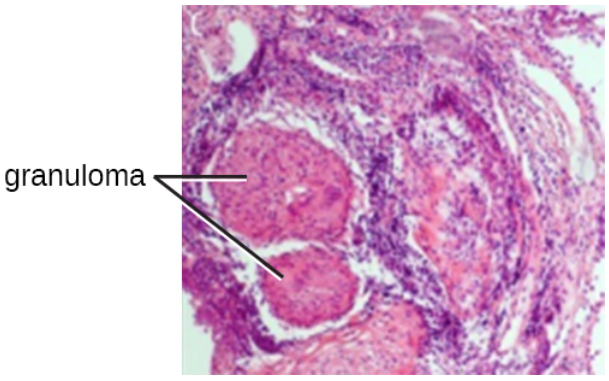


(a) Mast cells detect injury to nearby cells and release histamine, initiating an inflammatory response. (b) Histamine increases blood flow to the wound site, and increased vascular permeability allows fluid, proteins, phagocytes, and other immune cells to enter infected tissue. These events result in the swelling and reddening of the injured site, and the increased blood flow to the injured site causes it to feel warm. Inflammation is also associated with pain due to these events stimulating nerve pain receptors in the tissue. The interaction of phagocyte pattern recognition receptors (PRRs) with cellular distress signals and PAMPs and opsonins on the surface of pathogens leads to the release of more proinflammatory chemicals, enhancing the inflammatory response.

During the period of inflammation, the release of **bradykinin** causes capillaries to remain dilated, flooding tissues with fluids and leading to edema. Increasing numbers of neutrophils are recruited to the area to fight pathogens. As the fight rages on, **pus** forms from the accumulation of neutrophils, dead cells, tissue fluids, and lymph. Typically, after a few days, macrophages will help to clear out this pus. Eventually, tissue repair can begin in the wounded area.

Chronic Inflammation

When acute inflammation is unable to clear an infectious pathogen, **chronic inflammation** may occur. This often results in an ongoing (and sometimes futile) lower-level battle between the host organism and the pathogen. The wounded area may heal at a superficial level, but pathogens may still be present in deeper tissues, stimulating ongoing inflammation. Additionally, chronic inflammation may be involved in the progression of degenerative neurological diseases such as Alzheimer's and Parkinson's, heart disease, and metastatic cancer.



A ***tubercle*** *is a granuloma in the lung tissue of a patient with tuberculosis. In this micrograph, white blood cells (stained purple) have walled off a pocket of tissue infected with Mycobacterium tuberculosis. Granulomas also occur in many other forms of disease. (credit: modification of work by Piotrowski WJ, Górski P, Duda-Szymańska J, Kwiatkowska S)*

Chronic inflammation may lead to the formation of **granulomas**, pockets of infected tissue walled off and surrounded by WBCs. Macrophages and other phagocytes wage an unsuccessful battle to eliminate the pathogens and dead cellular materials within a granuloma. One example of a disease that produces chronic inflammation is **tuberculosis**, which results in the formation of granulomas in lung tissues. A tubercular granuloma is called a tubercle.

Chronic inflammation is not just associated with bacterial infections. Chronic inflammation can be an important cause of tissue damage from viral infections. The extensive scarring observed with hepatitis C infections and liver cirrhosis is the result of chronic inflammation.

Chronic Edema

In addition to granulomas, chronic inflammation can also result in long-term edema. A condition known as **lymphatic filariasis** (also known as elephantiasis) provides an extreme example. Lymphatic filariasis is caused by microscopic nematodes (parasitic worms) whose larvae are transmitted between human hosts by mosquitoes. Adult worms live in the lymphatic vessels, where their presence stimulates infiltration by lymphocytes, plasma cells, eosinophils, and thrombocytes (a condition known as lymphangitis). Because of the chronic nature of the illness, granulomas, fibrosis, and blocking of the lymphatic system may eventually occur. Over time, these blockages may worsen with repeated infections over decades, leading to skin thickened with edema and fibrosis. Lymph (extracellular tissue fluid) may spill out of the lymphatic areas and back into tissues, causing extreme swelling. Secondary bacterial infections commonly follow. Because it is a disease caused by a parasite, eosinophilia (a dramatic rise in the number of eosinophils in the blood) is characteristic of acute infection. However, this increase in antiparasite granulocytes is not sufficient to clear the infection in many cases.



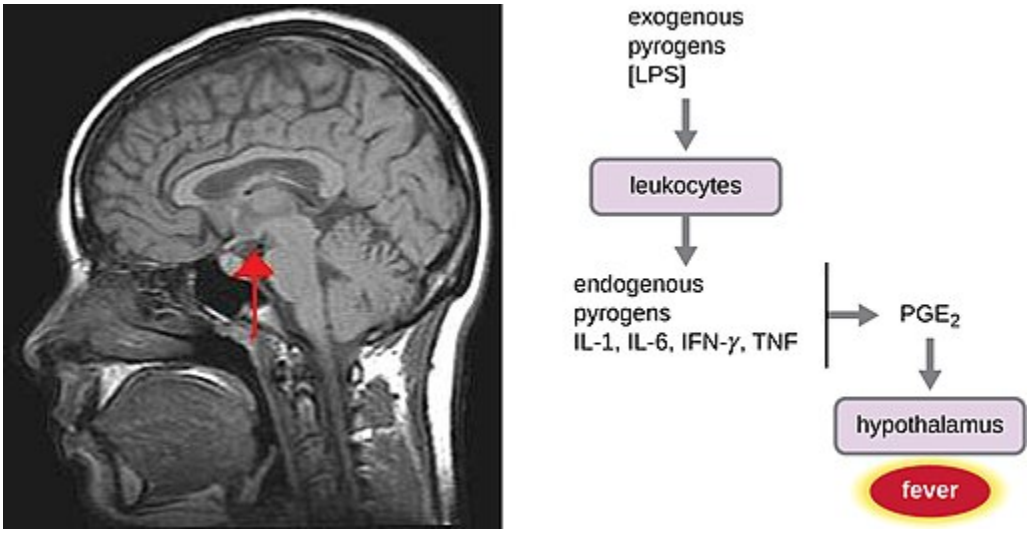
Elephantiasis (chronic edema) of the legs due to filariasis. (credit: modification of work by Centers for Disease Control and Prevention)

Lymphatic filariasis affects an estimated 120 million people worldwide, mostly concentrated in Africa and Asia.[1] Improved sanitation and mosquito control can reduce transmission rates.

Fever

A **fever** is an inflammatory response that extends beyond the site of infection and affects the entire body, resulting in an overall increase in body temperature. Body temperature is normally regulated and maintained by the hypothalamus, an anatomical section of the brain that functions to maintain homeostasis in the body. However, certain bacterial or viral infections can result in the production of **pyrogens**, chemicals that effectively alter the "thermostat setting" of the **hypothalamus** to elevate body temperature and cause fever. Pyrogens may be exogenous or endogenous. For example, the endotoxin lipopolysaccharide (LPS), produced by gram-negative bacteria, is an exogenous pyrogen that may induce the leukocytes to release endogenous pyrogens such as interleukin-1 (IL-1), IL-6, interferon-γ (IFN-γ), and tumour

necrosis factor (TNF). In a cascading effect, these molecules can then lead to the release of prostaglandin E2 (PGE_2) from other cells, resetting the hypothalamus to initiate fever.



The role of the hypothalamus in the inflammatory response. Macrophages recognize pathogens in an area and release cytokines that trigger inflammation. The cytokines also send a signal up the vagus nerve to the hypothalamus.

Like other forms of inflammation, a fever enhances the innate immune defenses by stimulating leukocytes to kill pathogens. The rise in body temperature also may inhibit the growth of many pathogens since human pathogens have optimum growth occurring around 35 °C (95 °F). In addition, some studies suggest that fever may also stimulate release of iron-sequestering compounds from the liver, thereby starving out microbes that rely on iron for growth.[2]

During **fever**, the skin may appear pale due to **vasoconstriction** of the blood vessels in the skin, which is mediated by the hypothalamus to divert blood flow away from extremities, minimizing the loss of heat and raising the core temperature. The hypothalamus will also stimulate shivering of muscles, another effective mechanism of generating heat and raising the core temperature.

The crisis phase occurs when the fever breaks. The hypothalamus stimulates **vasodilation**, resulting in a return of blood flow to the skin and a subsequent release of heat from the body. The hypothalamus also stimulates sweating, which cools the skin as the sweat evaporates.

Although a low-level fever may help an individual overcome an illness, in some instances, this immune response can be too strong, causing tissue and organ damage and, in severe cases, even death. The inflammatory response to bacterial **superantigens** is one scenario in which a life-threatening fever may develop. Superantigens are bacterial or viral proteins that can cause an excessive activation of T cells from the specific adaptive immune defense, as well as an excessive release of cytokines that overstimulates the inflammatory response. For example, *Staphylococcus aureus* and *Streptococcus pyogenes* are capable of producing superantigens that cause toxic shock syndrome and **scarlet fever**, respectively. Both of these conditions can be associated with very high, life-threatening fevers in excess of 42 °C (108 °F).

Section Review

- Inflammation results from the collective response of chemical mediators and cellular defenses to an injury or infection.
- Acute inflammation is short lived and localized to the site of injury or infection. Chronic inflammation occurs when the inflammatory response is unsuccessful, and may result in the formation of granulomas (e.g., with tuberculosis) and scarring (e.g., with hepatitis C viral infections and liver cirrhosis).
- The five cardinal signs of inflammation are erythema, edema, heat, pain, and altered function. These largely result from innate responses that draw increased blood flow to the injured or infected tissue.
- Fever is a system-wide sign of inflammation that raises the body temperature and stimulates the immune response.
- Both inflammation and fever can be harmful if the inflammatory response is too severe.

Review Questions

1. Which refers to swelling as a result of inflammation?

- Erythema
- Edema
- Granuloma
- Vasodilation

2. Which type of inflammation occurs at the site of an injury or infection?

- Acute
- Chronic
- Endogenous
- Exogenous

3. Fill in the blank.

A(n) _____ is a walled-off area of infected tissue that exhibits chronic inflammation.

4. Fill in the blank.

The _____ is the part of the body responsible for regulating body temperature.

5. Fill in the blank.

Heat and redness, or _____, occur when the small blood vessels in an inflamed area dilate (open up), bringing more blood much closer to the surface of the skin.

6. Name the five stages of inflammation.

Answer Key

1. Edema
2. Acute
3. Granuloma
4. Hypothalamus
5. Erythema
6. Heat, redness, swelling (erythema), pain, and altered function

Adaption

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Notes

1. Centers for Disease Control and Prevention. "Parasites–Lymphatic Filiariasis." 2016. http://www.cdc.gov/parasites/lymphaticfilariasis/gen_info/faqs.html.
2. N. Parrow et al. "Sequestration and Scavenging of Iron in Infection." *Infection and Immunity* 81 no. 10 (2013):3503–3514

Chronic Inflammation and Tissue Remodelling

JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Briefly explain how the body will remodel after repeated injury and inflammation.

It is inefficient for the body to replace tissue that is repeatedly injured with the same tissue. Yet, that is what is happening in acute inflammation. During chronic inflammation, the body begins to replace the damaged tissue with tissue that can handle the repeated injury better. In essence, the tissue remodels – i.e. changes from one tissue type to another. This is possible as cells that can still mitose can undergo differentiation – i.e. change from one mature cell type to another.

In most parts of the body, tissue remodeling often involves connective tissue replacing original tissue. As a result, the connective tissue does not have the same properties: often, the remodeled tissue is stiffer and more durable. This causes noticeable changes as there is a shrinkage and tightening of once-elastic tissues (contracture), a narrowing of a luminal space (stricture), or attachment of structures which normally don't attach (adhesions). The exception to this rule is the lung: lung tissue remodeling causes an expansion of the lung, as opposed to shrinkage. This will become evident as we discuss the pathophysiology of emphysema.

Section Review

- To adapt to repeated injury and subsequent inflammation, tissue will remodel and change its make-up in order to tolerate the repeated injury better.
- Remodelled tissue no longer has the properties of the original tissue. Often, remodelled tissue is more stiff and durable (i.e. addition of tough connective tissue during remodeling) thus affecting an organs original elasticity, compliance, and lumen size.

Review Questions

1. Think of 2 possible causes of chronic inflammation and 2 possible causes of acute inflammation in the lungs. What characteristic distinguishes between acute and chronic inflammation?

Answer Key

1. There are many possible answers. Note that acute inflammation is caused by short-term exposure to irritants, while chronic inflammation is caused by long-term exposure to irritants. Examples of causes of chronic inflammation: daily cigarette smoking and occupational exposure to dust/chemicals. Examples of causes of acute inflammation: Short-term infection of the lungs and short-term exposure to wildfire smoke

Pathophysiology of Emphysema

JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Outline the physiological cause of emphysema as a disease of repeated injury, inflammation and remodelling.
- Define the role of alpha-1-antitrypsin (AAT) in health and its role during the development of emphysema.
- Identify key features of emphysema in lung tissue on a gross and histological level.
- Explain how chronic inflammation and remodelling during emphysema leads to exhalation being an active process.

Emphysema is a progressive respiratory disease whereby chronic injury and inflammation to the airways & alveoli result in their deformation and destruction. The end result is a significant loss of gas exchange surface and serious impairment of the lung's natural elasticity needed for ventilation – particularly exhalation. Emphysema manifests in the mid to later stages of life.

Causes of Emphysema

For emphysema to develop, the lungs have had years worth of constant, repeated damage to the airways and alveoli, thus involving chronic inflammation and tissue remodeling. Causes that are considered modifiable (i.e. there's an opportunity to remove the recurrent injury) and non-modifiable (i.e. cannot avoid the recurrent injury).

Modifiable and Non-modifiable Causes of Emphysema

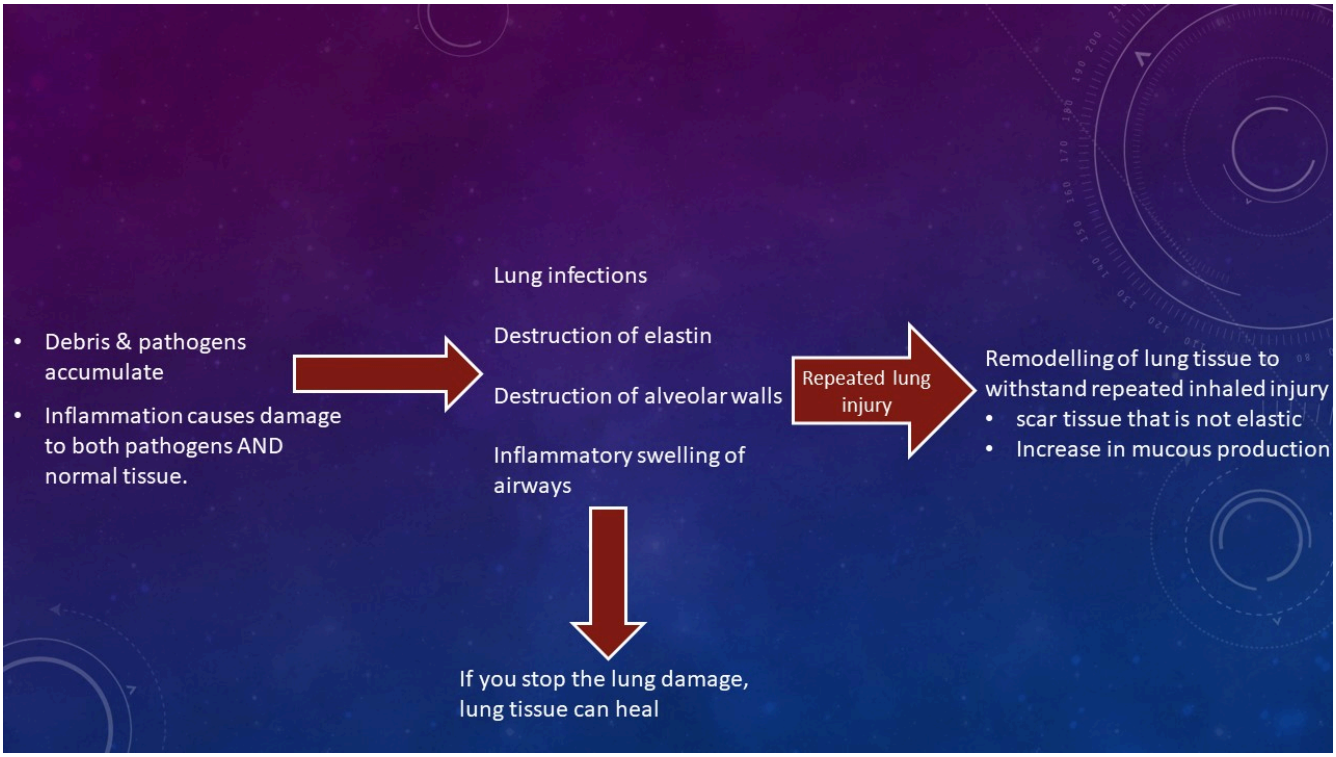
Modifiable causes	Non-modifiable causes
Chronic inhalation of foreign particulate (e.g. air pollution, second hand smoke, working with fine dust or powders)	A rare, inheritable alpha-1-anti-trypsin deficiency
Chronic infection/inflammation of the lungs – especially in childhood	

Recall that emphysema is one of the diseases lumped under the umbrella term COPD. Thus, emphysema can concurrently occur with other COPD conditions like chronic bronchitis.

Pathophysiology of Emphysema

Regardless of the cause, emphysema is caused by repeated injury and inflammatory response in the lung tissue. As part of the inflammatory response, leukocytes – especially neutrophils – are recruited to the site of injury. Neutrophils release enzymes which degrade proteins in the irritant/pathogen. Such enzymes (i.e. **proteases** such as trypsin, elastase) can also degrade one's own tissue's proteins if it weren't for the special protein **alpha-1-antitrypsin** (AAT) that deactivates any proteases approaching normal cells – akin to a protective forcefield. AAT is predominantly made in the liver, circulates continuously in the blood, and accumulates in lungs since lungs are exposed to pathogens (and hence, possible infection) with each breath.

But what happens if one frequently inhales harmful irritants? The acute inflammatory process works as needed, but the lungs run out of AAT. Rather, AAT is consumed by the frequent inflammatory response, faster than the liver can make it and circulate. As a result, the proteases released by neutrophils during inflammation will go uninhibited: digesting the proteins in both the irritant/pathogen AND the lungs. As a result, the lungs get damaged by its own cells – causing more of an inflammatory response and so forth. The result: loss of lung tissue and remodeling of airways to a non-elastic tissue (since proteases repeatedly digest the lung's natural elastin). The loss of lung tissue particularly alveolar walls is noticed microscopically and by gross inspection in that the fine holes/bubbles in lung tissue are larger, distorted blebs as airspaces from digested alveoli coalesce to form a single larger air space. Similarly, alveoli & airways, particularly bronchioles, are remodeled due to chronic inflammation, becoming inelastic. This is particularly noticeable in the airways as the airways have narrowed and lost its ability to stay open during exhalation (i.e. airways collapse). At the same time, alveoli, with their larger than normal airspace, can't recoil to a smaller volume during exhalation due to their remodeled inelastic nature. The end effect is that air is "trapped" inside lungs because the elastic-driving force of exhalation has been lost to remodeling.



Pathophysiology of Emphysema

Gross Pathology of Emphysema

For a stark contrast in the effects of emphysema, compare the normal lung to the emphysema specimen – suspended in formalin.

DHPLC specimen: A000 – *Normal Lung Tissue With Blood Washed Out.* All rights reserved

Note the striking difference in colour: the emphysema lung is black with the cigarette tar of frequent tobacco use. The emphysema lungs have 'shaggy' tissue with large holes – one hole is so large that is perforates through the entire specimen (top left). Notice that bronchioles in normal lung are numerous and can be easily identified whereas the emphysema specimen airways are smaller in number and not as discretely identifiable.

This video is awaiting licensing approval and will be available shortly. Key Features of Emphysema at Gross Level by Jennifer Kong, licensed under All rights reserved

To visualize the smaller and finer bronchioles, we now present Gough sections of normal and emphysema lung, both photographed at the level of the naked eye.

Normal lung (Gough section). All rights reserved

The emphysema specimen gives the impression of a decaying leaf, which is a good comparison considering the amount of lung tissue lost during years of chronic injury and inflammation. The emphysema lung has obvious signs of large air spaces, a result of alveolar wall destruction and coalescing of air spaces. Much of the lung tissue has become very thick with the impression of being stiff. Like the previous specimens, the emphysema lung retains much of the black residue from cigarette usage.

Histopathology of Emphysema

Critical thinking Exercise

Before viewing histopathologist Jon's video, consider what you already know about emphysema and what you would expect to see histologically. Privately record your answers to these questions before viewing the video

- In the histology chapter, you learned there are certain epithelial types you see within lung tissue. Which cell type would form the alveolar wall? The airways?
- What do you expect to see with respects to alveolar size, knowing there is destruction & remodeling?
- What do you think those enlarged airspaces, easily visible with the naked eye, will look like

microscopically?

- What do you think the overall pattern of the emphysema tissue sample be? Will it be a predictable, homogeneous pattern?
- What do you think cigarette residue within lung tissue will look like microscopically?
- How would you observe the remodeling of lung tissue into inelastic connective tissue?

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://pressbooks.bccampus.ca/pathology/?p=638#video-638-1

This video is awaiting licensing approval and will be available shortly. Histopathology of Emphysema by Jonathan Bush, licensed under All rights reserved

Section Review

- Due to chronic injury and/or insufficiency of alpha-1-antitrypsin in the lung, the inflammatory process destroys both the inhaled irritant AND normal healthy lung tissue. As a result, there is loss of lung tissue, particularly evident in alveolar walls, and remodeling of lung tissue to thicker, stiffer, less compliant properties.
- Because the lungs have lost their elasticity through remodeling, airways are narrowed and collapsible, especially during exhalation, resulting in an incomplete exhalation of the normal expiratory volume. The end result is some air being 'trapped' in the alveoli and thus lungs with each breath.
- Exhalation becomes progressively more difficult as the elastic recoil of healthy lung tissue is lost and the airways become narrowed and more likely to collapse. As a result, exhalation changes from a passive process to an active effort.
- Repeated inflammation causes loss of alveolar tissue. Thus causing expansion of alveolar air spaces with less area for gas exchange. These coalesced air spaces are visible histologically.
- Emphysema lung tissue may retain some of the inhaled irritants, thus changing the colour of lung tissue.

Review Questions

1. Fill in the blanks. During inflammatory processes, _____ are recruited to the site of injury/infection and begin releasing enzymes to degrade the irritants or pathogens. Alpha-1-antitrypsin is made in the _____ and circulates continuously in the _____, where it can accumulate in the lungs. Alpha-1-antitrypsin is responsible for deactivating _____ that are released by immune cells during inflammation. These enzymes can also degrade _____ lung tissue if they are unregulated.

2. Which of the following statements are true? Select all that apply.

- AAT is released from the liver after inflammation occurs, and is responsible for preventing damage to healthy tissue.

- Extensive tissue remodelling occurs in response to an acute inflammatory event, where inelastic scar tissue prevents proper functioning of the alveoli.
- AAT helps to regulate inflammatory-mediated damage to healthy lung tissue in acute events, but can run out in cases where there is frequent exposure to irritants or pathogens that cause an immune response.
- If the exposure to lung irritants stops, lung tissue is able to heal.

3. Describe some differences you can expect in the gross appearance of emphysema lung tissue versus healthy lung tissue.

4. List 3 ways in which breathing for a lung with emphysema will be more difficult than for a healthy lung. Recall the pathophysiology of emphysema, and relate that to the clinical picture.

Answer Key

1. Leukocytes/neutrophils,liver, blood, proteases,normal/healthy
2. AAT helps to regulate inflammatory-mediated damage to healthy lung tissue in acute events, but can run out in cases where there is frequent exposure to irritants or pathogens that cause an immune response.
3. **Example answer:** Depending on the cause of emphysema, the lung tissue may have noticeable pigmentation (e.g. due to repeated smoke inhalation, cigarette tar). Some black spots are normal in lung due to everyday inhalation of pollutants, but the lung of a lifetime smoker with emphysema may appear nearly completely black. A lung with emphysema will have a "shaggy" appearance: there will be large holes where the walls between alveoli (air sacks) have been destroyed and the air spaces coalesced, and these large holes can be seen with the naked eye. There will also be noticeable thickening of the walls of the larger airways compared to healthy lung tissue.
4. **Example answer:**
   i) Due to tissue remodelling, the lungs lose elasticity which leads to narrowed and collapsible airways (having trouble staying open, particularly during exhalation). ii) The alveoli, which also become inelastic through tissue remodelling, are unable to recoil during exhalation which "traps" air inside of the lungs and causes incomplete exhalations.
   iii) Many of the alveoli, which are responsible for the actual gas exchange in the lungs, have been destroyed and their air spaces have coalesced. This leaves less area for gas exchange to occur.

Media Attributions

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Signs and Symptoms of Emphysema

JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Explain how histological changes in lungs manifests as common signs and symptoms of emphysema.
- Define exacerbation of emphysema and explain its urgency for treatment.

As emphysema may take years to develop, signs and symptoms may be quite mild at the start. However, emphysema is a progressive decline in respiratory function, particularly exhalation, due to the loss of the alveolar tissue and remodelling with inelastic tissue. As emphysema progresses, the patient will accumulate "trapped air" yet have signs of poor oxygenation and increased work of breathing since energy is now needed to both inhale and exhale (recall that exhalation is passive due to the elastic nature of the lungs).

Clinical Manifestations of Emphysema based on the Pathology

Pathology findings	Clinical manifestations
Lungs filled with irritants & chemicals	**Dyspnea** with coughing = problems with gas exchange due to loss of alveolar tissue and thickened walls Increased mucous production to trap irritants
Airspaces are enlarged with air that can't be exhaled	Can't quite exhale all of the volume leading to lungs slowly increasing in chest volume –> barrel chest Chest sounds are **tympanic**
Significant loss of alveolar membranes	Low blood oxygen = **cyanosis** High blood CO2 levels = hypercapnic
Airways are narrower with scar tissue and increased mucous production	Coughing, with or without mucous **Wheezes** – especially during exhalation Coughing isn't efficient in clearing mucous with debris –> increased risk of lung infections

Exacerbations of Emphysema

As emphysema progresses, the patient's ability to exhale decreases yet work of breathing increases. As such, emphysema patients may not be able to cough as deeply or forcibly as needed, due to the decreased exhalation abilities. Normally, the cough reflex is helpful in expelling mucous, which has trapped inhaled irritants or pathogens: hopefully, before the pathogens have a chance to infect. Thus, emphysema patients are more susceptible to lung infections.

Similarly, patients with emphysema are experiencing chronic inflammation from the frequent injury to the lungs (e.g. daily cigarette smoking). An additional injury to the lungs (e.g. environmental pollution from forest fire smoke), on top of the daily injuries, will induce more of an inflammatory reaction, which will make the signs and symptoms worse. This is known as **exacerbation**. Exacerbations are, hopefully, temporary as withdrawal of the additional injury will stop the worsening of symptoms. However, dyspnea and changes in gas exchange between alveoli and blood will cause great discomfort in patients without medical intervention.

Section Review

- Remodeling leads to stiffer, less compliant lung tissue which progressively makes exhalation more difficult requiring expenditure of energy.
- As emphysema progresses, the accumulated loss of alveolar membrane tissue leads to decreased gas exchange resulting in less oxygenation of blood and insufficient elimination of CO2. Thus blood gases are affected (i.e. hypoxic and hypercapnic). As blood is less oxygenated, all tissues will be less nourished resulting in impaired function (e.g. weakness, fatigue) and the sensation of difficult breathing (dyspnea).
- As emphysema progresses, there is an accumulation of "trapped air" leading to a hyperinflation of lungs, and hence, chest volume.
- Remodeling can also lead to an increase in mucous production to help protect airways from inhaled irritants, resulting in increased coughing to expel the mucous. However, coughing is an active process requiring open airways, thus coughing become less effective.
- As emphysema progresses, the patient can manage their daily activities based on how well their lungs tolerate the physical demand. However, any additional challenge to the lungs (e.g. increased irritants in the air due to forest fire smoke, lung infection) can lead to a sudden worsening of lung function (i.e. exacerbation of emphysema) that can cause dyspnea, insufficient oxygenation of blood, and fatigue from the increased work of breathing an this additional challenge. Medical intervention is required as the patient will have difficulty adapting.

Review Questions

1. Fill in the blanks. As emphysema progresses, a patient's ability to _____ decreases, causing a decreased ability to cough as forcibly as might be needed. The cough reflex is needed to expel _____ which can contain trapped irritants and pathogens. Patients with emphysema can also experience _____ of their condition if they experience additional irritants which can worsen their symptoms.

2. What signs and symptoms might you expect from a serial smoker who developed emphysema? How might these correlate with histological findings?

Answer Key

1. Exhale, mucous/mucus, exacerbations/exacerbation
2. Example answer:
   Due to chronic inflammation, there is tissue damage causing loss of alveolar tissue and thickened septae. This impairs gas exchange, leading to low blood oxygen/high blood CO2 and dyspnea (feeling of breathlessness) with compensatory increase in respiratory rate. Constant exposure to irritants will also lead to increased mucous production (goblet cell metaplasia – increase in the cells which produce mucous) which is the body's response to try to trap more of the irritants before they make it to the lungs. This will lead to increased coughing. The airways of the lungs are also narrower due to the development of scar tissue, leading to difficulty with exhalation which can be recognized by wheezing of the patient. This may also manifest with increased lung infections, as the patient will not be able to cough deeply and expel mucous which may carry pathogens.

Diagnosis and Treatment of Emphysema

JENNIFER KONG

Learning Objectives

At the end of this section, you will be able to:

- Explain how health care professionals collaborate in the diagnosis, treatment, and management of a patient with emphysema.
- Describe how emphysema is diagnosed and monitored for its progression.
- Briefly outline the roles of the nurse takes when assisting a patient admitted to emergency department for exacerbation of COPD.

Diagnosis

As emphysema progresses, the amount of volume exhaled decreases. This can be measured by a pulmonary function test called "Forced Expiratory Volume in 1 sec" (**FEV1**). In exhalation with normal lungs, FEV1 is 80% (i.e. 80% of the volume of exhaled gas leaves within the first second of exhalation). However, in emphysema, FEV1 < 80% and will progressively decline as the trapped air accumulates over years. This test is often done by a respiratory therapist.

Similarly, blood gases will change as emphysema progresses. Initially, oxygenation will be normal as inhalation is yet to be impaired by chronic inflammation. However, as emphysema develops, there will be a retention of CO2 (i.e. hypercapnia) and an insufficient oxygenation (i.e. hypoxemia). Blood oxygenation can be measured quickly with pulse oximetry by a nurse (see below) or blood chemistry by a medical laboratory technologist. Blood gas analysis, performed by a respiratory therapist, can quantify the oxygen, carbon dioxide, and pH of blood.

Computed Tomography (CT)

This increase in trapped air can be visualized with medical radiography, specifically computed tomography (CT)

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=656#h5p-60

Role of CT During Diagnosis and Management of Emphysema by Sarah Ho, licensed under All Rights Reserved

Treatment of Emphysema & Complications

There is no cure for emphysema as lung tissue, when chronically injured, can not regenerate. Rather, treatment is for relief of symptoms as the lungs slowly inflate, yet lose gas exchange abilities & ventilation. On occasion, an emphysema patient may not be able to manage their disease due to a change in their health or environment (i.e. an exacerbation of emphysema), thus needing medical care.

Role of Nursing During Exacerbations from Emphysema

Listen to Rob Kruger, a long-time nurse, speak about the journey a patient with an exacerbation will take from entry into Emergency Department. He speaks about the many health care professionals the patient will encounter, with the nurse managing and coordinating the patient's care. He also describes the current roles in nursing and how many nurses are working in the Lower Mainland and within the province of BC. He also shares a fun fact about nursing!

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=656#h5p-61

Management of a Patient with an Exacerbation of Emphysema by Rob Kruger, licensed under All Rights Reserved

Section Review

- Emphysema is diagnosed with several data pointing to obstructed airways, particularly during exhalation. This can be measured by the volume forcefully exhaled in 1 second (FEV1 performed by respiratory therapists) or imaged using medical radiography (CT). Similarly, blood tests will reveal the amount of oxygen and carbon dioxide which may suggest COPD.
- Emphysema patients may encounter an additional respiratory challenge causing an exacerbation which may require medical intervention. Should the patient be admitted into the Emergency Department or health care facility, a nurse will manage the patient and provide patient support while coordinating their investigations and treatments during their stay. Upon leaving, the nurse will also educate the patient on how to manage their condition at home and avoid future exacerbations.

Review Questions

1. Which of the following statements are true for emphysema? Select all that apply.

- Emphysema patients experience low blood oxygen (hypoxemia) and low blood CO2 (hypocapnia) due to impaired gas exchange in the alveoli of the lungs.
- As emphysema progresses, patients have a harder time exhaling due to trapped air within enlarged alveolar air spaces. This can be measured by pulmonary function tests to help in the diagnosis and monitoring of emphysema.
- Blood gas analysis of a patient with unmanaged emphysema will likely show high CO2 levels, low blood oxygen, and an abnormal blood pH.
- Computer tomography can be used to visualize trapped air in the lungs in emphysemic patients.

2. A nurse will work with an array of physicians (e.g. emergency, respirologist), diagnostic techs (e.g. medical radiography techs, medical laboratory techs, cardiology techs), and fellow nurses (triage, emergency) for managing and coordinating a patient who arrives at the ER with exacerbated COPD.

- True
- False

3. List 3 tests that may be used for the diagnosis/monitoring of a patient with emphysema, and how they apply.

Answer Key

1. i) As emphysema progresses, patients have a harder time exhaling due to trapped air within enlarged alveolar air spaces. This can be measured by pulmonary function tests to help in the diagnosis and monitoring of emphysema.
   ii) Blood gas analysis of a patient with unmanaged emphysema will likely show high CO2 levels, low blood oxygen, and an abnormal blood pH.
   iii) Computer tomography can be used to visualize trapped air in the lungs in emphysemic patients.
2. True
3. i) Blood gas analysis: patients with emphysema are expected to have low blood oxygen, high blood CO2, and may have high blood pH due to impaired gas exchange and breathing.
   ii) Medical radiography/computed tomography (CT): CT can be used to visualize trapped air in an emphysema patient's lungs.
   iii) Forced Expiratory Volume in 1 sec (FEV1) can be used to demonstrate the volume of gas exhaled from the patient's lung in 1 second, which will be low (<80%) in a patient with emphysema.

Clinical Side of COPD

JENNIFER KONG

Want more practice with the clinical side of COPD? Or to read what it's like for a patient to have an exacerbation of COPD and a subsequent lung infection? See these additional Open Education resources.

A Patient's Journey Through the Health Care System

Meet fictional patient Erin Johns in the Appendices: Case Study for Chronic Obstructive Pulmonary Disease (COPD) where we follow her journey from an exacerbation of COPD and her hospital admission for a lung infection, as she meets many health care professionals working together on her diagnosis and care.

Select Clinical Skills Used by Health Care Providers

To learn about the skills of assessing a patient with signs and symptoms of heart failure, please read chapter 2 "Patient Assessment" from the Open Education resource Clinical Procedures for Safer Patient Care by Doyle & McCutcheon.

Emphysema Chapter Summary and Credits

JENNIFER KONG

Chapter Summary

Like all tissues, lungs respond to injury and infection through an inflammatory response. With repeated injury, the lung's supply of alpha-1-antitrypsin is exhausted thus leaving lung tissue vulnerable to injury from its own inflammatory process – thus causing more inflammation. Years worth of chronic inflammation will result in both loss of lung tissue (especially alveolar walls) and remodelling into non-elastic tissue that can tolerate repeated inflammatory attacks. Loss of elastic properties of the lungs now makes exhalation no longer a passive process: the body must work to push the lungs into a smaller volume. This remodelling also occurs in bronchioles, resulting in narrowed airways that can't snap open during exhalation. In some cases where emphysema is caused by inhaled irritants, there is an increased presence of cells that produce mucous (to trap the inhaled irritant), further narrowing the airway. Put them together, the lungs lose the alveolar surface necessary for gas exchange and airspaces coalesce into large blebs of air trapped within the lung tissue. The narrowed airways and increase work during exhalation results in less air being exhaled, thus trapping it within the lungs. The sensation of dyspnea will increase as lung tissue is lost and remodelled and fatigue occurs both due to low oxygenation of blood and increased work in breathing (especially exhalation). Loss of lung tissue and remodelling can be visualized with CT and loss of exhalation function can be measured with pulmonary function testing (i.e. FEV1). Because the lungs can't clear mucous and trapped pathogens/irritants as well (due to decreased exhalation abilities), emphysema patients are susceptible to lung infections. Thus, sudden changes in health status (e.g. lung infection) and/or environment (i.e. additional injury to lungs) can make emphysema symptoms worsen (exacerbation), thus requiring medical attention.

Credits

Author: Dr. Jennifer Kong (BCIT & UBC)

Gross anatomy video: Dr. Jennifer Kong (BCIT & UBC)

Histopathology video: Dr. Jonathan Bush (UBC, BC Children's Hospital)

Author of self-tests: Noah Stewart

Nurse: Rob Kruger (Specialty Nursing, BCIT)

Medical Radiography Technologist (CT): Sarah Ho (Medical Radiography, BCIT)

Videoproducer: Ian Whittlesey (BCIT), Adrian Marcuzzi (UBC medical student) and Dr. Jennifer Kong (BCIT & UBC)

Post-Test for Emphysema

JENNIFER KONG

1. There is a genetic cause to emphysema.

- True
- False

2. Repeated injury to the lungs, via inhaled irritants, will stimulate what response? Select all that apply.

- Recruitment of leukocytes to the lung tissue with the inhaled irritant
- Promotion of alveolar cell growth in size
- Remodelling of elastin-containing lung tissue into non-elastic fibrous tissue
- Increased production of elastin in lung tissue to trap inhaled irritants
- Decreased production of mucous to allow for easier inhalation

3. Fill in the blanks.

"Barrel chest" in emphysema develops because there is an _____ in chest volume. The chest volume is determined by alveolar air space which has _____ due to coalescing of alveolar air space after _____ is destroyed. In addition, the bronchioles have become _____ due to _____ production and loss of _____ thus making it easier to collapse and close during _____. The result is air trapping which progressively _____ the lung & chest volume, yet the actual amount of exhaled volume _____.

4. Fill in the blanks with the following words:

hypercapnia, weight loss, productive cough, fatigue, cyanosis, wheezing

_____ and _____ occurs when insufficient gas exchange occurs at the alveoli. _____ is felt when there is a decrease in oxygenated blood in circulation. _____ and _____ occur due to narrowed airways blocking air flow out during exhalation. _____ occurs due to the increased work of breathing.

Answer Key

1. False
2. Recruitment of leukocytes to the lung tissue with the inhaled irritant, remodelling of elastin-containing lung tissue into non-elastic fibrous tissue
3. Increase, increased, alveolar wall, narrowed, mucous, elastin, exhalation, increases, decreases
4. Cyanosis, hypercapnia, fatigue, wheezing, productive cough, weight loss

ATHEROSCLEROSIS AND ANGINA

Atherosclerosis Chapter Overview

JENNIFER KONG AND TETIANA POVSHEDNA

Chapter Learning Objectives

By the end of this chapter, you will be able to:

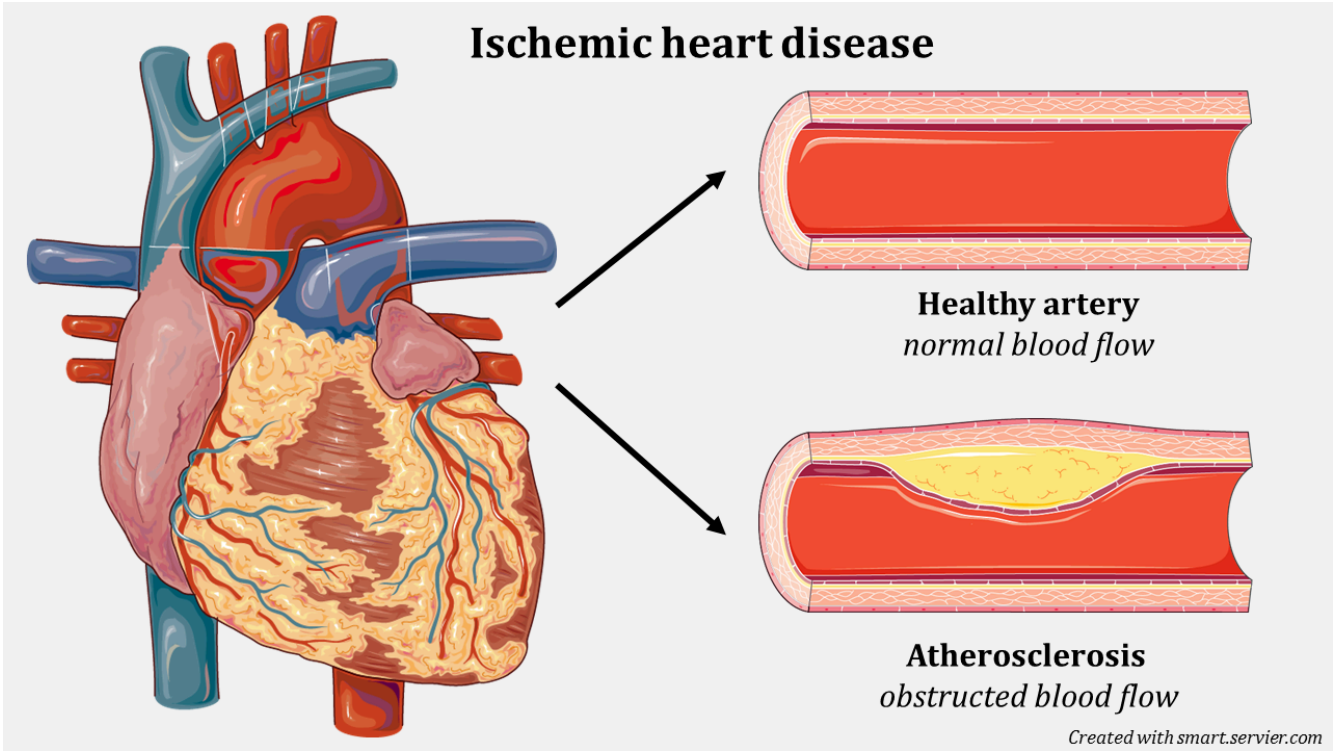
- Describe the gross development of atherosclerotic plaques as an inflammatory event.
- Describe the epidemiology, risk factors, and prevention strategies for atherosclerosis.
- Histologically, identify the presence of atherosclerotic plaques on vascular tissue.
- Correlate clinical findings and history with the pathology observed using atherosclerosis as an example.
- List possible consequences of atherosclerotic plaque development and rupture in the vessels of the heart and beyond.
- Briefly describe how interprofessional collaboration of health care professions works towards diagnosis of atherosclerosis and angina.

In 2020, the World Health Organization reported that ischemic heart disease was the leading cause of death in the world WHO top 10 causes of death. However, what exactly is ischemic heart disease?

Ischemic heart disease means that the heart is not getting enough oxygen – most likely because there is a restriction of flow of oxygenated blood to the heart tissues. One of the most common causes of this restricted blood flow is atherosclerosis, which involves fatty plaques formation and hardening of blood vessels. That impaired blood flow causes insufficient delivery of oxygen to the heart tissues – causing pain (known as angina) and loss of heart function.

Atherosclerosis is a chronic inflammatory process that involves accumulation of lipid particles (fatty streaks and plaques) on the vessel walls across the vascular tree (primarily vessels serving the heart, brain, lower limbs). Blood flow impairment caused by atherosclerosis can lead to acute atherosclerotic cardiovascular events, such as heart attack and stroke.

Keep in mind that atherosclerotic disease isn't limited to just the coronary vessels and is a systemic condition. Often, this disease process is evident in other parts of the vascular tree, which will similarly cause impaired blood flow and damage to blood vessels.



Ischemic Heart Disease

Abbreviations

The following abbreviations are used throughout the chapter.

CVD	Cardiovascular Disease
EKG	Electrocardiogram
HDL	High-Density Lipoprotein
IDL	Intermediate-Density Lipoproteins
LDL	Low-Density Lipoprotein
MAP	Mean Arterial Pressure
oxLDL	Oxidized LDL
TMAO	Trimethylamine N-Oxide
VLDL	Very Low-Density Lipoproteins
VSMCs	Vascular Smooth Muscle Cells
WSS	Wall Shear Stress

Media Attributions

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Pre-Test for Atherosclerosis

TETIANA POVSHEDNA

1. Finish the following sentence. Formation of atherosclerotic plaques that restrict blood flow can occur:

- In blood vessels of the heart
- In blood vessels of the brain
- In blood vessels of the lower/upper limb
- Anywhere within the vascular tree

2. Fill in the blank.

Atherosclerosis is one of the most common causes of _____ heart disease – a condition where heart doesn't get enough oxygen.

3. Risk of atherosclerosis development and progression depends only on genetic predisposition.

- True
- False

4. Fill in the blank.

At the core of atherosclerosis plaque formation is deposition of _____ particles within the blood vessel wall.

Answer Key

1. Anywhere within the vascular tree
2. Ischemic
3. False
4. Lipid

Structure and Function of Blood Vessels

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

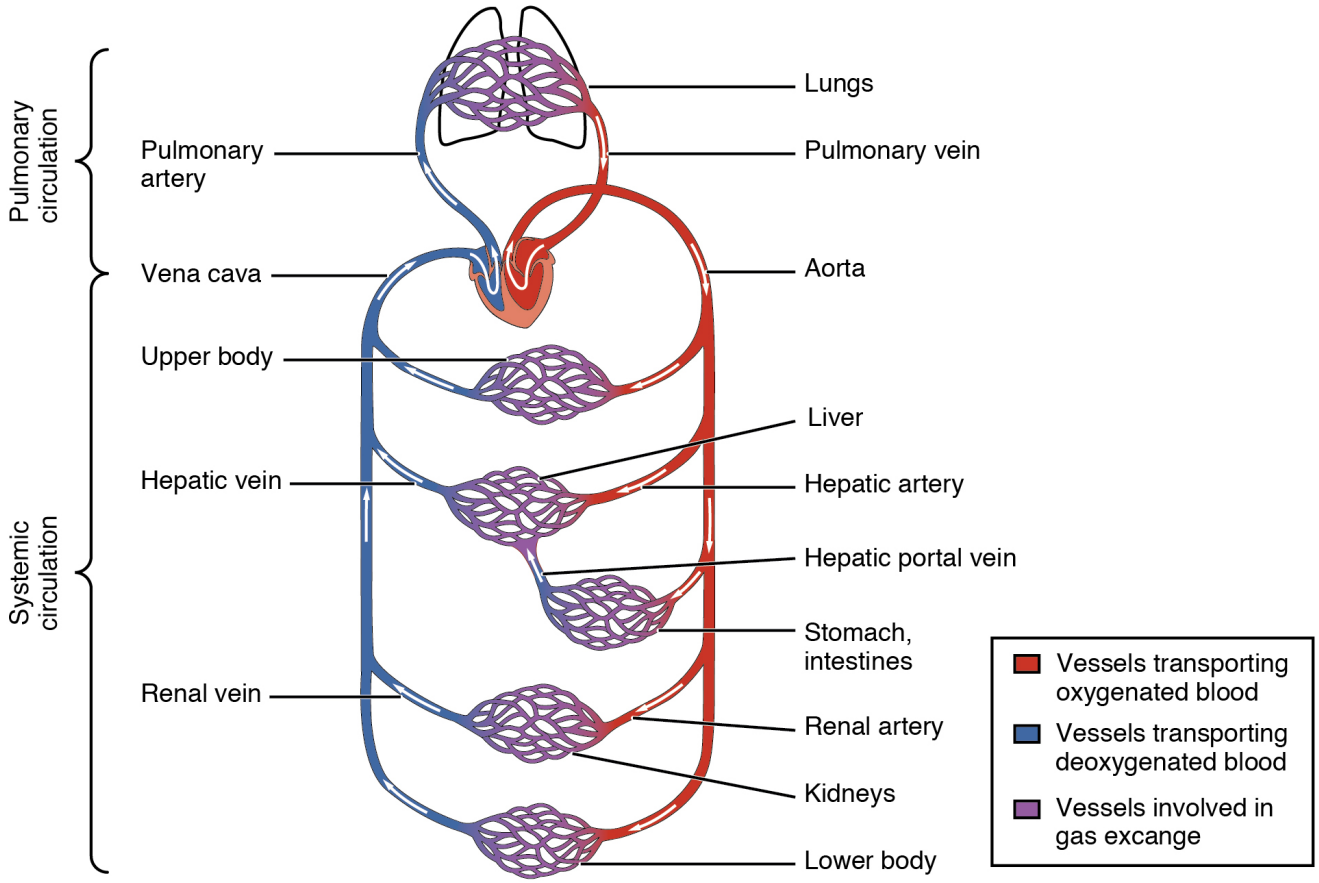
Learning Objectives

By the end of this section, you will be able to:

- Compare and contrast the three tunics that make up the walls of most blood vessels.
- Distinguish between elastic arteries, muscular arteries, and arterioles on the basis of structure, location, and function.
- Explain the structure and function of arteries vs veins.

Blood is carried through the body via blood vessels. An **artery** is a blood vessel that carries blood away from the heart, where it branches into ever-smaller vessels. Eventually, the smallest arteries, vessels called **arterioles**, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form **venules**, small blood vessels that carry blood to a **vein**, a larger blood vessel that returns blood to the heart.

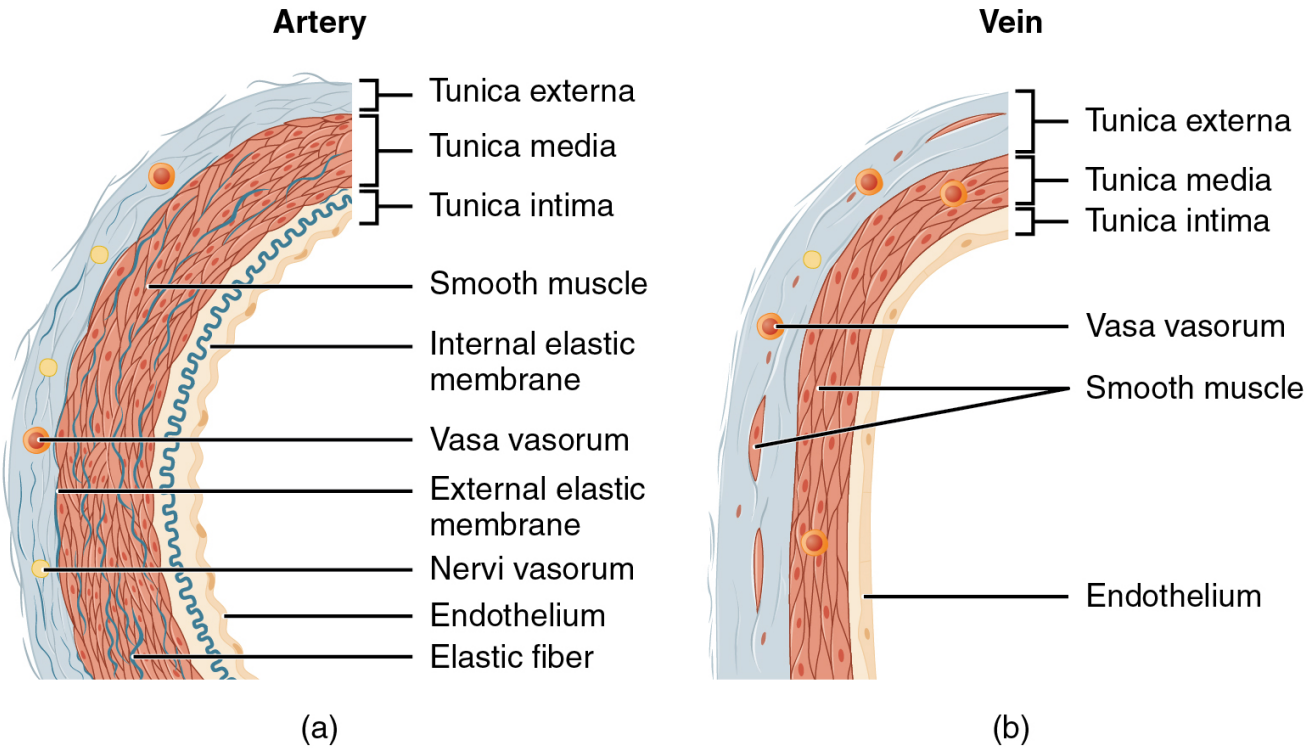
Arteries and veins transport blood in two distinct circuits: the ***systemic circuit*** and the ***pulmonary circuit***. ***Systemic arteries*** provide blood rich in oxygen to the body's tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has been delivered to the cells. In contrast, in the ***pulmonary circuit***, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.



Cardiovascular Circulation – *The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.*

Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. **Arteries** and **arterioles** have ***thicker walls*** than **veins** and **venules** because they are closer to the heart and receive blood that is surging at a far greater pressure). Each type of vessel has a **lumen**—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls and smaller diameters give arterial lumens a more rounded appearance in cross-section than the lumens of veins.


Artery
Tunica externa
Tunica media
Tunica intima
Smooth muscle
Internal elastic membrane
Vasa vasorum
External elastic membrane
Nervi vasorum
Endothelium
Elastic fiber
(a)
Vein
Tunica externa
Tunica media
Tunica intima
Vasa vasorum
Smooth muscle
Endothelium
(b)


Vein
Artery

(c)

Structure of Blood Vessels *(a) Arteries and (b) veins share the same general features, but the walls of arteries are much thicker because of the higher pressure of the blood that flows through them. (c) A micrograph shows the relative differences in thickness. LM × 160. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)*

In comparison to arteries, veins and venules withstand a much lower blood pressure, which is morphologically reflected in thinner walls and larger lumens. These adaptations allow for large volumes of blood to flow with less vessel resistance. Additionally, some veins in the limbs contain valves that assist the unidirectional flow, which is challenging in the extremities due to lower pressure and gravity.

Larger arteries and veins contain small blood vessels within their walls known as the **vasa vasorum**—literally "vessels of the vessel". Vasa vasorum are located in the outer layers of the vessel (Figure 2) and provide nutrients and allow for waste exchange for the cells and tissues composing the blood vessel wall. There are also minute nerves (known as **nervi vasorum** within the walls of both types of vessels that control the contraction and dilation of smooth muscle.

Both arteries and veins have the same three distinct tissue layers, called tunics. From the most interior layer to the outer, these tunics are the **tunica intima**, the **tunica media**, and the **tunica externa**.

Comparison of tunics within arteries and veins

	Arteries	**Veins**
General appearance	Thick walls with small lumens, appear rounded	Thin walls with large lumens, appear flattened
Tunica intima	Endothelium appears wavy due to constriction of smooth muscle. Internal elastic membrane present in larger vessels.	Endothelium appears smooth. Internal elastic membrane absent.
Tunica media	**Normally the thickest layer in arteries.** Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart). External elastic membrane present in larger vessels.	**Normally thinner than the tunica externa.** Smooth muscle cells and collagenous fibers predominate. Nervi vasorum and vasa vasorum present. External elastic membrane absent.
Tunica externa	**Normally thinner than the tunica media in all but the largest arteries.** Collagenous and elastic fibers. Nervi vasorum and vasa vasorum present.	**Normally the thickest layer in veins.** Collagenous and smooth fibers predominate. Some smooth muscle fibers. Nervi vasorum and vasa vasorum present.

Tunica Intima

The **tunica intima** (also called the tunica interna) is composed of epithelial (***endothelium***) and ***connective tissue*** layers.

- **endothelium** is the specialized **simple squamous epithelium**, makes up the lining of the blood vessel lumen and is continuous throughout the vascular system, including the heart. The permeable basement membrane is located underneath endothelium and provides strength while maintaining flexibility.
- thin layer of connective tissue that contains elastic and collagen fibers.

In larger arteries, there is also a thick, distinct layer of elastic fibers known as the **internal elastic membrane** (also called the internal elastic lamina) at the boundary with the tunica media. Like the other components of the tunica intima, the internal elastic membrane provides structure while allowing the vessel to stretch.

Under the microscope, the lumen and the entire tunica intima of a vein will appear smooth, whereas those of an artery

will normally appear wavy because of the partial constriction of the smooth muscle in the tunica media, the next layer of blood vessel walls.

Tunica Media

The tunica media is the thickest layer in arteries and consists of smooth muscle layers and connective tissue that is made up of elastic fibers, which appear wavy in histological slides.

Contraction and relaxation of the circular muscles decrease and increase the diameter of the vessel lumen, respectively. Specifically in arteries, **vasoconstriction** decreases blood flow as the smooth muscle in the walls of the tunica media contracts, making the lumen narrower and increasing blood pressure. Similarly, **vasodilation** increases blood flow as the smooth muscle relaxes, allowing the lumen to widen and blood pressure to drop. Both vasoconstriction and vasodilation are regulated in part by **nervi vasorum**.

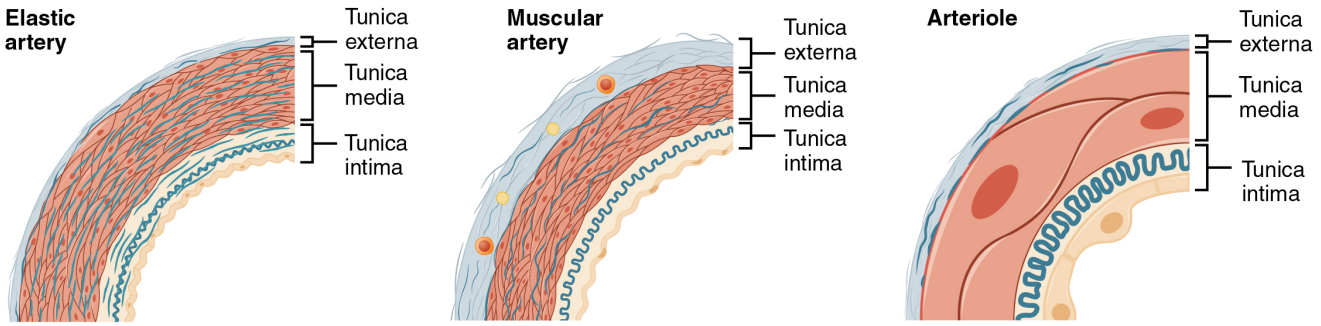
Separating the tunica media from the outer tunica externa in larger arteries is the **external elastic membrane** (also called the external elastic lamina). This structure is not usually seen in smaller arteries, nor is it seen in veins.

Tunica Externa

The outer tunic, the tunica externa (also called the tunica adventitia), is a substantial sheath of connective tissue composed primarily of collagenous fibers and some elastic fibers. The tunica externa in veins also contains groups of smooth muscle fibers. ***This is normally the thickest tunic in veins*** and may be thicker than the tunica media in some larger arteries. The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position. If you are able to palpate some of the superficial veins on your upper limbs and try to move them, you will find that the tunica externa prevents this. If the tunica externa did not hold the vessel in place, any movement would likely result in disruption of blood flow.

Arteries

An artery is a blood vessel that conducts blood away from the heart. All arteries have relatively thick walls that can withstand the high pressure of blood ejected from the heart. However, those close to the heart have the thickest walls, containing a ***high percentage of elastic fibers in all three of their tunics***. This type of artery is known as an **elastic artery**).. Vessels larger than 10 mm in diameter are typically elastic. Their abundant elastic fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to recoil after the surge has passed. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a ***conducting artery***, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.



Types of Arteries and Arterioles – *Comparison of the walls of an elastic artery, a muscular artery, and an arteriole is shown. In terms of scale, the diameter of an arteriole is measured in micrometers compared to millimeters for elastic and muscular arteries.*

Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery's tunica intima decreases and the amount of smooth muscle in its tunica media increases. The artery at this point is described as a **muscular artery**. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in **vasoconstriction**. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no "line of demarcation" where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

Arterioles

An arteriole is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin.

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as ***resistance vessels***.

Capillaries

A capillary is a microscopic channel that supplies blood to the tissues themselves, a process called **perfusion**. Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through. Flow through capillaries is often described as **microcirculation**.

The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth

muscle fibers. There is some variation in wall structure: In a large capillary, several endothelial cells bordering each other may line the lumen; in a small capillary, there may be only a single cell layer that wraps around to contact itself.

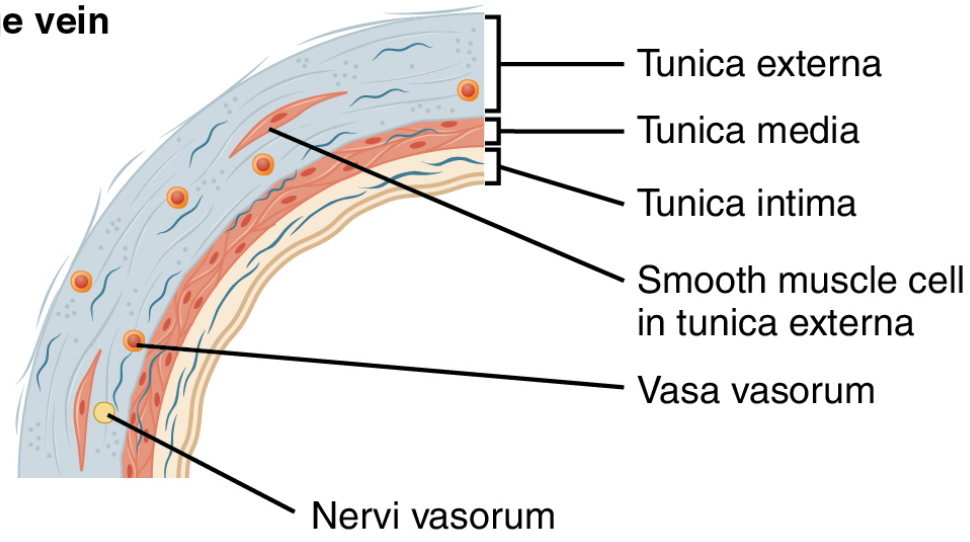
Venules

A venule is an extremely small vein, generally 8–100 micrometers in diameter. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa. Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

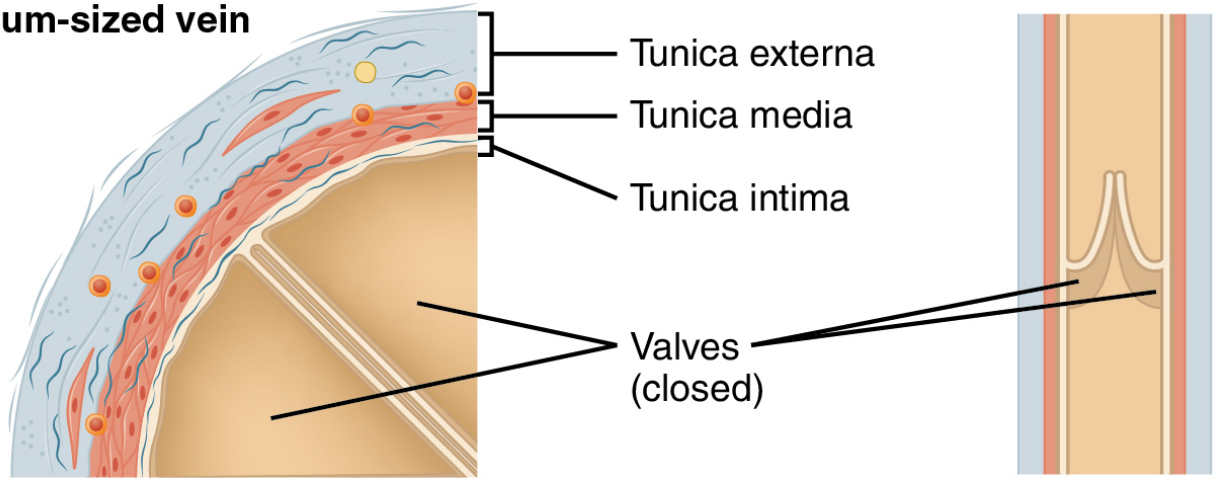
Veins

A vein is a blood vessel that conducts blood toward the heart. Compared to arteries, veins are thin-walled vessels with large and irregular lumens. Because they are low-pressure vessels, larger veins are commonly equipped with valves that promote the unidirectional flow of blood toward the heart and prevent backflow toward the capillaries caused by the inherent low blood pressure in veins as well as the pull of gravity.

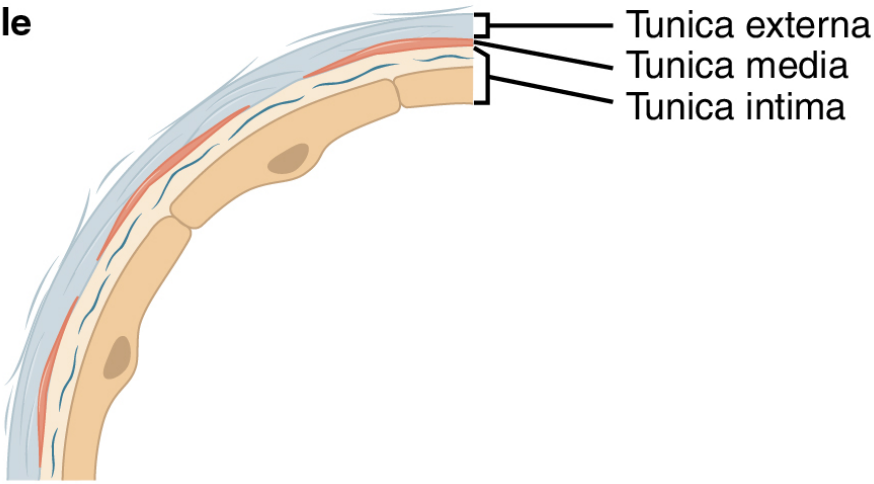
Large vein



Medium-sized vein



Venule



Comparison of Veins and Venules – *Many veins have valves to prevent back flow of blood, whereas venules do not. In terms of scale, the diameter of a venule is measured in micrometers compared to millimeters for veins.*

Comparison of Arteries and Veins

	Arteries	Veins
Direction of blood flow	Conducts blood away from the heard	Conducts blood toward the heard
General appearance	Rounded	Irregular, often collapsed
Pressure	High	Low
Wall thickness	Thick	Thin
Relative oxygen concentration	Higher in systemic arteries	Lower in systemic vein
	Lower in pulmonary arteries	Higher in pulmonary veins
Valves	Not present	Present most commonly in limbs and in veins inferior to the heart

Career Connection

Vascular Surgeons and Technicians Vascular surgery is a specialty in which the physician deals primarily with diseases of the vascular portion of the cardiovascular system. This includes repair and replacement of diseased or damaged vessels, removal of plaque from vessels, minimally invasive procedures including the insertion of venous catheters, and traditional surgery. Following completion of medical school, the physician generally completes a 5-year surgical residency followed by an additional 1 to 2 years of vascular specialty training. In the United States, most vascular surgeons are members of the Society of Vascular Surgery.

Vascular technicians are specialists in imaging technologies that provide information on the health of the vascular system. They may also assist physicians in treating disorders involving the arteries and veins. This profession often overlaps with cardiovascular technology, which would also include treatments involving the heart. Although recognized by the American Medical Association, there are currently no licensing requirements for vascular technicians, and licensing is voluntary. Vascular technicians typically have an Associate's degree or certificate, involving 18 months to 2 years of training. The United States Bureau of Labor projects this profession to grow by 29 percent from 2010 to 2020.

Visit this site to learn more about vascular surgery.

Visit this site to learn more about vascular technicians.

Section Review

Blood pumped by the heart flows through a series of vessels known as arteries, arterioles, capillaries, venules, and veins before returning to the heart. Arteries transport blood away from the heart and branch into smaller vessels, forming

arterioles. Arterioles distribute blood to capillary beds, the sites of exchange with the body tissues. Capillaries lead back to small vessels known as venules that flow into the larger veins and eventually back to the heart.

The arterial system is a relatively high-pressure system, so arteries have thick walls that appear round in cross-section. The venous system is a lower-pressure system, containing veins that have larger lumens and thinner walls. They often appear flattened. Arteries, arterioles, venules, and veins are composed of three tunics known as the **tunica intima**, **tunica media**, and **tunica externa**. Capillaries have only a tunica intima layer. The tunica intima is a thin layer composed of a simple squamous epithelium known as **endothelium** and a small amount of connective tissue. The tunica media is a thicker area composed of variable amounts of smooth muscle and connective tissue. It is the thickest layer in all but the largest arteries. The tunica externa is primarily a layer of connective tissue, although in veins, it also contains some smooth muscle. Blood flow through vessels can be dramatically influenced by **vasoconstriction** and **vasodilation** in their walls.

Review Questions

1. The endothelium is found in the:

- Tunica intima
- Tunica media
- Tunica adventitia
- Lumen

2. Closer to the heart, arteries would be expected to have a higher percentage of:

- Endothelium
- Smooth muscle fibres
- Elastin fibers
- Collagen fibers

3. Which of the following best describes veins?

- Thick walled, small lumens, low pressure, lack valves
- Thin walled, large lumens, low pressure, have valves
- Thin walled, small lumens, high pressure, have valves
- Thick walled, large lumens, high pressure, lack valves

Answer Key

1. Tunica intima
2. Elastin fibers
3. Thin walled, large lumens, low pressure, have valves

Adaption

This chapter is adapted from the following text:

Structure and function of blood vessels **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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Blood Flow and Blood Pressure

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Distinguish between systolic pressure, diastolic pressure, pulse pressure, and mean arterial pressure.
- Describe the clinical measurement of blood pressure.
- Identify and discuss five variables affecting arterial blood flow and blood pressure.

Blood flow refers to the movement of blood through a vessel, tissue, or organ, and is usually expressed in terms of volume of blood per unit of time. It is initiated by the contraction of the **ventricles** of the heart. Ventricular contraction ejects blood into the major arteries, resulting in flow from regions of higher pressure to regions of lower pressure, as blood encounters smaller arteries and arterioles, then capillaries, then the venules and veins of the venous system. This section discusses a number of critical variables that contribute to blood flow throughout the body. It also discusses the factors that impede or slow blood flow, a phenomenon known as **resistance**.

As noted earlier, hydrostatic pressure is the force exerted by a fluid due to gravitational pull, usually against the wall of the container in which it is located. One form of hydrostatic pressure is **blood pressure**, the force exerted by blood upon the walls of the blood vessels or the chambers of the heart. Blood pressure may be measured in capillaries and veins, as well as the vessels of the pulmonary circulation; however, the term blood pressure without any specific descriptors typically refers to systemic arterial blood pressure—that is, the pressure of blood flowing in the arteries of the systemic circulation. In clinical practice, this pressure is measured in mm Hg and is usually obtained using the brachial artery of the arm.

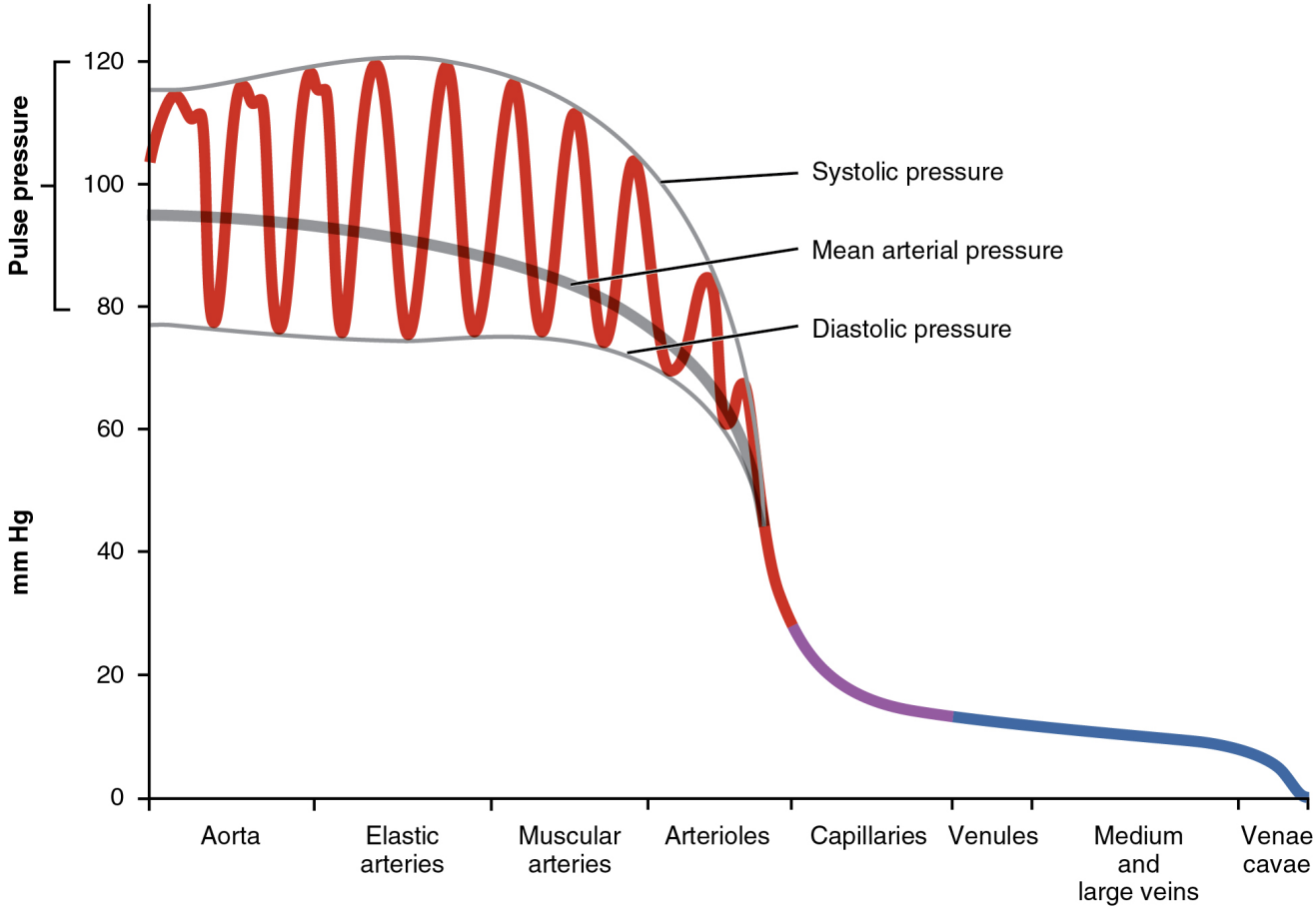
Components of Arterial Blood Pressure

Arterial blood pressure in the larger vessels consists of several distinct components: systolic and diastolic pressures, pulse pressure, and mean arterial pressure.

Systolic and Diastolic Pressures

When systemic arterial blood pressure is measured, it is recorded as a ratio of two numbers (e.g., 120/80 is a normal adult blood pressure), expressed as systolic pressure over diastolic pressure. The systolic pressure is the higher value (typically around 120 mm Hg) and reflects the arterial pressure resulting from the ejection of blood during ventricular

contraction, or **systole**. The diastolic pressure is the lower value (usually about 80 mm Hg) and represents the arterial pressure of blood during ventricular relaxation, or **diastole**.



Systemic Blood Pressure – *The graph shows the components of blood pressure throughout the blood vessels, including systolic, diastolic, mean arterial, and pulse pressures.*

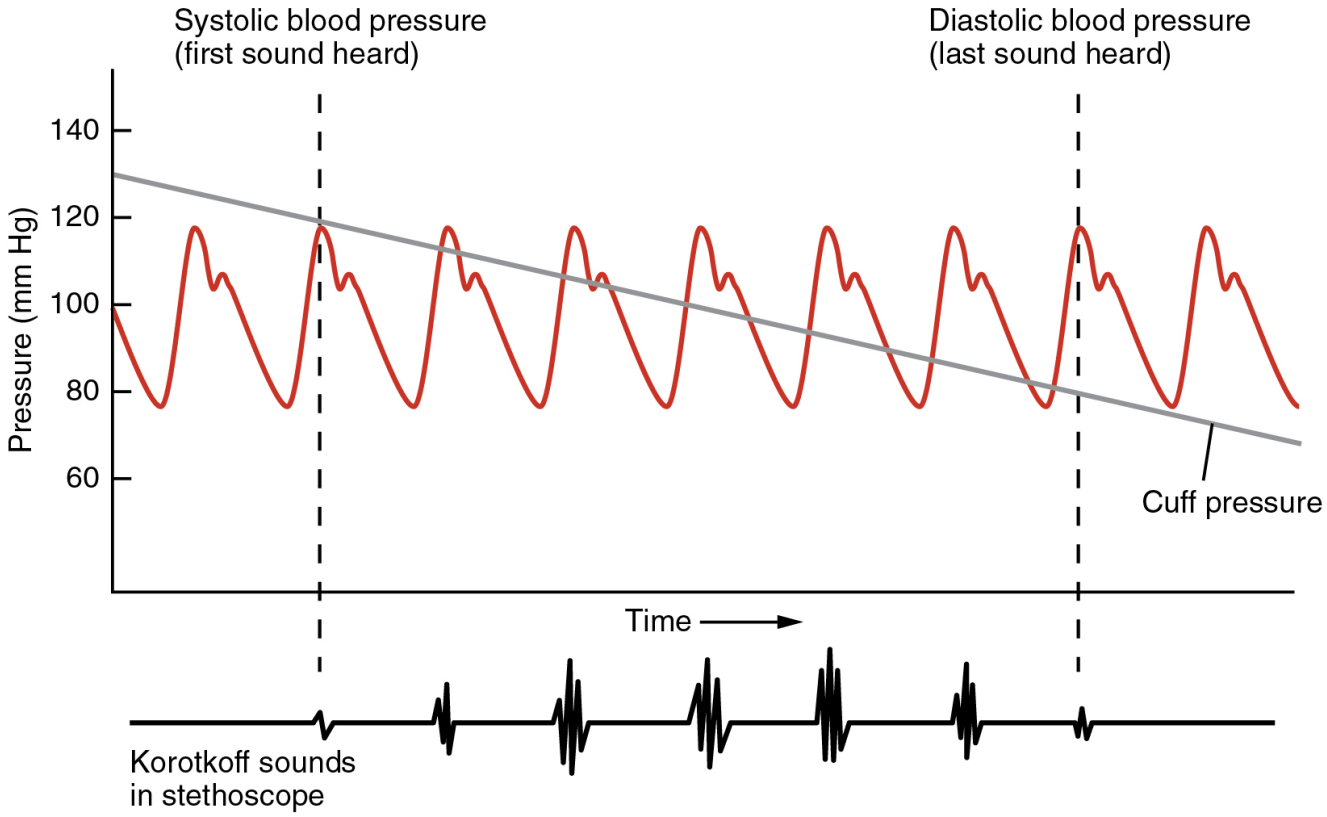
Measurement of Blood Pressure

Blood pressure is one of the critical parameters measured on virtually every patient in every healthcare setting. The technique used today was developed more than 100 years ago by a pioneering Russian physician, Dr. Nikolai Korotkoff. Turbulent blood flow through the vessels can be heard as a soft ticking while measuring blood pressure; these sounds are known as Korotkoff sounds. The technique of measuring blood pressure requires the use of a **sphygmomanometer** (a blood pressure cuff attached to a measuring device) and a stethoscope. The technique is as follows:

- The clinician wraps an inflatable cuff tightly around the patient's arm at about the level of the heart.
- The clinician squeezes a rubber pump to inject air into the cuff, raising pressure around the artery and temporarily cutting off blood flow into the patient's arm.
- The clinician places the stethoscope on the patient's antecubital region and, while gradually allowing air within the cuff to escape, listens for the Korotkoff sounds.

Although there are five recognized Korotkoff sounds, only two are normally recorded. Initially, no sounds are heard since there is no blood flow through the vessels, but as air pressure drops, the cuff relaxes, and blood flow returns to

the arm. As shown below, the first sound heard through the stethoscope—the first Korotkoff sound—indicates **systolic pressure**. As more air is released from the cuff, blood is able to flow freely through the brachial artery and all sounds disappear. The point at which the last sound is heard is recorded as the patient's **diastolic pressure**.



Blood Pressure *– Measurement When pressure in a sphygmomanometer cuff is released, a clinician can hear the Korotkoff sounds. In this graph, a blood pressure tracing is aligned to a measurement of systolic and diastolic pressures.*

The majority of hospitals and clinics have automated equipment for measuring blood pressure that work on the same principles. An even more recent innovation is a small instrument that wraps around a patient's wrist. The patient then holds the wrist over the heart while the device measures blood flow and records pressure.

Variables Affecting Blood Flow and Blood Pressure

Five variables influence blood flow and blood pressure:

- ***Cardiac output***: increase in heart rate or **stroke volume** will elevate blood pressure and promote blood flow, decrease in cardiac output will decrease arterial pressure and blood flow.
- ***Compliance***: veins are more compliant than arteries and can expand to hold more blood. Stiffness of arteris due to vascular disease reduces compliance and increases pressure within the vessel. This also increases the work of the heart.
- ***Volume of the blood*** – **hypovolemia** (can be caused by bleeding, dehydration, vomiting, etc) lowers blood pressure, **hypervolemia** (can be caused by heart failure, liver cirrhosis, kidney disease) elevates blood pressure.
- ***Viscosity of the blood*** – determined by formed elements (erythrocytes, etc) and plasma proteins. Anemia or liver

conditions can decrease viscosity, decrease resistance, and increase blood flow.
- ***Blood vessel length and diameter*** – the length of a vessel is directly proportional to its **resistance**: the longer the vessel, the greater the resistance and the lower the flow. The effect of diameter on resistance is inversely related to the resistance and flow.

Section Review

Blood flow is the movement of blood through a vessel, tissue, or organ. The slowing or blocking of blood flow is called resistance. Blood pressure is the force that blood exerts upon the walls of the blood vessels or chambers of the heart. The components of blood pressure include systolic pressure, which results from ventricular contraction, and diastolic pressure, which results from ventricular relaxation. Pulse pressure is the difference between systolic and diastolic measures, and mean arterial pressure is the "average" pressure of blood in the arterial system, driving blood into the tissues. Pulse, the expansion and recoiling of an artery, reflects the heartbeat. The variables affecting blood flow and blood pressure in the systemic circulation are cardiac output, compliance, blood volume, blood viscosity, and the length and diameter of the blood vessels. In the arterial system, vasodilation and vasoconstriction of the arterioles is a significant factor in systemic blood pressure: Slight vasodilation greatly decreases resistance and increases flow, whereas slight vasoconstriction greatly increases resistance and decreases flow. In the arterial system, as resistance increases, blood pressure increases and flow decreases. In the venous system, constriction increases blood pressure as it does in arteries; the increasing pressure helps to return blood to the heart. In addition, constriction causes the vessel lumen to become more rounded, decreasing resistance and increasing blood flow. Venoconstriction, while less important than arterial vasoconstriction, works with the skeletal muscle pump, the respiratory pump, and their valves to promote venous return to the heart.

Review Questions

1. In a blood pressure measurement of 110/70, the number 70 is the:

- Systolic pressure
- Diastolic pressure
- Pulse pressure
- Mean arterial pressure

2. A healthy elastic artery:

- Is compliant
- Reduces blood flow
- Is a resistance artery
- Has a thin wall and irregular lumen

3. Increased heart rate can result in increased blood pressure.

- True

- False

4. Fill in the blanks.

_____ of arteries due to vascular disease or atherosclerosis can _____ blood pressure.

Answer Key

1. Diastolic pressure
2. Is compliant
3. True
4. Stiffness, increase/elevate

Adaption

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Blood flow, pressure & resistance **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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Gross Anatomy and Histology of Normal Aorta

TETIANA POVSHEDNA

Learning Objectives

By the end of this chapter, you will be able to:

- Compare and contrast the main histological features of tissues that can be identified via H&E and elastic/trichrome stains.
- Identify three main layers (tunics) in the wall of the aorta and their main components.
- Relate the structural features of aorta to its function.

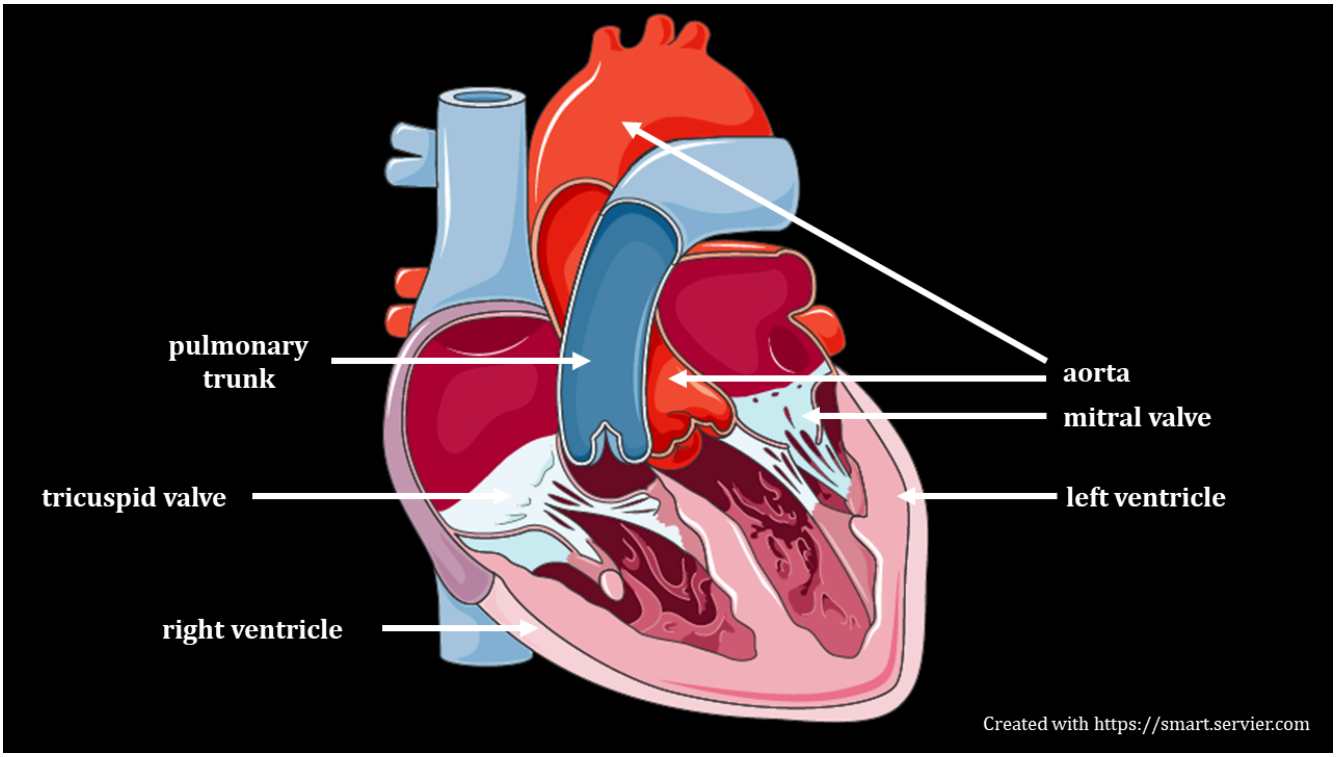
Arteries are blood vessels that transport and distribute oxygenated blood from the heart to all the organs in the body (*with one exception – pulmonary arteries transport deoxygenated blood from the heart to the lungs for gas exchange as a part of pulmonary circle*). The **aorta**, which originates from the aortic valve in the left ventricle, is the largest artery in the human body. Arteries are responsible for regulating blood pressure, which morphologically translates into a thick smooth muscle layer that facilitates contraction and dilatation in response to physiological stimuli.

Aorta is a unique example of an **elastic artery** and contains a lot of elastic fibers within its wall that allow for a large variation of the **lumen** size.

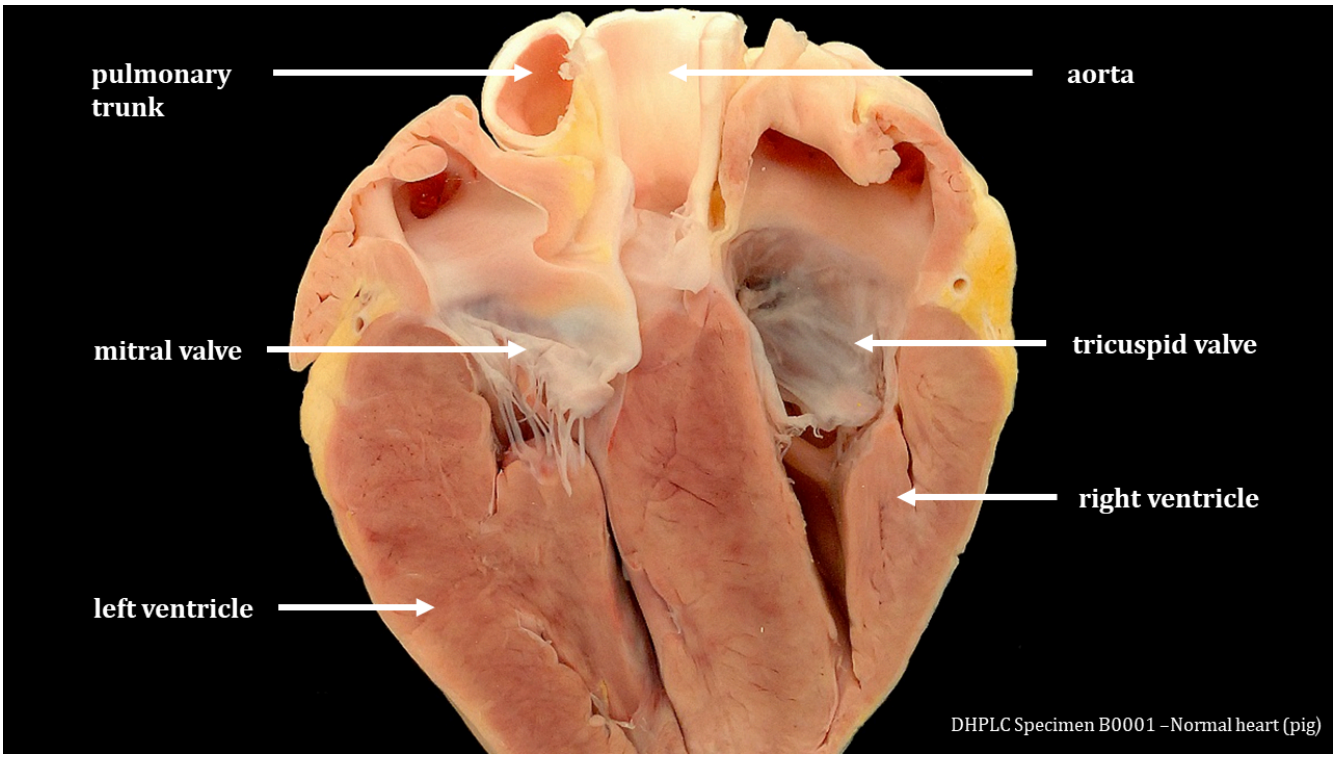
One the ***gross anatomy*** specimen that features **ascending aorta**, identify:

- smooth luminal surface, which is required for uninterrupted blood flow;
- wide diameter (around 20-30 mm in **ascending aorta**), necessary for allowing large volumes of oxygenated blood to be conducted from the heart into the vascular tree;
- thick walls (2-3 mm in the ascending aorta), which reflect high blood pressure in the aorta;
- color: aorta appears yellow/white due to a high amount of connective tissue fibers (collagen, elastin).

Please note: the classic depiction of normal heart anatomy usually examines the heart chambers and vessels from the anterior side. In this gross anatomy specimen, however, the heart chambers and vessels are examined from the posterior side. Thus, the left ventricle is on the left, and the aorta is in front of the **pulmonary trunk**.



Normal Heart Anatomy



DHPLC Specimen B0001 *Normal heart anatomy (pig). All rights reserved*

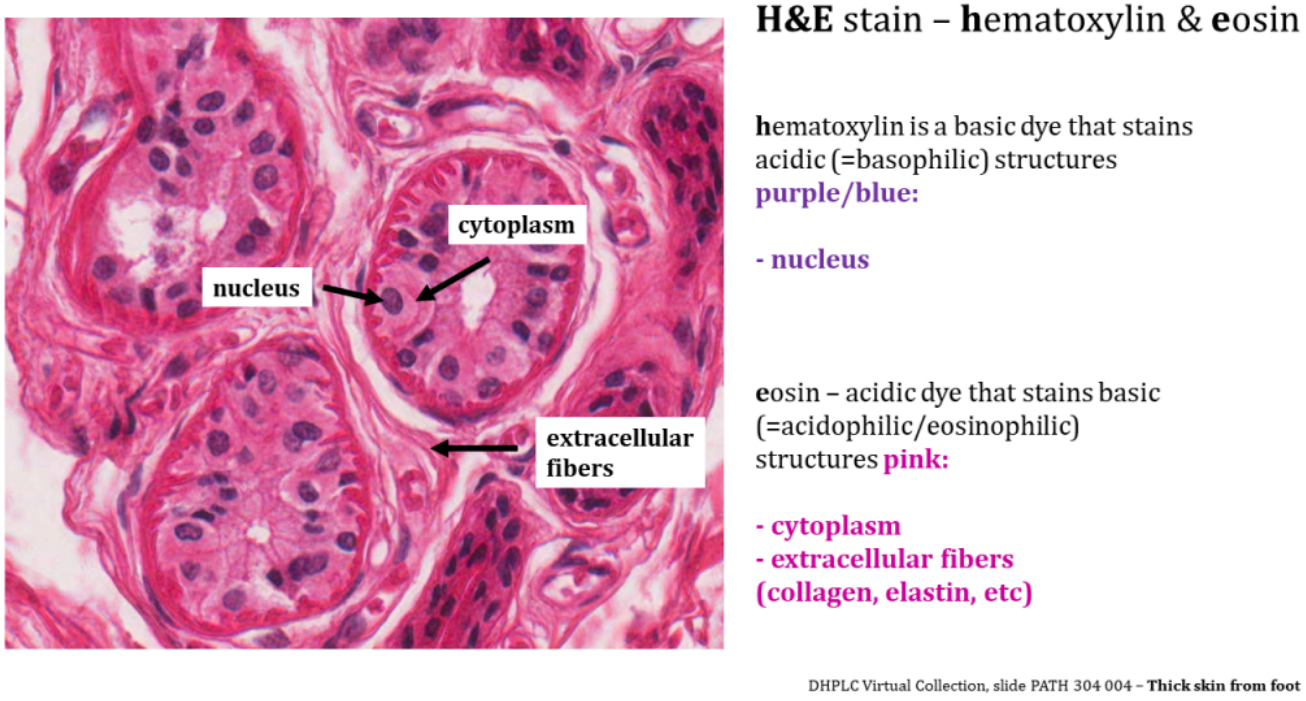
Histology of the Aorta

Before examining the histological sections of a normal human aorta, it is important to consider commonly used histological stains and their interpretation.
Generally, the stains are divided into non-specific, the ones that use dyes that stain all the cells within tissue in a similar manner, and special – the ones that use dyes that selectively bind to specific tissue/cell components.

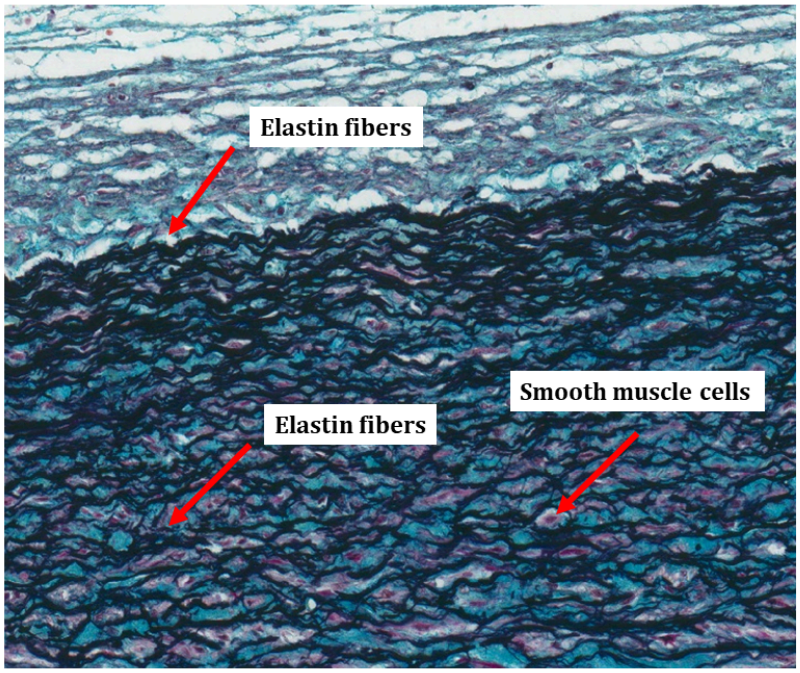
This section will examine the normal histology of the human aorta using histology slides stained with **hematoxylin** & **eosin** (***H&E, non-specific***) and ***elastin/trichrome (special)*** stains.

Please refer to the sections How Are the Specimens Obtained and Prepared? and Video Lessons on Histology to learn more about the stains and histology slide preparation.

H&E Stain Interpretation



DHPLC *e-slide* PATH 304 004 *Thick Skin Foot. All rights reserved*



Elastin/trichrome stain

Special stain to visualize connective tissue

Useful to visualize ***elastin fiber distribution*** within the wall of blood vessels

nuclei, elastin/collagen – **blue**/**black**,

muscle – **red**/**dark pink**

DHPLC Virtual Collection, slide PATH 304 024– **Normal Aorta**

DHPLC *e-slide* PATH 304 – 024 *Elastin/trichome stain of normal aorta. All rights reserved*

To better understand changes that occur in the blood vessel wall during the development of atherosclerosis, it's critical to understand the normal histology of large blood vessels.
Even though the morphology of blood vessels of different sizes and types (**arteries**, **veins**, **capillaries**) exhibits functional adaptations that reflect the location of a blood vessel and local blood pressure, the main features of the blood vessel wall remain the same across various types.

The wall of the aorta consists of 3 layers (tunics):

1. ***Tunica intima*** – thin innermost layer that includes:

a) **Endothelium** – a single layer of epithelial cells that forms the luminal surface of the vessel and is in direct contact with blood. Endothelium within the wall of blood vessels is continuous with the **endocardium** – the inner lining of the heart;

b) **Loose connective tissue** – a thin layer of connective tissue located under **endothelium**

2. ***Tunica media*** – the thickest layer in the aorta, includes:

a) Smooth muscle cells that allow for contraction and relaxation;

b) **Elastin fibers** that further expand the ability of aorta to dilate and contract; in aorta, numerous elastin fibers are located within tunica media, and some within tunica intima;

c) Connective tissue fibers and nerves.

3. ***Tunica adventitia*** -the outermost layer that includes:

a) Connective tissue for structural support and protection;

b) Nerve fascicles (**nervi vasorum**) and blood vessels (**vasa vasorum**) that supply and innervate the wall of the aorta

As an elastic artery, aorta contains a large amount of elastic fibers within the tunica media. This amount of elastin allows aorta to expand and recoil in response to blood pressure fluctuations (*similarly to how an elastic band behaves*) and conduct large volumes of blood that's ejected from the heart under high pressure.

In addition to being present within tunica media, elastin fibers also form two structures on the border between tunics:

a) Internal elastic lamina – on the border between tunica intima and tunica media;

b) External elastic lamina – on the border between tunica media and tunica adventitia

Both elastic laminas are thick bands of elastin fibers that appear wavy on the histological slide, which reflects the properties of elastin in a relaxed state. Elastic laminas are more easily identified in smaller arteries, where elastin fibers are located only within the laminas. In the aorta, which has numerous elastin fibers within tunica media, elastic laminas would be the fibers on the border between the tunics.



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=645#h5p-183

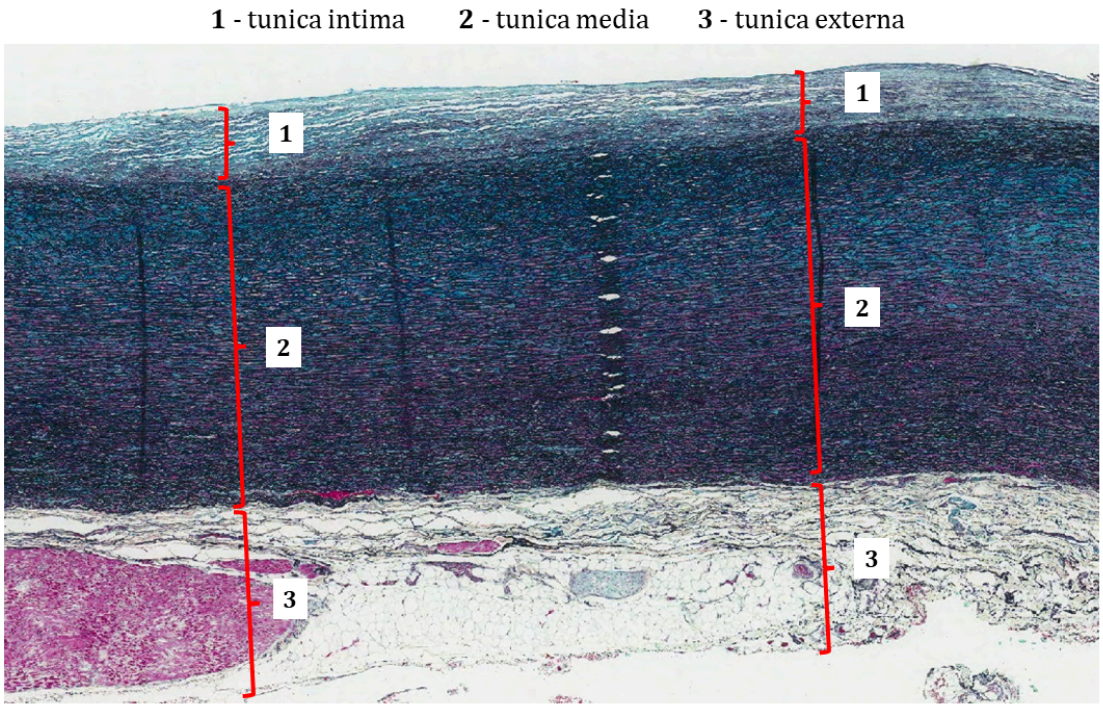
***Normal histology of aorta**. Created and presented by Tetiana Povshedna. Histology slides are DHPLC specimens PATH 304-023 (H&E) and PATH 304-024 (elastin/trichome). Illustrations were created under license with Biorender.com.*

Compare and Contrast the Histological Appearance of 3 Tunics in Various Blood Vessel Types

Please note the variation in the thickness of tunica media and the amount of elastic fibers between the two large vessels – aorta and vena cava.

These morphological adaptations reflect blood vessel location and blood pressure levels – both thickness of tunica media and amount of elastin fibers decrease in veins and venules compared to arteries. Note that **tunica media** is the thickest layer in aorta, but not in vena cava. **Tunica externa** of the **vena cava** is the thickest layer that also contains some smooth muscle fibers.

Aorta

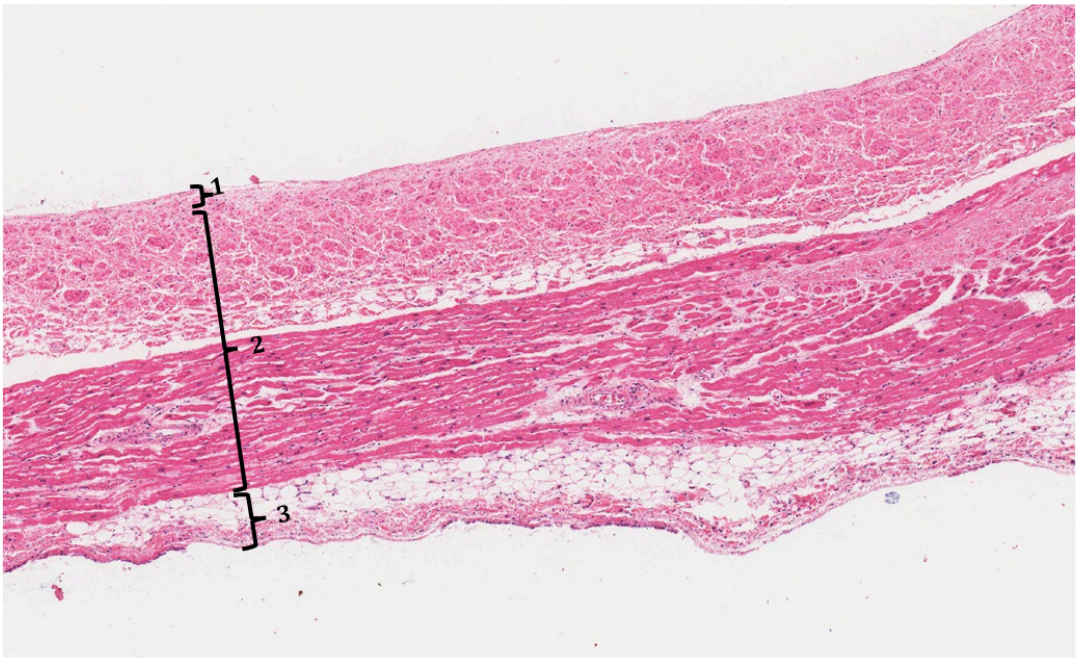


DHPLC Virtual Collection, slide PATH 304 024– **Normal Aorta**

***DHPLC e-slide* PATH 304-024** *Elastin/trichome stain of normal aorta. All rights reserved*

Vena Cava

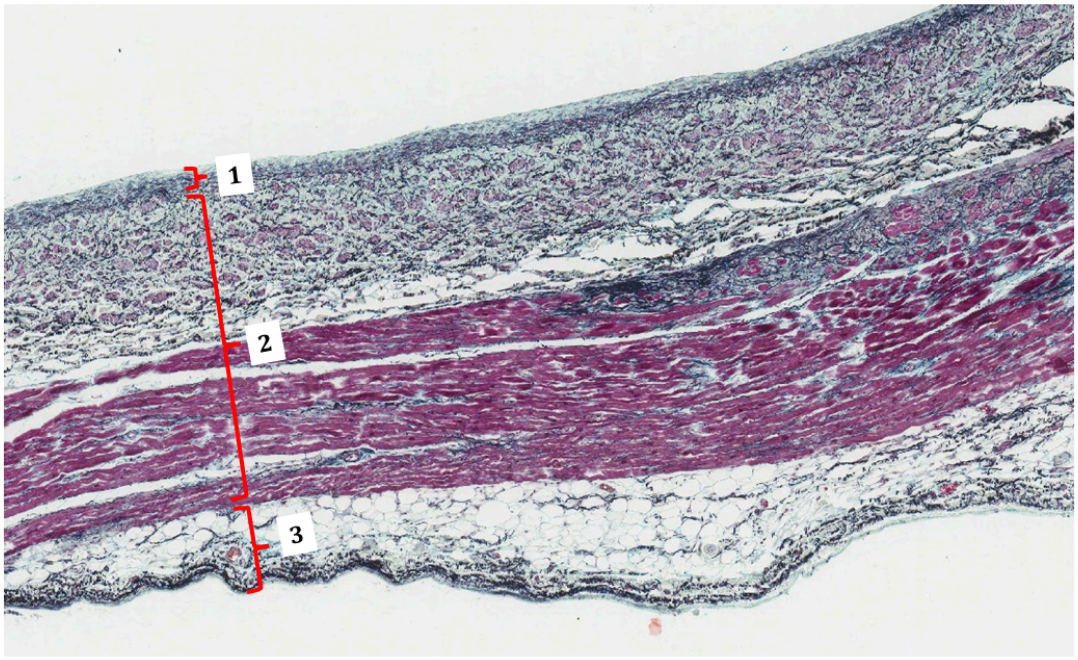
1 - tunica intima **2** - tunica media **3** - tunica externa



DHPLC Virtual Collection, slide PATH 304 025 – **Vena Cava**

***DHPLC e-slide* PATH 304 025** *H & E stain of vena cava. All rights reserved*

1 - tunica intima **2** - tunica media **3** - tunica externa



DHPLC Virtual Collection, slide PATH 304 026 – **Vena Cava**

DHPLC *e-slide* PATH 304 026 *Elastin/trichrome stain of vena cava. All rights reserved*

Section Review

Blood vessels across the vascular tree share a similar histological structure – their wall consists of three layers (also known as tunics). The thickness and characteristics of these layers (**tunica intima**, **tunica media**, **tunica externa**) vary depending on the blood vessel type (*artery vs vein*) and location (*closer or further from the heart*). Aorta, a major vessel that carries oxygenated blood from the heart and distributes it to organs and tissues, is an **elastic artery** that contains numerous elastic fibers across the layers, with the majority of them accumulated within the middle muscular layer (tunica media). This histological feature allows aorta to expand and recoil in response to blood pressure fluctuations, and carry large amounts of oxygenated blood from the heart.

Review Questions

1. Fill in the blanks. Aorta is the largest artery in the human body that carries _____ blood from the heart to tissues and organs.

2. Finish the following sentence. The wall of human aorta consists of three layers (also known as tunics): Select all that apply.

- Tunica interna

- Tunica media
- Tunica intermedialis
- Tunica extra

3. Generally, blood vessels of various types and sizes share a common histological structure.

- True
- False

4. Fill in the blanks.

Tunica _____ is the thickest layer in aorta, while tunica _____ is the thickest layer in vena cava.

5. Finish the following sentence. Large amount of elastic fibers in the tunica media of aorta allows for: Select all that apply.

- Dilation and contraction in response to blood pressure and fluctuations
- Variability of lumen size depending on physiological conditions
- Transport the large volumes of oxygenated blood outside the heart
- Blood pressure regulation
- Pulse variability

Answer Key

1. Oxygenated
2. Tunica interna, tunica externa, tunica media
3. True
4. Media, tunica, externa
5. Dilation and contraction in response to blood pressure fluctuations, variability of lumen size depending on physiological conditions, transport of large volumes of oxygenated blood outside of heart

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Risk Factors and Epidemiology of Atherosclerosis

TETIANA POVSHEDNA

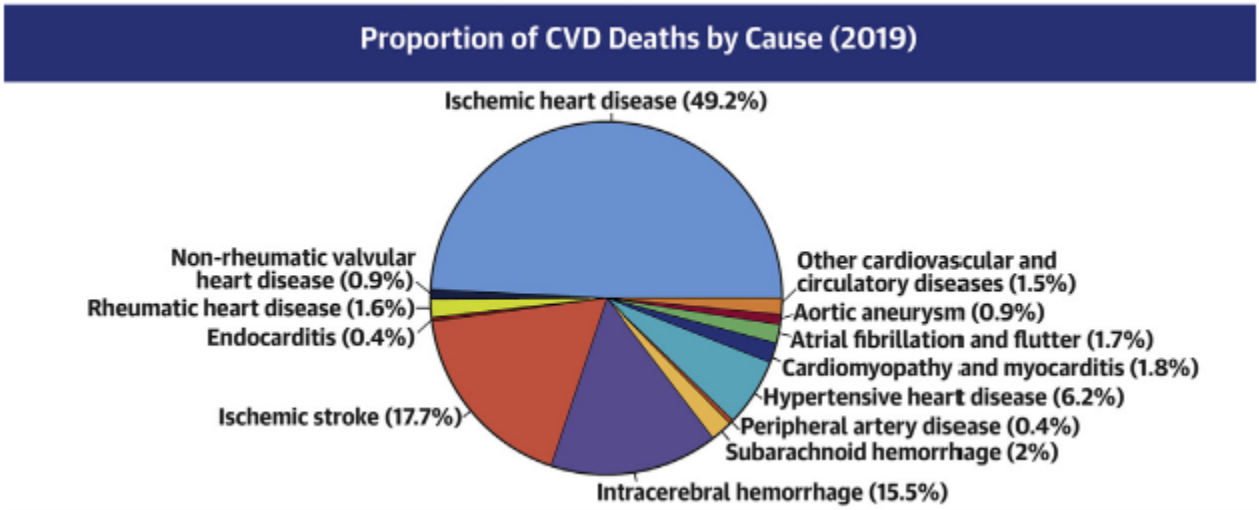
Learning Objectives

By the end of this chapter, you will be able to

- Identify the main modifiable and non-modifiable risk factors for the development of atherosclerosis.
- Describe the key epidemiological trends in the global burden of cardiovascular disease.
- Explain the role of public health measures in decreasing the burden of atherosclerosis.

The latest 2021 World Health Organization report that analyzed epidemiological data from 2019, stated that cardiovascular disease (ischemic heart disease, stroke, peripheral artery disease, etc) remains the ***leading cause of death*** globally. Despite advances in healthcare and medicine, cardiovascular disease-associated disability, prevalence, and mortality continue to increase. Cardiovascular disease rates and prevalence vary between countries and reflect access to healthcare, presence of national prevention programs, prevalence of risk factors, and general aging and growth of the human population. Strikingly, ***3/4 of acute cardiovascular events occur in low- and middle-income countries*** these days.

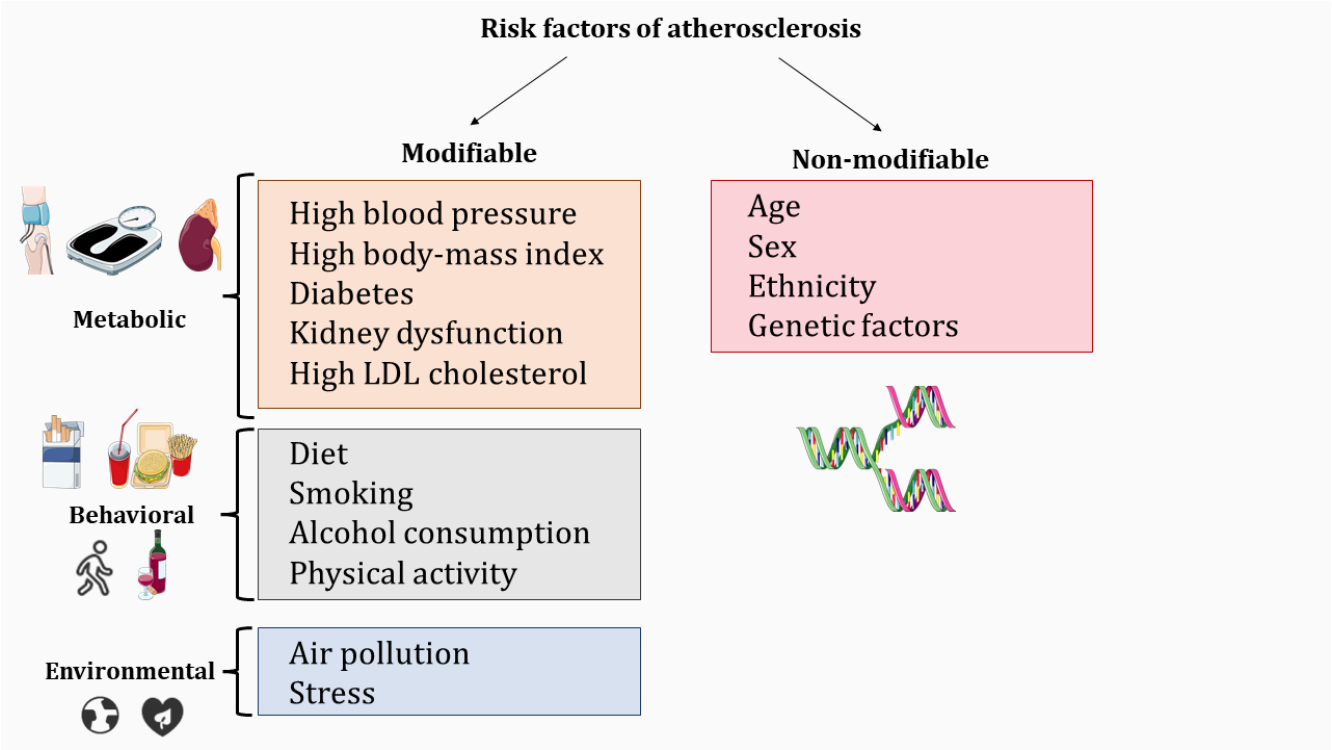
In 2019, cardiovascular disease accounted for 1/3 (17.9 million) deaths in the world, with the majority of them (85%) resulting from ischemic heart disease and stroke. These two acute types of cardiovascular disease are caused by occlusion of blood vessels in the heart/brain, which cuts off blood supply to these regions. The most common underlying reason of this blood flow restriction is ***atherosclerosis***.



Proportion of Cardiovascular Deaths by Cause.

Atherosclerosis is a chronic inflammatory process that involves the accumulation of lipid particles within the vessel walls across the vascular tree (primarily heart, brain, lower limb), which results in acute atherosclerotic cardiovascular disease (**ASCVD**) events, such as heart attack and stroke.

Certain**risk factors** have been identified as associated with increased susceptibility to the development of atherosclerosis.



Risk Factors of Atherosclerosis

Generally, risk factors can be divided into 2 groups:

- **Modifiable** – the ones that can be changed/minimized by targeted interventions
- **Non-modifiable** – the ones that cannot be changed but should be accounted for when estimating the risk of **ASCVD**

Non-modifiable factors include:

- **Age** – the risk of atherosclerosis naturally increases with age as the vascular tree is exposed to risk factors for a longer time;
- **Sex**– men and women experience **ASCVD** differently (before the age of 80, men are more likely to have a heart attack compared to women, but the trend reverses after 80 y.o.; at the same time, women are more likely to experience a stroke compared to men, even in younger age groups). This observation can be partially explained by different exposure of men vs women to some of the modifiable atherosclerosis risk factors (e.g. in some populations men are more likely to smoke, develop type 2 diabetes, and **hypertension** compared to women) or inherent differences between the sexes (hormones). However, a lot of cardiovascular events in younger women (15-20%) occur in the absence of known risk factors, which warrants future research.
- **Ethnicity** – some ethnicities experience a higher burden of type 2 diabetes and hypertension, which might affect increase their risk of ASCVD compared to the general population;
- **Genetic factors** – history of a cardiovascular event (heart attack/stroke in parents or siblings) increases individual risk of atherosclerosis and should be accounted for by healthcare providers

Perspective for future atherosclerosis research

Even though non-modifiable risk factors cannot be changed, they should be considered as independent variables in atherosclerosis research (data for men vs women, as well as different ethnicities, should be analyzed separately; this will allow for the identification of sex/ethnicity-specific trends or risk factors of atherosclerosis that, ultimately, can inform prevention and treatment strategies).

Epidemiological studies should represent the diversity of the global population, include young people, and account for socio-demographic factors (financial stability, employment status, mental health, stress levels)

Modifiable risk factors can be further divided into 3 groups:

1. **Metabolic**

- High blood pressure
- High body-mass index
- Diabetes
- Kidney dysfunction
- High LDL cholesterol

2. **Behavioural**

- Diet
- Smoking
- Alcohol consumption
- Low physical activity

3. **Environmental**

- Air pollution
- Stress

All these factors can be addressed/changed by targeted health behaviour interventions, which will be discussed further in the "Prevention, diagnosis, and treatment of atherosclerosis" section of this chapter.

Stress and Metabolic Health

When trying to understand and identify factors that predict clinical outcomes, it is important to take a holistic look at health and consider not only biological (laboratory/clinical/genetic) variables, but also socio-demographic factors that affect health and aging. The rise in cardiovascular mortality despite advances in healthcare and treatment might reflect an increase in common metabolic disorders over the past 30 years. These include common risk factors for atherosclerosis – liver disease, obesity, and diabetes (a 24% increase in men and women combined). Multiple studies have shown that stress (including childhood adversity) has an adverse impact on metabolic health and can result in 1.1-1.4 times higher risk of obesity, diabetes, and liver disease, as well as accelerated progression of existing metabolic conditions. Factors examined in the studies include home and work-related stress as well as socioeconomic disadvantage, including in childhood.

Thus, not only individual but also governmental efforts (access to healthcare, social protection and support programs, and working conditions) are important for reducing the global burden of atherosclerosis and its consequences.

From: Kivimäki, M., Bartolomucci, A. & Kawachi, I. The multiple roles of life stress in metabolic disorders. *Nat Rev Endocrinol* (2022). https://doi.org/10.1038/s41574-022-00746-8

Section Review

Atherosclerosis, a leading cause of mortality globally, remains a concern despite advancements in research and treatment approaches. Currently, the majority of cardiovascular deaths occur in low/middle-income countries, which highlights the importance of effective primary and secondary prevention strategies, access to healthcare, education, and other social determinants of health. Multiple risk factors have been identified as associated with atherosclerosis.

While modifiable factors (diet, smoking, physical activity, etc) can be changed by behavioural interventions, non-modifiable factors (sex, genetics, ethnicity) should be considered in research and treatment strategies.

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- https://www.sciencedirect.com/science/article/pii/S0735109720377755?via%3Dihub
- https://www.mdpi.com/1422-0067/23/6/3346
- https://www.nature.com/articles/s41574-022-00746-8

Review Questions

1. Acute manifestations of atherosclerosis cannot be prevented.

- True
- False

2. Finish the following sentence. Modifiable risk factors of atherosclerosis include:
Select all that apply.

- Physical activity level
- Sex
- Ethnicity
- Body-mass index

3. Finish the following sentence. Non-modifiable risk factors of atherosclerosis include:
Select all that apply.

- Lipid metabolism parameters
- Diabetes
- Stress levels
- Genetic factors
- Sex

4. Fill in the blanks.

The most common acute outcomes of atherosclerosis are _____ attack and _____.

Answer Key

1. False
2. Physical activity level, body-mass index
3. Genetic factors, sex
4. Heart, stroke

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Digestion and Absorption of Lipids

KARINE HAMM

Learning Objectives

By the end of this chapter you will be able to:

- Describe the main steps of lipid digestion and absorption.
- Explain the importance of lipoproteins (low-density and high-density) in the context of atherosclerosis.

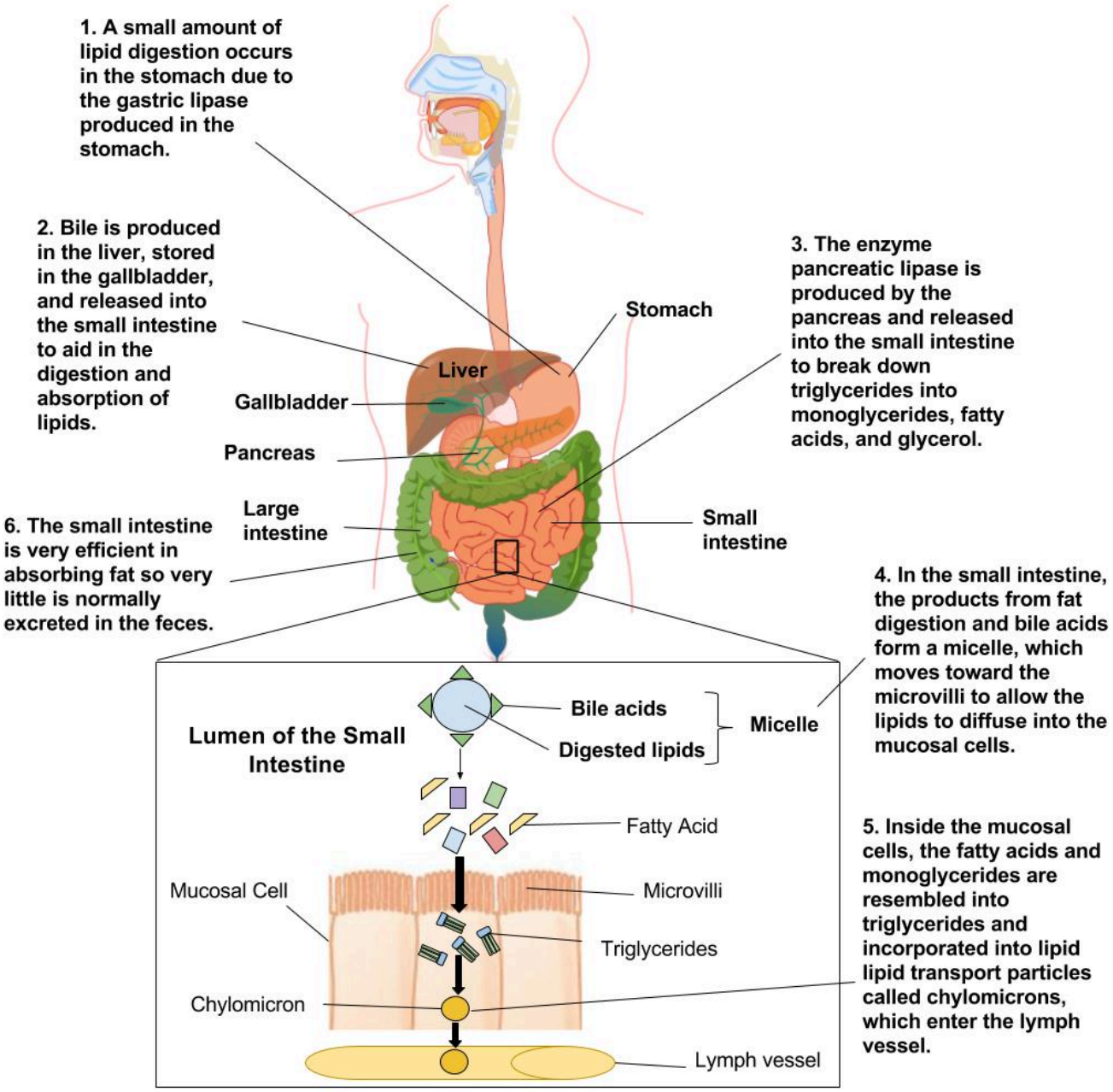
While numerous risk factors can increase the chance of atherosclerosis development, ***lipid deposition*** within the blood vessel wall is at the core of atherosclerosis initiation and progression.
This chapter will discuss key steps of lipid digestion and absorption, which are essential for understanding the pathophysiology of atherosclerosis.

Lipids are large molecules and generally are not water-soluble. Like carbohydrates and protein, lipids are broken into small components for absorption. Since most of our digestive **enzymes** are water-based, how does the body break down fat and make it available for the various functions it must perform in the human body?

Please note that this chapter uses the words "lipids" and "fats" interchangeably.

From the Mouth to the Stomach

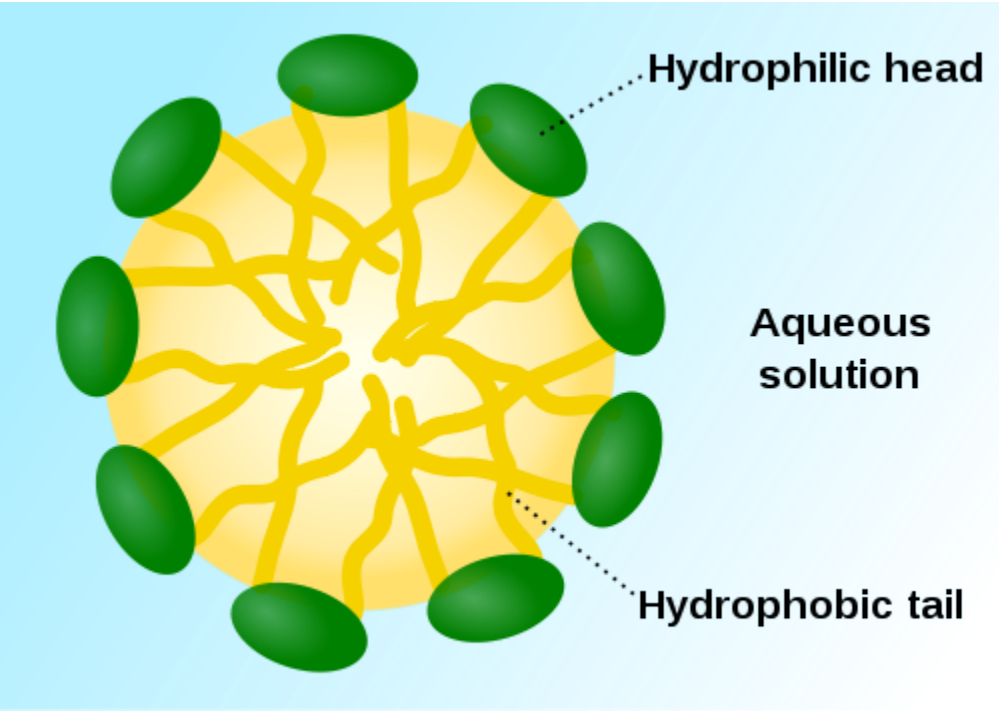
The process of lipid digestion begins in the mouth, where the action of chewing coupled with the action of a special enzyme (***lingual lipase***, which acts as an **emulsifier**) initiates the process. As a result, the fats become tiny droplets and separate from the watery components. Within two to four hours after eating a meal, roughly 30% of the **triglycerides** are converted to diglycerides and fatty acids by the stomach enzyme *gastric lipase*, yet very little fat digestion occurs in the stomach.



Lipid Digestion and Absorption

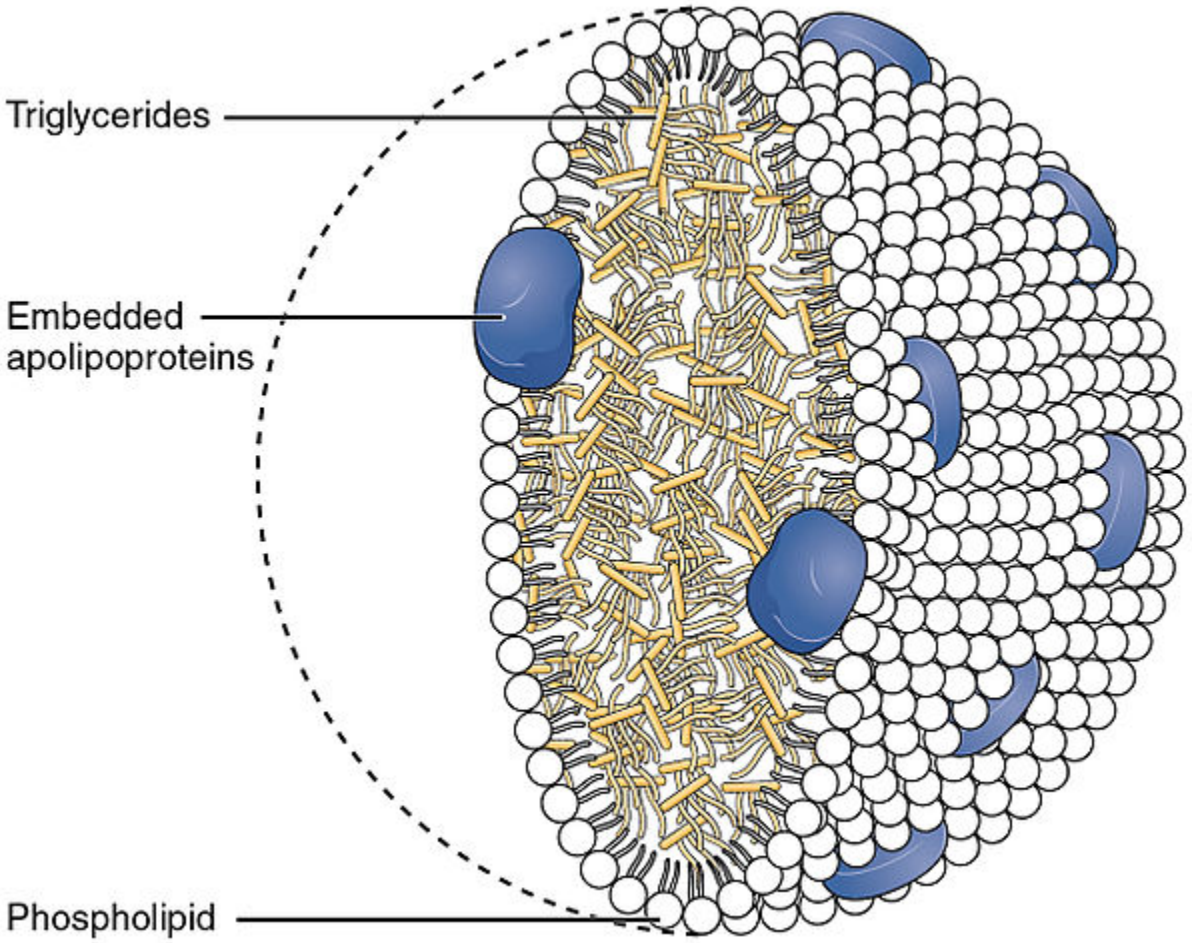
Going to the Bloodstream

As stomach contents enter the small intestine, **bile** acts as an **emulsifier** and makes lipids more accessible to digestive enzymes, such as *pancreatic* ***lipase*** that breaks down the fats into free fatty acids and monoglycerides. Bile also facilitates the formation of micelles necessary for the transportation of fats through the lining of the digestive tract. Micelles have a fatty acid core with a water-soluble exterior. This allows efficient transportation to the **intestinal microvillus**, where the fat components are released and disseminated into the cells of the digestive tract lining.



Micelle Formation – *Scheme of a micelle formed by phospholipids in an aqueous solution.*

Within the lining of the digestive tract, monoglycerides and fatty acids reassemble into triglycerides that form lipoproteins when joined with a protein carrier. **Lipoprotein**s have an inner core that is primarily made up of triglycerides and cholesterol esters (a cholesterol ester is a cholesterol linked to a fatty acid). The outer envelope is made of phospholipids interspersed with proteins and cholesterol. Together they form a **chylomicron**, which is a large lipoprotein that now enters the lymphatic system and will soon be released into the bloodstream via the jugular vein in the neck. Chylomicrons transport food fats perfectly through the body's water-based environment to specific destinations such as the liver and other body tissues.



Schematic Diagram Of A Chylomicron – *Chylomicrons Contain Triglycerides Cholesterol Molecules and other Lipids*

Cholesterols are poorly absorbed when compared to phospholipids and triglycerides. Cholesterol absorption is aided by an increase in dietary fat components and is hindered by high fiber content. This is the reason that a ***high intake of fiber is recommended to decrease blood cholesterol***. Foods high in fiber, such as fresh fruits, vegetables, and oats can bind bile salts and cholesterol, preventing their absorption and carrying them out of the colon.

Understanding Blood Cholesterol

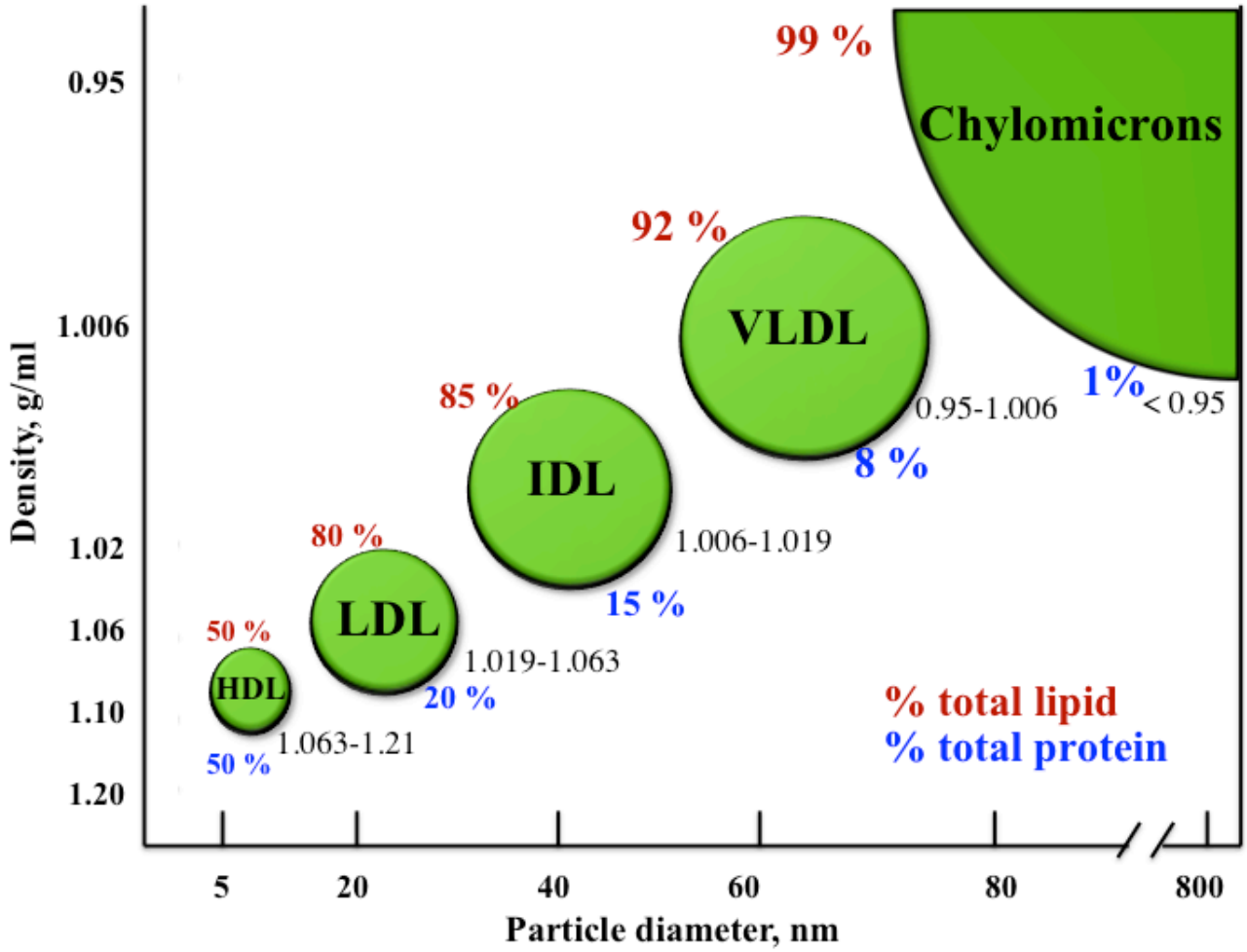
You may have heard of the abbreviations LDL and HDL with respect to heart health. These abbreviations refer to ***low-density lipoprotein*** (LDL) and ***high-density lipoprotein*** (HDL), respectively. **Lipoprotein**s are characterized by size,

density, and composition. As the size of the lipoprotein increases, the density decreases. This means that HDL is smaller than LDL. ***Why are they referred to as "good" and "bad" cholesterol?***

Major Lipoproteins

Recall that chylomicrons are transporters of fats throughout the watery environment within the body. After about ten hours of circulating throughout the body, chylomicrons gradually release their triglycerides until all that is left of their composition is cholesterol-rich remnants. These remnants are used as raw materials by the liver to formulate specific lipoproteins. Following is a list of the various lipoproteins and their functions:

- VLDLs: Very low-density lipoproteins are made in the liver from remnants of chylomicrons and transport triglycerides from the liver to various tissues in the body. As the VLDLs travel through the circulatory system, the lipoprotein lipase strips the VLDL of triglycerides. As triglyceride removal persists, the VLDLs become intermediate-density lipoproteins.
- IDLs: Intermediate-density lipoproteins transport a variety of fats and cholesterol in the bloodstream and are a little under half triglyceride in composition. While traveling in the bloodstream, cholesterol is gained from other lipoproteins while circulating enzymes strip its phospholipid component. When IDLs return to the liver, they are transformed into low-density lipoprotein.
- **LDL**s: As low-density lipoproteins are commonly known as the "bad cholesterol" it is imperative that we understand their function in the body so as to make healthy dietary and lifestyle choices. LDLs carry cholesterol and other lipids from the liver to tissue throughout the body. LDLs are comprised of very small amounts of triglycerides, and house over 50 percent cholesterol and cholesterol esters. How does the body receive the lipids contained therein? As the LDLs deliver cholesterol and other lipids to the cells, each cell's surface has receptor systems specifically designed to bind with LDLs. Circulating LDLs in the bloodstream bind to these LDL receptors and are consumed. Once inside the cell, the LDL is taken apart and its cholesterol is released. In liver cells these receptor systems aid in controlling blood cholesterol levels as they bind the LDLs. A deficiency of these LDL binding mechanisms will leave a high quantity of cholesterol traveling in the bloodstream, which can lead to heart disease or atherosclerosis. Diets rich in saturated fats will prohibit the LDL receptors which, are critical for regulating cholesterol levels.
- **HDL**s: High-density lipoproteins are responsible for carrying cholesterol out of the bloodstream and into the liver, where it is either reused or removed from the body with bile. HDLs have a very large protein composition coupled with low cholesterol content (20 to 30 percent) compared to the other lipoproteins. Hence, these high-density lipoproteins are commonly called "good cholesterol."



Lipoprotein Classes – *The classification of the major types of lipoproteins are based on their densities. Density range is shown as well as lipid (red) and protein (blue) content.*

Blood Cholesterol Considerations

For healthy total blood cholesterol, the desired range you would want to maintain is under 200 mg/dL. More specifically, when looking at individual lipid profiles, a low amount of LDL and a high amount of HDL prevents the excess buildup of cholesterol in the arteries and wards off potential health hazards. An LDL level of less than 100 milligrams per deciliter is ideal while an LDL level above 160 mg/dL would be considered high. In contrast, a low value of HDL is a telltale sign that a person is living with major risks for disease. Values of less than 40 mg/dL for men and 50 mg/dL for women mark a risk factor for developing heart disease. In short, elevated LDL blood lipid profiles indicate an increased risk of heart attack, while elevated HDL blood lipid profiles indicate a reduced risk.

Section Review

The process of **lipid** digestion involves multiple enzymes produced in different parts of the gastrointestinal tract (*lingual lipase* in the mouth, *gastric lipase* in the stomach, *pancreatic lipase*, and **bile**). Absorption of lipids happens primarily in the intestines, where lipids are combined with proteins to form **lipoproteins** – "vehicles" that can transport lipids in the bloodstream. In the context of atherosclerosis, two forms of lipoproteins (**LDL** of **HDL**) are of interest. LDLs, which transport lipid particles from the liver to the tissues/organs, are associated with an increased risk of atherosclerosis, while HDLs, which transport lipid particles from the tissue to the liver, are associated with a decreased risk. Smoking cessation, diets high in fiber and low in fat, and aerobic exercise i***ncrease the levels of HDL*** in the blood.

Review Questions

1. Finish the following sentence. Lipid absorption and digestion occur in the:

- Mouth
- Stomach
- Pancreas
- Intestines

2. Fill in the blank.

_____ is a general name of an enzyme that's involved in lipid digestion.

3. Bile is produced by pancreas and secreted into small intestine to facilitate lipid digestion.

- True
- False

4. Fill in the blank.

Bile is produced by the _____ and acts as emulsifier to facilitate lipid digestion.

5. Fill in the blanks.

_____, also known as "bad cholesterol" is associated with increased risk of atherosclerosis. _____, or "good cholesterol", is associated with lower risk of atherosclerosis initiation and progression.

Answer Key

1. Intestines
2. Lipase
3. False
4. Liver
5. LDL, HDL

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Pathophysiology of Atherosclerosis

TETIANA POVSHEDNA

Learning Objectives

By the end of this chapter, you will be able to:

- Identify and explain the main processes that occur during various stages of atherosclerotic plaque development.
- Describe the biological rationale for the most common locations of atherosclerotic plaques.
- Describe common clinical scenarios of atherosclerosis progression.

Atherosclerosis develops as a result of a continuous process that involves endothelial activation, lipid accumulation, atheroma plaque formation, vascular remodeling, and ultimate narrowing of the blood vessel lumen. This blood flow restriction due to atherosclerosis can manifest a variety of clinical diagnoses, which are named based on the location of atherosclerotic plaque (heart attack, stroke, and **peripheral artery disease**)

Atherosclerosis progression is initiated by **endothelial activation** in response to cardiovascular risk factors, such as **hypertension**, high blood glucose, smoking, increased cholesterol levels, etc.

Common Locations of Atherosclerotic Plaques

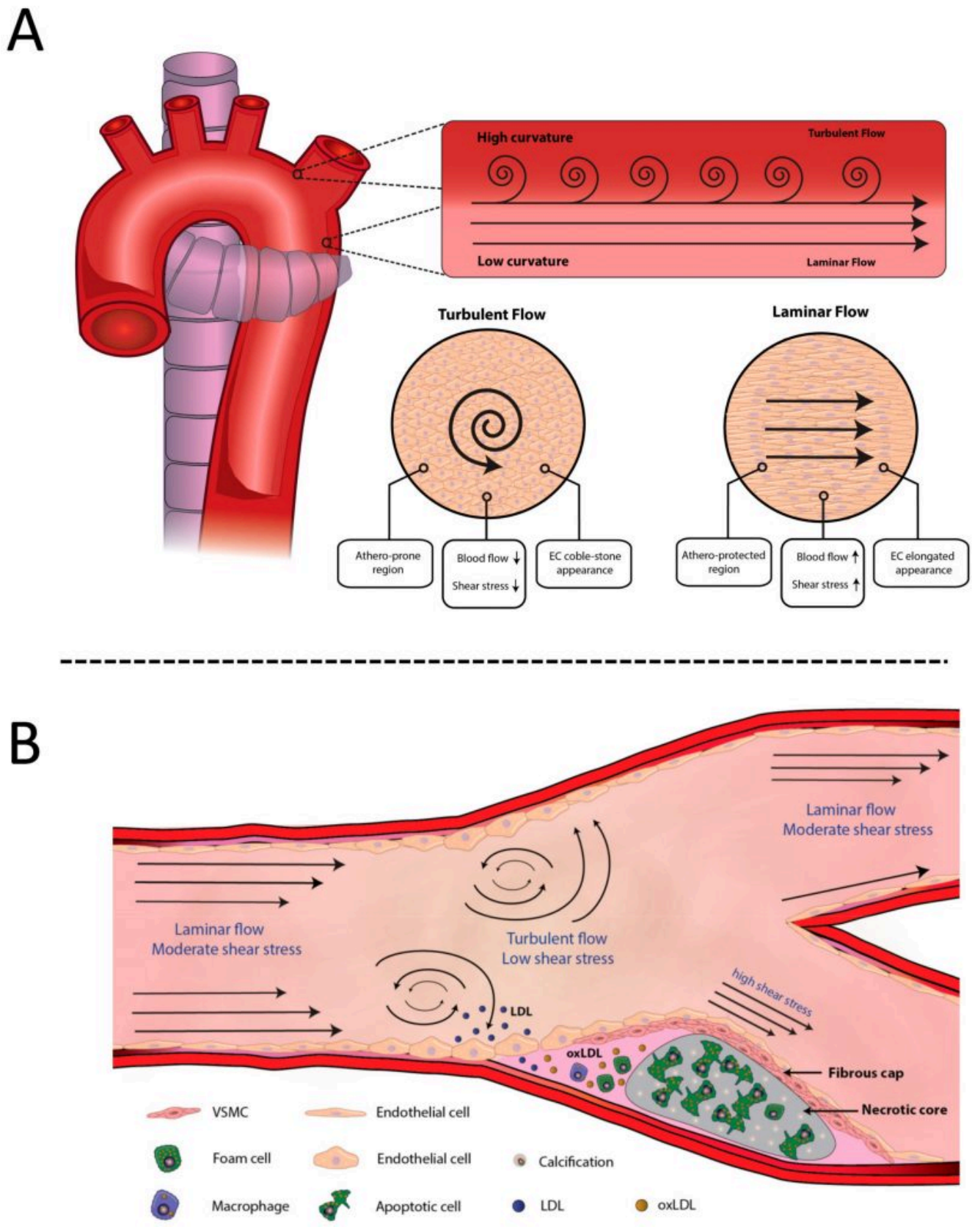
Even though the vascular tree is uniformly exposed to metabolic risk factors, ***some regions are more likely to form atherosclerotic plaques*** than others. This phenomenon can be partially explained by mechanical stress (wall shear stress, WSS) and type of blood flow (**laminar** vs **turbulent**).

Blood flow disturbance in branching points and **bifurcation**s of the vascular tree results in a specific distribution of atherosclerotic plaques, with the majority of them forming in these common atheroma-prone regions.

This trend highlights the importance of **arterial branches and bifurcations** in the diagnosis of atherosclerotic lesions.

Some examples of such locations include the bifurcations of:

- abdominal aorta into right and left iliac arteries
- common carotid arteries into external and internal carotic arteries
- left coronary artery into left anterior descending (LAD) and circumflex



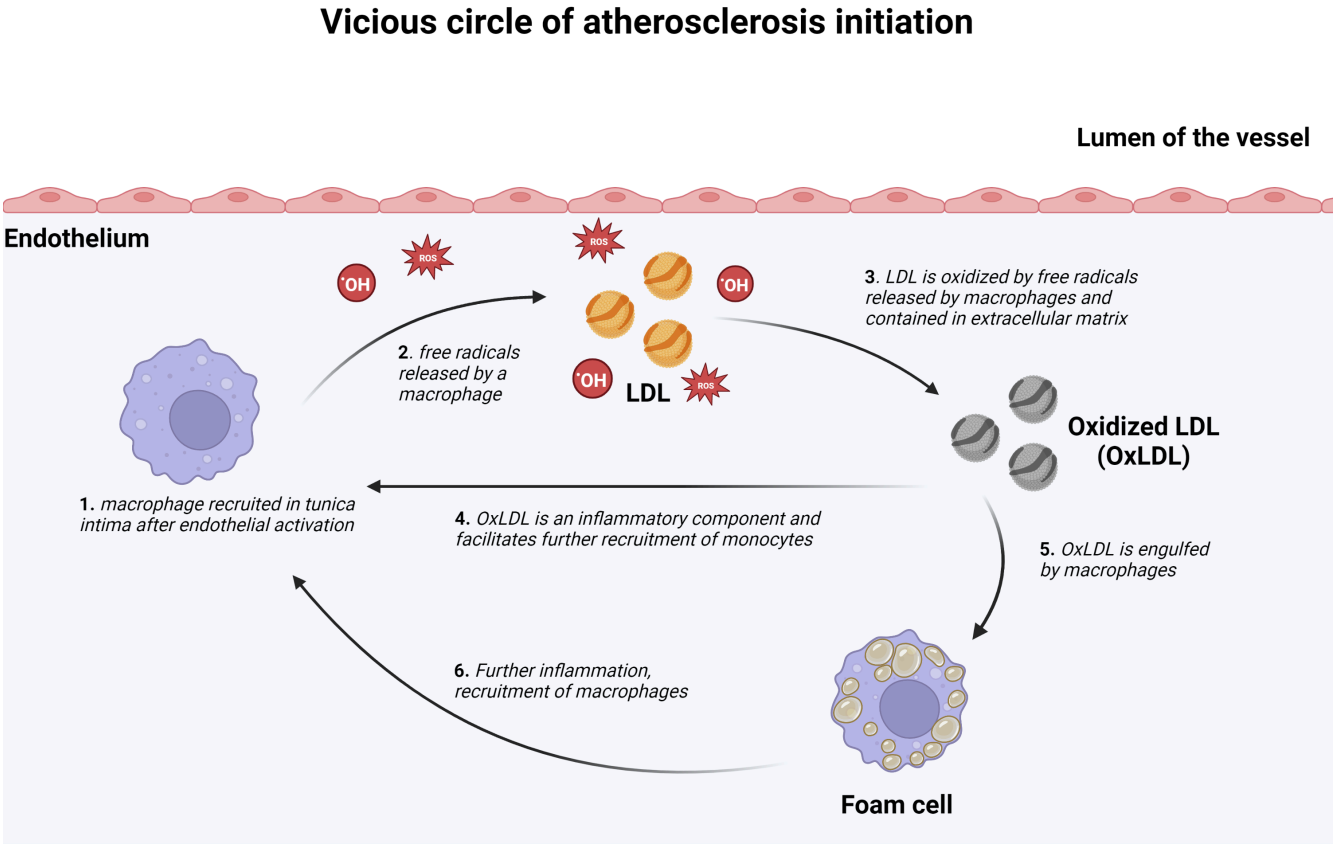
Effects of blood flow and mechanical stress on atherosclerotic plaque formation A) *Endothelial cells appear flat in straight vessel segments with laminar flow and physiological (moderate) WSS; High-curvature vessel segments (bifurcations and branch points) exhibit turbulent flow, reduced WSS, and cobblestone appearance of endothelial cells.* B) *Low shear stress promotes endothelial dysfunction and LDL accumulation, initiating atherosclerotic plaque formation in athero-prone regions.*

Atherosclerotic plaque formation starts with the fatty streak (accumulation of lipids within the intima) and progresses into the fibrous plaque with a necrotic core – a complex structure that can facilitate clot formation and/or detach and become an embolus.

Stages of Atherosclerotic Plaque Formation

1. **Lesion Initiation**

Atherosclerosis plaque formation begins with activation and/or damage to the **endothelium**, which disrupts the normal process of **LDL** intake and metabolism. As a result, LDL is modified and accumulated within the **tunica intima** of a vessel. Endothelial activation/damage affects its permeability, stimulates **leukocyte** adhesion to its surface, and **diapedesis**. The leukocytes recruited from the blood into the blood vessel wall are **monocyte**s, that become ***macrophages*** once they leave the systemic blood circulation and migrate into tissues.Once within the intimal layer, LDL particles are oxidized by free radicals that are contained in the extracellular matrix and/or produced by recruited **monocyte**s. **Oxidized LDL** (oxLDL) is a **key inflammatory component** that facilitates atherosclerosis progression. These initial processes create a "vicious circle" that results in further recruitment of monocytes, LDL retention, and oxLDL accumulation. Recruited monocytes and vascular smooth muscle cells (VSMCs) within the tunica intima engulf oxLDL and become "**foam cells**" – a name given to these cells because of a foamy appearance of the cytoplasm due to the oxLDL deposition.



Vicious Circle of Atherosclerosis Initiation

2. Fatty Streak

As the "vicious circle" progresses, LDL is deposited both inside cells and in the extracellular matrix, and cholesterol crystals form. The initial lesion increases in size and appears as a ***visible flat yellow streak*** on the luminal side of the vessel.

3. Fibrous Plaque

Foam cells (derived from macrophages and **VSMC**s) undergo cellular death (**apoptosis**) and release their contents within the tunica intima. These contents are further engulfed by macrophages in an attempt to "clean" the lesion site. However, an overwhelming amount of oxLDL, dead cells, cholesterol crystals, and extracellular debris form a soft **"necrotic" core** of growing atherosclerotic plaque. As the lesion progresses, it can accumulate calcium salts and harden over time, impairing the elasticity of blood vessels and their ability to dilate and contract in response to blood pressure fluctuations.

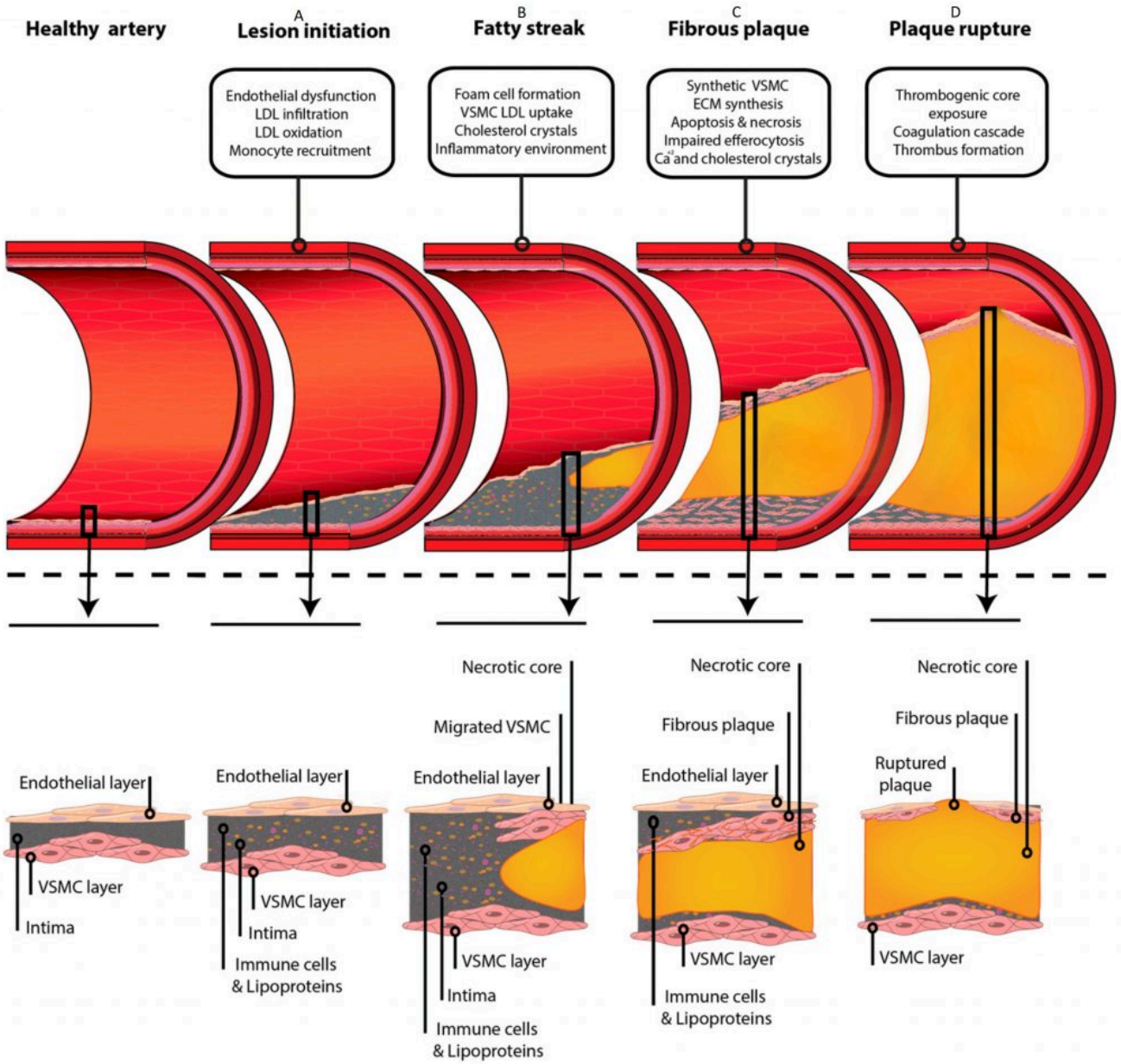
In response to the atherosclerotic lesion progression, more **VSMC**s are recruited from the **tunica media** to the **intima** to form a **fibrous cap** – a protective layer that covers the necrotic core. Normally, VSMCs facilitate contraction/dilation of blood vessels, but once recruited to tunica intima, they switch towards synthetic activity. VSMCs within the fibrous cap produce a large amount of extracellular matrix (collagen and elastin fibers, proteoglycans) to "cover" the soft necrotic

core and stabilize the plaque. The fibrous cap prevents plaque rupture and serves as a barrier between the lumen of the vessel and the necrotic core which, if exposed to the blood flow, can trigger the formation of a blood clot.

4. Outcomes

The thickness of the fibrous cap covering the soft necrotic core of an atherosclerotic lesion, as well as its composition (the amount of collagen/elastin fibers), affect the stability of the plaque and clinical outcomes. As atheroma increases in size, inflammation within the plaque (pro-inflammatory cytokines released by macrophages), as well as inflammatory **cytokines** in the bloodstream can affect the vulnerability of the plaque.

Atherosclerotic plaques can become more vulnerable if **VSMC**s within the fibrous cap respond to inflammation by producing enzymes that degrade components of the extracellular matrix, weakening the fibrous cap and making it more susceptible to rupture. A weaker fibrous cap increases the likelihood of the necrotic core getting exposed to the blood flow, which can result in clot formation on top of the plaque.



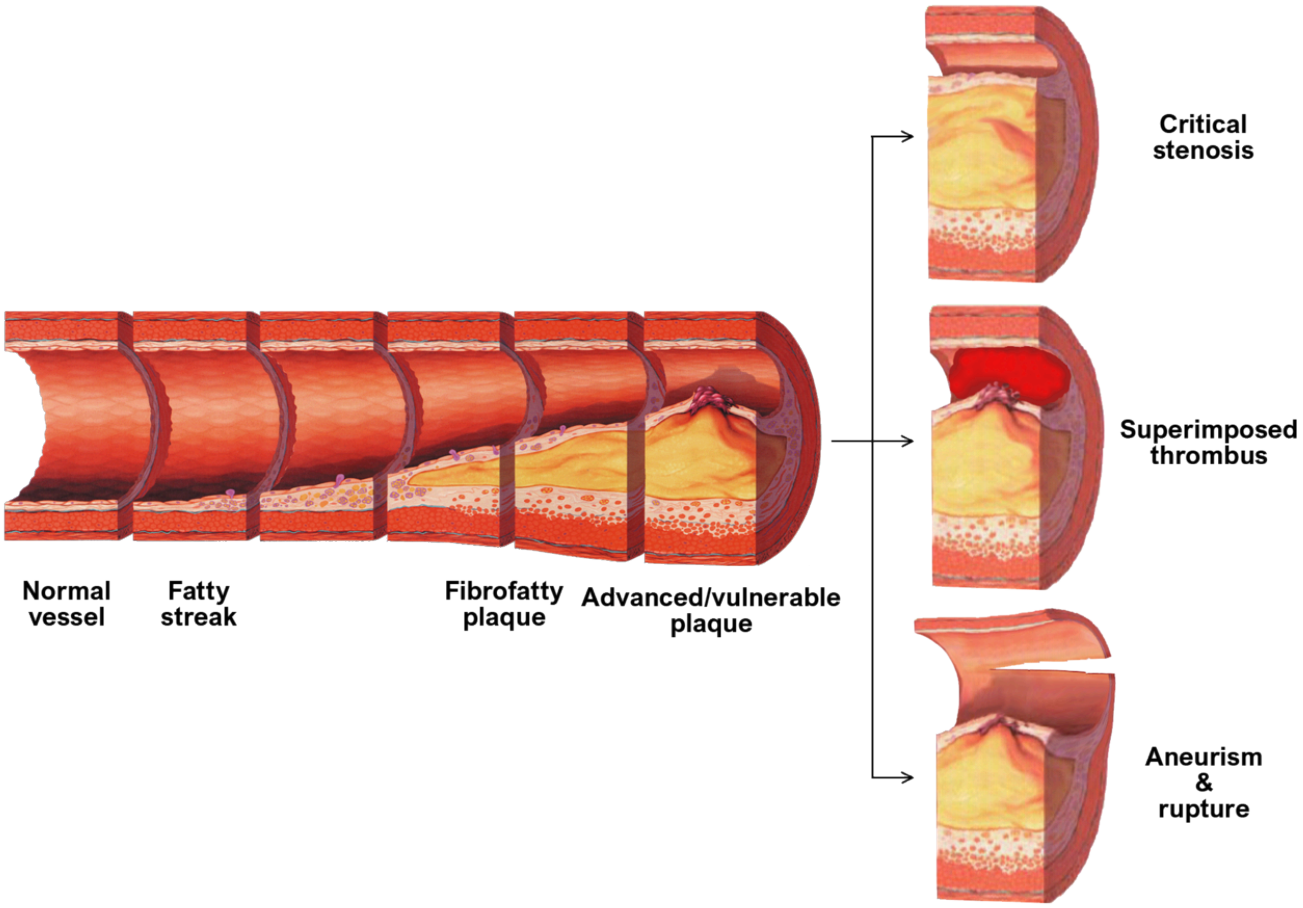
Schematic representation of atheroma plaque formation from a healthy artery to (A) Lesion formation, (B) Fatty streak, (C) Fibrous plaque, and (D) Plaque rupture underlying the most important events that contribute to its development in each stage.

Key Takeaways

1. Circulating monocytes (macrophages once outside of the bloodstream) play an important role in atherosclerosis initiation and progression and undergo morphological changes in the process.
2. Inflammation is relevant at all stages of atherosclerosis, from lesion initiation to its rupture.
3. Plaque stability determines the likelihood and severity of clinical complications.

Main Scenarios of the Atheroma Progression

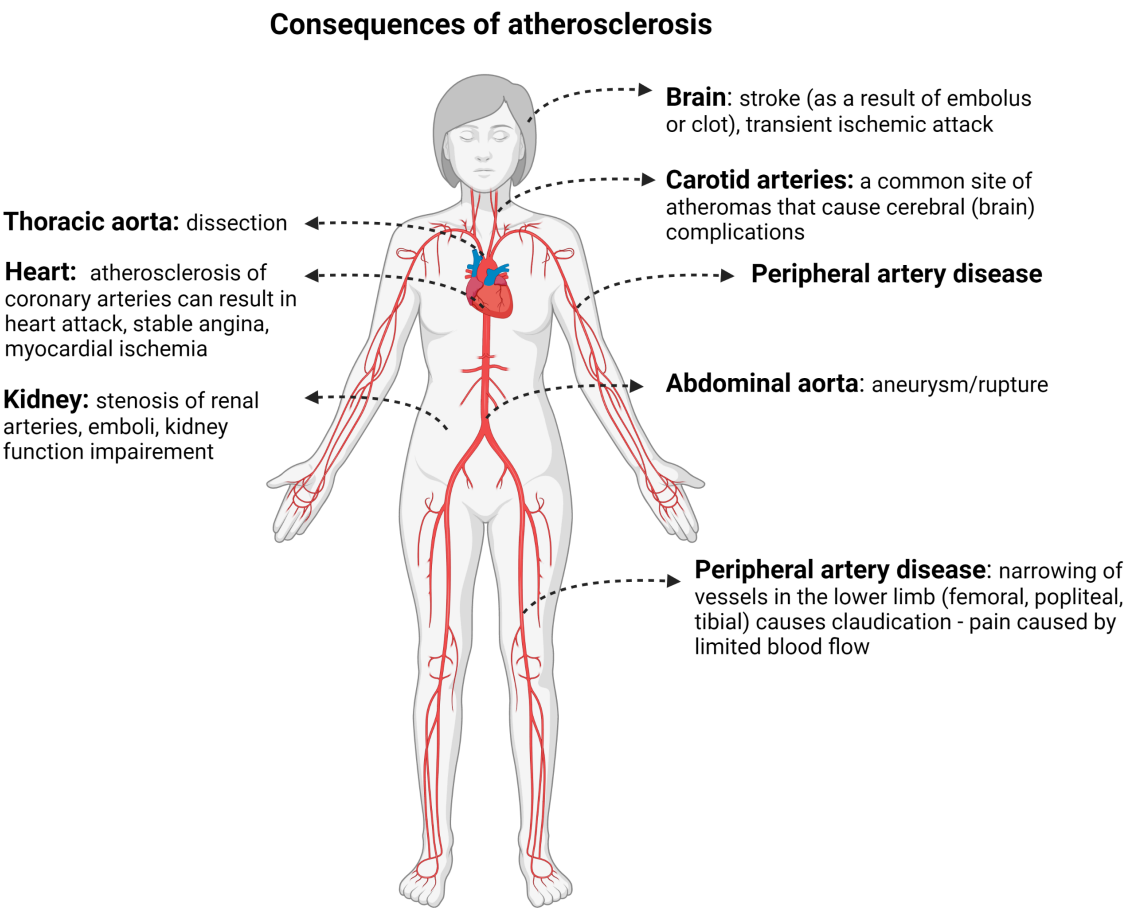
- growth of the plaque, progressive obstruction of the blood vessel lumen;
- erosion/rupture of the fibrous cap with subsequent clot formation on its surface;
- plaque/clot disruption and formation of the **embolus** in the bloodstream;
- increased susceptibility to **aneurysm** formation (Similarly to the process within the fibrous cap, extracellular matrix can be degraded within tunica media of the large vessels, weakening the muscular layer and making it more vulnerable to **dilatation**)



Late Complications of Atherosclerosis.

Clinical Scenarios of Atherosclerosis Progression

As mentioned earlier, the distribution of atheromas within the vascular tree is non-random and most commonly occurs at the branching points and bifurcation of large arteries.
As a result, clinical complications of atherosclerosis present as a wide array of symptoms and diagnoses.



Clinical Consequences of Atherosclerosis

Section Review

Microscopic and macroscopic changes that occur during the atherosclerosis progression are summarized below.

Stages of the atherosclerotic plaque formation

Plaque formation stage	Microscopic changes in the blood vessel wall (histology)	Outcome	Macroscopic changes in the blood vessel wall (gross anatomy)
1. Lesion initiation	Endothelial activation in response to risk factors (hypertension, lipid products, cigarette smoke, etc). Recruited monocytes and intimal VSMCs capture oxLDL and become foam cells	Initial LDL oxidation and infiltration within the intimal layer	–
2. Fatty streak	Recruited monocytes and intimal VSMCs become foam cells; cholesterol crystals form within the intima	Intracellular and extracellular LDL deposition	Bright yellow lesions on the luminal surface of the vessel; minimally raised
3. Fibrous plaque	Foam cells, recruited immune cells, and cholesterol crystals form a soft necrotic core. Impaired clearance of apoptotic cells, increased cellular death, and intraplaque hemorrhages facilitate its expansion. VSMCs from media are recruited to the intimal layer, secrete collagen-rich extracellular matrix, and form a protective fibrous cap.	Formation of the necrotic core and protective fibrous cap; thickness, composition, and collagen content of the fibrous cap determine stability of the plaque	Firm, visible, raised, homogenous, well-marked white areas on the luminal surface of the vessel; sometimes areas of calcification are present
4.1 Plaque rupture/ erosion	Erosion (loss of endothelium) or rupture (disturbed fibrous cap) expose the thrombogenic core of the plaque and initiate coagulation	Thrombus formation	Heterogeneous raised lesions associated with surface thrombosis
4.2. Plaque growth	Expansion of the necrotic core increases the size of the plaque	Lumen obstruction	Firm lesions that completely close the blood vessel lumen
4.3. Aneurysm formation and rupture	Weakening of the tunica media might appear as fragmentation in the superficial layers (border between tunica media and tunica intima). Muscular layer of the blood vessel wall can appear condensed, the amount of elastic fibers is decreased	Early stages – ballooning of the vessel wall, later stages – rupture	Rupture of the blood vessel (often fatal)

References

Jebari-Benslaiman, S., Galicia-García, U., Larrea-Sebal, A., Olaetxea, J. R., Alloza, I., Vandenbroeck, K., Benito-Vicente, A., & Martín, C. (2022). Pathophysiology of Atherosclerosis. International journal of molecular sciences, 23(6), 3346. https://doi.org/10.3390/ijms23063346

https://www.statpearls.com/ArticleLibrary/viewarticle/17943

Review Questions

1. Finish the following sentence. The first step of atherosclerosis lesion initiation is:

- Hypertension
- Lipid deposition within the blood vessel wall
- Endothelial activation/damage
- Clot formation

2. Fill in the blanks with the following words:

deposition, damage, branching points, bifurcations, turbulent, laminar

The most common locations for atherosclerotic plaque formation are _____ and _____ of arteries. This can be related to the type of blood flow as it changes from _____ to _____ , making these regions more prone to epithelial _____ and lipid _____.

3. Fill in the blank.

Macrophages and vascular smooth muscle cells become _____ after engulfing LDL particles.

4. Finish the following sentence. An advanced atherosclerotic plaque consists of:

- Soft necrotic core
- Protective fibrous cap
- A thick layer of smooth muscle
- A dense network of nerve fibers

5. Finish the following sentence. Common outcomes of advanced atherosclerosis DO NOT include:

- Plaque rupture
- Aneurysm
- Clot formation
- Spontaneous lesions reversal

Answer Key

1. Endothelial activation/damage
2. Branching points/bifurcations, branching points/bifurcations, laminar, turbulent, damage, deposition
3. Foam cells
4. Soft necrotic core, protective fibrous cap
5. Spontaneous lesion reversal

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Gross Anatomy and Histopathology of Atherosclerosis

TETIANA POVSHEDNA

Learning Objectives

By the end of this chapter, you will be able to:

- Identify macroscopic changes in the gross anatomy of the human aorta during different stages of atherosclerosis and its outcomes.
- Relate key pathophysiological changes in the progression of atherosclerosis to the cell/tissue changes visible on the histological slide.
- Interpret lipid and elastin histological stains.

Stages of Atherosclerosis (Gross Anatomy)

In this section, we will examine macroscopic changes that can occur in blood vessels of different sizes during atherosclerosis progression.

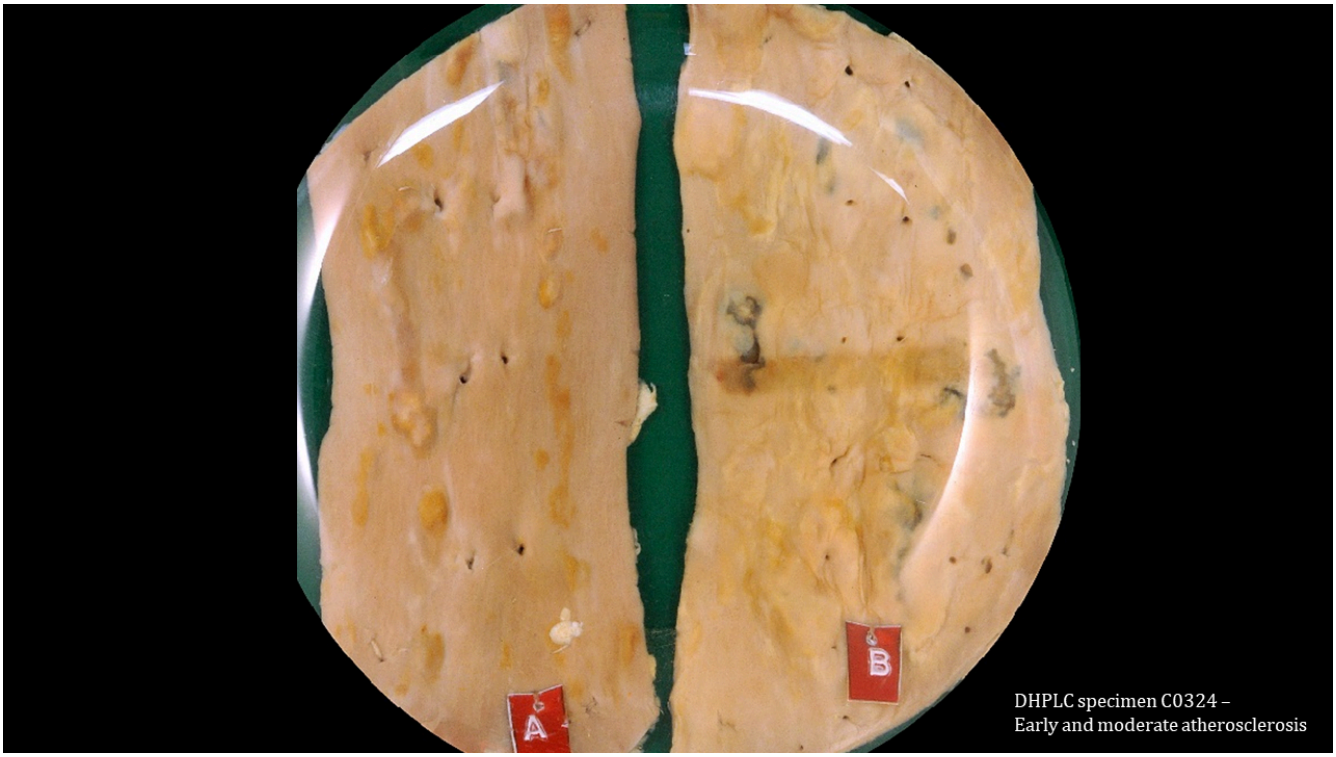
Early and Moderate Atherosclerosis

Please note: the gross specimen of the aorta appears flat because the artery (physiologically a tube) has been cut open to expose the luminal (inner) side of the vessel. Here, we are looking at the **tunica intima** – a place of atherosclerotic lesion initiation and a surface that physiologically in the human body is in direct contact with blood. Numerous openings on the aorta wall are origin sites of posterior intercostal arteries that branch off at this level of aorta and supply spine and rib cage with oxygenated blood.

Please note: the gross specimen of the aorta appears flat because the artery (physiologically a tube) has been cut open to expose the luminal (inner) side of the vessel. Here, we are looking at the **tunica intima** – a place of atherosclerotic lesion initiation and a surface that physiologically in the human body is in direct contact with blood. Numerous openings on the aorta wall are origin sites of posterior intercostal arteries that branch off at this level of aorta and supply spine and rib cage with oxygenated blood.

Key observations:

***Specimen* A:** mainly smooth **intimal** surface with early atherosclerotic lesions that appear as yellow cholesterol-containing plaques/streaks. Poorly defined pearly grey discoloration near openings of intercostal arteries demonstrates connective tissue proliferation
***Specimen* B**: note the increased number and size of lesions compared to specimen A and the more irregular surface of the luminal side of the aorta

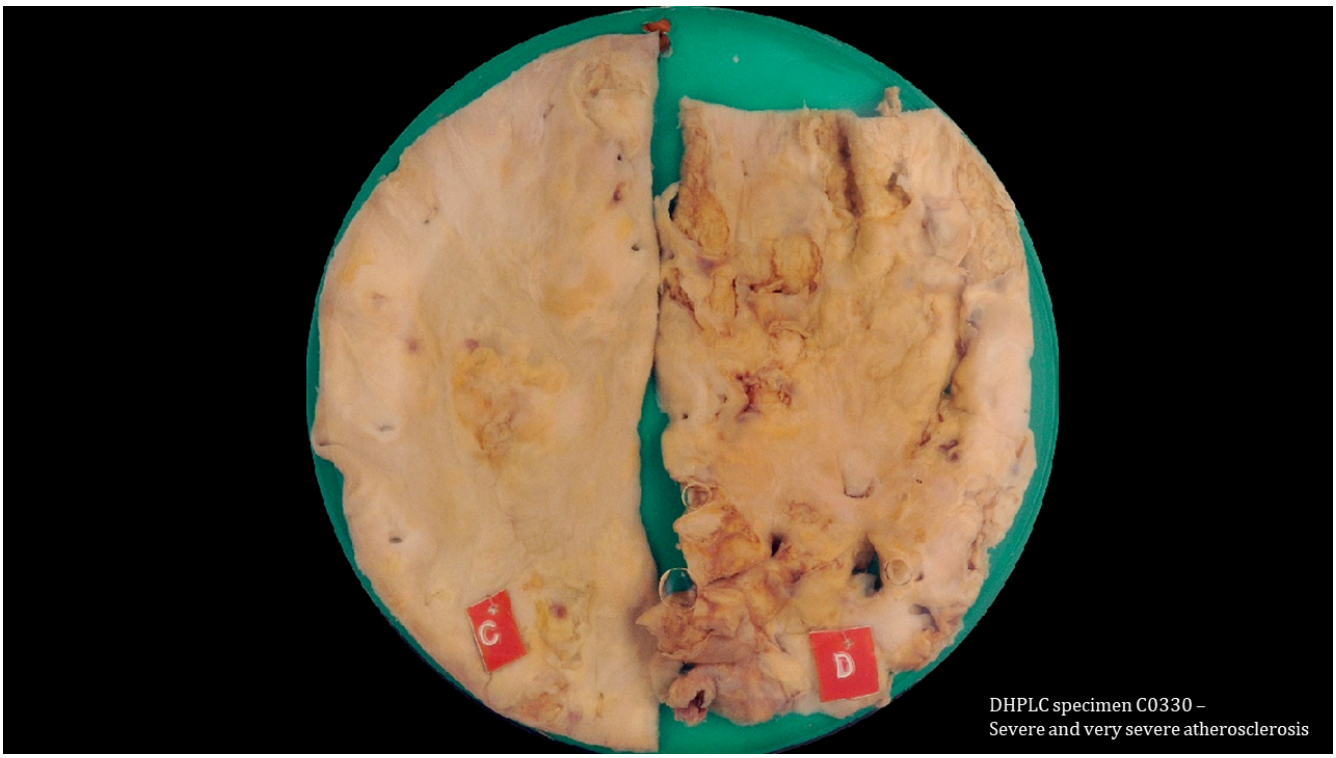


DHPLC specimen C0324 *Early and Moderate Atherosclerosis of Aorta. All rights reserved*

Severe and Very Severe Atherosclerosis

Key observations

***Specimen C*:** Severe atherosclerosis. The wall of the aorta appears stiff and reduced in elasticity. The inner surface contained irregular nodules, patches, and streaks of atherosclerotic plaques that appear dirty yellow. Intima is absent in some areas, leaving surface ulcers. During specimen preparation, numerous calcium flecks were noticed, which rendered the vessel brittle.
***Specimen D*:** Very severe atherosclerosis. The aorta is rigid and inelastic, with its surface completely altered by atherosclerotic lesions in various stages. Multiple surface ulcers are present. The brownish-black patches demonstrate **hemorrhage** under the atherosclerotic plaques. Thrombosis is occurring over some of the ulcerated lesions. The rigidity is due to calcium deposition.



DHPLC specimen C0330 *Severe and Very Severe Atherosclerosis of Aorta. All rights reserved*

Histopathology of Atherosclerosis

We will examine the histopathology of atherosclerosis using two slides of **atheroma** of the aorta coming from the same patient – a 65 y.o. man with a history of **hypertension** – one of the main risk factors of atherosclerosis.

Both slides are stained with special stains (fat stain and elastic tissue stain) that allow for visualization of specific tissue components that would not be clearly identifiable by the classic H&E stain.

While examining tissue slides, please note ***epithelial damage*** – an initial step of atherosclerosis progression that triggers subsequent inflammation and atherosclerotic plaque formation.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=3231#h5p-184

Histopathology of atherosclerosis (aorta) by Tetiana Povshedna licensed under CC BY 4.0 created with BioRender.com. Histology slides are DHPLC specimens PATH 425-032 (fat stain) and PATH 425-033 (elastin stain)

Fat Tissue Stain: Key Takeawats

- Irregularly thickened **tunica intima** as a result of lipid accumulation
- Numerous lipid deposits in both **tunica intima** and **tunica media**

On a cellular level, this stage of atherosclerosis development is associated with the pro-inflammatory state, macrophage recruitment, and foam cell formation with subsequent necrotic core development.

Elastin Stain: Key Takeaways .

- Irregularly thickened **tunica intima**; loss of elastic fibers in tunica intima (compare this elastic stain to an example of the normal human aorta in Gross anatomy and histology of normal aorta and note the amount of elastic fibers in tunica intima)
- Elastic tissue appears compressed and fragmented in the superficial layers of **tunica media**. This fragmentation and weakening of the aorta wall might facilitate the formation of **aneurysm**
- On higher magnification, cholesterol crystals appear as stellate empty spaces in **tunica intima**
- Areas of calcification appear as dark dense spots within tunica intima

While all the histological slides and gross anatomy specimens above focused on various regions of aorta as a site of atherosclerotic plaque formation, coronary arteries are also one of the common and clinically relevant sites of

atherosclerosis. Plaque formation within these arteries can cause **hypoxia** of the heart muscle which, if left untreated, can lead to a heart attack.

The video below examines the key features of atherosclerosis in **coronary arteries**. Clinically, these changes would reflect the pathophysiology of ischemic heart disease.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=3231#h5p-67

Histopathology of atherosclerosis (coronary artery). *Created and presented by Jonathan Bush. Histology slide is from private collection.*

Key Takeaways

- Numerous immune cells in **tunica externa** reflect inflammatory process triggered by atherosclerosis.
- A blood clot is obstructing the lumen, making tunica intima hard to identify.
- Fibrotic areas (appear pale pink and do not contain a lot of cell nuclei) reflect lipid accumulation.
- Foam cells that engulfed oxidized LDL in **tunica media** .

Clinical Outcomes of Severe Atherosclerosis (Gross Anatomy)

Thrombosis of Atherosclerotic Aorta

The formation of a clot is one of the common clinical outcomes of severe atherosclerosis. Thrombosis-induced **ischemia** can result in heart attack or stroke, depending on location. Clot formation as a result of atherosclerosis in coronary vessels can block the blood flow to the heart, and cause tissue damage as a result of **hypoxia**. Similar scenarios can occur anywhere along the vascular tree, including the brain (stroke), lower limb (peripheral artery disease), etc.

This specimen demonstrates a case of thrombosis in the abdominal aorta as a result of atherosclerosis.

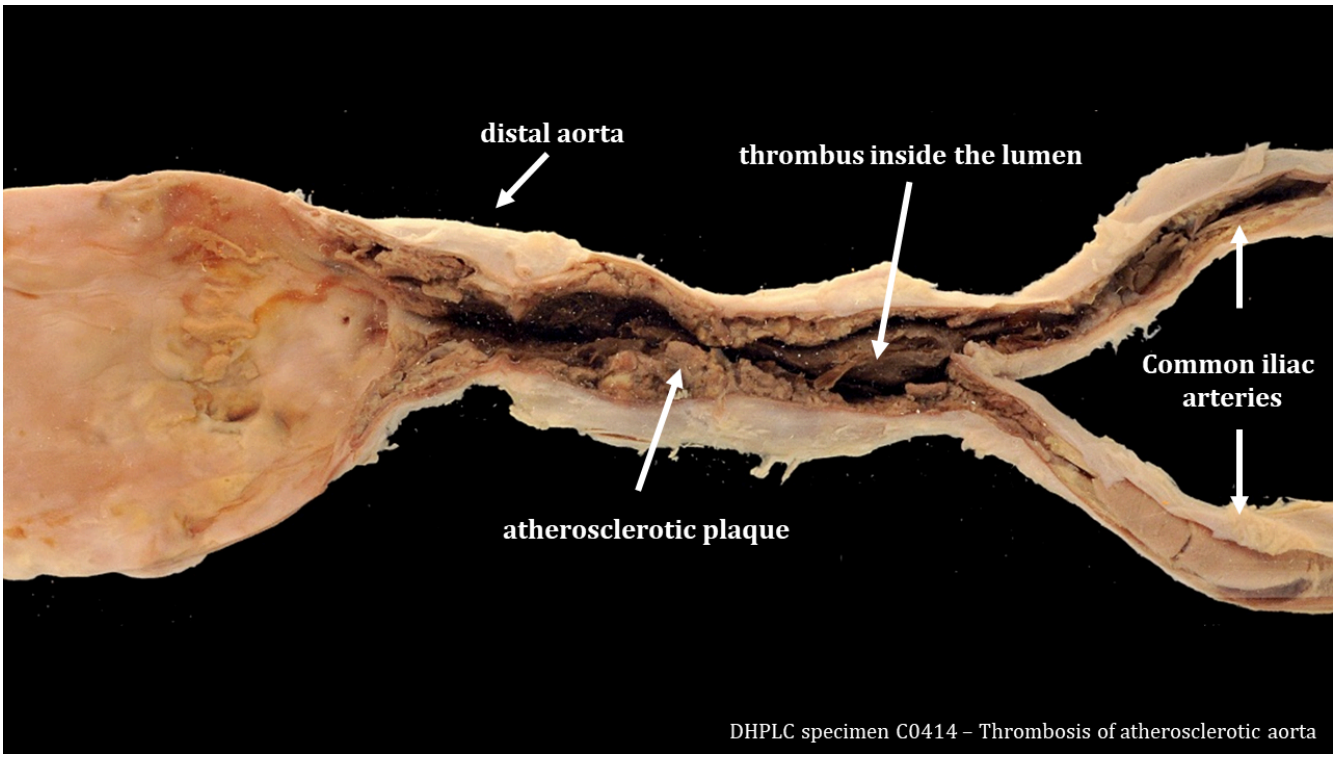
Patient history:

An elderly man with a history of peripheral artery disease – a manifestation of atherosclerosis in lower limbs, which resulted in bilateral leg amputation two years previously. Chief complaint on admission – pain. Cause of death – pneumonia; autopsy revealed generalized atherosclerosis.

The specimen demonstrates distal abdominal aorta as it divides into the right and left **common iliac arteries**.

Key observations:

- ***Narrowing*** of the distal aorta by a dark thrombus which extends into common iliac arteries
- ***Thickening*** of the aorta wall – numerous yellow atherosclerotic plaques that narrow the lumen
- Typical***location*** of the plaque and thrombus – **bifurcation** of a large vessel where the **laminar** flow becomes **turbulent**



DHPLC Specimen C0414 *Thrombosis of Atherosclerotic Aorta. All rights reserved*

Aneurysm of Atherosclerotic Aorta

Severe atherosclerosis can progress towards **aneurysm**, where the muscular layer of the vessel weakens and creates a bulge that can rupture and lead to internal bleeding.

This case demonstrates atherosclerotic aneurysm of the abdominal aorta.

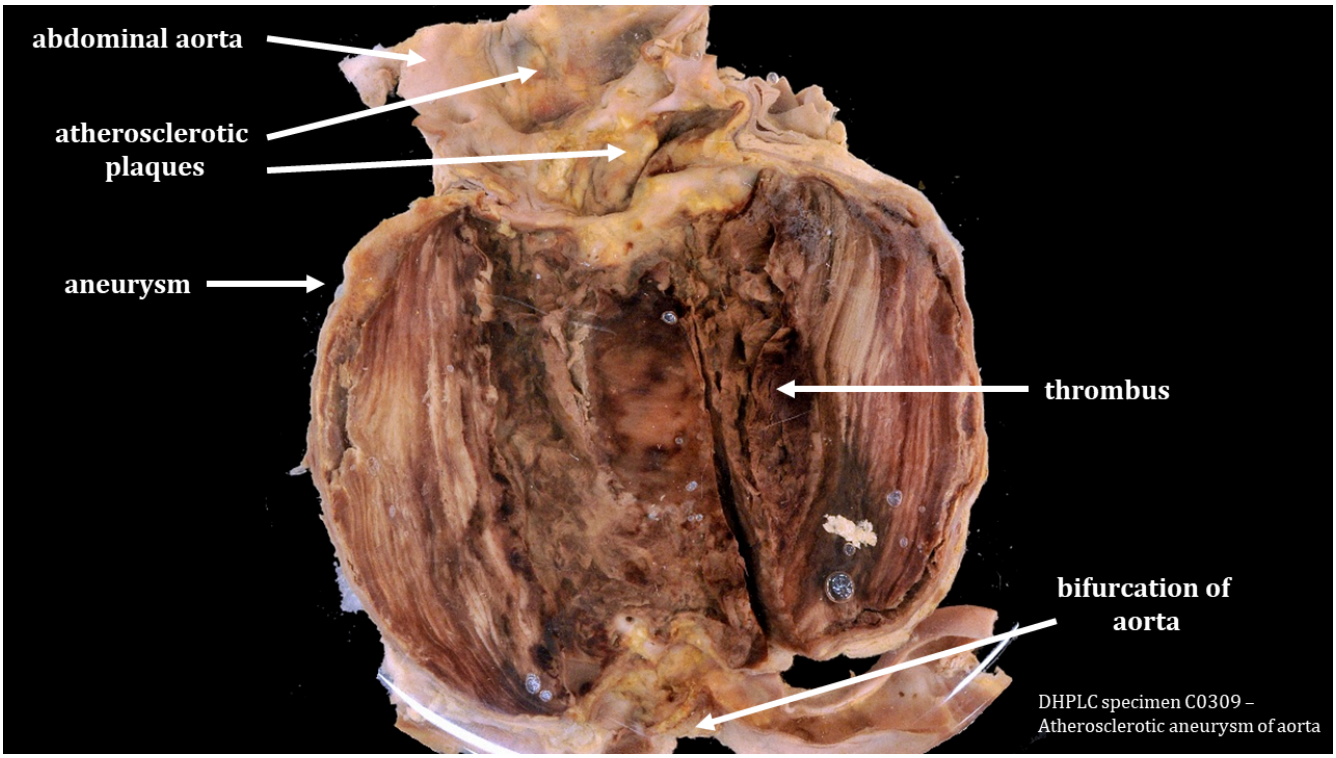
Patient history:

75 y.o. man with a known abdominal aortic aneurysm, presented with **epigastric** pain for several days. Physical examination of abdomen revealed a non-painful mass about 10 cm in diameter. Aneurysm **dissection** was suspected. The autopsy revealed atherosclerosis of **coronary** vessels, as well as an atherosclerotic abdominal aneurysm with a thrombus.

Key observations:

- Compare and contrast the diameter of abdominal aorta and aneurysm
- Note numerous atherosclerotic plaques in the proximal part of the aorta
- The lumen of the aneurysm if partially filled with a mural thrombus
- Typical location of atherosclerosis/aneurysm – at the bifurcation of the abdominal aorta into right and left **common iliac arteries**

Compare and contrast the diameter of the abdominal aorta in the above figure and the one below of DHPLC specimens C0414 and C0309



DHPLC specimen C0309 *Atherosclerotic Aneurysm of Aorta. All rights reserved*

Section Review

On gross anatomy specimens, early atherosclerotic lesions appear as yellow streaks/patches on the luminal side of the

vessel. As the severity of atherosclerosis increases, atherosclerotic plaques grow in size and number and can cause ulceration. Advanced atherosclerotic vessels have an irregular luminal surface, numerous plaques, areas of calcification, ulceration, and clot formation. One of the most common clinical outcomes of advanced atherosclerosis is an aneurysm or clot formation.

Histologically, lipid deposits are visible within the **tunica intima** and **tunica media** of atherosclerotic vessels. Endothelial damage, which is necessary for lesion initiation, is often present. During the advanced stages, cholesterol crystals and calcium deposits can be visualized in **tunica intima**, while **tunica media** can appear fragmented.

Review Questions

1. Fill in the blanks. On gross anatomy specimens, atherosclerotic plaques appear as _____ lesions. (*indicate colour*)

2. Finish the following sentence. Common clinical outcomes of advanced atherosclerosis include:
Select all that apply.

- Aneurysm formation
- Clot formation
- Decreased blood pressure
- Arythmias

3. Fill in the blank.

As atherosclerosis progresses, _____ can form on the luminal surface of the vessel, exposing underlying layers of the vessel wall.

4. Finish the following sentence. Aneurysm is usually a consequences of a weakened:

- Tunica intima
- Tunica media
- Tunica externa

5. Fill in the blank.

_____ damage is necessary for atherosclerotic lesion initiation.

6. In atherosclerosis, lipid deposits can accumulate in both tunica intima and tunica media.

- True
- False

7. Fill in the blank.

_____ deposits in advanced atherosclerosis harden the vessel wall and make it brittle.

Answer Key

1. Yellow
2. Aneurysm formation, clot formation
3. Ulcers
4. Tunica media
5. Endothelial
6. True
7. Calcium

Media Attributions

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Prevention, Diagnosis and Treatment of Atherosclerosis

TETIANA POVSHEDNA

Learning Objectives

By the end of this chapter you will be able to:

- Describe the actions toward primary and secondary prevention of atherosclerosis.
- Describe the common diagnosis and treatment strategies of atherosclerosis.
- Describe the role of interprofessional health teams in diagnosis and management of atherosclerosis.

Prevention efforts to minimize the global health impacts of atherosclerosis include primary and secondary prevention.

Primary prevention includes actions to prevent or delay the onset of atherosclerosis and focuses on addressing the impact of modifiable atherosclerosis risk factors (smoking cessation, dietary considerations, etc)
Secondary prevention includes actions to facilitate early diagnosis of existing diseases and prevent further disease progression/manifestations (lipid-lowering medication, anti-hypertensive medication, diagnostic tests to assess heart function)

It is important to recognize that atherosclerosis initiation can occur early in life, and the disease can be asymptomatic for decades before progressing and manifesting as an acute cardiovascular event.

This is why ***the prevention of atherosclerosis is a lifelong effort.***

Primary Prevention

Primary prevention strategies involve lifestyle considerations that aim to minimize the impact of modifiable risk factors. It is especially important to minimize the effect of these factors in childhood and adolescence because higher cumulative exposure to risk factors (e.g. decades of adherence to a high-fat diet, smoking, and sedentary lifestyle) can result in a higher incidence of **ASCVD** later in life. Therefore, the ideal primary prevention of atherosclerosis would involve adherence of a healthy lifestyle since childhood. Still, health behavior modifications for the prevention of atherosclerosis***provide benefits regardless of age and atherosclerosis stage***.

It's important to recognize that modifiable risk factors, even though distinct, often co-exist and can exacerbate each

other. On the other hand, certain lifestyle changes can affect multiple modifiable risk factors, "breaking down" the vicious circle of metabolic imbalance and atherosclerosis risk.

The interplay between modifiable risk factors in the context of atherosclerosis

Various modifiable risk factors can potentiate each other and thus increase the total risk of atherosclerosis progression and **ASCVD**.

Similarly, lifestyle and medical interventions towards one of the risk factors can modify and weaken the effect of other factors.

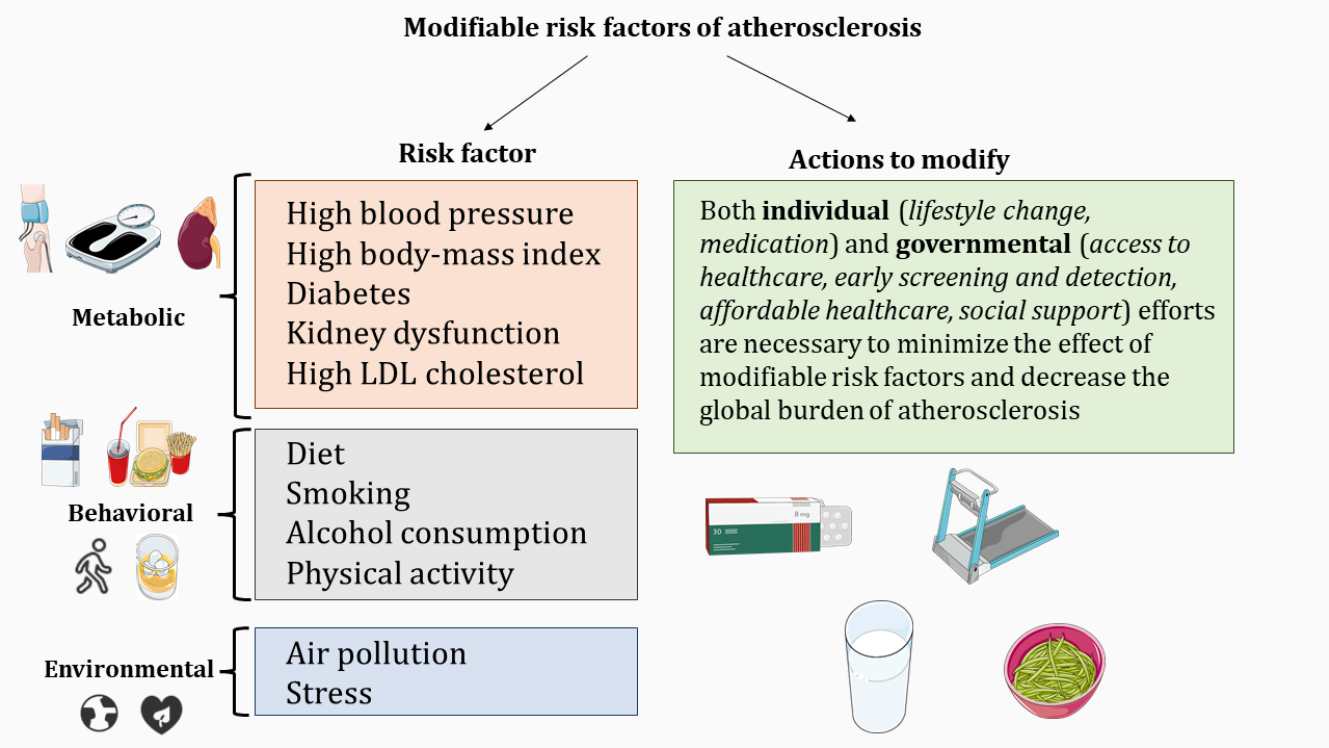
For example:

- Low rates of physical activity and poor diet are major ***behavioural risk factors*** that lead to caloric imbalance, higher rates of obesity, and type 2 diabetes (***metabolic risk factors***)
- Levels of LDL and HDL in the blood (***metabolic risk factors***) are affected by physical activity, diet, smoking (***behavioural interventions***), and body-mass index (***metabolic risk factor***)
- High body-mass index (***metabolic risk factor***) affects blood pressure, glucose metabolism, systemic inflammation, and cardiac structure and function (***metabolic risk factors***)
- Kidney function (***metabolic risk factor***) can be affected by hypertension and diabetes (***metabolic risk factor***)

Thus, a complex approach to modifiable risk factors, which includes recognition of their interplay, is necessary for effective primary prevention of atherosclerosis that, ideally, would address multiple modifiable risk factors.

In practice, ***primary prevention*** can include both individual efforts (lifestyle considerations regardless of age), and treatment strategies addressing modifiable risk factors.

The decision about prevention efforts is usually based on the ***risk assessment*** – a holistic assessment of a patient in the context of atherosclerosis. The image below, which includes laboratory tests, physical examination, and medical/family history collection.



Modifiable risk factors of atherosclerosis.

Healthcare professionals can also utilize ***risk calculators*** – clinical tools that integrate most of the known risk factors for atherosclerosis and can help guide clinical decision-making by providing estimates of 10-year risk of heart attack or other **ASCVD** outcomes.

Based on the risk assessment, patients are stratified as ***low***, ***intermediate***, or ***high risk*** in the context of primary prevention of atherosclerosis.

Primary atherosclerosis prevention: key recommendations from the Canadian Cardiovascular Society

- For those at ***low risk***: medications generally not recommended; focus on health behaviour modifications (smoking cessation, diet, exercise)
- For those at ***intermediate and high risk***: health behaviour modifications + lipid-lowering medication (details might vary for different risk groups)

Summary of recommended health behaviour modifications:

- ***Diet***: Mediterranean dietary pattern, Portfolio dietary pattern, Dietary Approaches to Stop Hypertension (DASH) dietary pattern, plant-based dietary pattern, dietary patters high in nuts, legumes, olive oil, fruits, vegetables, total fibre, and whole grains
- ***Exercise***: at least 150 minutes of vigorous aerobic activity per week + muscle- and bone-strengthening activities at least 2 days per week

Diagnosis and Secondary Prevention

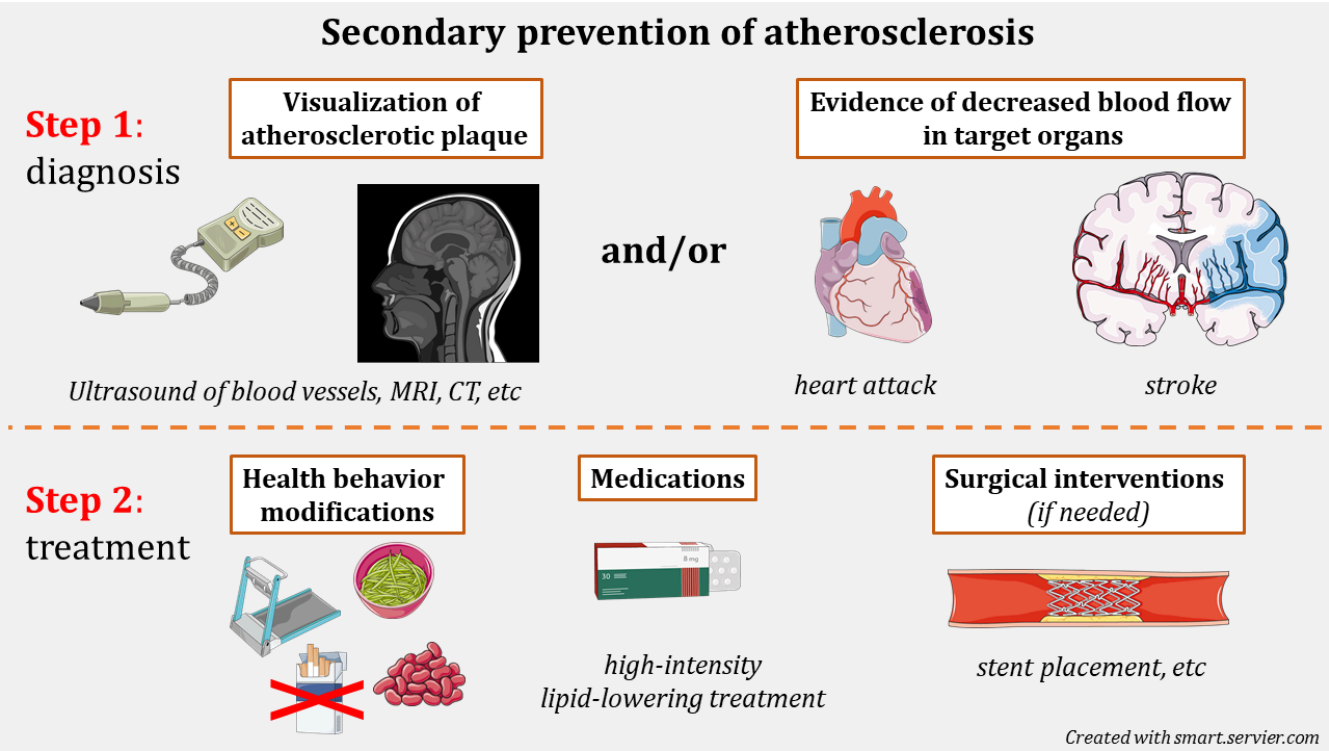
Secondary prevention efforts involve interprofessional health teams that work together to optimally manage patients with existing atherosclerosis with or without history of cardiovascular events (heart attack, stroke, etc) to prevent further disease progression and exacerbation.

> **Please note:** Some healthcare systems (including British Columbia) classify disease prevention as primary, secondary, and tertiary. In this case, ***primary prevention*** refers to efforts towards preventing the occurrence of the disease, ***secondary*** – efforts towards early diagnosis, and ***tertiary*** – efforts towards improvement of quality of life and reduction of symptoms in those with a diagnosed condition.
>
> Learn more: https://www.healthlinkbc.ca/healthy-eating-physical-activity/conditions/physical-activity-and-disease-prevention

Diagnosis of atherosclerosis generally involves:

1. direct visualization of atherosclerotic plaques (via ultrasound, computer tomography, or other imaging techniques)
2. definitive evidence of **ischemia** in target organs (evidence of heart muscle damage as a result of heart attack, etc)

As a general approach, patients with diagnosed atherosclerosis benefit from health behaviour modifications and high-intensity lipid-lowering therapy.
However, the location and characteristics of atherosclerotic plaque may warrant additional medical treatments/surgical interventions.



Diagnosis and Secondary Prevention of Atherosclerosis

Overall, ***prevention of atherosclerosis is a complex task that involves both behavioural and societal changes***.

The ability an individual to make health behaviour modifications to common risk factors of atherosclerosis (type of diet, stress levels, ability to exercise regularly, quality sleep, etc) depends on social factors, such as income level, education, employment, cultural/family habits, etc. It is important to recognize the role of public health measures and policies (availability and cost of different products, marketing strategies of unhealthy products, knowledge about impacts of various diets, etc) in the prevention of atherosclerosis. Thus, decreasing the global burden of atherosclerosis is not only an individual-level task but also an important public health responsibility and priority.

Role of Interprofessional Health Teams in the Prevention and Treatment of Atherosclerosis

In practice, a team of healthcare professionals (general practitioners, cardiologists, emergency doctors, cardiac technologists, nurses, radiologists, etc) works together during each case of acute or chronic atherosclerosis diagnosis and care.

One of the most common procedures that helps assess the blood flow of the heart and its function involves administering an electrocardiogram (EKG) or a stress test to a patient with suspected atherosclerosis/**ASCVD**.

Listen to Andrea Glew, a cardiac sciences technologist, as she discusses the experiences of patients who obtain an EKG or a stress test.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=827#h5p-62

Role of EKG and Stress Tests During Prevention and Treatment of Atherosclerosis by Andrea Glew, licensed under All Rights Reserved

Key Takeaways

EKG is a routine painless procedure that records electric impulses of the heart and provides information about heart blood supply and function. EKG can detect changes that occur as a result of reduced blood flow and heart damage – common symptoms of atherosclerosis. EKGs are often administered by cardiac technologists at the emergency departments where patients can present with signs and symptoms consistent with a heart attack. The EKG findings are then transferred to the physician/nurse for further assessment and decision-making.

The **stress tes**t is used to detect atherosclerosis outside of the emergency setting. The patient is connected to a cardiac monitor and is asked to walk on a treadmill. Certain changes detected by a heart monitor can occur as a result of increased heart rate and blood pressure, suggesting decreased blood flow to the heart. Often these changes can be missed by EKG administered at rest. A stress test can also help determine the degree of blood flow reduction/severity of atherosclerosis.

Section Review

While primary prevention of atherosclerosis focuses on changing/addressing modifiable risk factors (smoking, diet, exercise level, etc) to defer the onset of the disease, secondary prevention aims to delay the progression of diagnosed atherosclerosis. Secondary prevention methods include health behavior modifications (same as in primary prevention) and lipid-lowering medications (the dosage depends on the severity of atherosclerosis). Some advanced cases of atherosclerosis might require surgical interventions to renew the blood flow in obstructed vessels. Atherosclerosis diagnosis and management efforts involve interprofessional health teams that work together to design and help facilitate optimal prevention/treatment plans for each case of this lifelong condition.

Resources

https://www.onlinecjc.ca/article/S0828-282X(21)00165-3/fulltext

https://www.nature.com/articles/s41572-019-0106-z

Review Questions

1. Finish the following sentence. Primary prevention of atherosclerosis involves:
Select all that apply.

- Dietary considerations
- Exercise considerations
- Smoking cessation
- Genetic testing

2. Secondary prevention involves actions aimed to treat patients with diagnosed atherosclerosis to minimize it's future health impact.

- True
- False

3. Finish the following sentence. The most commonly used type of medications used in atherosclerosis prevention are:

- Lipid-lowering
- Glucose-lowering
- Anti-hypertensive
- Anti-inflammatory

4. Fill in the blank.

_____ is a routine procedure that helps assess heart function by recording its electric impulses.

5. Health behaviour modifications are the cornerstone of both primary and secondary atherosclerosis prevention strategies.

- True
- False

Answer Key

1. Dietary considerations, exercise considerations, smoking cessation

2. True
3. Lipid-lowering
4. EKG/ECG
5. True

Media Attributions

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- Secondary prevention © Tetiana Povshedna is licensed under a CC BY-NC (Attribution NonCommercial) license

Clinical Side of Angina

JENNIFER KONG

Want more practice with the clinical side of angina? Or to read what it's like for a patient to have unstable angina? See these additional Open Education resources.

A patient's journey through the health care system

Meet fictional patient Harj Singh in the Appendices: Case Study of Unstable Angina where we follow his journey from a severe anginal symptoms and visit to the ER, as he meets many health care professionals working together on his diagnosis and care.

Select clinical skills used by health care providers

To learn about the skills of assessing a patient with signs and symptoms of angina, please read chapter 2 "Patient Assessment" from the Open Education resource Clinical Procedures for Safer Patient Care by Doyle & McCutcheon.

Evolving Concepts and Research Frontiers - Atherosclerosis and Microbiota

TETIANA POVSHEDNA

The role of **gut microbiota** is actively being investigated in the context of cardiovascular disease in the past few decades. Some evidence implicating gut and oral microbiota in the development and progression of cardiovascular disease include ***altered microbial composition*** in individuals with CVD compared to controls and ***bacterial DNA in atherosclerotic plaques***. While mechanistic understanding of the relationship between microbiota and clinical outcomes is still lacking, multiple studies have pointed toward associations and mechanisms which might connect gut microbiota and the development of atherosclerosis. Some of these diet-related mechanisms are highlighted below and point toward possible behavioural interventions that could be incorporated into atherosclerosis prevention strategies if proven causal. So far, most of the data in the field are coming from animal studies, and there is no consensus about the relationship between diet, gut microbiota, and atherosclerosis. Thus, the research findings should not be interpreted as dietary or medical advice.

Possible Mechanisms that Connect Diet, Gut Microbiota, and Atherosclerosis

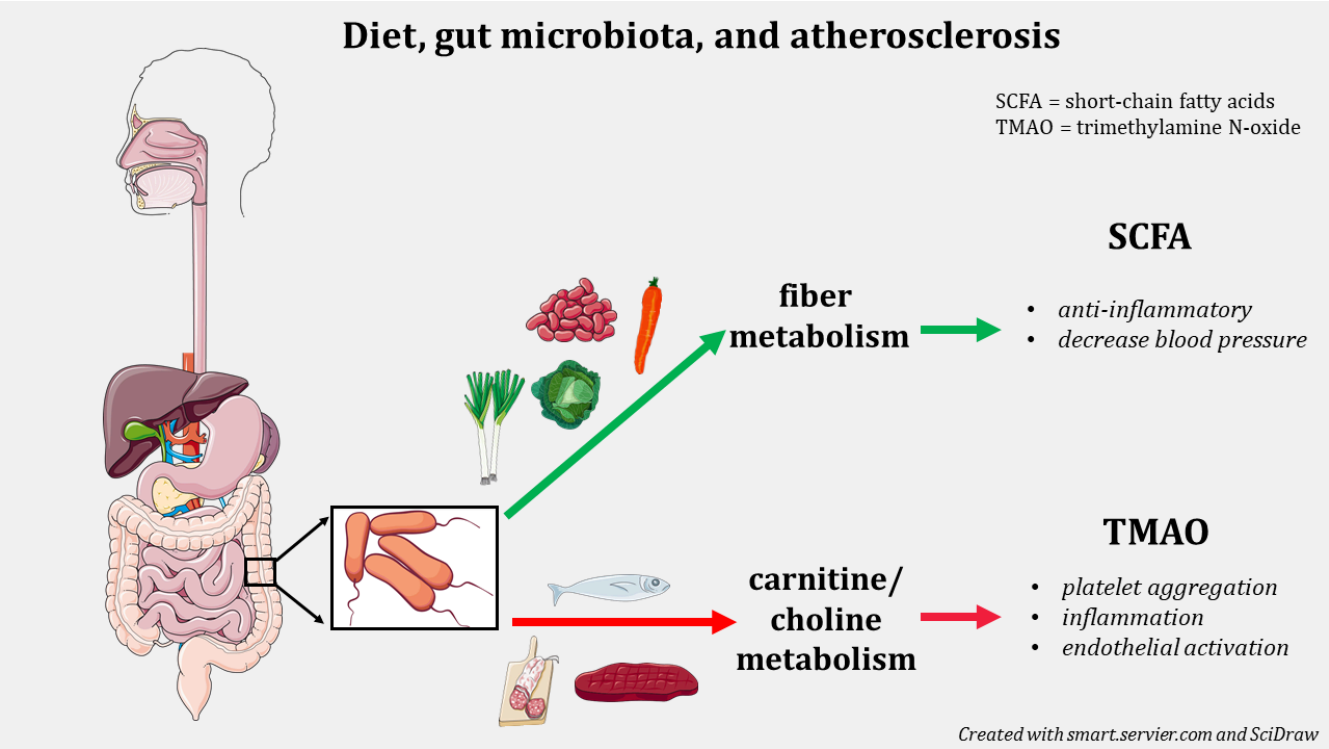
Short-chain Fatty Acids

Changes in intestinal wall permeability (the "leaky gut" concept), which occur in multiple disease states, including cardiovascular, allow for the transport of bacterial metabolites through the intestinal wall into the systemic circulation. Once in the systemic circulation, molecules produced by gut microbiota can induce a pro-inflammatory state in the host which, in turn, can worsen existing chronic conditions, including atherosclerosis. At the same time, some molecules produced by bacteria can have anti-inflammatory properties. The gut microbiota-derived **short-chain fatty acids**, which are produced during fiber fermentation by bacteria, can decrease blood pressure (a known risk factor for atherosclerosis), as shown in some animal and human studies. This possible link presents an interesting avenue for behavioral and therapeutic interventions and an opportunity to leverage the benefits of plant-based diets.

Trimethylamine N-oxide (TMAO)

TMAO is a dietary component that's produced by gut microbiota as a result of phosphatidylcholine, choline, and carnitine (contained in red meat, eggs, fish) metabolism. Some studies have found an association between higher amounts of this molecule, the likelihood of cardiovascular events (heart attack, stroke), and atherosclerosis severity. Some proposed mechanisms include TMAO's ability to facilitate platelet

aggregation (*a necessary step of clot formation*), inflammation (*a risk factor of atherosclerosis*), and endothelial activation (*often the first step in atherosclerosis lesion initiation*). A possible link between the amount of red meat consumption, TMAO levels, and the likelihood of **ASCVD** points towards the importance of dietary considerations for atherosclerosis prevention.



Diet, Gut Microbiota, and Atherosclerosis

As the body of evidence connecting gut microbiota and cardiovascular disease grows, scientists are exploring microbiota-targeted interventions to prevent atherosclerosis progression. These include:

- use of prebiotics (food/supplements that are used by beneficial gut microbiota)
- use of probiotics (foods/supplements that contain live microorganisms)
- TMAO production inhibitors
- dietary measures (variations of the plant-based diet with high dietary fiber and fermentable substrates content)
- targeting "leaky" intestinal membranes

Section Review

New research suggests that metabolites produced by gut microbiota can affect atherosclerosis development and progression. Numerous animal and human studies have shown intriguing associations between certain dietary patterns and atherosclerosis risk/outcomes. However, since the causal relationships between various diet components and atherosclerosis outcomes have not been established, these data should be interpreted with caution.

Review Questions

1. Finish the following sentence. The term "microbiota" refers to:

- Bacteria
- Fungi
- Parasites
- Bacteria, fungi, and viruses enhabiting a multicellular organism

2. Bacterial metabolites produced during fibre fermentation might decrease risk of atherosclerosis.

- True
- False

3. Fill in the blank.

One of the choline metabolites, _____, is pro-inflammatory and can increase risk of atherosclerosis.

Answer Key

1. Bacteria, fungi, and viruses enhabiting a multicellular organism
2. True
3. TMAO

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Atherosclerosis Chapter Summary and Credits

TETIANA POVSHEDNA

Chapter Summary

Atherosclerosis is the leading cause of ischemic heart disease worldwide, and its prevalence and impact continue to increase despite the advances in treatment and prevention strategies.

Formation of atherosclerotic plaques involves the activation/injury of **endothelium**, which triggers the deposition of lipids within the blood vessel wall. Plaques are most commonly located at the branching points of large arteries, which warrants close attention to these places during diagnosis. As atherosclerotic plaques progress, they can cause blood vessel lumen obstruction and/or clot formation, which results in ultimate blood flow restriction and **ischemia** of the target organ. Clinically, advanced atherosclerosis presents as heart attack, stroke, peripheral artery disease, aneurysm, etc. While all these conditions occur at various locations within the vascular tree and cause impairment to different organs, it's important to remember that they share the same underlying cause – a ***preventable*** condition (atherosclerosis).

While some non-modifiable factors (sex, ethnicity, genetic changes) affect an individual risk of atherosclerosis, it's important to recognize the effect of some modifiable factors (smoking, low activity levels, unhealthy diet, high blood pressure, etc) on atherosclerosis risk and progression. Primary and secondary prevention efforts at the individual and public health levels are important to prevent atherosclerosis onset and early diagnosis. Health behaviour changes that address modifiable risk factors are at the core of primary and secondary prevention and usually preceded lipid-lowering medication considerations.

Credits

Author: Tetiana Povshedna (UBC graduate student)

Author of questions and exercises: Tetiana Povshedna (UBC graduate student)

Gross anatomy and histology videos: Tetiana Povshedna (UBC graduate student) with supervision of Dr. Gang Wang (UBC, Director of DHPLC)

Cardiac Technologist: Andrea Glew (Cardiac Sciences Technology, BCIT)

Video editing: Dr. Jennifer Kong

Post-Test for Atherosclerosis

JENNIFER KONG

1. Fill in the blank. Atherosclerosis is the leading cause of _____, which contributes to the majority of deaths globally.

2. Fill in the blanks.

Most of the blood vessels share a similar structure and consist of three layers.

The innermost layer, also known as _____, consists of a single layer of endothelium and some connective tissue. The atherosclerotic process is initiated within this layer. The middle layer, _____, contains smooth muscle, allows for blood vessel contraction/distension, and helps regulate _____. Lastly, _____ contains connective tissue fibers, blood vessels that supply the tissues within the blood vessel wall, and nerves.

3. Finish the following sentence. Aorta, the largest artery in the human body, is able to conduct large volumes of blood ejected from the heart and respond to blood pressure fluctuations due to high content of:

- Collagen fibers
- Elastin fibers
- Proteoglycans
- Phospholipids

4. High-density cholesterol is also known as "bad cholesterol" and is associated with an increased risk of atherosclerosis.

- True
- False

5. Cellular changes that occur during the atherosclerotic plaque development DO NOT include:

- Deposition of lipid particles within the tunica intima and tunica media
- Formation of foam cells
- Deposition of calcium that hardens the vessel wall and decreases it's elasticity
- Formation of a soft necrotic core and a protective fibrous cap
- Deposition of cholesterol crystals
- Formation of new blood vessels within the plaque to ensure sufficient blood supply to the lesion

6. Finish the following sentence. Individual and public health efforts towards early diagnosis of atherosclerosis, as well as decrease of the burden of existing atherosclerosis, are called:

- Primary prevention
- Secondary prevention
- Prophylaxis
- Damage control

7. Modifiable risk factors of atherosclerosis that can be changed by targeted health behaviour interventions include: Select all that apply.

- Genetic predisposition
- Smoking
- Ethnicity
- Blood pressure
- Physical activity level

Answer Key

1. Ischemic heart disease
2. Tunica intima, tunica media, blood pressure, tunica adventitia
3. Elastin fibers
4. False
5. Formation of new blood vessels within the plaque to ensure sufficient blood supply to the lesion
6. Secondary prevention
7. Smoking, blood pressure, physical activity level

PNEUMONIA AND PULMONARY EDEMA

Pneumonia Chapter Overview

SIMON DUFFY AND MEIHUA E. SU

Chapter Learning Objectives

At the end of this chapter, you will be able to:

- Describe the pathophysiology of pulmonary edema as a consequence of severe bacterial and viral pneumonia.
- Identify key inflammatory events contributing to pulmonary edema.
- Outline expected clinical changes in a patient in response to infection, inflammation and respiratory distress.

This chapter is about pneumonia, a condition that involves infection of the lung and triggers an inflammatory response resulting in pulmonary edema. Pulmonary edema is a serious condition where the lungs fill with fluid instead of air, making it difficult to breath. Health care workers need to be acutely aware of the occurrence of pulmonary edema because it increases the likelihood that patients will need mechanical ventilation and because it is a major contributor to in-hospital mortality.

This chapter is subdivided into:

- Pre-test
- Lung anatomy
- Normal physiology of breathing and the cough reflex
- Pulmonary circulation, organs and structures of the respiratory zone
- Lung microbiome and barriers to infection
- Bacterial and viral pneumonia
- Inflammatory responses to infection
- Gross pathology and histopathology of infection
- Diagnosis and Treatment of Pulmonary Edema
- Interview with medical radiography technologist (Xray) and a medical lab technologist (microbiologist)
- Case study of two patients with pneumonia: Erin Johns (and English speaker and advocates for herself) and Miki Huang (a non-English speaker with family as her advocate)
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

CBC	Complete Blood Count
COVID-19	SARS-CoV-2 Virus
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
Hib	Haemophilus Influenzae Type B
HPIV	Human Parainfluenza Virus
IgA	Immunoglobulin A
PCV13	Pneumococcal Conjugate Vaccine
RSV	Respiratory Syncytial Virus

Pre-Test for Pneumonia

SIMON DUFFY

1. Finish the following sentence. Pneumonia is an infection of the lungs caused by:

- Bacteria
- Viruses
- Fungi
- All of these microbes

2. A person with pneumonia usually has a dry cough.

- True
- False

3. What is the best way to protect yourself from possibly developing severe viral pneumonia caused by influenza?

- Eating well and exercise
- Annual vaccine
- Regular hand hygiene
- Avoiding public transit

Answer Key

1. All of these microbes
2. False
3. Annual vaccine

Lung Anatomy

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

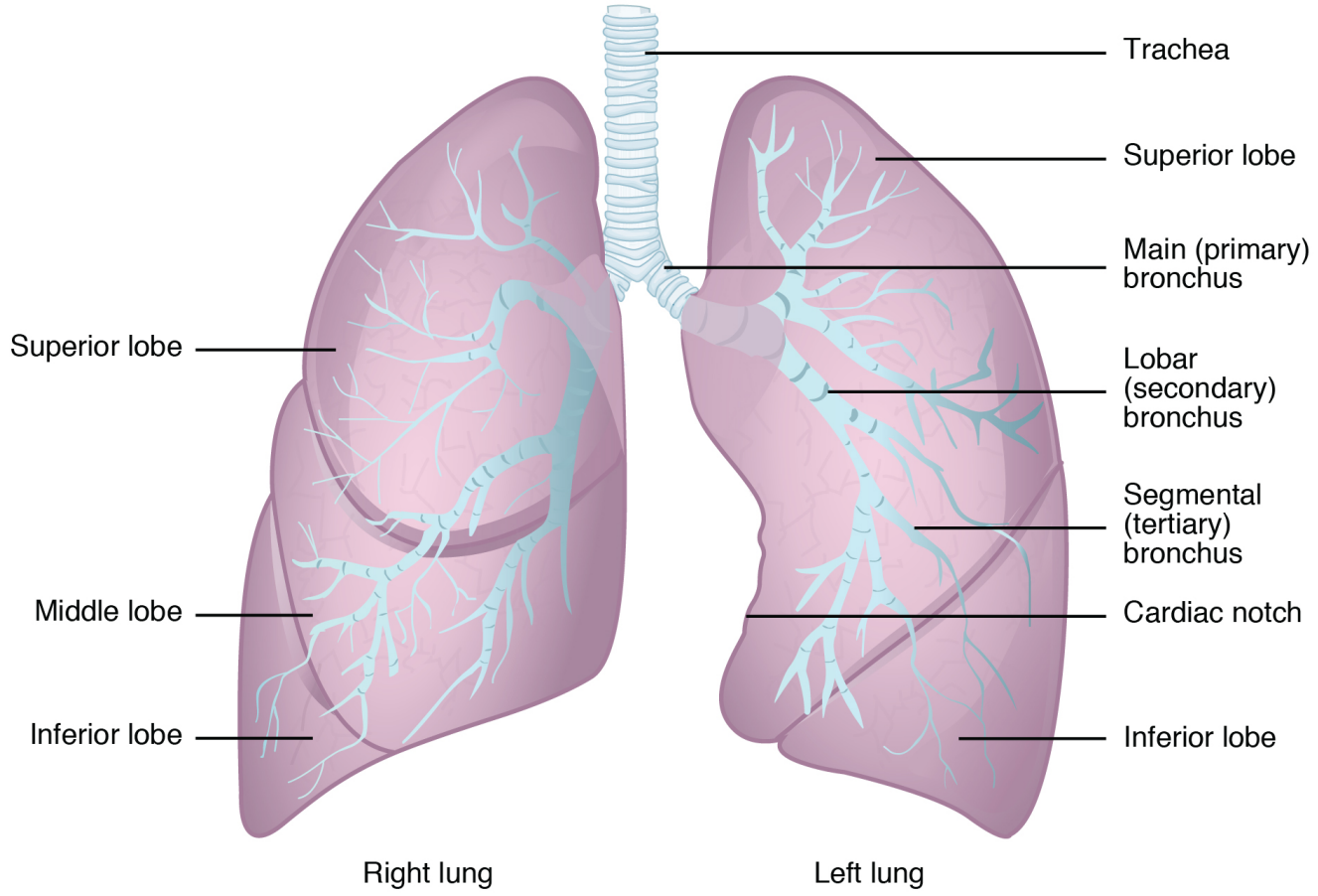
By the end of this section, you will be able to:

- Describe the overall function of the lung.
- Summarize the blood flow pattern associated with the lungs.
- Outline the anatomy of the blood supply to the lungs.
- Describe the pleura of the lungs and their function.

A major organ of the respiratory system, each **lung** houses structures of both the conducting and respiratory zones. The main function of the lungs is to perform the exchange of oxygen and carbon dioxide with air from the atmosphere. To this end, the lungs exchange respiratory gases across a very large epithelial surface area—about 70 square meters—that is highly permeable to gases.

Gross Anatomy of the Lungs

The lungs are pyramid-shaped, paired organs that are connected to the trachea by the right and left bronchi; on the inferior (lower) surface, the lungs are bordered by the diaphragm. The diaphragm is the flat, dome-shaped muscle located at the base of the lungs and thoracic cavity. The lungs are enclosed by the pleurae, which are attached to the mediastinum. The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right. The **cardiac notch** is an indentation on the surface of the left lung, and it allows space for the heart. The apex of the lung is the superior (upper) region, whereas the base is the opposite region near the diaphragm. The costal surface of the lung borders the ribs. The mediastinal surface faces the midline.



Gross anatomy of the lungs.

Each lung is composed of smaller units called lobes. Fissures separate these lobes from each other. The right lung consists of three lobes: the superior, middle, and inferior lobes. The left lung consists of two lobes: the superior and inferior lobes. A bronchopulmonary segment is a division of a lobe, and each lobe houses multiple bronchopulmonary segments. Each segment receives air from its own tertiary bronchus and is supplied with blood by its own artery. Some diseases of the lungs typically affect one or more bronchopulmonary segments, and in some cases, the diseased segments can be surgically removed with little influence on neighboring segments. A pulmonary lobule is a subdivision formed as the bronchi branch into bronchioles. Each lobule receives its own large bronchiole that has multiple branches. An interlobular septum is a wall, composed of connective tissue, which separates lobules from one another.

Blood Supply and Nervous Innervation of the Lungs

The blood supply of the lungs plays an important role in gas exchange and serves as a transport system for gases throughout the body. In addition, innervation by the both the parasympathetic and sympathetic nervous systems provides an important level of control through dilation and constriction of the airway.

Blood Supply

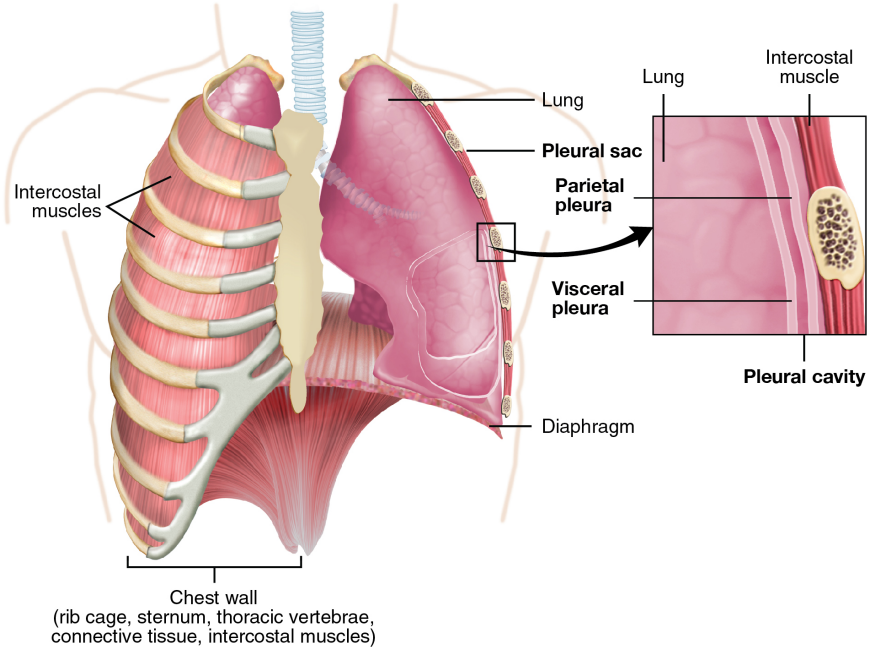
The major function of the lungs is to perform gas exchange, which requires blood from the pulmonary circulation. This blood supply contains deoxygenated blood and travels to the lungs where erythrocytes, also known as red blood cells, pick up oxygen to be transported to tissues throughout the body. The **pulmonary artery** is an artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli. The pulmonary artery branches multiple times as it follows the bronchi, and each branch becomes progressively smaller in diameter. One arteriole and an accompanying venule supply and drain one pulmonary lobule. As they near the alveoli, the pulmonary arteries become the pulmonary capillary network. The pulmonary capillary network consists of tiny vessels with very thin walls that lack smooth muscle fibers. The capillaries branch and follow the bronchioles and structure of the alveoli. It is at this point that the capillary wall meets the alveolar wall, creating the respiratory membrane. Once the blood is oxygenated, it drains from the alveoli by way of multiple pulmonary veins, which exit the lungs through the **hilum**.

Nervous Innervation

Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems. The parasympathetic system causes **bronchoconstriction** (narrowing of the bronchi), whereas the sympathetic nervous system stimulates **bronchodilation** (opening of the bronchi). Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control. Sensory nerve fibers arise from the vagus nerve, and from the second to fifth thoracic ganglia. The **pulmonary plexus** is a region on the lung root formed by the entrance of the nerves at the hilum. The nerves then follow the bronchi in the lungs and branch to innervate muscle fibers, glands, and blood vessels.

Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The **visceral pleura** is the layer that is superficial to the lungs, and extends into and lines the lung fissures ((Figure)). In contrast, the **parietal pleura** is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The **pleural cavity** is the space between the visceral and parietal layers.



Parietal and Visceral Pleurae of the Lungs

The pleurae perform two major functions: They produce **pleural fluid** and create cavities that separate the major organs. Pleural fluid is secreted by mesothelial cells from both pleural layers and acts to lubricate their surfaces. This lubrication reduces friction between the two layers to prevent trauma during breathing, and creates surface tension that helps maintain the position of the lungs against the thoracic wall. This adhesive characteristic of the pleural fluid causes the lungs to enlarge when the thoracic wall expands during ventilation, allowing the lungs to fill with air. The pleurae also create a division between major organs that prevents interference due to the movement of the organs, while preventing the spread of infection.

Critical Thinking Questions

Why is there a difference in size and shape between the right and left lungs?

The right and left lungs differ in size and shape to accommodate other organs that encroach on the thoracic region. The right lung consists of three lobes and is shorter than the left lung, due to the position of the liver underneath it. The left lung consist of two lobes and is longer and narrower than the right lung. The left lung has a concave region on the mediastinal surface called the cardiac notch that allows space for the heart.

Why are the pleurae not damaged during normal breathing?

There is a cavity, called the pleural cavity, between the parietal and visceral layers of the pleura. Mesothelial cells produce and secrete pleural fluid into the pleural cavity that acts as a lubricant. Therefore, as you breathe, the pleural fluid prevents the two layers of the pleura from rubbing against each other and causing damage due to friction.

Section Review

The lungs are the major organs of the respiratory system and are responsible for performing gas exchange. The lungs are paired and separated into lobes; The left lung consists of two lobes, whereas the right lung consists of three lobes. Blood circulation is very important, as blood is required to transport oxygen from the lungs to other tissues throughout the body. The function of the pulmonary circulation is to aid in gas exchange. The pulmonary artery provides deoxygenated blood to the capillaries that form respiratory membranes with the alveoli, and the pulmonary veins return newly oxygenated blood to the heart for further transport throughout the body. The lungs are innervated by the parasympathetic and sympathetic nervous systems, which coordinate the bronchodilation and bronchoconstriction of the airways. The lungs are enclosed by the pleura, a membrane that is composed of visceral and parietal pleural layers. The space between these two layers is called the pleural cavity. The mesothelial cells of the pleural membrane create pleural fluid, which serves as both a lubricant (to reduce friction during breathing) and as an adhesive to adhere the lungs to the thoracic wall (to facilitate movement of the lungs during ventilation).

Review Questions

1. Which of the following structures separates the lung into lobes?

- Mediastinum
- Fissure
- Root
- Pleura

2. Finish the following sentence. A section of the lung that receives its own tertiary bronchus is called the:

- Bronchopulmonary segment
- Pulmonary lobule
- Interpulmonary segment
- Respiratory segment

3. The _ _ _ _ _ circulation picks up oxygen for cellular use and drops off carbon dioxide for removal from the body.

- Pulmonary
- Interlobular
- Respiratory

- Bronchial

4. The pleura that surrounds the lungs consists of two layers. Name the layers.

- Visceral and parietal pleurae
- Mediastinum and parietal pleurae
- Visceral and mediastinum pleurae
- None of the above

Answer Key

1. Fissure
2. Bronchopulmonary segment
3. Respiratory
4. Visceral and parietal pleurae

Adaption

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Normal Physiology of Coughing

MAX YANG

Learning Objectives

By the end of this section, you will be able to:

- Define coughing and describe it as a protective physiological response of the respiratory system.
- Identify the components of an effective cough.
- Describe the importance of medical history, cough duration, and symptoms that can help differentiate between acute and chronic coughs.
- Identify potential causes of a cough from its characteristics.

Coughing is a normal physiological response of the body's defense and ventilation systems, controlled by voluntary (i.e. conscious control) or involuntary (i.e. reflex) means.

It is associated with a variety of different diseases or ailments; therefore, it is crucial to obtain a close examination of the patient's medical history, cough duration and other related symptoms to understand the cause.

These factors can differentiate between a short-term cough which could simply be a case of an obstructed airway (i.e. choking) or the presence of a long-term chronic cough that is more likely associated with an underlying disease.

Epidemiology

Coughing is one of the most common symptoms observed by doctors and has critical implications in health and disease management. They account for more than 30 million visits to the physician a year. A systematic review in 2015 uncovered that the global prevalence of a chronic cough was 9.6% with the greatest affected areas in Oceania and Europe [1].

Physiology

A cough is a 3-part response triggered by the activation of airway mechanosensory receptors called slowly adapting receptors (SARS) and rapidly adapting receptors (RARS).

- **Detection/Sensing**: For a cough to be triggered, it must first activate afferent sensory pathways where the RARS acts as a sensor leading to a specific output (like a switch). RARS are the major contributors in triggering a cough which detects mechanical and/or chemical irritation like foreign particles, smoke, etc. The output in this case is the cough.

Once triggered, the action of a cough can be split into three main components: inspiration, compression and expiration.

1. **Inspiration**: The main muscles of normal inspiration (diaphragm and external intercostal muscles) activate and expand the volume of the thoracic cavity. Accessory muscles including the sternocleidomastoid and scalene muscles draw additional air into the lung to increase air volume within the chest. This subsequently increases the effectiveness of the later stages of the cough.
2. **Compression**: The glottis, a valve between the vocal folds in the larynx, closes tightly. This seals in the air that was inhaled during inspiration. The expiration muscles begin to contract via the passive recoil of the lungs' elastic properties and accessory expiration muscles (abdominal and internal intercostal muscles). By decreasing the chest volume, there is a short-lasting build-up of high-pressure air in the lungs that's ready to be expired.
3. **Expiration**: In the last stage, the glottis opens which allows the build-up of air to escape quickly and rapidly. Further activation of accessory expiratory muscles forcefully expels the remaining air out. This rapid movement of air exiting the lungs and through the mouth helps dislodge mucous or irritants trapped within the lining of the respiratory tract. Through multiple cycles of these 3 stages, the body can clear out any foreign material or irritants located in the respiratory tract.

A cough can be classified depending on its duration. Those lasting less than 3 weeks would be considered acute, coughs lasting 3-8 weeks are considered subacute and coughs lasting more than 8 weeks are considered chronic.

- Acute cough (<3 weeks)
- Subacute (3-8 weeks)
- Chronic (>8 weeks)

Examples of an Acute Cough

- **Acute Pneumonia:** An infection within the respiratory system where the lungs could fill with liquid resulting in consolidation during imaging. RARs will detect inflammatory markers and excess fluid in the airway thereby triggering a cough.
    - **Why?**: The lungs and the body are attempting to remove pathogens and congestion from the clogged respiratory tract.
- **Foreign Body Aspiration (Choking)**: When an object becomes lodged within the respiratory tract (especially the trachea or main bronchi)and triggers mechanosensory RARs inducing a cough.
    - **Why?**: Pressure build up in the respiratory tract triggers the body to have a rapid emergency response to remove the object as quick as possible.

Examples of a Chronic Cough

- **Asthma**: A chronic inflammatory obstruction of the airways due to bronchial hypersensitivity which could be triggered by environmental or genetic causes.
    - **Why?**: Coughing is a natural response due to the inflamed/narrowed airway, allergen/environmental triggers or response to excess mucous secreted
- **COPD**: A progressive disease with characteristics of both chronic bronchitis and emphysema.
    - **Why?**: A persistent cough is present due to inflammatory markers, narrowed airways, mucous and failure of

efficient expiration (i.e. wheezing) triggering RARs and a subsequent cough.

Management Principles

- Understanding the underlying source of a cough is key in providing an effective treatment.
- A detailed medical history will help determine if the cough is acute (short-term) or chronic (long-term). History taking can reveal any symptoms which may have presented itself when the cough began. Uncovering the systems impacted (immune, gastrointestinal etc.) will give a better picture of the disease.
    - For example, a cough accompanied with a fever and productive cough often indicates an infection.
    - A cough accompanied by a sour taste/heart burn can indicate GERD.
    - Shortness of breath and other specific breathing patterns (i.e. shallow rapid breaths) could indicate COPD.
- A clinical examination should be performed by examining the nose (i.e. obstruction), oropharynx (i.e. swelling, strep throat), and chest (i.e. chest x-ray).
- Pneumonia caused by a bacteria would be managed with antibiotics whereas, a cough triggered by a lodged foreign object would require the removal of the object.
    - An interesting case in 2017 investigated a man who presented to the doctor with a chronic cough. To the doctor's surprise after a chest x-ray, they discover the patient swallowed a small traffic cone toy 40 years prior, has stayed undetected and lodged! [2]
- Cough medications, also known as antitussives, can be given to patients to help suppress a cough which interferes with the patients' quality of life during work, sleep or exercise. Mucolytics are another option which can be given to help break down mucous and aid in producing a productive cough. The origins and details of an acute or chronic cough helps health care teams understand and create treatment plans tailored to each individual patient for better outcomes.

Review Questions



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=9043#h5p-435

1. Which of the following is not needed to produce a cough?

- Functional respiratory and glottis muscles
- Normal lung volume
- Neurological control of diaphragm
- Stimulation of chemical receptors in the airway and surrounding structures

2. Coughing needs mucous.

- True
- False

3. Fill in the missing words.

All of us have bouts of involuntary coughing such as being on a dusty road. Inhalation of an _____ stimulates the chemical receptors in the airway, sending a message to the _____. This initiates a motor message to do a rapid _____, then _____ the glottis, and finally the contraction of the muscles normally needed to _____ – resulting in a buildup of pressure that will explode with enough force to removed the inhaled _____.

Answer Key

1. Stimulation of chemical receptors in the airway and surrounding structures
2. False
3. All of us have bouts of involuntary coughing such as being on a dusty road. Inhalation of an **irritant/allergen** stimulates the chemical receptors in the airway, sending a message to the **brain/cough centres**. This initiates a motor message to do a rapid **inhalation**, then **close** the glottis, and finally the contraction of the muscles normally needed to **exhale** – resulting in a buildup of pressure that will explode with enough force to removed the inhaled **irritant/allergen**.

Notes

1. Song, W.-J., Chang, Y.-S., Faruqi, S., Kim, J.-Y., Kang, M.-G., Kim, S., Jo, E.-J., Kim, M.-H., Plevkova, J., Park, H.-W., Cho, S. H., & Morice, A. H. (2015). The global epidemiology of chronic cough in adults: A systematic review and meta-analysis. European Respiratory Journal, 45(5), 1479–1481. https://doi.org/10.1183/09031936.00218714
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Pulmonary Circulation, Organs and Structures of the Respiratory Zone

J. GORDON BETTS; KELLY A. YOUNG; MARK WOMBLE; BRANDON POE; OKSANA KOROL; DEAN H. KRUSE; PETER DESAIX; JAMES A. WISE; JODY E. JOHNSON; AND EDDIE JOHNSON

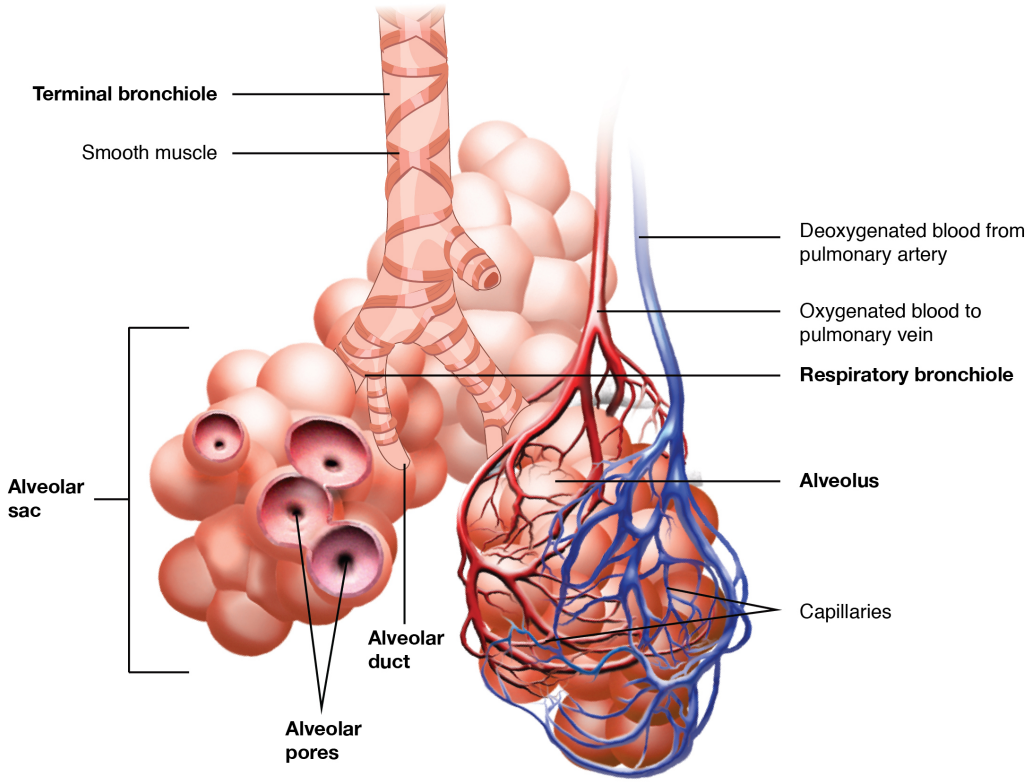
Learning Objectives

By the end of this section, you will be able to:

- List the structures that make up the respiratory zone.
- Describe how the respiratory system processes oxygen and CO2.
- Trace the path of oxygenated and deoxygenated blood as it arrives and leaves the alveoli.
- Identify the vessels through which blood travels within the pulmonary circuit, beginning from the right ventricle of the heart and ending at the left atrium.

Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. The respiratory zone begins where the terminal bronchioles join a respiratory bronchiole, the smallest type of bronchiole, which then leads to an alveolar duct, opening into a cluster of alveoli.

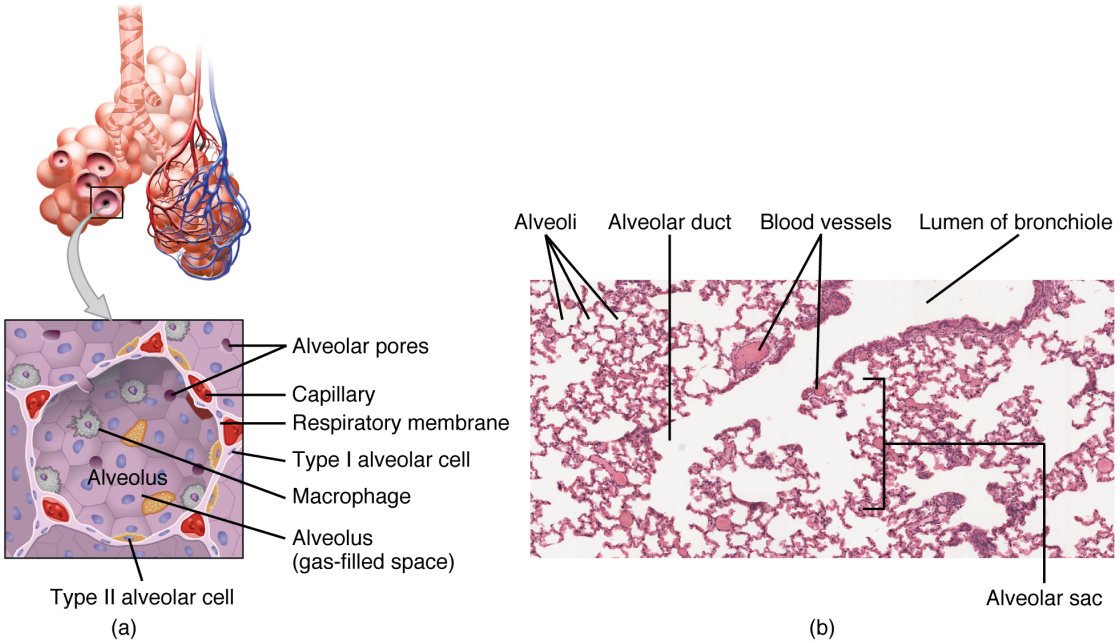


The Respiratory zone – *Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.*

Alveoli

Alveolar duct is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An alveolus is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An alveolar sac is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 μm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. The image below shows that alveoli are connected to their neighbors by alveolar pores, which help maintain equal air pressure throughout the alveoli and lung.



Structures of the Respiratory Zone *(a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

The alveolar wall consists of three major cell types: type I alveolar cells, type II alveolar cells, and alveolar macrophages. A type I alveolar cell is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. A type II alveolar cell is interspersed among the type I cells and secretes pulmonary surfactant, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli. Roaming around the alveolar wall is the alveolar macrophage, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a respiratory membrane that is approximately 0.5 µm (micrometers) thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO2 to be released into the air of the alveoli.

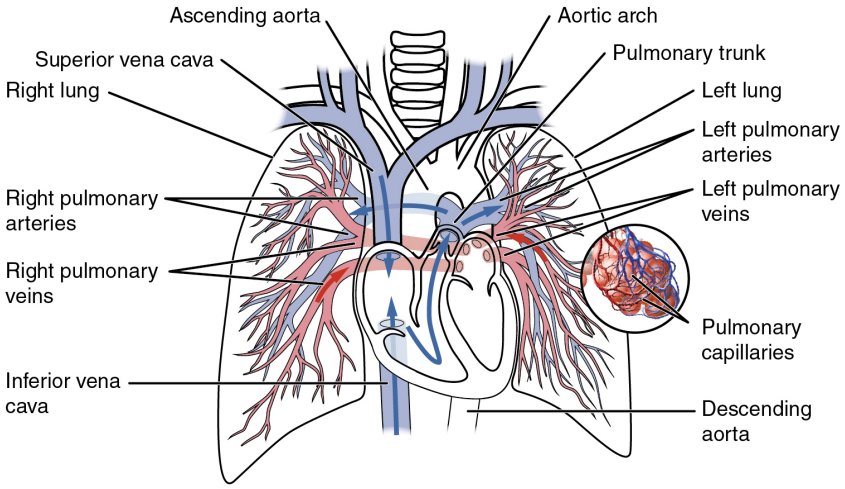
Pulmonary Circulation

Recall that blood returning from the systemic circuit enters the right atrium via the superior and inferior venae cavae and the coronary sinus, which drains the blood supply of the heart muscle. These vessels will be described more fully later in this section. This blood is relatively low in oxygen and relatively high in carbon dioxide, since much of the oxygen has been extracted for use by the tissues and the waste gas carbon dioxide was picked up to be transported to the lungs for elimination. From the right atrium, blood moves into the right ventricle, which pumps it to the lungs for gas exchange. This system of vessels is referred to as the pulmonary circuit.

The single vessel exiting the right ventricle is the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve, which prevents backflow of blood into the right ventricle during ventricular diastole. As the pulmonary

trunk reaches the superior surface of the heart, it curves posteriorly and rapidly bifurcates (divides) into two branches, a left and a right pulmonary artery. To prevent confusion between these vessels, it is important to refer to the vessel exiting the heart as the pulmonary trunk, rather than also calling it a pulmonary artery. The pulmonary arteries in turn branch many times within the lung, forming a series of smaller arteries and arterioles that eventually lead to the pulmonary capillaries. The pulmonary capillaries surround lung structures known as alveoli that are the sites of oxygen and carbon dioxide exchange.

Once gas exchange is completed, oxygenated blood flows from the pulmonary capillaries into a series of pulmonary venules that eventually lead to a series of larger pulmonary veins. Four pulmonary veins, two on the left and two on the right, return blood to the left atrium. At this point, the pulmonary circuit is complete (see the diagram below) defines the major arteries and veins of the pulmonary circuit discussed in the text.



Pulmonary Circuit – *Blood, exiting from the right ventricle, flows into the pulmonary trunk, which bifurcates into the two pulmonary arteries. These vessels branch to supply blood to the pulmonary capillaries, where gas exchange occurs within the lung alveoli. Blood returns via the pulmonary veins to the left atrium.*

Pulmonary Arteries and Veins	
Vessel	**Description**
Pulmonary trunk	Single large vessel exiting the right ventricle that divides to form the right and left pulmonary arteries
Pulmonary arteries	Left and right vessels that form from the pulmonary trunk and lead to smaller arterioles and eventually to the pulmonary capillaries
Pulmonary veins	Two sets of paired vessels—one pair on each side—that are formed from the small venules, leading away from the pulmonary capillaries to flow into the left atrium

Section Review

The lining of the conducting zone is composed mostly of pseudostratified ciliated columnar epithelium with goblet cells. The mucus traps pathogens and debris, whereas beating cilia move the mucus superiorly toward the throat, where it is swallowed. As the bronchioles become smaller and smaller, and nearer the alveoli, the epithelium thins and is simple squamous epithelium in the alveoli. The endothelium of the surrounding capillaries, together with the alveolar epithelium, forms the respiratory membrane. This is a blood-air barrier through which gas exchange occurs by simple

diffusion. The right ventricle pumps oxygen-depleted blood into the pulmonary trunk and right and left pulmonary arteries, which carry it to the right and left lungs for gas exchange. Oxygen-rich blood is transported by pulmonary veins to the left atrium after gas exchange occurs across the respiratory membrane inside the capillaries of the lung. The left ventricle pumps this blood into the aorta.

Review Questions

1. Fill in the blanks. The _____ ventricle of the heart pumps oxygen-depleted blood to the lungs via the pulmonary _____ which will continue to branch until they become pulmonary capillaries which envelop the _____ where gas exhange occurs. The vessels that leave now carry oxygenated blood via the pulmonary _____ back to the _____ atrium.

2. What is the role of alveolar macrophages?

- To secrete pulmonary surfactant
- To secrete antimicrobial proteins
- To remove pathogens and debris
- To facilitate gas exchange

3. What would be the consequence of the respiratory membrane suddenly getting thicker (e.g. during inflammation)?

- Reduced gas exchange
- Reduced blood flow to the alveoli
- Reduced blood flow away from the alveoli
- Improved gas exchange

Answer Key

1. Right, arteries/trunk, alveoli, veins, left
2. To remove pathogens and debris
3. Reduced gas exchange

Adaptation

This chapter is adapted from the following text:

Pulmonary Circulatory Pathway and Organs and Structures of the Respiratory Zone and Pulmonary Circulation **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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Lung Microbiome and Barriers to Infection

SIMON DUFFY

Learning Objectives

By the end of this section, you will be able to:

- Describe the nature of the normal microbiome of the lung.
- Describe why the lung is specifically at risk for infection.
- Explain the principles of mucociliary clearance.
- Outline the physical and immunological barriers to infection of the respiratory tract.

The upper airways of the respiratory tract are relatively rich in microbes. Sampling of the lower airways of the lung have shown that there is a much lower biomass and much fewer microbes present. However, the lower airways are not sterile and have a considerable diversity of microbes. These microbes collectively form an ecological community that share this space, called a microbiome. This microbiome consist of symbiotic and commensal microbes that support the healthy lung but can also include pathogenic microbes that can contribute to lung and other diseases.

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Normal lung microbiome created by Sarah Perkins, licensed under CC BY NC ND license

Microbiome of the Lung

Throughout the 1900s it was widely believed that the lung was a sterile space where microbes could not grow. Modern techniques involving DNA sequencing-based microbe identification have since revealed that the microbiome is an important part of a healthy lung and that microbes may protect the lung from injury and the development of allergies. The resident microbes of the lung exist in a natural balance and are part of lung homeostasis. During infection, these microbes may communicate with and alert our immune system to increase mucus secretion and other host defenses. Chronic lung disease disrupt the microbial balance and may leave the lung more susceptible to infection.

Lung Epithelium as a Barrier to Infection

A person will breath 10,000L of air each day and this this air will contact lung epithelium that spans a vast surface area (over 100 m^2) in order to enable efficient gas exchange. Tightly packed epithelium cells are needed to keep microbes from entering human tissues. In the airways, these cells secrete an additional protective layer of mucus, while the alveoli are protected by secretion of surfactant. It is important to note that the walls of the alveoli are very thin to allow for efficient gas exchange. When pathogens penetrate this thin alveolar wall, the tissue becomes inflamed and immune cells enter into the alveolar sac as pus. This immune response to infection is pneumonia.

Mucociliary Clearance

The trachea, bronchi and larger bronchioles contain mucus-producing goblet cells and submucosal glands. The airway is also lined with epithelial cells that have hair-like projections called cilia, which work in conjunction to goblet cells in order to maintain a nearly sterile lung through the process of mucociliary clearance. Mucus is a sticky and viscous substance that often contains antimicrobial components, such as lysozyme enzyme or immunoglobulin A (IgA). Small particulate dust or pollutants, allergens, infectious agents become trapped in the viscous mucus. The movement of cilia on the surface of airway epithelia carries mucus-encapsulated particles away from the respiratory zone of the lung .

Secretion of mucus entraps foreign particles and infectious agents, while the movement of cilia carries these entrapped particles away from the lung.

Barriers to Alveolar Infection

Throughout the respiratory tract, the airway lumen is lined with epithelial cells that associate by tight junctions to prevent infection. Mucus also serves as a physical barrier and a carrier for mucociliary clearance. However, the mucociliary system does not extend to the alveoli because mucus impedes airflow and gas exchange. Instead, alveolar cells consist of type I pneumocytes, which are optimized for gas exchange, and type II pneumocytes, which are more numerous and perform secretory functions.

Alveolar pneumocytes still form epithelial tight junctions, but unlike the thicker pseudostratified cell layers of the bronchi, the alveolar cells form a squamous thin layer of cells. Type II pneumocytes secrete surfactant to primarily reduce surface tension and prevent alveolar collapse. However, surfactant also contains proteins that opsonize foreign cells, making them more likely to be consumed by phagocytes.

Immune cells, such as macrophages and dendritic cells, play an important role in removing debris and infectious agents within the alveoli. Macrophages and dendritic cells are phagocytes, meaning that they consume foreign material. These cells may remain within the epithelium or enter the air spaces to eliminate infectious agents, toxins, or allergens. In the context of an infection, these cells are potent inducers of inflammation and in persistent infection they alert the T-cells and B-cells of the adaptive immune response, through a process called antigen presentation.

Section Review

- The upper respiratory tract is typically colonized by commensal microbes, collectively known as the microbiome.
- The lower respiratory tract, including the lungs, have a microbiome consisting of significantly fewer microbes.
- The microbe-poor alveoli of the lung are maintained by preventing microbes from reaching the alveoli via mucus secretion and ciliary clearance of the mucus-encapsulated microbes in the upper airway.
- Surfactant secretion as well as resident macrophage immune cells are barriers to infection in the alveoli.
- Macrophages can also trigger inflammation that is characteristic of pneumonia.

Review Questions

1. Why are the lung alveoli at particularly high risk for infection?

- The alveolar epithelium is thin to allow for gas exchange.
- Unlike the upper airway, which secretes mucus, the alveoli do not secrete fluid that performs a protective function.
- The alveoli have a smaller surface area, resulting in a concentration of microbial cells along their surface.

2. Fill in the blank with the following words.

IgA	epithelia
goblet	lysozyme

Mucus is secreted into the airway by _____ cells. This mucus is viscous and contains antimicrobial compounds such as _____ enzyme and _____ antibodies. Specialized _____ cells of the airway have cilia cell extensions that sweep the mucus up and out of the respiratory tract.

3. Immune cells enter into the alveolar air spaces in order to eliminate potential pathogens and to remove debris.

- True
- False

Answer Key

1. The alveolar epithelium is thin to allow for gas exchange.
2. Mucus is secreted into the airway by **goblet** cells. This mucus is viscous and contains antimicrobial compounds such as **lysozyme** enzyme and **IgA** antibodies. Specialized **epithelia** cells of the airway have cilia cell extensions that sweep the mucus up and out of the respiratory tract.
3. True

Bacterial and Viral Pneumonia

SIMON DUFFY

Learning Objectives

By the end of this section, you will be able to:

- Identify clinically relevant forms of bacterial and viral pneumonia.
- Compare and contrast major characteristics of different bacterial pneumonia.
- Compare and contrast major characteristics of different viral pneumonia.

Pneumonia involves an acute respiratory infection that is most commonly caused by viruses or bacteria. The consequence of infection is inflammation, which results in an accumulation of fluid and immune cells in the alveoli. As the alveoli fill with fluid, breathing becomes painful and oxygen intake is limited.

Bacterial Pneumonia

Pneumonia involves infection of the lungs, which results in inflammation, accumulation of fluid and migration of immune cells into the alveolar space. Bacterial pneumonia is both prevalent and can potentially contribute to serious illness. A common cause of bacterial pneumonia is *Streptococcus pneumoniae* (pneumococcus). Children and elderly are most affected by this disease, and it is estimated that one million children die every year from pneumococcal disease.

Examples of Bacterial Pneumonia

Streptococcus Pneumoniae (also known as Pneumococcus)

Most common cause of community-acquired bacterial pneumonia. In addition to pneumonia, pneumoncoccus accounts for half of cases of bacterial meningitis and can cause post-infection arthritis. Fortunately, the availability of pneumococcal conjugate vaccine (PCV13) is thought to prevent over 60,000 deaths every year[1].

Pneumococcal bacteria evade ingestion by macrophages and other phagocyte immune cells because the cell surface is encased in a polysaccharide capsule. The bacterium also releases pneumolysin O protein that forms pores in host cells, contributing to inflammation and bloody sputum. Some pneumococcal bacteria have developed resistance to penicillins and similar β-lactam antibiotics, requiring alternative antibiotics such as macrolides and fluoroquinalones.

Haemophilus Influenzae Type B (Hib)

Hib cause serious infection, especially in infants. In addition to pneumonia, meningitis is the most common clinical manifestation. Death occurs in 3-6% of cases and survivors may experience hearing impairment. The incidence of invasive Hib has decline by 99% since the introduction of routine childhood immunization.

Klebsiella Pneumoniae

These bacteria may be found in the intestine and nose of healthy individuals and are often spread by contamination of hands. The rates of people who are carriers for this pathogen are particularly high in hospital environments. Immune compromised individuals may develop pneumonia, which is associated with 30-50% mortality. Part of the reason for this poor prognosis is due to increasing antibiotic resistance among these bacteria.

Pseudomonas Aeruginosa

These bacteria are commonly found in soil, water and throughout the environment. *P. aeruginosa* can cause serious bacterial pneumonia in patients with cystic fibrosis because these patients have a genetic defect that impairs mucociliary clearance. *P. aeruginosa* also cause pneumonia in patients that rely on an artificial ventilator because the bacteria are aspirated directly into the lung.

Viral Pneumonia

Pneumonia caused by viral infection occurs more frequently than bacterial pneumonia and result in infectious diseases, such as the flu (influenza virus) and COVID-19 (SARS-CoV-2 virus). Some people may experience viral infections of the naval cavity, called the "common cold". These *cold viruses* include rhinoviruses, adenoviruses and coronaviruses. Some cold viruses can disseminate from the nasal cavity to the lung to produce pneumonia.

Most viral pneumonias do not have a specific treatment but people typically get better on their own. While antibiotics are used to treat bacterial infection, these same medications are not effective against viruses. However, a viral pneumonia may place a person at greater risk of also contracting a bacterial infection, which would then have to be treated with antibiotics.

Examples of Viral Pneumonia

Adenovirus

Adenoviruses can cause infection of the digestive or urinary tract but must frequently contribute to respiratory illness. Adenoviruses are relatively resistant to disinfection and can spread on surfaces (e.g. doorknob, light switch). Respiratory illness can range from cold to pneumonia, croup and bronchitis.

Influenza Virus

Influenza virus can infect the nose, throat or lungs. It causes a respiratory illness called flu, which typically has more abrupt and intense symptoms that than the common cold. Also, people with the flu are more likely to experience fever and chills than people with the common cold. Flu can progress to pneumonia and may contribute to death in people with a weakened immune system.

Flu can spread from person to person by droplets made when people cough, sneeze or speak. These droplets harbouring virus can infect people up to 2 meters (6 feet) away or can contaminate surfaces. Flu is a vaccine-preventable disease and immunization significantly reduces a persons likelihood of needing medical support or hospitalization, following infection.

Human Parainfluenza Virus (HPIV)

People may get re-infected with HPIV multiple times in their life but those most frequently infected include infants, young children and people with a weakened immune system. Infected people may experience a range of illness, from clod-like symptoms to croup, bronchitis, bronchiolitis and pneumonia. HPIV is spread by droplets that fall within 2 meters (6 feet) or may remain airborne for over an hour.

Respiratory Syncytial Virus (RSV)

One of the most common childhood illnesses, RSV infection causes a cold-like illness. In some cases, this infection may contribute to pneumonia. Severe infection in infants, young children and those who are immune compromised may require hospitalization.

Coronavirus

Seven types of coronavirus are known to infect people. Four types cause mild-to-moderate upper respiratory infection. Three types (SARS-CoV, SARS-CoV-2, MERS-CoV) can cause severe pneumonia potentially resulting in death. SARS-CoV-2 is responsible for COVID-19, an infectious disease that spread as a global pandemic that contributed to the death of over 15 million people[2].

Review Questions

1. Place each term in the correct column. HiB, RSV, SARS-CoV, Pneumococcus, K. pneumoniae, HPIV

Virus	Bacterium

Answer Key

1.

Virus	Bacterium
SARS-CoV HPIV RSV	K. pneumoniae HiB Pneumococcus

Notes

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Pathophysiology of Pneumonia

NOAH STEWART

Learning Objectives

By the end of this section, you will be able to:

- Explain why certain individuals may be more predisposed to developing pneumonia than others.
- Outline the different inflammatory patterns present in pneumonia.
- Describe how inflammation in the lungs contributes to the symptomology of pneumonia.
- Describe the role of pulmonary edema in pneumonia.

Who Gets Pneumonia?

As discussed in the previous chapter, pneumonia is an infection of one or both lungs that is characterized by inflammation of the alveoli and interstitial tissue. The many pathogens that may cause pneumonia do not express explicit related features to infect the lower respiratory tract. Instead, pneumonia is largely considered to be the result of failure in the host response to pathogens, although the individual properties of microorganisms do contribute to their ability to cause pneumonia. For this reason, pneumonia most commonly affects children <5 years of age, adults >70 years of age, and patients with ongoing health problems – those whose defenses against infection are either not fully developed or may be weakened. Nevertheless, anybody may develop pneumonia. Pneumonia may be a primary condition, where there are no apparent pre-existing conditions that may predispose a patient to developing pneumonia, or a secondary condition where the patient has another condition that may predispose them to developing pneumonia, such as COPD, cystic fibrosis, or aspiration pneumonia.

Initial Infection and Colonization of the Lower Respiratory Tract

The first step in the pathophysiology of pneumonia is exposure to the pathogen. Owing to the variety of pathogens that can cause pneumonia, the ways in which they can first infect a person can vary. Most commonly the pathogens that cause pneumonia are spread when an infected individual coughs or sneezes and releases oropharyngeal secretions in the form of droplets into the air, which contain the pathogen. These droplets are suspended in the air and can be breathed in by others. Rarely, pathogens may spread to the lungs through the blood following an initial infection at another site of the body.

Failure of pulmonary protective mechanisms, in addition to features of the pathogen that help it infect the airways, can lead to penetration and proliferation of the pathogen in the lower respiratory tract. For example, in comatose patients whose cough reflex is impaired, or in chronic cigarette smokers whose mucociliary clearance is impaired, the ability

to prevent infection in the lower respiratory tract is diminished. The fine balance between the healthy and tolerated endogenous bacteria of the lower respiratory tract and the local and systemic defense mechanisms of the host is disrupted, thus leading to inflammation of the functional tissue of the lung (pneumonia).

Examples of Impaired Pulmonary Protective Mechanisms Seen in Pneumonia

Defense mechanism	Possible cause
Impaired cough reflex	Comatose patient, certain substances of abuse
Impaired mucociliary clearance	Cigarette smoking, Kartergerner syndrome
Accumulation of secretions	Cystic fibrosis, bronchial obstruction
Impaired systemic defense mechanisms	Cigarette smoking (suppressed neutrophil function), chemotherapy, HIV

The Immune Response to Infection

Following penetration and proliferation of the pathogen in the lower airways and alveoli, the immune system responds to eliminate the pathogens. The body's response to infection is what causes the clinical and histopathological findings of pneumonia, which will be discussed in more detail in later chapters. Infection and tissue damage spurs a systemic inflammatory response when chemical messengers called cytokines are released, although the exact inflammatory response depends on the type of pathogen. Cytokines are released when cells are damaged or when they recognize pathogens. Lung epithelial cells, when activated, release antimicrobial proteins and cytokines into the surrounding tissue to recruit neutrophils to the site of infection. Macrophages present in the alveoli play a large role in the innate immune response to infection. Alveolar macrophages are able to ingest (phagocytose) and kill pathogens, promote local inflammation, and release cytokines to attract other immune cells to the site of inflammation. To make it easier for immune cells to find and enter the site of infection from the bloodstream, the released cytokines cause dilation of nearby blood vessels leading to increased blood flow and leaky capillaries. This inflammatory response aims to destroy invading pathogens and infected cells, but also causes damage to the healthy lung tissue. The systemic cytokine release during pneumonia also acts on the hypothalamus in the brain and disrupts normal thermoregulation, causing fever and chills.

Patterns of Inflammation

There are three main inflammatory patterns depending on the cause of pneumonia and the areas that are affected: **lobar pneumonia**, **bronchopneumonia**, and **interstitial pneumonia**. Lobar pneumonia affects an entire lobe of the lung, and the inflammatory response causes the accumulation of cells, protein, and fluids leaking out of nearby capillaries in the lungs and into the alveoli of the affected lobe. The buildup of fluid and debris, known as plasma exudate, in alveoli prevents gas exchange from taking place, leading to less oxygen making it to the blood and a compensatory increase in respiratory rate and difficulty breathing. The fluid buildup also leads to irritation and attempted clearance of the airway by coughing, which leads to the production of phlegm. This is known as a productive cough.



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Pathophysiology of Lobar Pneumonia created by Sarah Perkins, licensed under CC BY NC ND license

Pulmonary Edema in Pneumonia

The abnormal buildup of fluid inside the lungs is called **pulmonary edema**. The most common cause of pulmonary edema is pressure-induced, where the circulatory system is unable to remove enough blood from the pulmonary circulation and thus causes it to leak into the lungs. This has been discussed in the chapter on Heart Failure. Pneumonia instead may cause pulmonary edema through inflammatory mechanisms by increasing the permeability of blood vessels in response to infection and tissue damage in the lungs, causing fluid to leak into the lungs.

On the other hand, certain pathogens cause what is known as interstitial pneumonia. Interstitial pneumonia affects the walls between alveoli, in contrast to lobar pneumonia which is caused by the buildup of inflammatory cells, fluid, and proteins inside of the alveolar spaces. Similar to lobar pneumonia, interstitial pneumonia results in the impairment of gas exchange and difficulty breathing. However, in the case of interstitial pneumonia, impairment of gas exchange is caused by the thickening of the alveolar walls which makes it difficult for gases to diffuse due to the increased distance between the blood vessels and the alveolar air space. Thickening of the alveolar walls is caused by the buildup of immune cells and cellular debris in the space between the alveoli and the blood vessels. The inflammatory response in the alveolar walls cause irritation and also trigger the cough reflex. In lobar pneumonia, coughing led to the production of phlegm via the fluid trapped inside the alveoli. Because there is no fluid buildup inside the alveolar airspace in interstitial pneumonia, a dry cough is produced.

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Pathophysiology of Interstitial Pneumonia created by Sarah Pinault, licensed under CC BY NC ND license

Bronchopneumonia, as the name suggests, is caused by the inflammation of the bronchi and nearby alveoli. Bronchopneumonia is similar to lobar pneumonia in its features, and often transforms into lobar pneumonia as the infection progresses. Bronchopneumia is hallmarked by the accumulation of inflammatory cells, debris, and fluid in the bronchi and/or bronchioles and adjacent alveoli in inflamed patches around the lung. This contrasts with lobar pneumonia, where the entire lobe of a lung and its alveoli are affected.

There are many ways to classify pneumonias. Classification by the pattern of involvement, as is presented above, is relevant histologically when lung tissue is viewed under the microscope (as will be discussed in the next chapter) as well as when looking at certain lab findings, such as chest X-rays. Other ways pneumonia can be classified are by the type of pathogen, how/where it is spread, and by how the patient presents.

Section Review

- Pneumonia is the result of pathogens overcoming the protective mechanisms of the body and penetrating into the lower respiratory tract.
- Patients who have reduced functioning of these barriers are at a greater risk for developing pneumonia.
- The clinical manifestations of pneumonia are the result of the body's inflammatory immune response to the invading pathogen.
- The pattern of inflammation can vary depending on the invading pathogen, but all may lead to the characteristic symptoms of fever/chills, fatigue, and dyspnea.
- Gas exchange can be impaired in pneumonia by the accumulation of fluid in the alveoli (pulmonary edema) or by the thickening of the space between alveoli and capillaries.

Review Questions

1. Place the phrases under the appropriate column. Phrases may be used more than once.

Low blood oxygenation	Productive cough
Fever	Nonproductive cough
Inflammation of the lungs	Fluid buildup in the airspace of the lung
Coughing	Thickening of lung tissue

Lobar pneumonia	Bronchopneumonia	Interstitial pneumonia

2. Pneumonia most commonly affects those with weakened or developing immunological defences.

- True
- False

3. Pneumonia can only occur as a secondary condition (i.e. due to the occurrence of another condition in the patient, such as COPD).

- True

- False

4. The pathogens that cause pneumonia are most commonly spread when an infected person coughs/sneezes, causing them to expel droplets from their respiratory tract that contain the pathogen into the environment.

- True
- False

5. Lobar pneumonia affects an entire lobe of the lung, and manifests with shortness of breath in the patient due to a buildup of immune cells and debris in the walls between alveoli and capillaries.

- True
- False

6. Explain, in terms of what happens microscopically, how someone can develop bacterial pneumonia and why they may experience trouble breathing. It may be useful to create a flowchart or stepwise plan to describe your thinking.

Answer Key

1.

Lobar pneumonia	Bronchopneumonia	Interstitial pneumonia
Low blood oxygenation Fever Inflammation in the lungs Coughing Productive cough Fluid buildup in the airspace of the lungs	Low blood oxygenation Fever Inflammation in the lungs Coughing Productive cough Fluid buildup in the airspace of the lung	Low blood oxygenation Fever Inflammation in the lungs Coughing Nonproductive cough Thickening of the lung tissue

2. True
3. False
4. True
5. False
6. **Example answer:**
   Prior to infection, a pathogen is typically inhaled (e.g. through respiratory droplets from another infected individual). Due to a failure in the innate defences of the host (cough reflex, mucus, ciliated respiratory epithelium, immune response,...) the pathogen can gain access to the lower respiratory tract (lungs). After the pathogen colonizes the lungs, it begins to multiply and the body responds when local cells release chemical messengers that recruit immune cells and cause inflammation. This inflammatory response is what causes the symptoms seen in pneumonia, and the pattern of inflammation can change depending on the pathogen and where it first colonizes along the lower

respiratory tract. For example, in lobar pneumonia and bronchopneumonia, inflammation concentrates within the airspace of the alveoli (and bronchi/bronchioles) leading to consolidation of the alveoli as they fill with fluid from leaky blood vessels, cellular debris, fibrin, and inflammatory cells. This congestion of the alveoli prevents gas exchange from occurring, leading to dyspnea (difficulty breathing) and tachypnea (increased rate of breathing). The majority of bacterial pneumonia lead to lobar or bronchopneumonia, and are most commonly caused by Streptococcus pneumoniae. However, pathogens may also infect the interstitium of the lungs, causing interstitial pneumonia. In interstitial pneumonia, the inflammatory response is concentrated in the alveolar walls (septae), which causes thickening of the space between capillaries and the alveolar air spaces with inflammatory cells, cellular debris, fluid, and possible scar tissue formation. Because of this, gas exchange cannot be carried out efficiently, leading to the similar symptoms of dyspnea/tachypnea.

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Video Lessons on Normal Lung: Gross Anatomy and Histology

NOAH STEWART AND JENNIFER KONG

Watch the following video lessons of the gross anatomy and histology of a normal lung.

Normal Gross Anatomy of the Lung

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Normal Histology of the Lung

The next 4 video lessons look at the histology of lung tissue from the spots along the respiratory tract: bronchi, bronchioles, and alveoli. The make up of tissue changes as one progresses from the upper respiratory tract (i.e. bronchi) to the lower (i.e. alveoli).

Overview of Lung Histology

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Bronchi

Bronchi are the largest airways (tubes) in the lung, with an average diameter in the centimeter scale. The defining

features of a bronchus histologically are the cartilaginous plates that provide structural support for the large airway which can be found around the edge of the bronchus, similar to the trachea in the upper respiratory tract. Bronchi, like other airways in the lung, are arranged in layers of cells. These layers, starting from the most luminal cells, are made up of:

A. Pseudostratified columnar epithelium ("respiratory epithelium") with 2 main cell types:

- **Goblet cells** – mucus-secreting, "balloon"-like. The mucus traps bacteria and debris and prevents it from reach the smaller airways
- **Ciliated cells** – columnar/"rectangular" with finger-like projections (cilia) facing the lumen of the airway. The cilia help to push the mucus with trapped substances upwards and towards the esophagus.

"Pseudostratified" refers to the fact that it appears like there are multiple layers of cells in the epithelium, however it is actually a single layer of densely packed cells that "stack up" on one another. All of these cells in this single layer are anchored to a thin layer of protein called the basement membrane

B. Lamina propria – wavy layer of loose connective tissue that lies beneath the epithelium

C. **Smooth muscle layer** – made up of distinctive wavy cells with stretched nuclei

D. **Mucous glands** – round arrangements of of secretory cells that secrete mucus and other products into a central lumen

E. **Fat cells** on the same layer as mucous glands

F. **Cartilage plates** (hyaline cartilage) – plates of thick, distinctive material that appear shiny under light microscopy and distinguish bronchi from bronchioles. The cartilage plates line the smooth muscle layer. Cells (called chondrocytes) can be found within "holes" (lacunae) within the cartilage.



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Bronchioles

Bronchioles are another type of airway in the lung. They can be classified into different types depending on their position within the airway (between bronchi and alveoli). They are smaller than bronchi but larger than other airways in the lung, with an average luminal diameter of less than one millimetre. Their structure is very similar to that of the bronchi, with notable differences being their **lack of cartilage or mucous glands**. The respiratory epithelium also becomes more cuboidal (cube-like)/shorter and there are less goblet cells present in the epithelium as you move farther down the airways towards the alveoli. A bronchiole that opens up and begins to branch into the alveoli is called a terminal bronchiole (average diameter of around 0.1 millimeters).

Alveoli

Alveoli are the smallest airways (sack) in the lung with an average diameter of around 0.5 μm. They are the functional unit of the lung and are the structures responsible for the actual gas exchange that occurs. Under the microscope they appear as isolated sacs in the lung, and consist of two distinct parts: the very thin alveolar walls or septae (made up of pneumocytes and capillaries), and the lumen (where the air fills).

Unlike the larger airways, the alveoli are no longer lined by respiratory epithelium. They have completely distinct cell types present, which are:

- **Type I pneumocytes** – very thin cells that form the thin wall of the alveolus, which is necessary for gases to diffuse across. Nucleus appears elongated, and the rest of the cell body stretches far and thin to cover a lot of area.

- **Type II pneumocytes** – a cuboidal cell also in the wall of the alveolus, that secretes surfactant into the lumen (and thus can appear "foamy") to prevent collapse of the alveoli.
- The **capillaries**, made up of endothelial cell(s) with red blood cells in the lumen – usually a single endothelial cell wraps around itself to form a very small lumen, where blood cells can pass through and carry out gas exchange across the very thin wall made by type I pneumocytes.
- **Alveolar macrophages** – present in small quantities in the lumen, carry out immunological surveillance of the lung and can eat up debris and thus commonly appear darkly pigmented under the microscope.



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Section Review

The lung contains many different tissue types, each with their own function. The upper respiratory tract (i.e. trachea, primary bronchi) contain many cartilaginous rings and plates to allow for a physical opening of the airways, independent of nervous control. As the airways get smaller, there is a reduction of cartilage and an increased presence of smooth muscle. Smooth muscle is neurally controlled and can allow for fine-tuned airway opening/closing dependent on the situation.

There are many cell types involved in the respiratory defense of the lungs. Goblet cells with ciliated epithelia work together the trap pathogens and debris in mucous made by goblet cells. The cilia then brush that mucous up towards the pharynx for either swallowing or coughing. Coughing is a neurologically controlled reflex that detects inhaled irritants and expel them with force. Alveolar macrophages reside in the alveolar air space and roams around looking for irritants and pathogens that escaped the aforementioned defenses.

There are 3 major cell types in the alveoli: type I pneumocytes that make up the bulk of the alveolar wall; type II pneumocyte which makes surfactant to prevent the collapse of alveoli; and capillary endothelial cells which allow for quick gas exchange between blood and the type I pneumocyte.

Review Questions

Critical Thinking Exercises

How do the microscopic appearances relate to their function in the lung: ciliated epithelial cells, goblet cells, smooth muscle cells, type I and II pneumocytes, capillary endothelial cells, alveolar macrophages?

- Ciliated cells: cilia faces the lumen of the airway to push the mucus (and trapped substances) up towards the esophagus.
- Goblet cells: goblet faces lumen of airway and are filled with clear, "balloon"-like sacs of mucus. Mucus is exported out of the cell into the airway so the mucus traps bacteria and debris for expulsion by coughing or swallowing.
- Smooth muscle cells – spindly, wavy cells with stretched nuclei. When contracted, the waves fold in resulting in shrinking of the cells. As the smooth muscle cells totally enclose the entire circumference of the airway, this will cause a shrinking of the airway diameter, thus restricted air entry.
- Type I pneumocytes – very thin, elongated cells that make up the alveolar wall. The cell has to be thin to both increase surface area and reduce diffusion distance between the alveoli air space and the capillaries.
- Type II pneumocytes – a cuboidal cell with a large round nucleus. Cuboidal cells are packed with organelles that produce and secrete surfactant into the lumen of the alveoli.
- Capillary endothelial cells – usually a single thin endothelial cell that fully wraps itself around to form a very small lumen, where blood cells can pass. The thin cell makes a small diffusion distance between the blood, type I pneumocyte, and the alveolar air space.
- Alveolar macrophages – large irregular shaped cells in the alveolar lumen. Commonly appear darkly pigmented due to the number of enzymes it can release when it encounters a pathogen.

Gross Pathology and Histopathology of Pneumonia

NOAH STEWART

Learning Objectives

By the end of this section, you will be able to:

- Distinguish between symptoms of lobar pneumonia, bronchopneumonia and interstitial pneumonia.
- Describe the unique features of each type of pneumonia.
- Explain how different types of pneumonia uniquely affect the gross features of the lung.

Histopathology of Pneumonia

Lobar Pneumonia

Lobar pneumonia occurs when entire lobe(s) become acutely inflamed, leading to the alveoli filling with fluid, cell debris, inflammatory cells, and fibrin (**consolidation**). Both grossly and under the microscope, the affected lobe(s) are clearly distinct compared to surrounding normal lobes and will be visibly discoloured, lose their spongy appearance, and will appear consolidated.

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Histologically, the alveolar walls will remain intact and thin, with stained material filling the lumen. The inflammation will affect the entire lobe(s) uniformly, with complete or nearly complete consolidation of the alveoli. As with other inflammatory processes, the blood vessels become congested. There are four main stages of lobar pneumonia that can be identified depending on what types of materials or cells can be found within the alveolar fluids:

Stage	Alveolar fluid findings
Congestion	Alveolar fluid with microorganisms, few RBCs/neutrophils
Red hepatization	Many RBCs, neutrophils and fibrin
Grey hepatization	RBC breakdown, fibrinopurulent exudate (pus)
Resolution	Clearance of exudate by macrophages, possible scar tissue formation

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Bronchopneumonia

Bronchopneumonia occurs when the infection begins within the bronchi/bronchioles, and then descends into the nearby alveoli. Because of this, consolidation of the alveoli occurs in patches around the affected bronchi/bronchioles. This pattern may or may not be localized to a single lobe of the lung.

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University of Michigan virtual Slide Box 151127 Histology slide of H&E stained lung with bronchopneumonia presented by Noah Stewart, licensed under a CC-BY-NC license

Interstitial Pneumonia

Unlike lobar or bronchopneumonia, interstitial pneumonia is characterized by the inflammation and congestion of the **alveolar walls/interstitial tissue**. Interstitial pneumonia can be identified by diffuse, patchy areas of inflamed interstitial tissue. The alveolar lumens will be mostly normal. Within the inflamed areas, the alveolar walls will be congested and may appear thicker than the alveolar lumens as they become filled with fluid, inflammatory cells, debris, and possibly scar tissue.

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DHPLC e-slide: PATH 425-014 Histology slide of H&E stained lung with interstitial pneumonia presented by Noah Stewart, licensed under a CC-BY-NC license

Outcomes of Pneumonia

A patient may present with different signs and symptoms, based on the type of pneumonia affecting them. Lobar pneumonia and bronchopneumonia normally present as *typical* pneumonia. This includes malaise, fever/chills, productive cough with purulent sputum (pus), difficulty breathing (dyspnea) or an increased rate of breathing (tachypnea). Interstitial pneumonia often presents as *atypical* pneumonia, which has a slow onset, malaise, fever without chills, muscle soreness, headaches, nonproductive (dry) cough.

Pneumonia has a wide range of outcomes depending on patient factors, the specific pathogen, the severity of infection, and the length of infection, among others. Severe complications, such as the formation of lung abscesses can occur in rare cases. An abscess is a cavity that contains liquefied necrotic (dead) tissue, pus, and microorganisms.



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Section Review

- Lobar pneumonia presents as a typical pneumonia and affects one or more lobes of the lung uniformly. Inflammation makes blood vessels more prominent while consolidation contributes to hepatization of the affected lobe(s).
- Bronchopneumonia presents as a typical pneumonia, originating in the larger airways and radiating to nearby alveoli. Consolidation is patchy and may be diffuse throughout the lung, but may progress to the more uniformly distributed lobar pneumonia.
- Interstitial pneumonia presents as an atypical pneumonia. Consolidation is absent but interstitial tissue may become inflamed and thicken and/or scar.

Review Questions

Normal lung histology

1. Which of the following features can be found in the terminal bronchioles? Select all that apply.

- Smooth muscle
- Glands present in the submucosa
- Cartilaginous plates
- Goblet cells
- Ciliated epithelial cells

2. Which cells can be found in the alveoli of normal lungs? Select all that apply.

- Goblet cells
- Alveolar macrophages
- Type I pneumocytes
- Type III pneumocytes
- Ciliated epithelium
- Type II pneumocytes
- Chondrocytes

3. Describe the microscopic appearance of the normal lung under a) low magnification and b) high magnification, at different levels within the airway.

4. Fill in the blanks.

The thin walls that separate the vascular _____ and the air-filled _____ is made up of Type _____ pneumocytes and Type II pneumocytes which are responsible for making _____. This allows for the exchange of gases and known as the blood-air barrier.

Pneumonia histopathology

1. Which of the following statements are true? Select all that apply.

- The clinical symptoms seen in lobar pneumonia are primarily due to thickening of the alveolar walls, which impairs the exchange of gas across the blood-air barrier.
- Bronchopneumonia and interstitial pneumonia appear very similar under the microscope, except bronchopneumonia involves consolidation of alveoli around the bronchi whereas the entire lobe(s) of lung is uniformly affected in interstitial pneumonia.
- In bronchopneumonia, the infection occurs first within the larger airways and then spreads to adjacent alveoli.
- Interstitial pneumonia occurs uniformly throughout an affected lobe of lung.

2. Fill in the provided table to compare and contrast lobar, broncho-, and interstitial pneumonias according to their clinical symptoms, unique histological features, and unique gross features.

Pneumonia	Clinical Symptoms	Unique Histological Features	Unique Gross Features
Lobar pneumonia			
Bronchopneumonia			
Interstitial Pneumonia			

Answer Key

Normal lung histology

1. Ciliated epithelial cells
2. Alveolar macrophages, Type I pneumocytes, Type II pneumocytes
3. **a)** At low magnification, the lung architecture appears spongy, with plenty of white space as the majority of the lung will be made up of the alveoli. You can also identify larger airways (bronchi) with their outer cartilaginous plates, smaller airways (bronchioles) and larger blood vessels. Veins and arteries can be distinguished primarily by the thickness of the layer of muscle surrounding the endothelium, however because the arteries of the lung are under lower pressure than other areas in the body, this difference can be less obvious.
   b) At high magnification, bronchi are distinguishable by the ciliated columnar epithelium with interspersed goblet cells, larger size, with glands present in the submucosa and cartilage present around the outer edge of the structure. Smooth muscle is also present below the epithelium, which allows for contraction of the bronchi. The submucosal glands will appear cuboidal (box-like) and in circular arrangements surrounding a common duct into which they will empty their secretory products (which can be seen in their cytoplasm). Under H&E staining, cartilage will appear bluish compared to the surrounding tissue, with chondrocytes present in “holes” (lacunae) within the cartilage. Moving down the airway, bronchioles can be identified by having a similar organization to the bronchi, but lacking cartilage and submucosal glands. They will generally be thinner, and will still be surrounded by a layer of smooth muscle. Depending on the depth within the bronchiole, the epithelium may appear less columnar (more cuboidal) and will have a higher proportion of goblet cells present. Continuing down the airway, the alveoli lose the ciliated epithelium, and instead contain thin septae with an epithelium consisting predominantly of type I pneumocytes (thin, spindly cells with elongated nuclei). Nuclei stain black/dark blue using H&E staining. Within the septae in high proportions are capillaries, made up typically of a single endothelial cell (blood vessel cell) wrapped

around itself to create a thin wall within which blood can flow. The thin capillary wall and alveolar epithelium allow for easy gas exchange within the lungs. Type II pneumocytes appear as cuboidal cells also within the alveolar epithelium, but take up only ~5% of the space. They are responsible for secreting surfactant, and thus appear foamy due to the products present in their cytoplasm. Lastly, alveolar macrophages can be identified by their large, round or ovoid appearance with a single acentric (off-centred) nucleus, and commonly appear with a dark/brown pigment due to update of various debris in the lungs, giving them the name “dust cells”.

4. Capillaries/pulmonary capillaries, alveoli, I/1, surfactant

Pneumonia histopathology

1. In bronchopneumonia, the infection occurs first within the larger airways and then spreads to adjacent alveoli.
2. See table below.

Pneumonia	Clinical Symptoms	Unique Histological Features	Unique Gross Features
Lobar pneumonia	Typical pneumonia: Malaise, fever/chills, productive cough with purulent sputum (pus), difficulty breathing/ increased rate of breathing (dyspnea, tachypnea).	Involves one or more lobes uniformly. Appearance may change depending on stage. Alveoli become consolidated (filled with fluid, cell debris, inflammatory cells, fibrin). Blood vessels become more prominent due to inflammation (dilate and increase in volume). Inflammation takes place within the lumen of the alveoli. Minimal damage to interstitium; alveoli are mostly intact and remain thin.	One (or more) lobes will appear affected while other lobes may appear normal. The affected lung will appear consolidated, larger and more dense due to exudate filling the alveoli. The lobe may appear similar to liver tissue (intermediate lobar pneumonia). Depending on the stage, the colour of the affected lobe(s) may change. For example, at one stage (gray hepatization), much of the blood in the tissue will have been broken down, giving the affected lobes a gray appearance.

Pneumonia	Clinical Symptoms	Unique Histological Features	Unique Gross Features
Bronchopneumonia	Typical pneumonia: Malaise, fever/chills, productive cough with purulent sputum (pus), difficulty breathing/ increased rate of breathing (dyspnea, tachypnea)	Accumulation of fluid, inflammatory cells, cell debris, fibrin in the bronchi and/or bronchioles in inflamed patches around the lung. May appear very similar to lobar pneumonia, and commonly progresses to lobar pneumonia	The lung will exhibit diffuse consolidation. It may spread to multiple lobes (unevenly), and appear in patchy areas where the lung tissue is obviously affected (difference in colour, white/black versus the normal healthy red/ brown lung colour). NB black spots around the lung are found in normal lung (anthrocotic pigments) due to everyday pollution, and not the result of pneumonia.

Pneumonia	Clinical Symptoms	Unique Histological Features	Unique Gross Features
Interstitial Pneumonia	Atypical pneumonia: Slow onset, malaise, fever without chills, muscle soreness, headaches, nonproductive (dry) cough	Unlike other inflammatory patterns, there is no consolidation (exudate buildup) of alveoli. Instead, interstitial pneumonia is marked by the diffuse thickening of interstitial tissue (alveolar septae) by inflammation (inflammatory cells, fluid, debris) and scar tissue. Alveolar walls will appear very thick in some parts of the lung, but others will appear relatively normal within the same lobe.	Unique appearance on chest X-ray. In interstitial pneumonia, affected areas may appear as fine white nodules (e.g. on the millimeter scale) where there are areas of acute inflammation. Visible airways (bronchi) in affected areas will not appear empty and open as they normally would due to thickening of the interstitial tissue.

Diagnosis and Treatment of Pneumonia

SIMON DUFFY AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Relate pathophysiology with clinical diagnosis of pneumonia.
- Briefly describe what X-ray is and how it is used in the diagnosis of pneumonia.
- Briefly describe what microbiology testing (medical laboratory sciences) is and how it is used in the diagnosis of pneumonia.
- Describe common treatment options for pneumonia.

Diagnosis of Pneumonia: Physical Examination

The lungs are not immediately visible because they are contained inside the chest cavity. However, a clinical professional can use their senses of sight, hearing, and touch in order to get clues for possible infection.

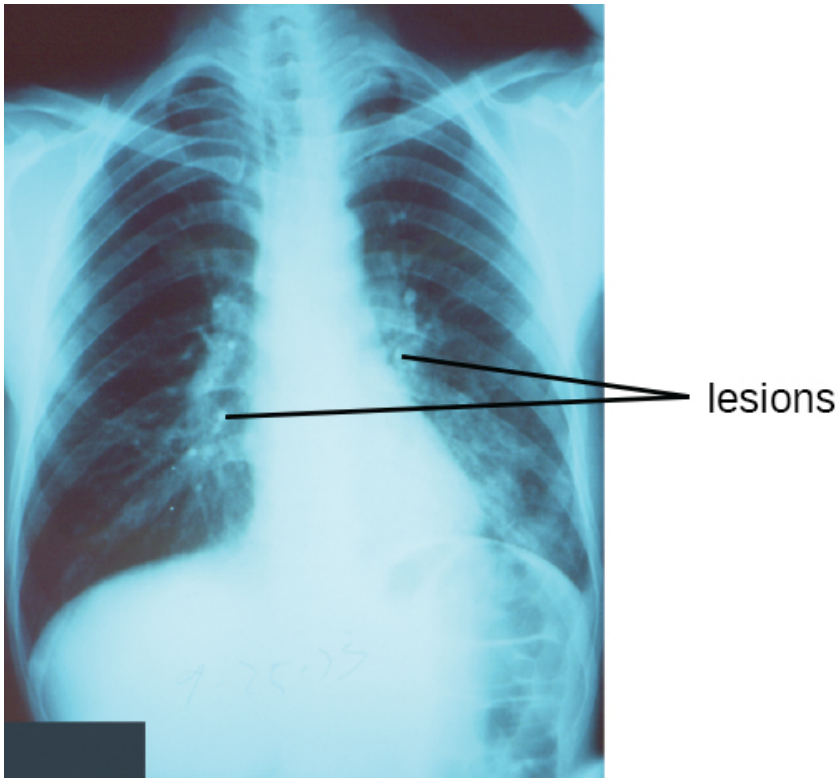
The sense of sight can be used to observe a patient's breathing. A person with pneumonia may not be getting enough oxygen, resulting this the need for a more rapid respiration rate (**tachypnea**). Also, this person will breath using muscles not normally engaged during breathing, called accessory muscles. The patient is working harder to breathe and may also complain of this sensation (**dyspnea**).

The sense of hearing can be used when performing auscultation (with or without percussion) during a physical exam. Listening for signs of infection – and when it happens during inhalation/exhalation – will involve the use of a stethoscope (**auscultation**). For example, the thick, sticky exudate in pneumonia may cause the lung to make abnormal sounds upon auscultation: a 'course crackle" in the affected lung. Percussion is tapping on the affected area of the chest. When listening during percussion, the flow of air can be easily heard during inhalation and exhalation. However, in pneumonia, the exudate – being mostly fluid – will dampen sound, resulting in a 'dull" or diminished breath sounds during auscultation. Auscultation while the patient is speaking can also help during examination. When a person speaks, the vocalizations may be transmitted more efficiently in the fluid that builds up within the lung. (recall that sound travels better in water than in air). Hence, these vocalizations will sound louder than normal using the stethoscope on the affected side.

The sense of touch can involve palpation, the process of using hands and fingers in order to feel evidence of illness. In normal breathing, you feel equal respiratory expansion on both sides of the body. However, in lobar pneumonia a whole section of the lung is not functioning and you would feel an asymmetric during chest expansion.

Diagnosis of Pneumonia: Medical Imaging (X-ray)

Consolidation of the lung can be easily visualized by X-ray. Recall that X-rays will make air-filled structures (like the lung) as black (radioluscent). However, the production of exudate in pneumonia (i.e. consolidation) will show up as white (radioopaque). Any abnormalities in the X-ray are defined as 'lesions'. Hence, X-rays are a fast and easily accessible method to determine the location and extent of consolidation.



Chest x-ray of a person with pneumonia. Lesions in the image represent regions of consolidation.

Listen to Michelle Beauchamp, a medical radiography technologist (X-ray), introduce how X-rays work. She explains the experience a patient with pneumonia (possibly due to heart failure complications) will have when coming in for a chest X-ray. She speaks about the important role medical radiography plays in a health care team in diagnosis of a disease. She also shares a fun fact about the diverse work environments of a medical radiography technologists!

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Medical Radiography (X-Ray) created by Michelle Beauchamp & Jennifer Kong, licensed under CC-BY-NC

Diagnosis of Pneumonia: Sputum Analysis

Sputum is the mucus that is coughed up from the lower airways of the respiratory tract, and can have many clues for a possible infection. The sputum colour may be informative. For example, a yellow or green colour may result from immune cells forming as pus within the airway. A rusty, pink or red colour may reflect blood-tinged sputum due to infectious exudate.

Visual inspection of sputum may not be enough to confirm infection, so sputum may be cultured in a laboratory to grow and analyze the microbes in it. Few microbes should grow in the lung sputum and the culture is considered *positive* when the number of microbes exceeds a safe range. Lab tests can aim to identify whether known pathogens are present in order to guide clinical decisions. In addition to a microbial culture to grow microbes, the microbes may be tested for sensitivity to antimicrobials (e.g. antibiotics). Culture & Sensitivity testing is an important step in selecting the most effective therapy for a patient.

Listen to Marion Regan, a medical laboratory technologist (microbiology), introduce her field and subspecialties. She speak about the journey the sputum specimen (from a patient with suspected pneumonia) takes from collection to identification. She also describes the important role of medical laboratory science in a health care team as their tests aid in the diagnosis of diseases. She also shares a fun fact about what it's like to work in a medical laboratory facility!



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Medical Laboratory Sciences (Microbiology) and Pneumonia created by Marion Regan & Jennifer Kong, licensed under CC-BY-NC

Diagnosis of Pneumonia: Blood Analysis

Blood tests can be used to generally assess a person's health by looking at the body's response to infection and the expected ensuing inflammatory response. A complete blood count (CBC) measures the overproduction of immune cells that may be due to infection. Erythrocyte sedimentation rate (ESR) is based on a phenomenon where red blood cells become more dense when people experience inflammation. Some blood molecules, such as C-reactive protein (CRP) and pro-calcitonin can be measured at high amount during inflammation. Blood oxygen levels may also be measured using methods like pulse oximetry. If the lung is not functioning properly, the content of oxygen in the blood might decrease while carbon dioxide levels may rise.

Blood tests can also monitor for potentially harmful infections of the blood, called septicemia. These involve culture and sensitivity tests, described in the sputum analysis section above. Infections of the bloodstream must be carefully managed because they can result in a severe immune response, called sepsis. Sepsis is the body's extreme response to infection, where there is a chain reaction of inflammation throughout the body. Due to the severity of this immune response, sepsis can rapidly lead to permanent tissue damage, organ failure and even death.

Treatment of Pneumonia

Treatment of pneumonia depends largely on what microbe is involved in the infection as well as how the illness presents. As well, treatment must also include methods to help the patient's feeling of dyspnea and lessen the effort of breathing during pneumonia. Until C&S results determine the specific antimicrobial, the health care team may implement changes to aid breathing. Medications can be given to help widen airways and, if necessary, dampen the swelling in airways due to inflammation. The best method to deliver this medication is through metered dose inhalers – more commonly known as 'puffers'. Similarly, if consolidation is significant enough to decrease gas exchange, blood oxygenation will be decreased and assessed with a pulse oximeter. If blood oxygen saturation becomes less than 95%, extra oxygen may be inhaled to enrich each breath during inspiration.

Interprofessional Collaboration During Diagnosis and Treatment of Pneumonia

As you can imagine, there is a large health care team involved when treating someone with pneumonia – especially if they have comorbidities and/or are hospitalized. Please read the following patient case studies to get a glimpse of the members of the health care team.

Listen to author Simon Duffy's interview with nurse Anna Kornienko as she describes her experience caring for a patient with pneumonia and coordinating patient access with the members of the health care team.



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Nursing management of pneumonia. Created by chapter author Simon Duffy and nurse Anna Kornienko, licensed under CC-BY-NC

Section Review

- A physical examination involving observation of breathing patterns, breathing sounds and palpation can provide evidence for pneumonia.
- Medical radiography technologists take X-rays, a type of radiation which helps visualize the body based on a tissue's density which can stop X-rays (radiopaque) or not (radiolucent). Chest X-rays allow for visualization of the size of the heart and whether there is fluid in the lungs – useful in the diagnosis of pneumonia.
- Microbiology, a specialty of medical laboratory science, can analyze blood and sputum samples to determine the identity of the pathogen which is causing infection and the antimicrobials which can treat the infection (e.g. antibiotics). Microbiology is integral to a primary care provider to choosing the appropriate antimicrobial to treat the pneumonia
- Treatment of pneumonia involves antimicrobials to manage the infection but also medications to support breathing and tissue oxygenation.

Review Questions

1. Which of the following statements is NOT true in regards to chest X-rays?

- X-rays use ionizing radiation to image the body for the diagnosis or monitoring of injury or disease.
- X-rays pass easily through air and are stopped by dense substances like bone.
- Patients undergoing a chest X-ray will typically have two images taken at 90 degrees of one another, to help make sure nothing is missed.
- When looking at a chest X-ray, normal lung will appear as white (radioopaque) while consolidated sections of lung will appear as black (radioluscent).

2. Which of the following could point towards a case of pneumonia? Select all that apply.

- A yellow/green or rusty colour to the patient's sputum sample
- A culture from patient sputum with a number of microbes below the threshold
- Blood tests show that the patient has a high complete blood count (CBC) and erythrocyte sedimentation rate (ESR)
- Chest X-ray showing multiple lesions throughout the lung

3. Explain how physical examination, medical imaging, sputum analysis, and blood analysis all contribute to the management of a patient with suspected pneumonia. Think about how a test might contribute to diagnosis or treatment.

Answer Key

1. When looking at a chest X-ray, normal lung will appear as white (radioopaque) while consolidated sections of lung will appear as black (radioluscent).
2. A yellow/green or rusty colour to the patient's sputum sample, blood tests show that the patient has a high complete blood count (CBC) and erythrocyte sedimentation rate (ESR), chest X-ray showing multiple lesions throughout the lung

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Pneumonia Chapter Summary and Credits

NOAH STEWART

Chapter Summary

The healthy lung hosts a diverse array of microbes that collectively form a microbiome. These resident microbes exist in a natural balance with the body's immune system, and can communicate with and alert the immune system to invading pathogens. In addition to the lung microbiome, other host defenses which protect the lung from infection include: mucociliary clearance (when the cilia of the respiratory epithelium sweeps mucus and its trapped contents toward the upper respiratory tract), anti-microbial components secreted into the airways, the tight coupling of airway epithelial cells via tight junctional proteins, opsonins present in surfactant secreted by type II pneumocytes in the alveoli, and resident immune cells such as alveolar macrophages in the lung. When these barriers to infection are weakened and overcome, pathogens may descend into and infect the lungs. It is for this reason that those with an already weak immune system or other barriers, such as the old, children, or patients with preexisting conditions, are at a greater risk of developing pneumonia.

Pneumonia most commonly involves an acute respiratory infection caused by bacteria or viruses which penetrate into the lower respiratory tract. Although both bacterial and viral pneumonias are prevalent and can contribute to serious illness, viral infection is the more common cause of pneumonia. Streptococcus pneumoniae (Pneumococcus) is the most common cause of community-acquired bacterial pneumonia. Viruses that can infect the nasal cavity (causing the "common cold") can also descend into the lungs and cause pneumonia.

Common infective causes of pneumonia

Bacterial	**Viral**
Streptococcus pneumoniae	Adenovirus
Haemophilus influenzae type b (Hib)	Influenza virus
Klebsiella pneumoniae	Human Parainfluenza virus (HPIV)
Pseudomonas aeruginosa	Respiratory syncytial virus (RSV)
	Coronavirus

When the body responds to an ongoing infection, chemical messengers (cytokines and chemokines) are released which cause and inflammatory response and recruit immune cells to the area to help deal with the infection. It is the inflammatory response to infection which causes pneumonia through infiltration of immune cells and fluid into the lung, and by the tissue damage that occurs as the body fights the infection. Depending on the pathogen and where it colonizes along the lower respiratory tract, different inflammatory patterns (lobar pneumonias, bronchopneumonias, interstitial pneumonias) can be seen microscopically. The clinical symptoms of short breath and increased rate of breathing are caused by consolidation of the alveoli as they fill with fluid, inflammatory cells and other substances (lobar/bronchopneumonias) or by thickening of the alveolar walls which (interstitial pneumonia), both of which limit the gas exchange that can occur between the blood in the capillaries and the air in the alveoli. The abnormal buildup of fluid in the lungs, in this case caused by inflammatory mechanisms, is called pulmonary edema.

Clinical professionals can get a hint of infection by performing a physical examination on patients who show symptoms of pneumonia. This involves performing auscultation (with a stethoscope) to listen for signs of infection through

abnormal sounds caused by the buildup of fluids in the lungs, using their hands/fingers to feel evidence of infection (palpitation) as the patient breathes, and watching the patient's breathing rate and what muscles are being used during breathing as an indication of infection. Chest X-rays can be used to visualize consolidation in the lungs based on the density of the tissue in the lungs, causing areas of fluid buildup to appear white on an X-ray. Analysis of patient sputum that is coughed up from the lower airways can also give indication to infection by visual analysis (if pus or blood is present). The sputum can also be sent to a microbiology laboratory to grow and analyze the microbes in it and to test antibiotic susceptibility, which helps choose the most effective therapy for a patient. Blood tests may also be used for diagnosis, as some molecules in blood indicate inflammation at high levels (due to infection) and abnormal blood-gas levels can indicate an issue in the function of the lungs. Blood tests can also be used to monitor for infections in the blood (septicemia) which can be extremely dangerous.

The treatment of pneumonia depends largely on the identity of the microbe involved in the infection and the presentation of the patient. A healthcare team can implement changes to aid breathing and medications can be given to widen the airways and decrease swelling due to inflammation. Extra oxygen may also be given to the patient if blood oxygen saturation becomes too low. Culture and sputum results can determine the specific antimicrobial that can be used to help fight the infection.

Credits

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Patient narratives of Pneumonia

JENNIFER KONG

There are two case studies on pneumonia with COPD.

Both case studies follow similar – but not identical – health journeys of elderly women with COPD who develop pneumonia, thus exacerbating their COPD. Both case studies demonstrate the many similarities in the diagnosis of pneumonia, treatment, and interactions with health care team.

In one case study, Miki Huang is a non English-speaker and relies heavily on her daughter as her translator and patient advocate Appendices: Case study for Pneumonia (Miki Huang). Contrast this with the other case study of Erin Johns who is an English-speaker and has no problem being her own patient advocate Appendices: Case Study for Chronic Obstructive Pulmonary Disease and pneumonia (Erin Johns). Although the underlying pathology is the same (ie pneumonia causing an exacerbation of COPD), Miki and Erin's perspectives are quite different.

Miki's case study was written by UBC English student Annabelle Liao in 2022. Erin Johns case study is from the Open Ed textbook "Health Case Studies" written by Rees, Kruger, & Morrison.

Post-Test for Pneumonia

SIMON DUFFY

1. The pathogens that can cause pneumonia always share similar explicit features that make them able to infect the lungs.

- True
- False

2. Cystic fibrosis is an inherited disorder in the CFTR gene that regulates the movement of chloride and sodium into and out of cells. Dysfunction of this gene leads to a buildup of abnormally thick mucous in the airways. Using what you've learned so far in this chapter, give a stepwise explanation as to why someone with cystic fibrosis may be at an increased risk of developing pneumonia.

3. Fill in the blanks.

Lobar pneumonia involves _____ filling the _____, preventing good gas exchange and producing a productive cough with phlegm. The airways are normal sized. In interstitial or bronchopneumonia, the airways are inflamed and swollen causing a _____ in size. This will also impair gas exchange and difficulty breathing also known as _____. However, the cough reflex is to help ventilation and will not produce phlegm.

4. Black spots seen in the gross visual inspection of lung is normal and expected.

- True
- False

5. Finish the following sentence. Consolidation appears on gross inspection of lungs as:

- A deep red/brown colour with spongy appearance
- Red, with black spots spread diffusely
- Patches of pale red, white, or grey either localized or spread diffusely
- Consolidation can only be visualized with X-ray

Answer Key

1. False
2. Multiple answers possible. Example answer: Patients with cystic fibrosis have a dysfunctional CFTR protein, which is responsible for the transport of chloride and sodium ions in cells. In the airway, CFTR dysfunction may cause issues in mucus secretion and/or mucus reabsorption, leading to the development of an abnormally thick mucus layer in the airways. In the airways, mucus is normally able to trap debris and potential pathogens before they reach the lungs, and then cleared when pushed back up towards the

esophagus. The abnormal mucus in cystic fibrosis patients can impede mucociliary clearance in the host when the airway-lining cilia are unable to beat efficiently due to the high viscosity of the surrounding mucus. Because of this, the cilia are unable to sufficiently propel the mucus towards the esophagus and thus pathogens such as bacteria are allowed to persist in the airway, where they can replicate and spread to the lower respiratory tract and lungs to cause pneumonia.

3. Exudate, alveoli, decrease, dyspnea

4. True

5. Patches of pale red, white, or grey either localized or spread diffusely

ACUTE KIDNEY INJURY

Acute Kidney Injury Chapter Overview

JENNIFER KONG AND LYZ BOYD

Chapter Learning Objectives

By the end of this chapter, you will be able to:

1. Define kidney injury and differentiate between acute and chronic types.
2. Explain how injury leads to acute death of nephrons based on its cause originating before, within, or after the kidney.
3. Identify histological features in the nephron associated with acute kidney injury.
4. List common clinical manifestations of acute kidney injury and explain the pathophysiology behind each.
5. Briefly describe how interprofessional collaboration of health care professions work towards diagnosis of acute kidney injury.

While most people are aware of the general functions of their heart, lungs, or brain, the functions of the kidneys are rarely thought of or referred to in day-to-day life. Throughout your life, your kidneys quietly perform their important tasks without your knowledge. However, if a pathological process affects the function of the kidneys, you will quickly become sick and the situation may become life threatening. In this chapter, we will explore various pathologies that impact the kidneys on both gross and histological levels. We will also examine clinical correlations to acute kidney injury (AKI), which is defined as a rapid decrease in kidney function.

This chapter is subdivided into:

- Pre-test
- Gross & Microscopic anatomy of kidney
- Physiology of urine formation
- Gross anatomy of normal kidney
- Histology of normal kidney
- Clinical presentations of AKI
- Gross pathology of AKI
- Histopathology of AKI
- Treatment and prognosis of AKI
- Consequences of AKI in other systems
- Diagnosis of AKI and interprofessional collaboration
- Chapter summary
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

ADH	Antidiuretic Hormone
AKI	Acute Kidney Injury
ATN	Acute Tubular Necrosis
BPH	Benign Prostatic Hypertrophy
CKD	Chronic Kidney Disease
DCT	Distal Convoluted Tubule
GFR	Glomerular Filtration Rate
LoH	Loop of Henle
NFP	Net Filtration Pressure
PCT	Proximal Convoluted Tubule
RAAS	Renin Angiotensin Aldosterone System
UTIs	Urinary Tract Infections

Pre-Test for Acute Kidney Injury

JENNIFER KONG AND LYZ BOYD

1. True or False? Urine production decreases in acute kidney injury.

- True
- False

2. Finish the following sentence. A key criteria to diagnose acute kidney injury is:

- Low blood pressure (hypotension)
- Protein in the urine (proteinuria)
- Flank pain (lower back pain)
- Increased creatinine in the blood
- Confusion

3. Fill in the blanks with the following words.

angiotensin II, nephrons, K+, creatinine

Kidneys are responsible for filtering the blood and removing wastes such as _____. The kidneys are made of millions of individual functional units known as _____. These units are also responsible for fluid homeostasis by controlling the amount of fluid that is reabsorbed, using hormones such as _____. What fluid is not reabsorbed will be eliminated, along with wastes and undesirable ions such as _____ and acids.

4. Which of the following diseases can cause acute kidney injury by causing glomerulonephritis?

- Chronic high blood pressure (hypertension)
- Kidney stone
- Hypovolemic shock (e.g. hemorrhage)
- Systemic lupus erythematosus (lupus)

Answer Key

1. True
2. Increased creatinine in the blood
3. Kidneys are responsible for filtering the blood and removing wastes such as **creatinine**. The kidneys are made of millions of individual functional units known as **nephrons**. These units are also responsible for fluid homeostasis by controlling the amount of fluid that is reabsorbed, using hormones such as **angiotensin II**. What fluid is not reabsorbed will be eliminated, along with wastes and undesirable ions such as **K+** and acids.

4. Systemic lupus erythematosus (lupus)

Gross Anatomy of the Kidney

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

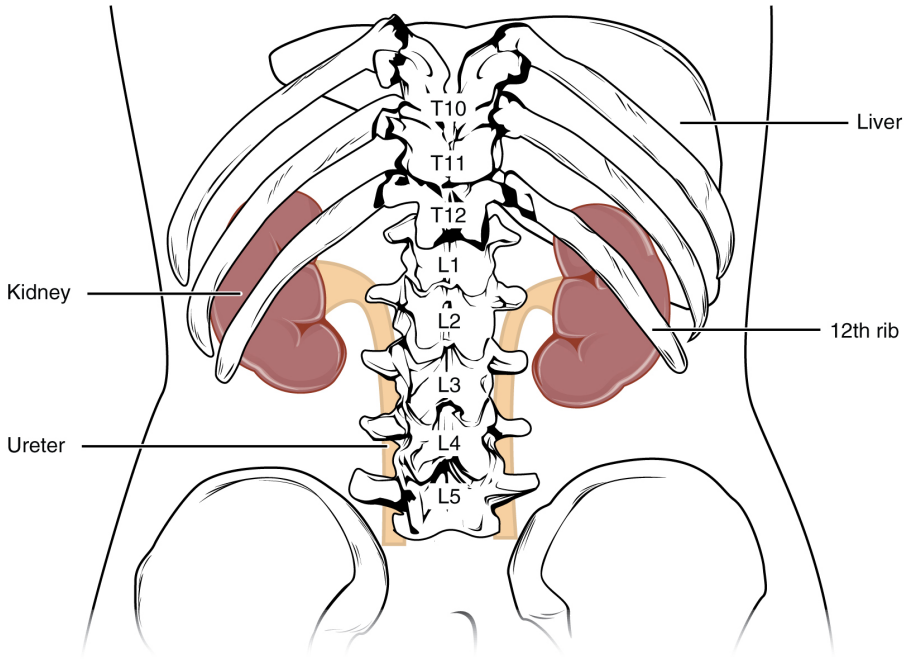
By the end of this section, you will be able to:

- Describe the external structure of the kidney, including its location, support structures, and covering.
- Identify the major internal divisions and structures of the kidney.
- Identify the major blood vessels associated with the kidney and trace the path of blood through the kidney.
- Name structures found in the cortex and medulla.
- Describe the physiological characteristics of the cortex and medulla.
- Identify the ureters, urinary bladder, and urethra, as well as their location, structure, histology, and function.
- Compare and contrast male and female urethras.

The kidneys lie on either side of the spine against the back of the abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist. The kidneys require a lot of blood flow, receiving about 25 percent of the blood pumped by the heart at rest.

External Anatomy

The right kidney is located slightly lower than the left, due to displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs and are also surrounded and protected by a connective tissue capsule and surrounding fat.

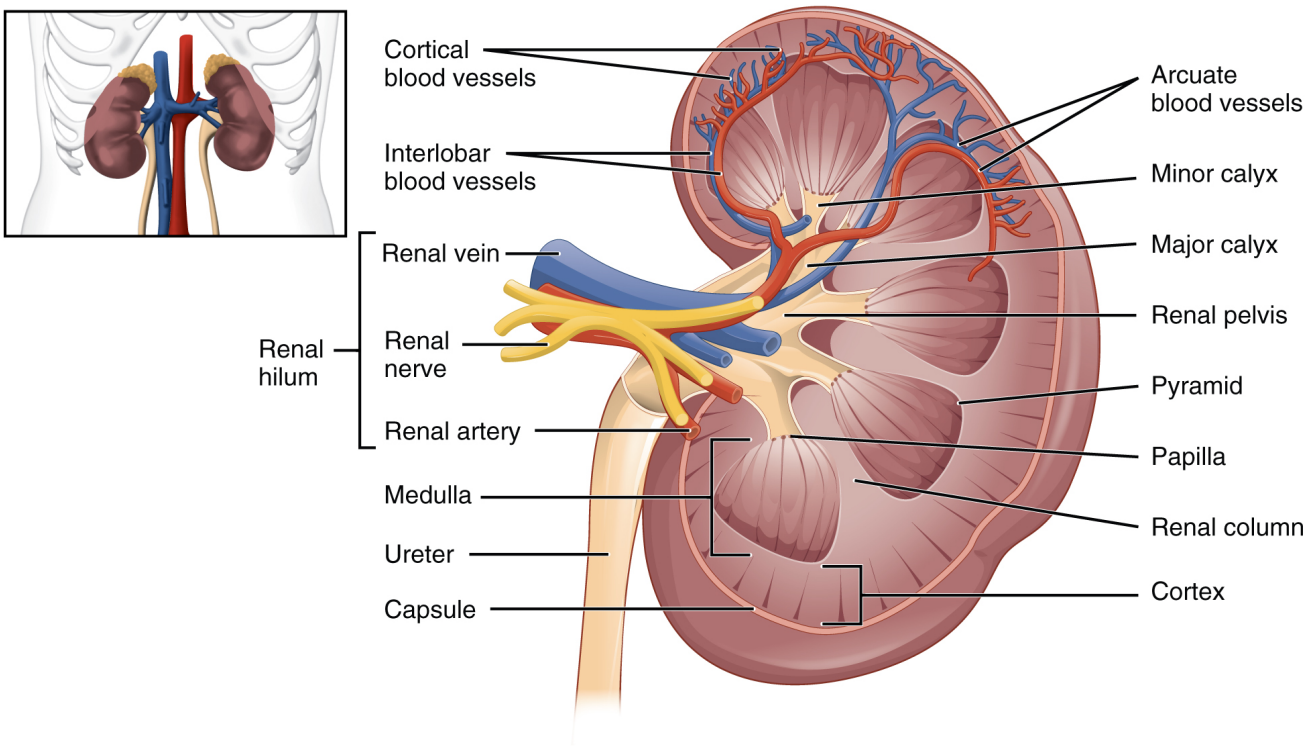


The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

Atop each kidney is an adrenal gland. The adrenal cortex, or outer layer of the adrenal gland, influences renal function by producing the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

Inside the kidney there is an outer region called the **renal cortex** and an inner region called the **medulla**, as shown in the figure below. The **renal columns** are connective tissue extensions that pass from the cortex through the medulla to separate the **renal pyramids** (triangular segments formed of tissue from the medulla) and **renal papillae**. The papillae are bundles of collecting ducts that transport urine made by the functional tissue of the kidney to the **calyces** of the kidney for excretion.



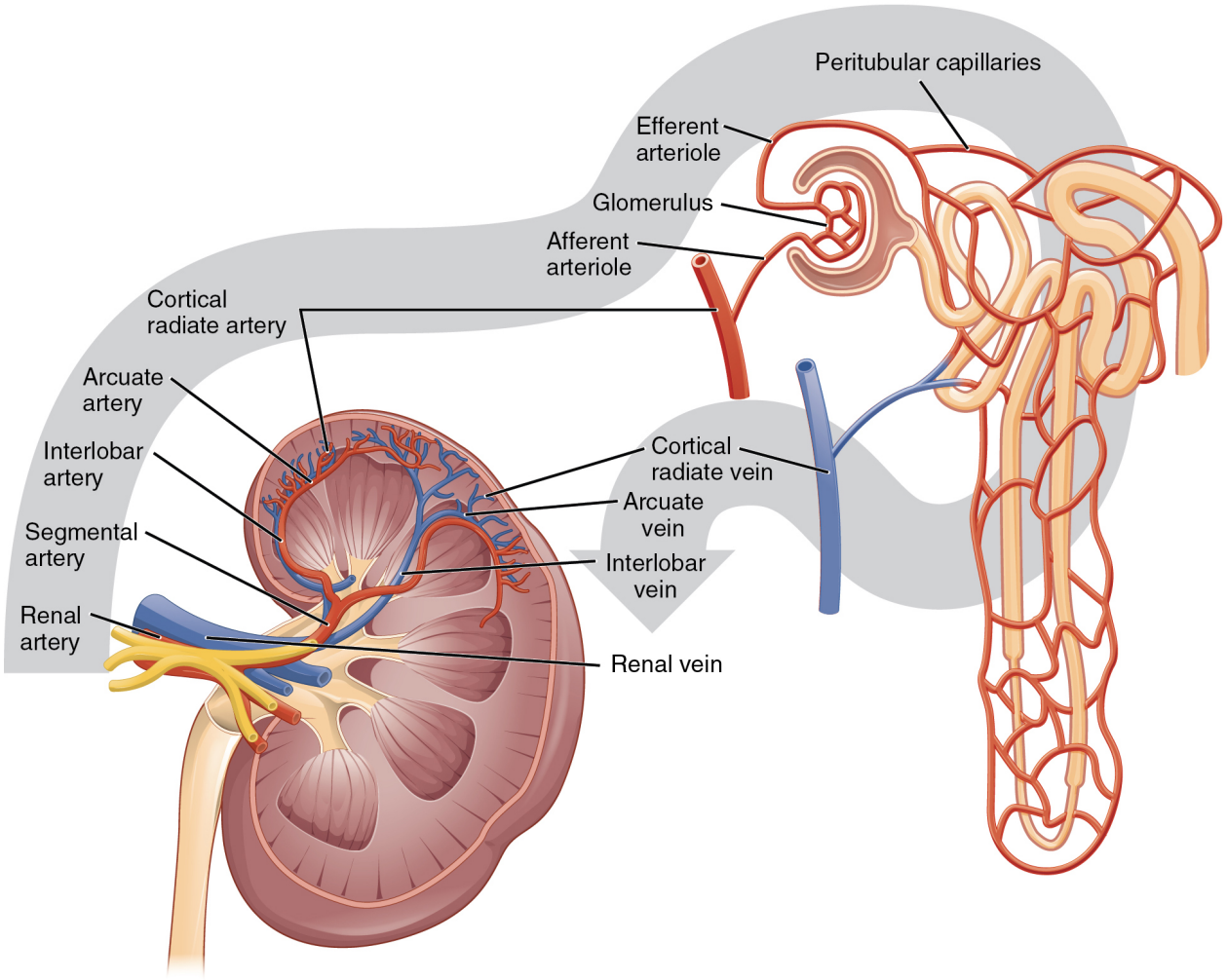
The left kidney with renal hilum

Renal Hilum

The **renal hilum** is the entry and exit site for structures servicing the kidneys: blood vessels (artery and vein), nerves, lymphatics, and ureters.

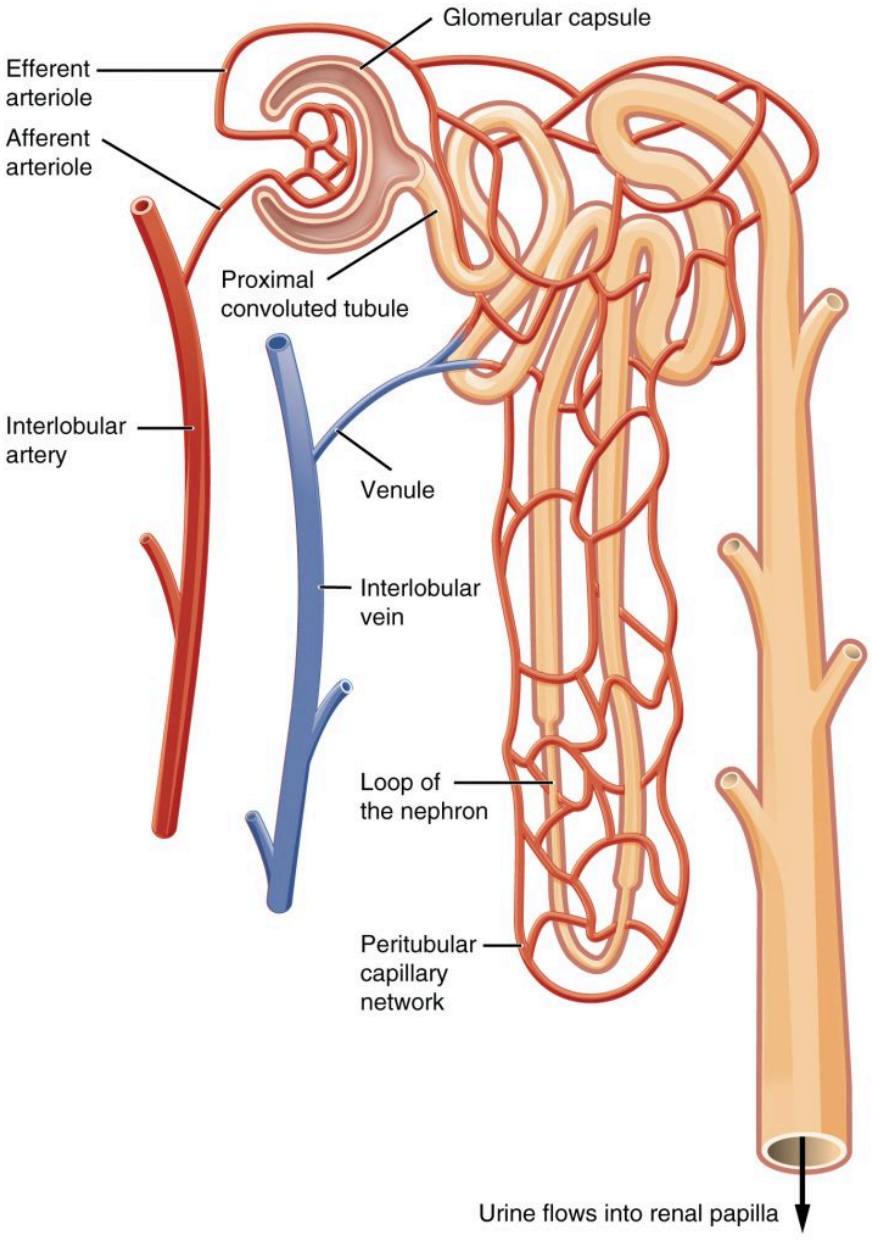
Nephrons and Vessels

The renal arteries branch into smaller and smaller vessels, eventually forming afferent arterioles, as seen in the figure below. The afferent arterioles feed the capillaries in the glomeruli that are vital to the function of the kidney.



Blood Flow in the Kidney

Nephrons are the "functional units" of the kidney; they cleanse the blood and balance water and electrolytes, like sodium and potassium. The diagram below shows the blood flow and urine formation in the nephron. The afferent arterioles form the capillaries of the glomeruli (sing. **glomerulus**). The glomerulus is surrounded by **Bowman's capsule**, which forms a space around the glomerulus called Bowman's space. The nephron is composed of tubules that are continuous with Bowman's space. The glomerulus and Bowman's capsule together form the **renal corpuscle**. These glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the **efferent arteriole**. These will next form the **peritubular capillary** network around the more distal portions of the nephron tubule before returning to the venous system. As the glomerular filtrate passes through the nephron, these peritubular capillary networks recover most of the solutes, nutrients, and water, and return them to the circulation.



Blood Flow in the Nephron

Urine requires specialized structures to remove it from the body safely and efficiently, and to store it until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye.

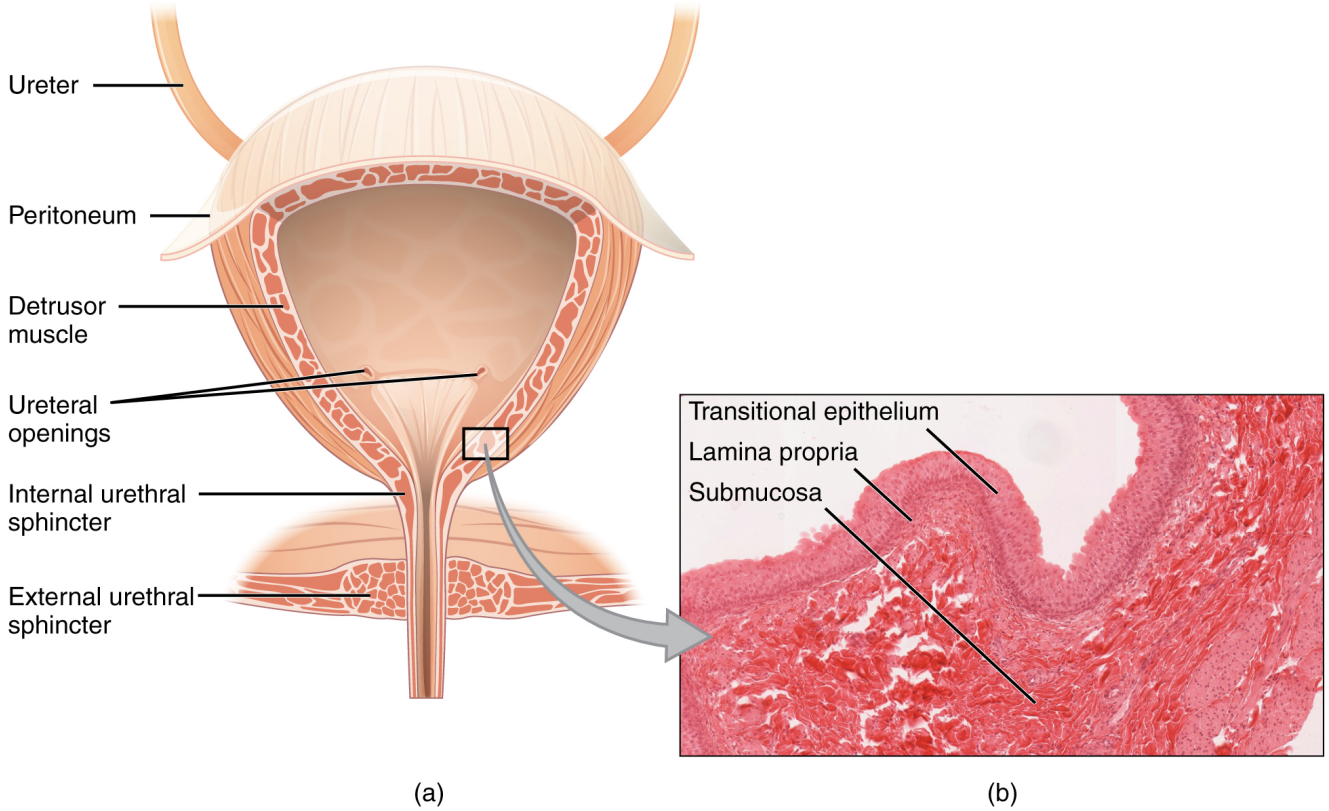
Ureters

As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The renal pelvis narrows to become the ureter of each kidney. As the ureters approach the bladder,

they turn and enter the bladder at an angle. This creates a one-way valve that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter.

Bladder

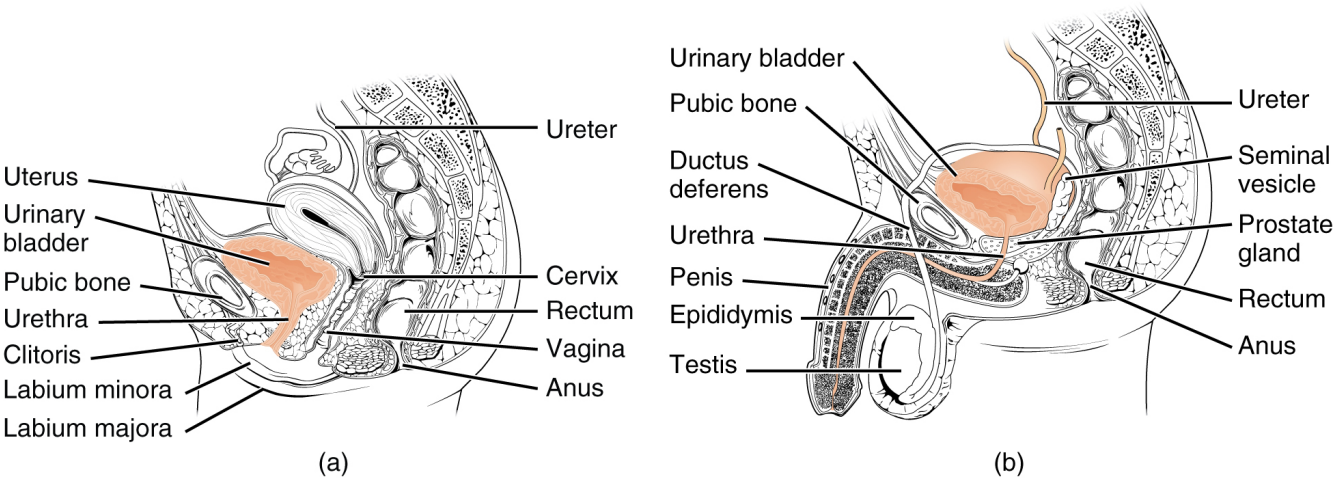
The urinary bladder collects urine from the ureters and lies in front of the uterus in females, behind the pubic bone and in front of the rectum. In males, the anatomy is similar, minus the uterus, and with the addition of the prostate below the bladder, surrounding the **urethra**.



Urinary Bladder *(a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)*

Urethra

The urethra transports urine from the bladder to the outside of the body for disposal. The urethra is the only part of the urinary system that shows any significant anatomic difference between males and females; all other urine transport structures are identical.



Female and Male Urethras – *The urethra transports urine from the bladder to the outside of the body. (a) a female urethra and (b) a male urethra.*

The urethra in both males and females begins inferior and central to the two ureteral openings.

Female Urethra

The main difference between the from the male urethra is the female urethra's short length of about 4 cm. This makes it less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of urinary tract infections (UTIs) in women.

Male Urethra

The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis. The length of the male urethra varies but averages 20 cm in length.

Section Review

The structure of the kidney is divided into two main regions—the peripheral rim of cortex and the central medulla. The two kidneys receive about 25 percent of cardiac output (amount of blood pumped by the heart). They are protected by fat and overlying ribs and muscle. Ureters, blood vessels, lymph vessels, and nerves enter and leave at the renal hilum. There are about 1.3 million nephrons per kidney and these are the "functional units" that perform the important physiologic functions. The glomerulus (a specialized capillary bed) filters blood and the filtrate is captured by Bowman's capsule. Most water and solutes are recovered by a second capillary bed that surrounds the tubules of the nephron. This filtrate is processed into urine by the renal tubules and finally flows into collecting ducts that drain into the minor calyces, which merge to form major calyces. The urine then proceeds to the renal pelvis and finally the ureters to

the bladder. Urine is stored in the bladder until urination. The male and female urethras differ in their length and the presence of a prostate in males.

Review Questions

1. Finish the following sentence. The renal pyramids are separated from each other by extensions of the renal cortex called:

- Renal medulla
- Minor calyces
- Medullary cortices
- Renal columns

2. Finish the following sentence. The primary structure found within the medulla is the:

- Loop of Henle
- Minor calyces
- Portal System
- Ureter

3. Finish the following sentence. The right kidney is slightly lower because:

- It is displaced by the liver
- It is displaced by the heart
- It is slightly smaller
- It needs protection of the lower ribs

4. Fill in the blanks.

The sturdy _____ and conformable _____ provide physical protection to the kidney.

5. What is NOT part of the renal hilum?

- Bladder
- Renal Artery
- Renal Vein
- Ureter
- Lymphatics
- Nerves

6. Fill in the blanks.

Females are more likely to develop bladder infections than males because _____ must travel farther in the _____ urethra, making it less likely for infections.

Answer Key

1. Renal columns
2. Loop of Henle
3. It is displaced by the liver
4. ribs, fat pads
5. Bladder
6. bacteria, male

Adaption

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Microscopic Anatomy of the Kidney

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the structure of the filtration membrane.
- Identify the major structures and subdivisions of the renal corpuscles, renal tubules, and renal capillaries.
- Describe the histology of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts.

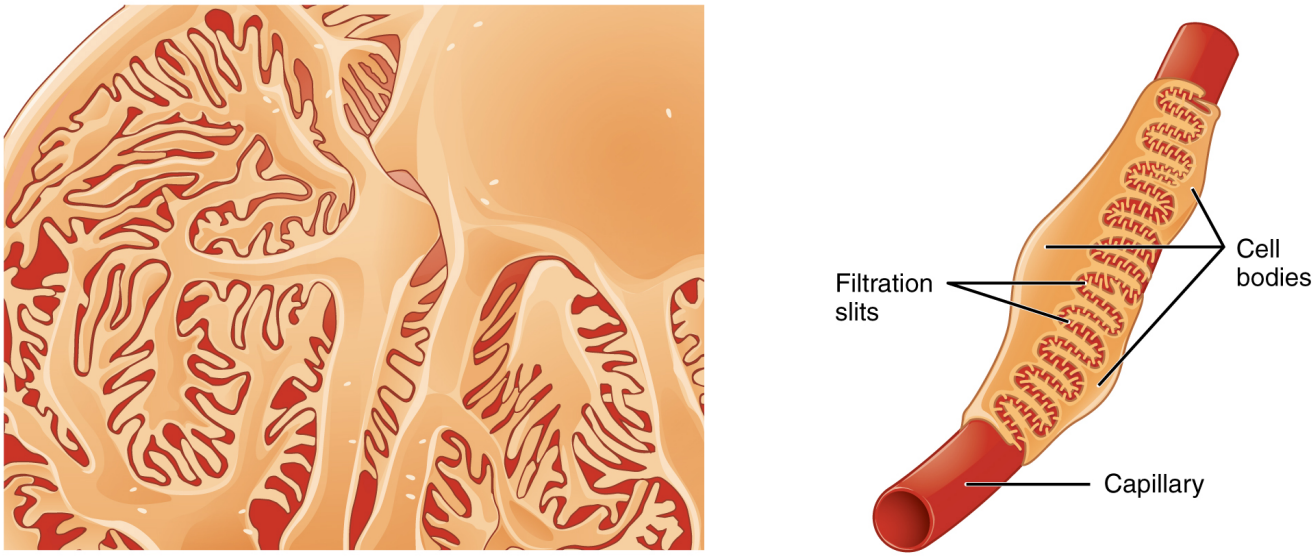
The renal structures that contribute to the function of the kidney cannot be seen by the naked eye. Therefore, microscopy is required to reveal these structures.

Nephrons: The Functional Unit

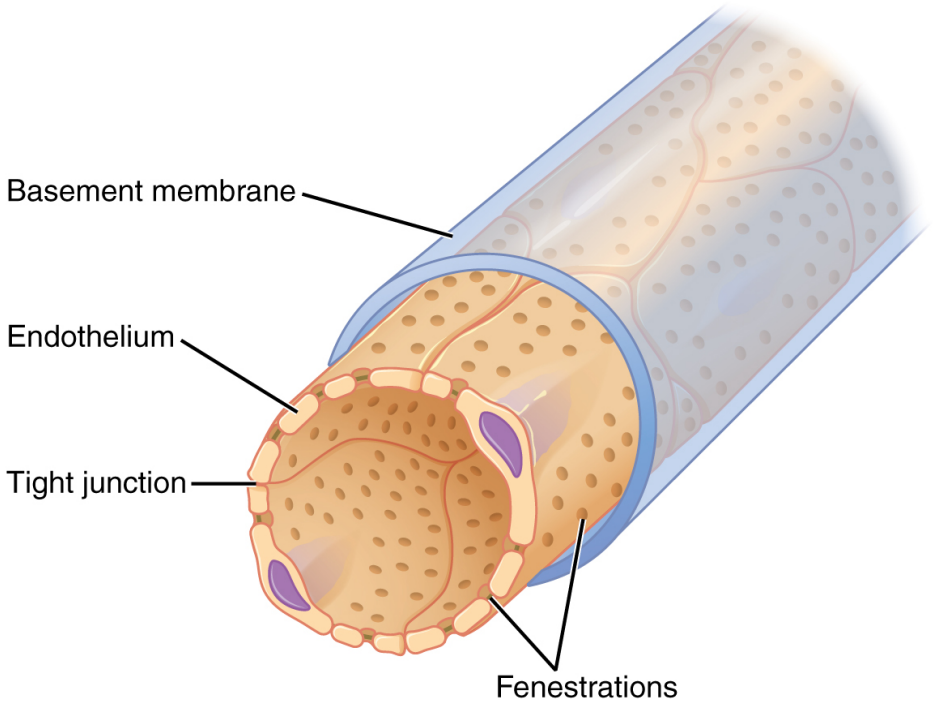
Nephrons take a simple filtrate of the blood and modify it into urine. The filtrate is altered through reabsorption of nutrients and secretion of waste products until urine is formed. The term "forming urine" will be used to describe the filtrate as it is modified into "true urine". The main tasks of the nephrons is to regulate the composition of the blood to achieve homeostasis and to excrete waste products and potential toxins in the urine. They do this by accomplishing three primary functions—filtration, reabsorption, and secretion.

Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a network of capillaries called the glomerulus that is surrounded by Bowman's (glomerular) capsule. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the **proximal convoluted tubule** (PCT). Podocytes are the cells that cover the glomerular capillaries by extending finger-like arms called pedicels over them. Between the pedicels there are specialized slits that allow for filtration of the blood. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. The glomerular capillaries have fenestrations, or "windows" in their walls that allow the filtrate to exit the capillary and be filtered by the pedicels. The fenestrations prevent filtration of blood cells or large proteins, but allow the passage of most other blood components, like water, electrolytes, and small molecules.



Podocytes – Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.



Fenestrated Capillary – Fenestrations allow many substances to diffuse from the blood based primarily on size.

Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its twisting path. A single layer of cells line the tubule and have folding of their cell membranes which creates microvilli, forming a brush border. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na^+, Cl^-, glucose, etc.), which is the main function of this portion of the nephron. These cells actively transport ions across their membranes, so they have many mitochondria to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the **loop of Henle** are continuations of the same tubule which descends into the deep cortex and medulla and returns to the cortex to form the **distal convoluted tubule**. Its function will be discussed in a subsequent section.

Distal Convoluted Tubule (DCT)

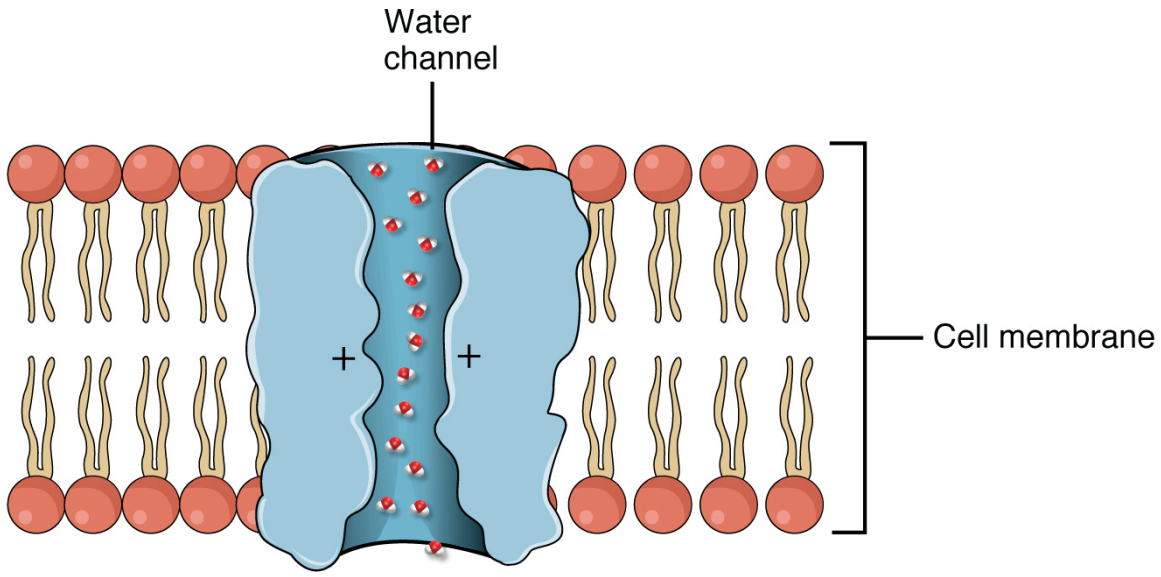
The DCT, like the PCT, is twisty, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, they have fewer microvilli. These cells also require ATP to pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend into the medulla and empty at papillae. In states when the body needs to keep more water, a hormone called antidiuretic hormone (ADH) signals the cells of the collecting ducts to produce protein channels called aquaporins, which selectively allow water to be reabsorbed instead of excreted in the urine.

Aquaporin Water Channel

Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.



Aquaporin water channel – Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.

Section Review

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman's capsule and directed to the PCT. The filtrate enters the PCT where absorption and secretion of several substances occur. The loop of Henle descends into the medulla then returns to the cortex. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to hormone signals by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

Review Questions

1. Finish the following sentence. Blood filtrate is captured in the lumen of the:

- Glomerulus
- Bowman's capsule
- Calyces
- Renal papillae

2. Finish the following sentence. The functional unit of the kidney is called the:

- Hilum
- Corpuscle
- Nephron
- Bowman's capsule

Answer Key

1. Bowman's capsule
2. Nephron

Adaption

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Physiology of Urine Formation

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the hydrostatic and osmotic forces that influence renal filtration.
- Define glomerular filtration rate (GFR).
- List specific transport mechanisms occurring in different parts of the nephron, including active transport, osmosis, facilitated diffusion, and passive electrochemical gradients.
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation.
- Describe how and where water, organic compounds, and ions are reabsorbed in the nephron.
- List the locations in the nephron where tubular secretion occurs.

Having reviewed the anatomy and microanatomy of the urinary system, now is the time to focus on the physiology. You will discover that different parts of the nephron use filtration, reabsorption, and secretion to produce urine. You will learn how each of these processes works and where they occur along the nephron and collecting ducts. The physiologic goal is to modify the composition of the glomerular filtrate and produce the waste product urine.

Glomerular Filtration Rate (GFR)

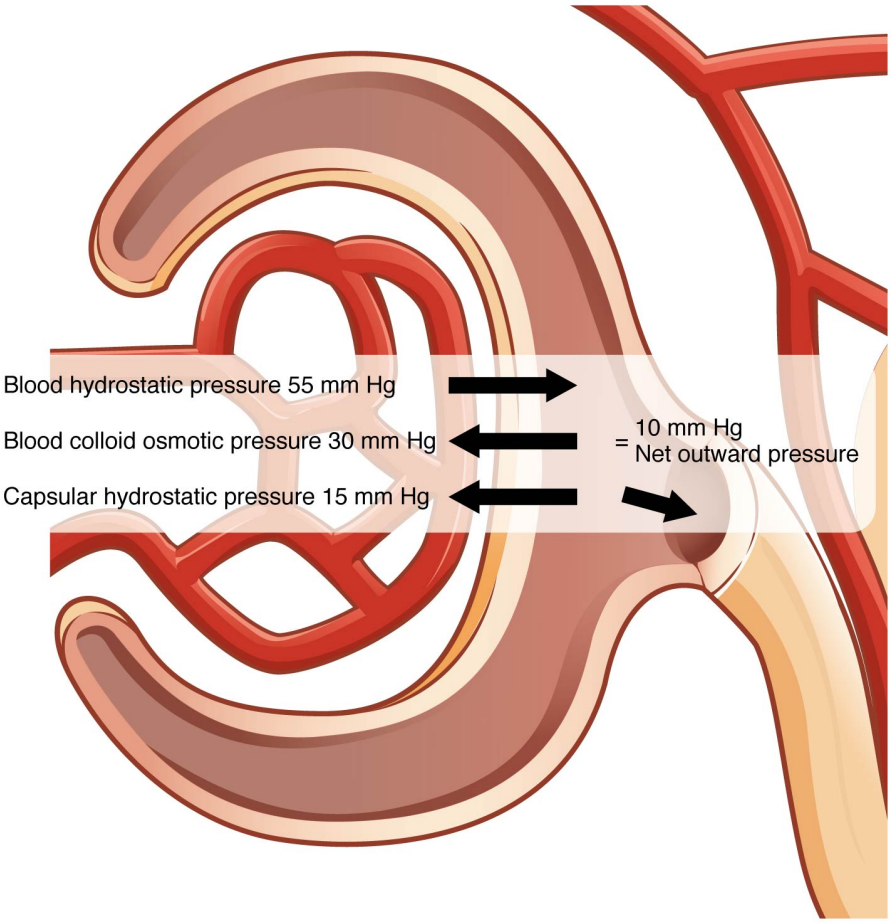
The volume of filtrate formed by both kidneys per minute is termed the **glomerular filtration rate** (GFR). The volume of filtrate produced by the kidneys per day is about 180 L in males and 150 L in females. Ninety-nine percent of this filtrate is returned to the circulation by reabsorption so that only about 1–2 liters of urine are produced per day.

GFR is influenced by the hydrostatic pressure and osmotic pressure on either side of the capillary membrane of the glomerulus. Filtration occurs as pressure forces fluid and solutes through a semipermeable barrier with the solute movement constrained by particle size. Hydrostatic pressure is the pressure produced by a fluid against a surface. If you have a fluid on both sides of a barrier, both fluids exert a pressure in opposing directions. Net fluid movement will be in the direction of the lower pressure.

Osmosis is the movement of solvent (water) across a semipermeable membrane from an area of low solute concentration to an area of high solute concentration in an attempt to balance the concentration on both sides. This creates a pressure, osmotic pressure, which will exist until the solute concentration is the same on both sides of a semipermeable membrane. As long as the concentration differs, water will move.

Glomerular filtration occurs when glomerular hydrostatic pressure exceeds the hydrostatic pressure of Bowman's space.

Osmotic pressure tends to oppose filtration because solute concentration is typically higher in the glomerular capillary. This is because there is a size limitation on the substances that can pass into the filtrate, leading to higher solute concentrations in the blood compared to the filtrate. The sum of all of the influences, both osmotic and hydrostatic, results in a **net filtration pressure** (NFP) of about 10 mm Hg.



Net Filtration Pressure (NFP) is the sum of osmotic and hydrostatic pressures.

A proper concentration of solutes in the blood is important in maintaining osmotic pressure both in the glomerulus and systemically. There are disorders in which too much protein passes through the filtration slits into the kidney filtrate. This excess protein in the filtrate leads to a deficiency of proteins in the blood. Because there is less circulating protein, the osmotic pressure of the blood falls. Less osmotic pressure pulling water into the capillaries tips the balance towards hydrostatic pressure, which tends to push it out of the capillaries. The overall effect is that water is lost from the circulation to interstitial tissues and cells. This "plumps up" the tissues and cells, causing a condition termed **systemic edema**.

Net Filtration Pressure (NFP)

When combining hydrostatic and osmotic pressures, as illustrated in this figure, there is a low net pressure across the filtration membrane. Therefore, minor changes in osmolarity of the blood or capillary blood pressure result in major changes in the amount of filtrate formed. The kidney is able to cope with a wide range of blood pressures because the

smooth muscle in the afferent arterioles that feed the glomerular capillaries is autoregulatory. When you stretch it, it contracts. Thus, when blood pressure goes up, smooth muscle in the afferent arterioles contracts to limit any increase in blood flow and filtration rate. When blood pressure drops, the same arterioles relax to let more blood through and maintain filtration rate. This autoregulation can compensate for a wide range of blood pressures, but will start being unable to compensate below a mean arterial pressure of around 60 mmHg. Blood pressures below this level will impair renal function and cause systemic disorders that are severe enough to threaten survival. This condition is called shock.

Clinical use of GFR

Determination of GFR is important clinically. For example, many dyes and drugs are excreted by the kidneys. In patients with impaired renal function, drug dose adjustments may be required to avoid accumulation of the drug to a toxic level. The GFR is used in this calculation.

But how do we determine a patient's GFR? It is calculated by measuring creatinine present in the blood. Creatinine is a protein-derived molecule produced by muscle tissue that is freely filtered at the glomerulus and is not significantly secreted or reabsorbed by the renal tubules, making it a good candidate to assess GFR. If kidney function is impaired, creatinine will rise because it is not being adequately filtered out by the kidneys.

- Medical Lab technologists receive blood samples to measure the amount of creatinine and nitrogenous waste products (e.g. urea). These wastes should be in low amounts in the blood when the kidney is functioning properly to eliminate these wastes every minute of the day.
- Medical imaging and nuclear medicine tests sometimes use dyes or radioisotopes to help visualize their images (e.g. MRI, CT) or function tests (e.g. myocardial perfusion test). However, these dyes and radioisotopes must be eliminated from the body once the imaging/tests have been completed. Thus, GFR must be within normal range to allow for such dyes in these procedures, knowing that they can be safely eliminated

Tubular Reabsorption

Seeing as up to 180 liters of fluid pass through the nephrons of the kidney per day, it is important that most of that water be reabsorbed, along with the electrolytes and nutrients that also pass into the filtrate. The term "reabsorption" is used because these substances originated in the blood and are returning to the blood, in contrast to the digestive system in which nutrients are absorbed from food. The main functions of the kidney tubules are reabsorption of nutrients, maintenance of homeostasis, and elimination of waste, all of which they accomplish by selective reabsorption of nutrients, electrolytes, and water. This is a brief overview of the mechanisms of reabsorption and the functions of the different parts of the nephron, but if you are interested in more detail, please refer to Tubular Reabsorption.

The kidney has some additional functions that won't be explored in this chapter. These include regulation of electrolytes and hormone activation and/or release (e.g. vitamin D activation, release of the hormone erythropoietin for RBC synthesis). For more detail on these topics, refer to Endocrine regulation of kidneys and Regulation of fluid volume and electrolytes.

Mechanisms of Reabsorption

You may be wondering how this process of reabsorption occurs. The tubules are lined by a single layer of cells and the luminal side (the side on the inside of tubule, where the filtrate is) contains transport proteins that help to move nutrients via the mechanisms outlined below.

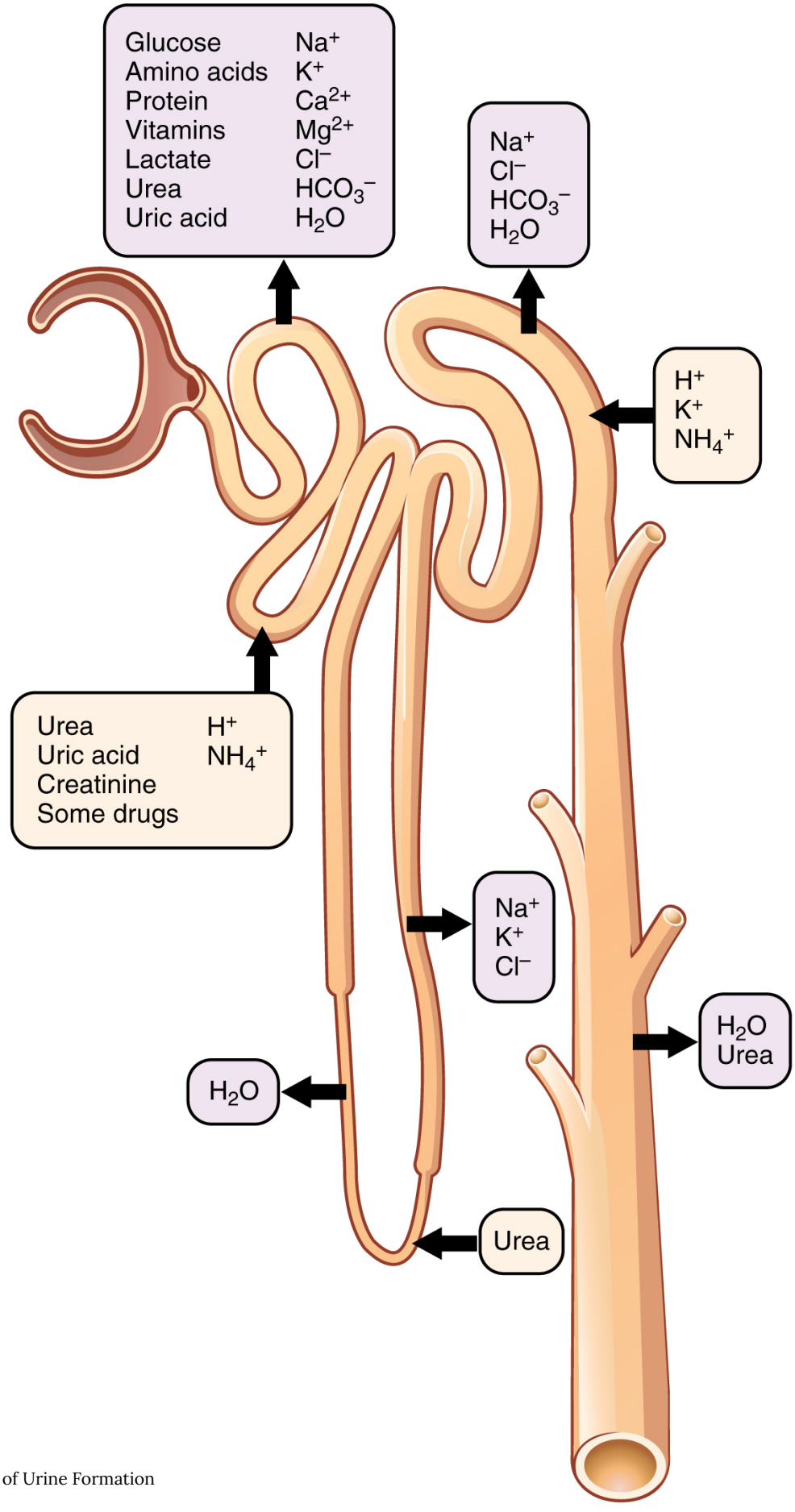
- Active transport: Substances travel against their concentration gradient via a protein "pump" that consumes ATP
  - Example: In the proximal convoluted tubule (PCT), a protein actively transports sodium.
- Facilitated diffusion: Substances follow their concentration gradient using a transport protein to cross the cell membrane. This process does not require energy.
  - Example: Glucose transport in the PCT.
- Simple diffusion: Substances follow their concentration gradient and diffuse across a membrane. In order to do so, their chemical properties need to allow them to cross the cell membrane, therefore they cannot be charged or too large.
  - Example: In parts of the Loop of Henle, urea diffuses across the cell membrane.
- Osmosis: movement of water across the membrane to equalize a concentration gradient of a substance that cannot cross the membrane.
  - Example: Water follows actively pumped ions, like Na^+.

The Role of Secretion

In addition to reabsorbing important substances, the nephron also secretes certain substances. These are often waste compounds that the body is removing via excretion in the urine. Examples of such waste components are urea and certain drugs. The nephron also uses secretion to balance the body's pH, usually by secreting H^+ and $NH4^+$ to make the urine more acidic and the body more alkaline.

Functions of Renal Tubules

The following section will outline the function of each part of the nephron. Refer to the figure below for an overview.


Glucose
Amino acids
Protein
Vitamins
Lactate
Urea
Uric acid
Na+
K+
Ca2+
Mg2+
Cl−
HCO3−
H2O
Na+
Cl−
HCO3−
H2O
H+
K+
NH4+
Urea
Uric acid
Creatinine
Some drugs
H+
NH4+
Na+
K+
Cl−
H2O
Urea
H2O
Urea

Proximal Convoluted Tubule (PCT)

Once the filtrate is filtered into Bowman's space, the first structure it enters is the PCT. Hence, this is the part of the nephron where the filtrate contains the highest amount of substances that need to be reabsorbed, like water, sodium, glucose, amino acids, small proteins, calcium, potassium, magnesium, and chloride. Hence, there are transport proteins located in the PCT to enable reabsorption of all these substances by the mechanisms outlined previously. This is also where the majority of water reabsorption occurs.

Many parts of the nephron have a role in maintaining pH balance and the PCT is one of them. It does this by reabsorbing bicarbonate ($HCO3^-$), which acts as a buffer to balance blood pH. pH balance in the body is vital, because outside of the narrow normal pH range proteins begin to take on or lose hydrogen ions and lose their shape, and therefore their function. In cases of kidney pathology, one of the signs can be acidemia (blood that is too acidic) because the kidneys are not able to adequately balance the pH.

Loop of Henle (LoH)

The main function of the LoH is to reabsorb water and electrolytes. The loop descends towards or into the medulla, where there is a higher concentration of salt and urea. In the descending limb, water responds to the hyperosmotic environment by leaving the tubule by osmosis. The ascending portion is impermeable to water, so the previously reabsorbed water doesn't just return to the tubule. Here, electrolytes are actively pumped out to maintain the hyperosmotic environment around the LoH.

Distal Convoluted Tubule (DCT)

After passing through the LoH, the filtrate returns to the cortex and enters the DCT. At this point, 80% of the water in the filtrate has been reabsorbed and the DCT recovers another 10-15%. It also has a role in the reabsorption of sodium, chloride, and calcium.

Collecting Ducts

The collecting ducts are not technically part of the nephron and several nephrons will drain into a single collecting duct. However, they still play an important role in controlling the recovery of water. If the body detects a need to retain water, a hormone called antidiuretic hormone (ADH) will be released, which causes aquaporins (water channels) to be inserted into the membranes of the otherwise water-impermeable collecting duct cells. This allows water to be reabsorbed by facilitated diffusion as the filtrate passes through the hyperosmotic medulla on its way to the renal collecting system.

The collecting ducts also have a role in increasing blood pressure when under the influence of the hormone aldosterone. Aldosterone is formed by a chain of events that begin elsewhere in the kidney. The macula densa is a structure that is

located where the LoH returns to the cortex and becomes the DCT. It detects the amount of sodium in the filtrate and if it is low, it begins a cascade of events to increase blood pressure and GFR. This is because in a healthy individual, low sodium in this portion of the nephron is usually due to low renal perfusion. The hormone renin is released, which converts angiotensinogen to angiotensin I, which is then converted to angiotensin II. Angiotensin II acts on the vasculature to cause vasoconstriction and also causes release of aldosterone from the adrenal glands, which sit above the kidneys. Aldosterone increases retention of sodium in the collecting duct. When water passively follows, the result is to increase blood volume and assist in maintaining the blood pressure and perfusion of the kidneys. This complex system is often referred to as the RAAS, short for the renin-angiotensin-aldosterone system.

Critical thinking Exercise

Thinking back on the normal physiology of urine formation (one of the main functions of the kidney), that things are possible to appear in the urine? And what is supposed to be there?

- Now speculate what could have happened for you to see RBCs in the urine? What about very large proteins?

Section Review

The entire volume of the blood is filtered through the kidneys about 300 times per day, and 99 percent of the water filtered is recovered. The GFR is influenced by hydrostatic pressure and osmotic pressure. Under normal circumstances, hydrostatic pressure is greater and filtration occurs. The hydrostatic pressure of the glomerulus depends on systemic blood pressure and autoregulatory mechanisms, among other mechanisms. The kidney can function normally under a wide range of blood pressures due to the autoregulatory nature of smooth muscle.

The kidney regulates water recovery and blood pressure by producing the enzyme renin, thus starting the Renin-Angiotensin-Aldosterone (RAAS) system. The result of RAAS activation is vasoconstriction and retention of salt and water. Water recovery is also powerfully and directly influenced by the hormone ADH. Even so, it only influences the last 10 percent of water available for recovery after filtration at the glomerulus, because 90 percent of water is recovered before reaching the collecting ducts.

Mechanisms of solute recovery include active transport, simple diffusion, and facilitated diffusion. Most filtered substances are reabsorbed. Urea, NH_3, creatinine, and some drugs are filtered or secreted as wastes. H^+ and HCO_3^- are secreted or reabsorbed as needed to maintain acid–base balance. Movement of water from the glomerulus is primarily due to pressure, whereas that of peritubular capillaries and vasa recta is due to osmolarity and concentration gradients. Almost 100 percent of glucose, amino acids, and vitamins are recovered in the PCT. The recovery of solutes creates an osmotic gradient to promote the recovery of water. The descending loop promotes recovery of water. The ascending loop is impervious to water but actively recovers Na^+, reducing filtrate osmolarity. The vasa recta recover the solute and water in the medulla, returning them to the circulation. Nearly 90 percent of water is recovered before the forming urine reaches the DCT, which will recover another 10 percent.

Review Questions

1. Fill in the blank._____ pressure must be greater on the capillary side of the filtration membrane to achieve filtration.

2. Production of urine to modify plasma makeup is the result of :

- Filtration
- Absorption
- Secretion
- All of the above

Answer Key

1. Hydrostatic
2. All of the above

Adaption

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Tubular reabsorption **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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- 2618_Nephron_Secretion_Reabsorption © OSCRiceUniversity is licensed under a CC BY (Attribution) license

Gross Anatomy of Normal Kidney

JENNIFER KONG AND MEIHUA E. SU

Learning Objectives

By the end of this chapter, you will be able to:

- Identify gross structures of the kidney.
- Explain the functions of the major kidney structures.
- List the path of blood flow and urine filtration.

The kidneys are amazing organs as they filter all of the blood through millions of microscopic nephrons. To the naked eye, these nephrons and blood vessels look like dense, smooth red/brown tissue. Yet, these nephrons help separate unwanted wastes from blood, draining them into structures that collect urine. At the same time, these nephrons help retain valuable nutrients, electrolytes, and water which is reabsorbed back into the blood vessels of the kidney and put back into the general circulation.

Normal Gross Anatomy of the Kidney – created and presented by Eva M. Su

Video Summary: the kidney is a red/brown colour due to the high amount of blood that is being filtered. Blood enters and leaves the kidney via the renal hilum. The kidney is covered in a thin, invisible capsule. The outer rim of the kidney is the renal cortex, containing the blood vessels and glomeruli. The inner portion of the kidney is the renal medulla which contain the renal pyramids, separated by renal columns which contain renal vessels going to/from the cortex. The renal pyramids contain the nephron loops. At the tip of each pyramid, the renal papilla connects the pyramid to the minor calyces, a funnel-like structure which drains the urine from the nephrons. Minor calyces drain into major calyces which merge to form the renal pelvis. The ureter is attached to the renal pelvis and drains the urine in an inferior direction towards the bladder.



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2509#h5p-123

Overview of the Nephrons and Blood & Urine Flow – created and presented by Eva M. Su. Figure presented is from the Open Ed text "Anatomy & Physiolology" by CCCOnline (CC-BY-SA) and work by Cenveo, licensed under a Creative Commons Attribution 3.0

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An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2509#h5p-121

Summary and Post-test of normal kidney anatomy – created and presented by Eva M. Su

Key Definitions

- **Vasa Recta** – Branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries.
- **Renal Fat Pad** – Adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney.

Histology of Normal Kidney

LYZ BOYD

Learning Objectives

By the end of this section, you will be able to:

- Identify the renal cortex and medulla of a kidney with H&E staining.
- Correlate the staining of the cytoplasm and nuclei with the function of the cells within the nephron.
- Identify glomerulus and Bowmans capsule within the renal cortex.
- Distinguish between a renal arteriole and vein.

In the following video, we will learn what the kidney looks like microscopically and identify the structures we learned about in previous sections.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2513#h5p-85

DHPLC specimen PATH 304-020 normal rabbit kidney created and presented by Lyz Boyd, licensed under [All Rights Reserved]

Key Definitions:

- **Epithelium** – The layer of cells that covers all internal and external surfaces of the body, including the renal tubules.
- **Podocytes** – Specialized cells present in the glomeruli of the kidneys that create the filtration barrier, allowing fluid and small molecules to pass through while keeping larger proteins and cells in the blood.
- Bowman's Space – The space surrounding the glomerulus that the filtrate initially passes into.
- **Bowman's Capsule** – The membrane surrounding Bowman's space.
- **Brush Border** – A feature of the cells of the proximal convoluted tubule that creates increased surface area for absorption.
- **Lumen** – The space inside a structure in the body, for example, the space that contains the filtrate in a renal tubule.

Section Review

Nephrons are microscopic structures which filter blood to eliminate wastes via urine. Histologically, the cortex of the nephron comprises the glomeruli, Bowmans capsules, PCT, and DCT. The nephron loops (or Loop of Henle) are at the border of the cortex and medulla and form the renal pyramids. The collecting ducts travel from the cortex, through the medulla, and converge to form the renal papillae at the tip of the pyramids.

Glomeruli are easily recognized by its round structure (full of many capillaries and RBC), surrounded by a thin membrane (Bowmans capsule), separated by a slight space (Bowmans space). PCTs are recognized by its eosinophilic appearance and 'fuzzy' lumen which represents the brush border/microvilli that PCT uses to reabsorb nutrients out of the filtrate. In contrast, the loop, DCT, and collecting duct structures have a clear lumen.

Review Questions

1. The lumen of the proximal convoluted tubule should be fuzzy.

- True
- False

2. Which cells are found in the glomerulus? Check all that apply.

- Capillary endothelial cells
- Red blood cells
- Antibodies/Immune cells
- Brush border
- Melanocytes
- Podocytes

3. Fill in the blanks.

The renal cortex contains the round _____ surrounded by its _____ capsule, _____ convoluted tubule with its brush border on the luminal side, and the _____ with is clear luminal space.

Answer Key

1. True
2. Capillary endothelial cells, Red blood cells, Podocytes
3. glomerulus/glomerui, Bowman's, proximal, distal convoluted tubule

Pathology of Acute Kidney Injury

LYZ BOYD

Learning Objectives

By the end of this chapter, you will be able to:

- Define acute kidney injury (AKI).
- Differentiate between pre-, intra-, and post-renal categories and name examples of each.

Introduction to Acute Kidney Injury

Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function that occurs over the course of hours to days and results in changes to urine production, waste elimination, and the important homeostatic functions of the kidney. Synonyms for AKI include acute renal injury, acute kidney failure, and acute renal failure, however the terms that include "failure" are considered outdated and are no longer actively being used.

Types of AKI

As demonstrated above, the definition of AKI is very broad. Therefore, AKI is truly an umbrella term for many disease entities. These causes of AKI fall into 3 major categories:

1. Prerenal: Injury to the kidney caused by decreased renal blood flow. In order for the kidneys to filter the blood and modify the filtrate to produce urine, they need adequate blood flow. Additionally, the cells of the nephron tubules are highly metabolically active and so require adequate oxygen and nutrition in order to function, so decreased blood flow causes dysfunction and possibly death of these cells. Therefore, any disease state that causes decreased renal or systemic perfusion can cause prerenal AKI, including extreme hypotension, blood loss, and vasoconstriction of the renal arteries.
2. Renal or intrarenal: Direct injury to the renal tubules or glomeruli. A variety of conditions can cause this type of AKI and examples of these will be provided later in the chapter.
3. Postrenal: Alteration of kidney function caused by obstruction downstream of the kidney that causes pressure backup in the urinary system and disrupts the glomerular pressure gradient. Recall that blood is filtered in the glomerulus from the bloodstream into the renal tubules and this process relies on the pressure in the capillary being higher than that in Bowman's space. If pressure in the urinary system increases, increasing the pressure in Bowman's space, this filtration will not be able to occur normally.

Prerenal AKI

Prerenal AKI can be subcategorized into cases where there is a decrease in absolute blood volume and cases where there is a decrease in effective blood volume. A decrease in absolute blood volume describes a loss of blood or fluid, such as from a massive hemorrhage (bleed), dehydration, or excessive diarrhea or vomiting. A decrease in effective blood volume means that the body has not lost fluid, but the blood is unable to circulate properly. There are many causes for this, some include congestive heart failure (a loss of heart muscle function, such that it is no longer able to pump adequately), sepsis (excessive blood vessel dilation due to a systemic inflammatory response), or a blockage in the vasculature, such as a pulmonary embolism (blood clot in the blood vessels of the lung). These are all causes of medical shock, which is defined as a sudden drop in blood flow to the body and may be caused by decreases in absolute or effective blood volume.

In some cases, the decrease in blood flow is specific to the kidneys. For example, hepatorenal syndrome occurs in liver disease when hormones are released that cause excessive renal vasoconstriction. Certain drugs also impact the ability of the glomeruli to maintain filtration and may also cause prerenal AKI if used incorrectly.

Intrarenal AKI

Intrarenal AKI can involve disease processes at the level of the glomeruli, the renal tubules, or the interstitium (fluid filled spaces around the cells) of the kidney.

The most common cause of intrarenal AKI is called acute tubular necrosis (ATN) and occurs when ischemia (inadequate blood flow) or a toxin damages the renal tubules and causes the cells that line them to undergo necrosis (cell death). A prolonged prerenal AKI can progress to ATN if the decreased blood flow to the kidneys begins to result in necrosis of the cells in the tubules.

An example of an intrarenal cause of AKI affecting the glomerulus is glomerulonephritis. Glomerulonephritis also has a variety of causes, but most are related to autoimmune conditions such as lupus. It can also occur after certain infections such as streptococcus (e.g: “strep throat”) where the infection triggers a type of allergic reaction that results in deposition of immune system components like antibodies and immune cells in the glomeruli. The immune deposits activate an inflammatory response which damages the glomeruli and interferes with their function.

A problem that can occur in the interstitium of the kidney is acute interstitial nephritis. This is similar to an allergic reaction within the interstitial spaces of the kidney and is usually caused by a reaction to a new medication. Clinically, this may present with a rash, fever, and increased number of eosinophils, a type of white blood cell associated with allergic reactions and parasitic infections, in the blood.

Postrenal AKI

Any obstruction of the urinary system downstream of the kidney has the potential to cause a postrenal AKI. Examples include blockage of the ureter or urethra by a kidney or bladder stone, scar tissue, tumour, or benign prostatic hypertrophy (BPH) (enlarged prostate gland) (biological males only). BPH is the most common cause of post-renal AKI, especially in older males.

In cases where the obstruction is gradual and affects only one kidney, for example a tumour compressing one of the two ureters, AKI is usually not the result. This is because only one of the kidneys is affected and over time the other is usually

able to compensate. Therefore, it is more common for obstruction of the bladder outlet to cause AKI, seeing as there is only one urethra, but two kidneys and two ureters.

Section Review

AKI occurs when the kidney(s) are injured suddenly and significantly such that many nephrons are damaged or even die. Causes of AKI are various but can be classified based on the location of the injury. Pre-renal causes result in decreased blood flow to the kidney, thus preventing both perfusion of the kidney and filtration of blood. This can be due to either low blood volume or low blood flow to the kidneys specifically. Intrarenal causes tend to cause direct damage to the nephrons – whether it be chemical (e.g. drugs), immunologic (e.g. nephritis), or physical. Post-renal causes are most commonly caused by obstructions in the urinary tract (e.g. kidney stones, benign prostatic hyperplasia) that causes a back up of urine into the kidneys causing physical damage with the backpressure.

Review Questions

1. Fill in the blanks. There are three categories of AKI. _____ injury is classified by decreased blood flow in the kidneys. _____ is an injury to the renal tubules or glomeruli. _____ injuries are classified by blockages after the kidneys that affect the glomerular pressure gradient.

2. Place the following in the correct column.

Extreme Hypotension Toxin Damages to Renal Tubules Acute Tubular Necrosis (ATN) Glomerulonephritis Blockage of Urethra	Bladder Stone Kidney Stone Benign Prostatic Hypertrophy (BPH) Decreased Renal Blood Flow Vasoconstriction of Renal Arteries Blockage of Urethra	Direct Injury to Renal Tubules or Glomeruli Dehydration Excessive Diarrhea & Vomiting Obstruction Downstream of Kidneys Sepsis Hemorrhages

Prerenal AKI	Renal/Intrarenal AKI	Postrenal AKI

3. Fill in the blank.

In kidneys with normal function, the pressure in capillaries is _____ than the pressure in the Bowman's space.

4. A decrease in absolute blood volume and effective blood volume means the same thing.

- True
- False

Answer Key

1. Prerenal, Renal/intrarenal, Postrenal
2.

Prerenal AKI	Renal/Intrarenal AKI	Postrenal AKI
Extreme Hypotension Vasoconstriction of Renal Arteries Hemorrhages Dehydration Excessive Diarrhea & Vomiting Sepsis Decreased Renal Blood Flow	Acute Tubular Necrosis (ATN) Toxin Damages to Renal Tubules Glomerulonephritis Direct Injury to Renal Tubules or Glomeruli	Blockage of Ureter Blockage of Urethra Bladder Stone Kidney Stone Benign Prostatic Hypertrophy (BPH) Obstruction Downstream of Kidneys

3. Higher
4. False

Clinical Presentation and Causes of AKI

LYZ BOYD

Learning Objectives

By the end of this chapter, you will be able to:

- Identify common blood test values which determine kidney function.
- Explain common signs and symptoms of AKI based on pre-, intra-, and postrenal causes.

General Presentation

As you might imagine, the clinical presentation of AKI can differ depending on the cause. However, the basic criteria for AKI apply to all causes which include:

- An increase in serum creatinine OR
- An abnormally small volume of urine production

Let's briefly learn about what creatinine is and how it relates to the function of the kidneys. Creatinine is a waste molecule produced by muscle tissue that is excreted by the kidneys. It is produced at a relatively constant rate every day, and therefore excreted in the same way. A sudden rise in creatinine in the blood can be indicative of AKI because it reflects the fact that the kidneys are not excreting it properly into the urine. Seeing as creatinine levels are related to muscle mass, everyone's normal level is different depending on factors like sex, age, and weight. Therefore, it's best when healthcare providers have a previous value to compare to, but that is not always available.

Both an increase in serum creatinine or a decrease in urine production indicate that the kidneys are not working normally and an AKI is present.

Key Takeaways

- Nephrons are damaged and can no longer control urine formation, leading to changes in volume of urination (little or no urine production) AND excess fluid in tissues (edema).
- Nephrons are damaged and can no longer control reabsorption of useful substrates nor eliminate waste. This causes a rise in nitrogenous wastes in blood (since it can't be excreted).

Regardless of the cause, if AKI is not corrected it will progress, resulting in a build up of toxic waste products in the body, along with other disruptions to the delicate balances of the body, such as pH balance and electrolyte concentrations. Build up of waste products like urea may progress to a condition called uremic encephalopathy, where the function of the brain becomes impacted by these toxins. Symptoms of uremic encephalopathy include confusion, seizures, and coma.

Specific Presentations

The following table summarizes the specific presentations of different causes of AKI, in addition to increase in blood creatinine levels and low urine output:

Cause of AKI	Description of Pathology	Clinical presentation
Prerenal causes		
Acute hemorrhage (hypovolemic/hemorrhagic shock)	Decreased blood pressure due to blood loss and therefore decreased blood volume	Low blood pressure, tachycardia, tachypnea, reduced level of consciousness, evidence of hemorrhage (may be internal or external)
Gastrointestinal fluid losses (hypovolemic shock)	Decreased blood pressure due to fluid losses	Low blood pressure, tachycardia, tachypnea, recent or current vomiting/diarrhea
Acute congestive heart failure exacerbation (cardiogenic shock)	Decreased heart function due to heart pathology (eg: cardiomyopathy, muscle damage from a past ischemic event) such that the heart can no longer maintain adequate blood flow to the body	Electrocardiogram (ECG) abnormalities, low blood pressure, tachycardia, shortness of breath, enlarged heart. Pulmonary edema (fluid build up) from fluid backup into lungs, may hear crackles with a stethoscope. Peripheral edema from fluid build-up in the periphery (usually the lower legs).
Sepsis (septic shock)	Systemic inflammatory response to an infection, often a bloodstream infection. Inability to maintain adequate blood pressure due to dilation of blood vessels all over the body (vasodilation).	Fever, warm extremities (from vasodilation), low blood pressure, tachycardia, history or signs of an infectious source (eg: skin wound, pneumonia)
Massive pulmonary embolism (obstructive shock)	Obstruction of the pulmonary (lung) blood vessels (usually by a blood clot) that increases pressure in the right side of the heart and reduces blood returning to the left side of the heart to a degree that impairs blood flow to the body.	Low blood pressure, tachycardia, shortness of breath, chest pain, cough, hemoptysis (coughing up blood).
Intrarenal causes		
Acute tubular necrosis	Damage to renal tubule cells from ischemia (lack of blood flow) or toxin. Examples of toxins include medications or toxin release from another pathological process, such as rhabdomyolysis (muscle breakdown, myoglobin release) or hemolytic uremic syndrome (E. coli toxin from intestinal infection).	History of prolonged renal ischemia, history of medication known to cause ATN, muscle tenderness (rhabdomyolysis), or history of gastrointestinal illness.
Glomerulonephritis	Various causes are possible, but all are encompassed by immune-mediated damage to components of the renal corpuscle.	Hematuria (blood in the urine), proteinuria (protein in the urine), highly elevated blood pressure which may further cause confusion or headache, edema (usually in the periphery or around the eyes)
Acute interstitial nephritis	A type of allergic reaction to a drug or pathogen that affects the interstitium of the kidneys.	Variable, can be asymptomatic or may have nausea, vomiting, and/or flank pain. Skin rash and a fever are also possible.
Postrenal causes		

Benign prostatic hyperplasia	The prostate gland (present in biological males) located around the urethra near the bladder outlet, gradually enlarges over time. If the obstruction of the urethra becomes severe enough, it can entirely block urination and cause AKI by urine backing up into the urinary system.	History of lower urinary tract symptoms which include weak stream, straining to urinate, hesitancy (difficulty initiating urination), nocturia (frequent waking at night to urinate), frequency (needing to urinate many times during the day), and urgency (sensation of an urgent need to urinate). Abdominal or flank pain
Tumour	Tumours of the urinary system, abdomen, or reproductive system can compress structures involved in urine transport which may result in AKI.	non-specific symptoms that affect the whole body and are often associated with cancer or infection – such as unintentional weight loss, fever, excessive sweating at night, and fatigue. In the case of prostate carcinoma, metastasis to the bone is common, so bone pain or back pain is possible.
Kidney stone	Stones that form in the kidneys may become suddenly stuck in a ureter, causing obstruction and impaired kidney function if the other kidney is unable to compensate or if stones are present on both sides.	Flank pain with radiation to the groin.

Critical Thinking Exercises

Answer these questions for yourself

- Select all the patients below that are at risk for acute intra-renal injury?
    - A. A 45 year old male with a renal calculus.
    - B. A 65 year old male with benign prostatic hyperplasia.
    - C. A 25 year old female receiving chemotherapy.
    - D. A 36 year old female with renal artery stenosis.
    - E. A 6 year old male with acute glomerulonephritis.
    - F. An 87 year old male who is taking an aminoglycoside medication for an infection.
- In caring for the patient with AKI, of what should the nurse be aware?
    - A. The most common cause of death in AKI is irreversible metabolic acidosis.
    - B. During the oliguric phase of AKI, daily fluid intake is limited to 1000 mL plus the prior day's measured fluid loss.
    - C. Dietary sodium and potassium during the oliguric phase of AKI are managed according to the patient's urinary output.
    - D. One of the most important nursing measures in managing fluid balance in the patient with AKI is taking accurate daily weights.

Answer Key

1. correct answers are C, E, F
    - option A is incorect because usually blockage AFTER the nephrons (but might still be in the calyces. As intr-renal means within nephrons, a calculus in the calyces or ureter would be post-renal
    - option B is incorect because it would be true for post-renal as the kidneys are fine but the backup of urine will hurt them
    - option C is corect becasue many chemo agents are toxic and will kill nephrons as it's being eliminated in urine
    - option D is incorect becasue this is an example of pre-renal injury in that the kindeys are fine but there is a reduction fo blood getting to them.
    - option E is corect becasue glomerulonephritis involves immune damage to the nephrons & glomerulus which reside within the kidney.
    - option F is corect becasuethis medication is known to cause death of nephrons.
2. correct answer is D
    - option B is incorect becasue the fluid limitation in the oliguric phase is 600 mL plus the prior day's measured fluid loss.
    - omption C is incorect because dietary sodium and potassium intake are managed according to plasma levels.
    - option D is corect becasue measuring daily weights with the same scale at the same time each day allows for the evaluation and detection of excessive body fluid gains or losses. Infection is the leading cause of death in AKI, so meticulous aseptic technique is critical.

Section Review

Manifestations of AKI are varied due to the underlying cause of the kidney injury. Because nephrons are damaged and can no longer control blood filtration and urine formation, renal manifestations would be changes in volume of urination (little or no urine production), excess fluid in tissues (edema), rise of nitrogenous wastes in the blood (e.g. high serum creatinine). These manifestations are in addition to those seen with the original cause. Manifestations of pre-renal causes will have signs of poor blood flow and/or low blood volume (e.g. low blood pressure). Intrarenal causes could have signs of inflammation (e.g. fever). Post-renal causes would have difficulty with urination and possible pain at the location of the obstruction.

Review Questions



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2517#h5p-77

Gross Pathology of AKI

LYZ BOYD AND JENNIFER KONG

Learning Objectives

By the end of this chapter, you will be able to:

- Identify changes in colour and size of kidney and relate it to the pathology.
- Identify absence and presence of gross anatomy structures and relate it to the pathology.
- Correlate pre-renal, intra-renal, and post-renal causes and the pathological changes in gross anatomy specimens.

In this section, we'll learn about examples of different causes of AKI using gross pathology specimens from the DHPLC.

Prerenal: Shock Kidney

Recall that prerenal acute kidney injury occurs when there is inadequate blood flow to the kidneys for them to be able to continue their function of excreting waste and balancing fluid and electrolytes. In this example, the cause of the AKI was hemorrhagic shock.

Pathophysiology

Aneurysms are bulges in arteries that can occur as a result of weak connective tissue or prolonged hypertension. This 58 year old patient with a history of hypertension and diabetes had an aneurysm of their abdominal aorta. Due to the weakened vessel walls, this aneurysm ruptured. The abdominal aorta carries all the blood supply for the lower body, so with rupture of the aneurysm, there was massive bleeding into the abdominal cavity, resulting in hemorrhagic shock. In addition to the blood loss and other negative consequences of the ruptured aneurysm, this shock state also caused an AKI in this patient.

Clinical Features

The rupture of the aneurysm caused severe abdominal pain and the blood loss caused shock, which presented as an extremely low blood pressure of 60/0 mmHg (normal: approximately 120/80 mmHg). Surgeons attempted to repair the rupture with a graft, but after the operation the patient had persistent hypotension and anuria (lack of urination), which reflected the AKI that accompanied this pathology.

Gross Pathology Features

Compared to the normal kidney, the cortex is pale and the medulla is darkened. These findings are typical of prolonged shock.

This video is awaiting licensing approval and will be available shortly. **DHPLC specimen D0310** Shock kidney presented by Jennifer Kong, licensed under [License Type Here]

Intrarenal: Glomerulonephritis

Intrarenal causes of AKI are a group of conditions that cause kidney damage via a process that occurs within the tissue of the kidney. In this example, the cause was glomerulonephritis which is an inflammatory response that targets the glomeruli.

Pathophysiology

The term glomerulonephritis encompasses a group of causes of kidney disease that all involve damage done to components of the glomerulus by the immune system. For example systemic lupus erythematosus (colloquially known as "lupus") is an autoimmune condition that involves deposition of immune complexes and inflammatory responses in a wide array of body systems. One of these is the kidneys and this ongoing immune insult to the kidneys may affect renal function. Another example of a cause of glomerulonephritis is post-streptococcal glomerulonephritis. After an infection with streptococcal bacteria, some people develop a damaging immune response in the kidneys that affects the glomeruli. There are many other causes of glomerulonephritis, but in most cases the recruitment of immune cells and proteins (like antibodies) impair the ability of the glomerulus to perform filtration. Not all of these causes usually result in AKI; some of them have a tendency to cause more gradual changes to kidney function which is termed Chronic Kidney Disease (CKD).

The impaired filtration and damage to the glomeruli results in protein and red blood cells that would normally be too large for the filtration barrier of the glomerulus leaking into the urine. This can result in inadequate protein in the blood, decreasing the osmotic force drawing fluid back into the blood and resulting in edema. The nephron has an internal mechanism of sensing filtration and adjusting blood pressure accordingly, so when filtration is impaired, factors are released in an attempt to increase kidney perfusion. Unlike prerenal causes where activation of mechanisms to raise blood pressure may be helpful, in glomerulonephritis the systemic blood pressure is usually normal to begin with, so this effect may cause dangerously elevated blood pressure.

In the case of the specimen we will see shortly, clinicians were unable to determine a precise cause, but acute glomerulonephritis was confirmed to be present.

Clinical Features

In this patient, the initial symptoms were facial and peripheral edema (swelling in the face and extremities), which were likely related to protein loss in the urine. They then developed headaches, blurred vision, and dark urine. When they presented for medical care, their blood pressure was extremely elevated at 220/120 and their urine contained protein and red blood cells. The headaches were most likely caused by the increased blood pressure, as was the blurred vision. The small blood vessels that supply the retina are delicate and can burst when blood pressure is extremely elevated. Dark urine was caused by the leakage of red blood cells through the damaged glomeruli and into the filtrate. The patient died from a bleed in their brain (cerebral hemorrhage) before treatment could be completed, which was also caused by the highly elevated blood pressure because the blood vessels could not continue to withstand the pressure.

Gross Pathology Features

This video is awaiting licensing approval and will be available shortly. **DHPLC specimen D0201** Glomerulonephritis presented by Jennifer Kong, licensed under [License Type Here]

In the cortex of the kidney that we can see on the cross section view of the specimen there are many small red dots. These are called petechiae and they represent hemorrhages resulting from the damage the disease caused to the glomeruli. These dots are only present in the cortex because that is where the glomeruli are located.

Section Review

Two examples of AKI are shock kidney and glomerulonephritis. Shock kidney is a prerenal cause as shock is preventing blood flowing to the kidney. As such, the kidneys are pale and the pyramids are showing signs of necrosis. Glomerulonephritis is an intrarenal cause where antibodies have damaged the glomeruli. As a result, damage is evident in the cortex – pale with signs of bleeds (petechia) whereas the medulla (loop of Henle & collecting ducts) are spared.

Review Questions

1. Compared to a normal kidney, which of the following would indicate a kidney that experienced prolonged shock?

- A pale cortex and darkened medulla
- A darkened cortex and pale medulla
- A darkened cortex and darkened medulla
- A pale cortex and pale medulla

2. Fill in the blanks.

_____ part of Bill's kidney is inflamed if he has glomerulonephritis.

3. Fill in the blanks. What gross pathological feature is often observed in the kidney from someone with glomerulonephritis? Where is the feature located?

_____ observed in the _____ of kidneys.

Answer Key

1. A pale cortex and darkened medulla
2. Glomerulus/Glomeruli
3. Petechiae, cortex

Histopathology of AKI

LYZ BOYD

Learning Objectives

By the end of this section, you will be able to:

- Identify debris within the nephron tubule and explain how it is an indication of kidney injury.
- Recognize changes in cellular populations in the glomeruli and correlate with pathology.
- Identify the loss of cellular components (e.g. nuclei, cell volume, brush border) and correlate with the pathology.

As mentioned in a previous section, AKI is a clinical diagnosis defined by an increase in serum creatinine or an abnormal decrease in urine output. Therefore, when discussing histopathology, the term AKI doesn't really apply and instead we describe the pathological changes we see within the kidney itself.

The categories of causes of AKI (prerenal, intrarenal, and postrenal) don't apply to the histopathology either. Generally, we will see only intrarenal damage when observing the kidneys microscopically, but this could be a result of any of AKI from any of the 3 categories.

Review the following sections and videos to learn more about the histopathology of AKI.

Shock Kidney

As we discussed earlier, medical shock occurs when there is a serious decrease in either effective or absolute circulating blood volume and may cause a prerenal AKI. A persistent prerenal AKI can cause intrarenal kidney damage, when the high metabolic demands of the cells in the renal tubules are not met and they begin to degenerate.

The following video reviews the histological findings in the kidney of someone with hemorrhagic shock.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2528#h5p-86

Histopathology of kidney experiencing shock. DHPLC specimen PATH 425-058 presented by Lyz Boyd

Video Summary – Clinical context: The patient was a 29 year old male who was involved in a traffic accident and fractured his pelvis. Pelvic

fractures are often associated with massive internal bleeding, which in this case caused shock and therefore a prerenal cause of AKI. He developed AKI and died 7 days later.
Pathology: The blood loss caused hemorrhagic shock which resulted in a type of prerenal kidney injury. Prolonged lack of blood to the kidneys resulted in pathology that can be seen microscopically, termed acute tubular injury.
Histopathological findings: The following changes to the renal tubules can be observed:
– Renal tubules are filled with debris and/or blood as a result of damage to the tubules and degradation of the epithelial cells lining the tubules.
– Nuclei of the cells lining the tubules disappear or appear faint.
– The brush border of the proximal convoluted tubules is lost or reduced.
– The cells lining the tubules flatten, making the lining of the tubules appear thinner.
– Mitotic figures are present, indicating that the surviving cells are attempting to divide and regenerate the tubules.

Glomerulonephritis

As mentioned in a previous section, glomerulonephritis is an inflammatory response that targets the glomeruli and interferes with their function. In this case, glomerulonephritis was triggered by strep throat.

The following video outlines the histopathological findings of glomerulonephritis.



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2528#h5p-84

Histopathology of glomerulonephritis. DHPLC specimen PATH 425-049 presented by Lyz Boyd
Video Summary:
Clinical context: The patient was a 10 year old child who had a strep throat infection, which is an infection with a bacteria called streptococcus. A couple of weeks later they developed fever, edema, headaches, and “smoky” urine. Their urine contained protein, red blood cells, and white blood cells and their blood contained excess urea, a metabolic waste product.
Pathology: In some cases, a streptococcus infection results in a misguided immune response that attacks the glomeruli of the kidneys, termed streptococcal glomerulonephritis.
Histopathological findings:
– The tubules of the kidney have observable debris and damage, similar to the shock kidney.
– The glomeruli are hypercellular because they are filled with inflammatory cells that are impairing the function of the glomeruli.
– Some glomeruli demonstrate crescents, which are areas of scarring in response to the inflammatory damage; others have been entirely obliterated.

Section Review

Histologically, the damage caused in AKI is quite dramatic. In shock kidney, blood is not perfusing the nephrons causing starvation and death of cells. As a result, the nephron tubules are filled with debris and/or blood with signs of nuclear activity (i.e. life in the cell) waning as cellular structures appear faint (e.g. nuclei) or diminished (e.g. loss of brush border in PCT, flattened cells). Similarly in glomerulonephritis, the damage to glomeruli by antibody complexes are evident in observable debris and damage in the nephrons. Glomeruli are hypercellular because they are filled with inflammatory

cells in addition to the glomerular capillaries and blood. Taken together with the changes in gross anatomy, the damage to nephrons are serious.

Review Questions

1. Place the following into the correct columns.

Mitotic figures are present (surviving cells are attempting to divide and regenerate tubules). The cells lining the tubules flatten (lining of tubules appear thinner). Tubules have observable debris and inflammatory damage. Renal tubules filled with debris and/or blood (result of damaged tubules and degradation of tubule epithelial cells).	Glomeruli crescents Areas of obliterated glomeruli. Nuclei of the cells lining the tubules disappear or appear faint. Hypercellular glomeruli because they are filled with inflammatory cells that are impairing glomeruli function. Brush border of proximal convoluted tubules is lost or reduced.

Histopathological Features of Glomerulonephritis Kidney	**Histopathological Features of Hemorrhagic Shock Kidney**

Answer Key

1.

Histopathological Features of Glomerulonephritis Kidney	Histopathological Features of Hemorrhagic Shock Kidney
Tubules have observable debris and inflammatory damage. Hypercellular glomeruli because they are filled with inflammatory cells that are impairing glomeruli function. Glomeruli crescents Areas of obliterated glomeruli.	Renal tubules filled with debris and/or blood (result of damaged tubules and degradation of tubule epithelial cells). Nuclei of the cells lining the tubules disappear or appear faint. Brush border of proximal convoluted tubules is lost or reduced. The cells lining the tubules flatten (lining of tubules appear thinner). Mitotic figures are present (surviving cells are attempting to divide and regenerate tubules).

Treatment and Prognosis of AKI

LYZ BOYD

Learning Objectives

By the end of this chapter, you will be able to:

- Explain why addressing the underlying cause will ultimately treat the acute kidney injury.
- Briefly describe the process of dialysis to treat AKI.

You may be wondering, once a patient has developed AKI, what happens? This section will address the treatment and prognosis of AKI.

Treatment

As we've seen so far in this chapter, the causes of AKI are widely varied. Therefore, the treatments also vary and are aimed at addressing the underlying cause of the AKI as well as managing some of the symptoms. Here are some examples of treatments for the different types of causes of AKI:

Type of AKI	Example pathology	Examples of treatment strategies
Prerenal	Hemorrhagic shock	Surgery to control the source of the bleeding, replacement of blood volume with IV fluids and/or blood transfusion
Intrarenal	Acute streptococcal glomerulonephritis	Administration of antibiotics to treat the bacterial infection and of medications to decrease blood pressure if elevated. Immunosuppressive medications lack evidence for this condition, but they may be used if the condition is severe or worsening based on kidney biopsy.
Postrenal	Obstruction of the urethra caused by BPH	Insertion of a catheter into the urethra to keep it open and relieve the obstruction.

If the kidney dysfunction is severe enough that the patient experiences dangerous imbalance in pH or electrolytes or build up of waste products, dialysis may be necessary. Dialysis is a process that uses a machine to mimic the function of the kidney outside the body. During the process, the patient's blood is passed along a membrane that mimics the function of the glomerulus and allows waste products to be removed from the blood by passing through a semipermeable membrane. The blood is then returned to the patient. While this is a life-saving treatment, it is not perfect and does not entirely mimic the function of the kidneys. It is also a time-consuming procedure that needs to be performed every 2-3 days.

Prognosis

Just as the causes and treatments vary, the anticipated long term outcomes of AKI vary as well. The severity and cause of the AKI have a large impact on the prognosis.

As we've seen in some of the cases presented throughout previous sections, death is unfortunately a relatively common outcome of AKI. In some cases, AKI itself is responsible for the death of the patient, but more often, the underlying critical illness, such as medical shock, leads to both AKI and death.

Many patients survive, but still have some impairment of their kidney function and become part of the population who has chronic kidney disease (CKD). CKD can vary widely in severity, from requiring only medications and dietary restrictions to manage it to requiring ongoing dialysis or even renal transplant.

Some patients make a full recovery after the underlying cause of the AKI has been treated. Some of these patients may require dialysis temporarily while their kidney function recovers.

Section Review

The treatments and prognoses of AKI are just as varied as the causes of AKI. The treatments aim to address the underlying cause and/or treat the symptoms. Some patients unfortunately pass away as a result of AKI or the cause of the AKI and others live with ongoing impairment of their kidney function. However, some patients do make a full recovery.

Review Questions

1. Fill in the blanks. Treatments of AKI are varied and are based on the _____ cause. Prognosis also varies and is based on the _____ and cause.

2. When may dialysis be necessary? Select all the apply.

- pH imbalance
- Electrolyte imbalance
- Build-up of waste products
- Slightly increased blood pressure
- Slightly decreased blood pressure

3. Fill in the blanks.

Impairment of kidney function as a result from AKI can result in _____ in the long run.

Answer Key

1. underlying, severity
2. pH imbalance, Electrolyte imbalance, Build-up of waste products
3. chronic kidney disease/CKD

Consequences of AKI in Other Systems

JENNIFER KONG

Learning Objectives

By the end of this chapter, you will be able to:

- Explain the consequences of fluid overload, caused by AKI, in the cardiovascular and pulmonary systems.
- Describe the outcomes of excessive circulating nitrogenous wastes, caused by AKI, on the GI and nervous systems.
- Explain how pH imbalances, due to AKI, will affect electrically excitable tissues and rate/depth of breathing.

As mentioned, the effects of rising blood levels of wastes and the inability to excrete said wastes and fluid will have profound effects on almost every system in the body.

Fluid overload (because volume can't be excreted) will cause problems with

- Cardiovascular: increased blood volume will increase blood pressure and work for the heart. This can push a heart into failure if it can not maintain pumping this excessive volume.
- Pulmonary: increased blood volume may increase blood pressure in pulmonary circulation. As a result, some plasma-like fluid leaks out of the pulmonary capillaries and into alveolar space, manifesting as pulmonary edema which can be heard upon auscultation of the chest

Excessive circulating nitrogenous wastes will cause problems with

- Gastrointestinal: nitrogenous wastes like urea and ammonia are very irritating to tissues that have fluid, given their ability to dissolve in water easily. Thus, the entire GI tract will be irritated, manifesting in nausea and vomiting.
- Nervous: Similarly, excessive nitrogenous wastes will dissolve in the cerebrospinal fluid and thus irritate the CNS, manifesting as confusion and CNS depression (i.e. reduced level of consciousness, altered cognition)

Imbalance of pH and electrolyte imbalances (because excretion/absorption is impaired) will cause problems with

- Cardiovascular: disturbances in electrolytes – especially potassium – will have effects on all electrically excitable cells: especially the heart. Thus electrolyte imbalances due to AKI can cause arrhythmias
- Nervous: similarly, electrolyte disturbances will affect the CNS – manifesting in altered cognition, CNS depression, and possibly seizures.
- Pulmonary: pH imbalances will affect the rate and depth of breathing as the respiratory system tries to maintain pH balance. AKI prevents acid from being excreted – so a faster breathing rate (tachypnea) will occur causing the body to work harder to breathe.

Section Review

As kidneys fail, wastes accumulate in the blood causing direct damage to the CNS and GI systems. This presents as CNS depression (altered consciousness and cognition) and GI distress (e.g. nausea, vomiting). Impaired kidney function will lead to problems with both fluid and electrolyte balance with an overload of fluid in vasculature and tissues. This fluid overload will have consequences on the heart (increased workload) and vessels (high blood pressure) with excess fluid wanting to enter third spaces (e.g. alveoli) causing complications in other systems. Electrolyte disturbances will affect anything that is electrically excitable such as the heart (e.g. arrhythmias) and CNS (e.g. cognition). Kidneys also help maintain pH homeostasis by excreting acid; hence loss of kidney function will lead to acidosis which the respiratory system will work faster and harder to compensate to maintain pH homeostasis.

Review questions

1. Which systems will be affected by AKI? Select all that apply.

- CNS
- Respiratory
- Cardiovascular
- Renal
- Gastrointestinal
- Reproductive

2. AKI can cause increased respiratory rate.

- True
- False

3. Fill in the blanks with the following words.

Edema	Interstitial fluid
Albumin	Tissues

_____ happens when excess fluid leaves the blood and enters the _____. There are two causes for this:

AKI has caused the loss of _____ in the urine, leading to a decrease in osmotic gradient in the blood; and increased fluid in vessels causes an increase in blood pressure that pushes plasma from the blood into the _____

Answer Key

1. CNS, Respiratory, Cardiovascular, Renal, Gastrointestinal
2. True
3. Edema, Interstitial fluid, Albumin, Tissues

Diagnosis of AKI and Interprofessional Collaboration

JENNIFER KONG

Learning Objectives

By the end of this chapter, you will be able to:

- Explain the role of blood and urine tests in the diagnosis of AKI.
- Briefly describe how ultrasound works and the role of the sonographer when diagnosing AKI.

Medical Lab Technologist

As mentioned earlier, kidney function is mainly determined on blood tests, urine composition, and urine volume. A medical lab technologist is responsible for collecting and analyzing both blood and urine samples. Blood tests will be analyzed for creatinine and nitrogen waste (e.g. urea) levels in the blood; urine tests can analyze for composition that suggests the kidney's ability to reabsorb useful nutrients, electrolytes, and overall fluid volume and density. In addition, blood tests can be analyzed to help identify the cause (i.e. pre-renal, intrarenal, or post-renal)

Sonographer

A sonographer uses ultrasound to help investigate the cause of AKI. Ultrasound can give real time information on kidney structure and the path of urine excretion. Ultrasound can also give information of blood flow to/from the kidney (Doppler for blood flow) which will help determine the cause of AKI being pre-renal vs intrarenal/post-renal causes.



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2535#h5p-126

Sonography and acute kidney injury. Created by Ken Marken and Jennifer Kong, licensed under CC-BY-NC

Section Review

Many health professionals work together to diagnose AKI and determine the severity. Medical lab technologists can test the presence of wastes in the blood, indicative of an impaired elimination from the renal system. Similarly, they can test for the presence of useful nutrients in the urine, indicative of impaired reabsorption at the nephron level. Sonographers can give real-time imaging of blood flow to the kidney and of the kidney itself. This is helpful for prerenal causes as sonographers can use the 'doppler' to measure blood flow to the kidney and for post-rental causes as an obstruction can be visualized.

Review questions

1. A medical lab technologist can help determine kidney function by measuring substances? Select all that apply.

- Blood plasma or serum
- Feces
- Urine
- Hair

2. Sonography can detect the presence of a blood clot to the kidney.

- True
- False

3. Why are medical lab technologists are measuring nitrogen waste levels in blood and not urine?

Answer Key

1. Blood plasma or serum, Urine
2. True
3. Kidney failure means you can't eliminate the nitrogenous wastes from your blood into your urine. You would expect to see nitrogen waste in urine at all times – but there should be much nitrogen in your blood if your kidneys work.

AKI Chapter Summary and Credits

JENNIFER KONG

Chapter Summary

AKI is a result of an insult to the kidneys – whether before (prerenal), within (intrarenal), or after the kidney (postrenal). Regardless of the cause, nephrons are damaged or destroyed due to the insult – which is evident in both gross and microscopic examination of the nephrons. The end result is impaired reabsorption of useful nutrients AND excretion of harmful wastes and excess fluid. As a result, the body retains the wastes and fluid causing disturbances in multiple systems and signs of fluid overload.

A common feature of AKI is high blood levels of nitrogenous wastes and creatinine at the same time as a reduction in urine output. In addition to these common features, there will be additional features that suggest the cause as being pre-, intra-, or post-renal. Diagnosis of AKI is usually by blood tests for creatinine and nitrogenous wastes in conjunction with urine output. Imaging of the kidney through ultrasound will help give information as to the cause being pre-, intra-, or post-renal.

Treatment of AKI is to address the underlying cause of the insult to the kidney.

Credits

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Histopathology video: Lyz Boyd (UBC medical student) with supervision of Dr. Jonathan Bush (UBC, Director of DHPLC)

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Post-Test for Acute Kidney Injury

LYZ BOYD AND JENNIFER KONG

1. Which of the following is an example of a prerenal cause of acute kidney injury?

- Severe dehydration
- Acute glomerulonephritis
- Pelvic tumour blocking the flow out of the urethra
- Taking too many medications that hurt the kidney (nephrotoxic)

2. Finish the following sentence. The damage to the kidney in post-renal causes is generally caused by:

- Inadequate blood flow to the kidney
- Toxic drugs
- The immune system
- Blockage of the drainage of urine

3. Which of the following signs is a result of protein loss in the urine from pathology that damages the glomerular filtration barrier?

- Elevated blood pressure (hypertension)
- Edema (swelling)
- Increased amounts of dark urine
- Increased temperature (fever)

4. Which of the following is a histological sign of acute tubular injury?

- Debris in the renal tubules
- Inflammatory cells filling the Bowmans space of the glomerulus
- Increase in brush border surface area in the PCT
- Increased number of neprhon cells (hyperplasia)

5. Fill in the blanks.

Acute glomerulonephritis is an example of a _____ cause of AKI. It begins with damage to the _____, usually caused by the body's own _____ system. As a result, _____ can leak out of the blood and into the _____. This can result in inadequate osmotic gradient protein in the _____, which decreases fluid to stay in the tissues rather than be kept in the blood. Clinically, this can be seen as _____, most noticeably in the lower limbs and face.

Answer Key

1. severe dehydration
2. Blockage of the drainage of urine
3. Edema (swelling)
4. Debris in the renal tubules
5. intrarenal, glomerulus, immune, proteins, urine, blood, edema

CIRRHOSIS

Cirrhosis Chapter Overview

JENNIFER KONG

Chapter Learning Objectives

1. Describe the anatomy and physiology of the liver.
2. Describe the pathogenesis and manifestations of liver cirrhosis.
3. Identify the main risk factors and causes for liver cirrhosis.
4. Explain how laboratory findings and diagnostics determine the cause and extent of liver damage.

Cirrhosis is end-stage liver failure. Many things can cause liver damage:

According to Health Canada and the Canadian Liver Foundation, 1 in 4 Canadians experience some degree of liver malfunction in their lifetime. There are over 100 liver diseases caused by a variety of factors including; viruses, toxins, genetics, alcohol, medications, biliary obstructions and unknown causes.
Regardless of the cause, repeated chronic liver damage will result in cirrhosis where the liver experiences persistent damage with ensuing inflammation, to the extent that liver regeneration is unable keep up, leading to lower hepatocyte numbers and permanent scarring (fibrosis).

This chapter is subdivided into:

- Pre-test
- Normal liver and gallbladder
- Gross anatomy and histology of normal liver
- Causes and pathophysiology of cirrhosis
- Gross pathology of cirrhotic liver
- Histopathology of cirrhosis
- Clinical manifestations of cirrhosis
- Treatment and prognosis of AKI
- Consequences of AKI in other systems
- Diagnosis of cirrhosis
- Interprofessional collaboration during the diagnosis and management of cirrhosis
- Chapter Summary
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

CBC	Complete Blood Count
INR	International Normalized Ratio
IVC	Inferior Vena Cava
LFTs	Liver Function Tests
PTT	Prothrombin Time Test
SVC	Superior Vena Cava

Cirrhosis Pre-Test

JENNIFER KONG

1. Cirrhosis can occur after repeated ingestion of toxins like alcohol.

- True
- False

2. Finish the following sentence. Cirrhosis can manifest as:
Select all that apply.

- fluid in the abdomen (ascites)
- hemorrhoids
- very bad breath
- menstrual irregularities
- development of breast tissue in males
- jaundice

3. Fill in the blanks. Liver failure can develop by:

- Cirrhosis is the final result of _____ injury to the liver over years. This injury can be chronic infections of the_____ virus or chronic ingestion of toxins such as _____ or medications or even chronic overfilling of the liver with blood due to _____ sided heart failure.

Answer Key

1. True
2. All of the above
3. repeated/continuous, hepatitis B/hepatitis C, alcohol, right

The Normal Liver and Gallbladder

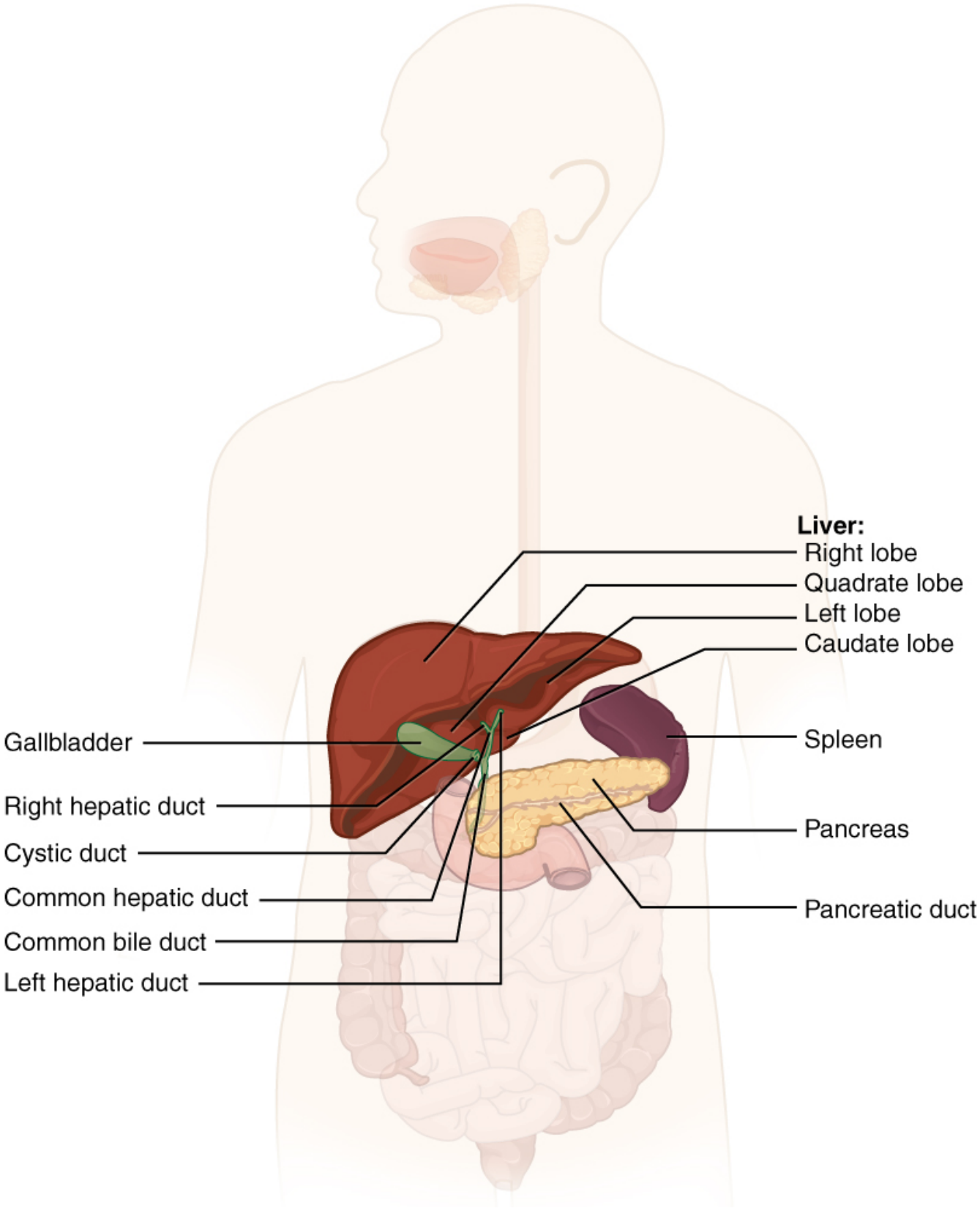
J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- State the main digestive roles of the liver and gallbladder.
- Identify three main features of liver histology that are critical to its function.
- Discuss the composition and function of bile.

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the **liver**, **pancreas**, and gallbladder. The digestive role of the liver is to produce **bile** and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile.



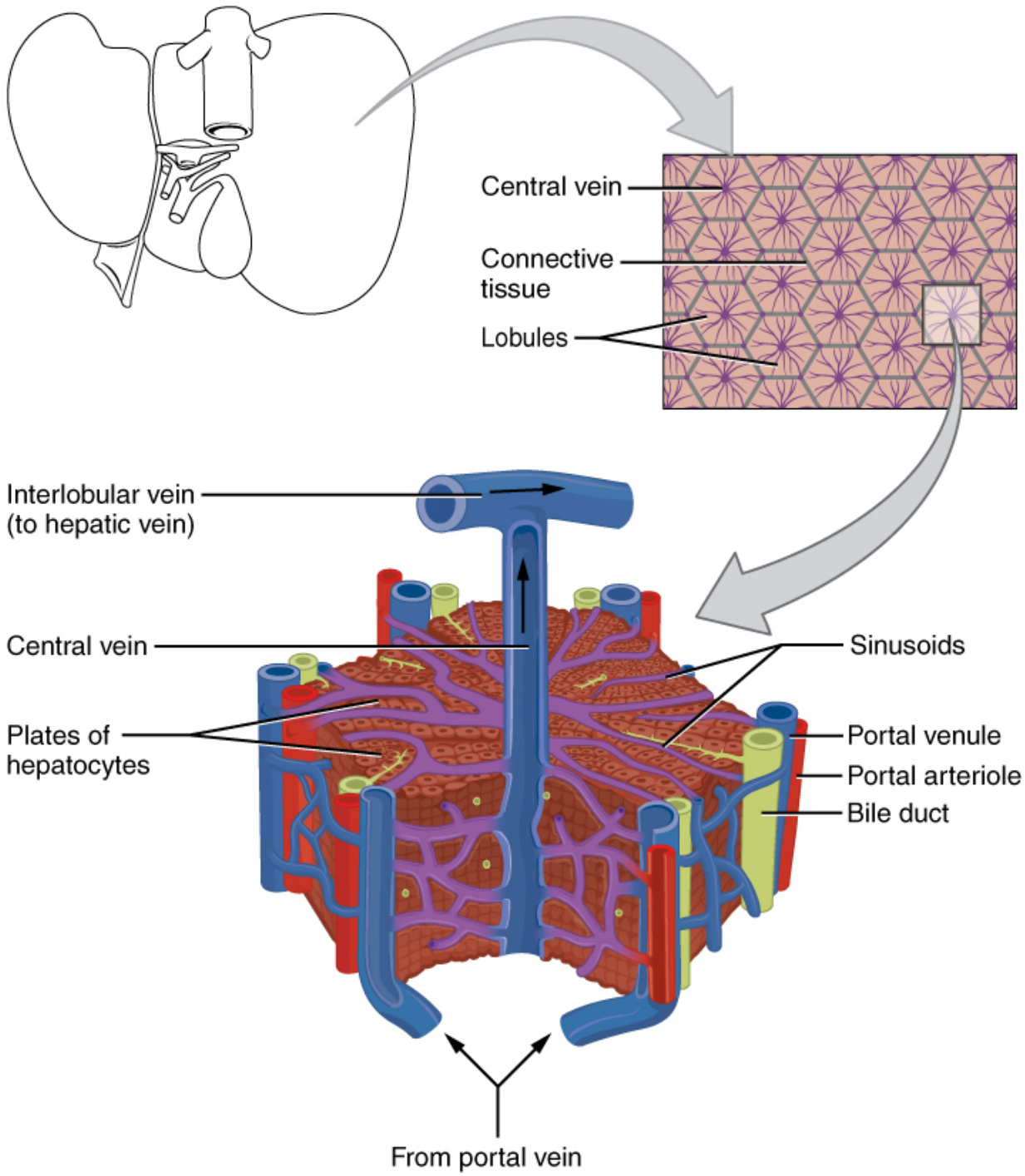
The Liver, Spleen, Pancreas and Upper Duodenum

The Liver

The liver is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles in metabolism and regulation of blood plasma composition. The liver lies inferior to the diaphragm in the right upper quadrant of the abdominal cavity and receives protection from the surrounding ribs.

The liver is divided into two primary lobes: a large right lobe and a much smaller left lobe. In the right lobe, some anatomists also identify an inferior quadrate lobe and a posterior caudate lobe, which are defined by internal features. The liver is connected to the abdominal wall and diaphragm by five peritoneal folds referred to as ligaments. These are the falciform ligament, the coronary ligament, two lateral ligaments, and the ligamentum teres hepatis. The falciform ligament and ligamentum teres hepatis are actually remnants of the umbilical vein, and separate the right and left lobes anteriorly. The lesser omentum tethers the liver to the lesser curvature of the stomach.

The **porta hepatis** ("gate/door to the liver") is where the **hepatic artery** and **hepatic portal vein** enter the liver. These two vessels, along with the **common hepatic duct**, run behind the lateral border of the lesser omentum on the way to their destinations. As shown in the figure below, the hepatic artery delivers oxygenated blood from the heart to the liver. The hepatic portal vein delivers approximately 80% of total blood flow to the liver; portal vein blood is partially deoxygenated, but contains nutrients absorbed from the small intestine and actually supplies more oxygen to the liver than do the much smaller hepatic arteries. In addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the **central vein** and then through the **hepatic vein** to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.



Microscopic Anatomy of the Liver – *The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.*

Histology

The liver has three main components: **hepatocytes**, bile canaliculi, and **hepatic sinusoids**. A hepatocyte is the liver's main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory,

metabolic, and endocrine functions. Plates of hepatocytes called hepatic laminae radiate outward from the central vein in each **hepatic lobule**.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each **bile canaliculus** (plural = canaliculi). These small ducts transport the bile that is produced and secreted by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the common hepatic duct. This duct then joins with the cystic duct from the gallbladder, forming the **common bile duct** through which bile flows into the duodenum of the small intestine.

Hepatic sinusoids are an open, porous blood space lined with simple squamous endothelial cells that takes the form of discontinuous fenestrated capillaries. Sinusoids are formed by the merging of nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries and therefore carry mixed blood containing nutrients from the alimentary canal as well as oxygen. Sinusoids are instrumental in that they infiltrate each hepatic laminae delivering their contents to the hepatocytes. From their central position, hepatocytes absorb and process the nutrients, toxins, and waste materials carried by the blood. Materials such as **bilirubin** are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids at levels that maintain specific levels within the blood. Hepatocytes have the ability to store excess lipid, carbohydrates and amino acids until the blood plasma levels become depleted. Maintaining blood plasma composition is very important as each of these blood plasma components are required by cells of the entire body. The liver therefore has an important role in ensuring maintenance, survival, and homeostasis of all of the tissues and organs.

Once the hepatic sinusoids have passed by the hepatocytes within each laminae, the sinusoids merge and send blood through a central vein. Blood then flows through a hepatic vein into the inferior vena cava (IVC). This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-shaped **reticuloendothelial cells** (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The **portal triad** is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

Bile

In order to underscore the importance of the bile that is produced by hepatocytes. It is important to remember that the food that is eaten does contain fat which is a valuable energy source and building block for the body. Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid globules, a process called emulsification. Bile is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, both of which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μm in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity. Emulsification is similar to way dish soap can disperse oil slicks or fats that can be seen on the top of dishwater.

Bile salts act as emulsifying agents, so they are also important for the intestine's ability to digest and then absorb lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the **enterohepatic circulation**. Once

bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes absorb and then excrete the bile salts as part of the newly formed bile. Thus, this precious resource is recycled.

Bilirubin, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is processed and then excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic colour! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats are able to be broken down or absorbed in the absence of bile.

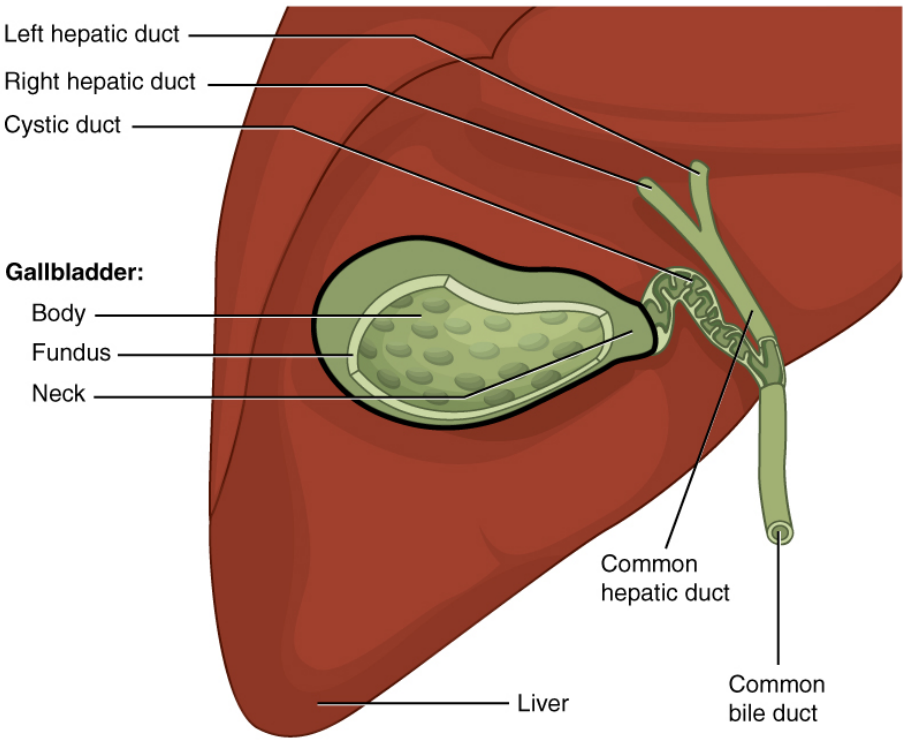
Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like hepatopancreatic ampulla closes, allowing bile to divert to the **gallbladder**, where it is concentrated and stored until the next meal.

Watch this video on liver to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

The Gallbladder

The gallbladder is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The **cystic duct** is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the cystic duct and into the bile duct. Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.



Gallbladder – *The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.*

Section Review

Chemical digestion in the small intestine cannot occur without the help of the liver and pancreas. The liver produces bile and delivers it to the common hepatic duct. Bile contains bile salts and phospholipids, which emulsify large lipid globules into tiny lipid droplets, a necessary step in lipid digestion and absorption. The gallbladder stores and concentrates bile, releasing it when it is needed by the small intestine.

The pancreas produces the enzyme- and bicarbonate-rich **pancreatic juice** and delivers it to the duodenum of the small intestine through ducts. Pancreatic juice buffers the acidic gastric juice in chyme, inactivates pepsin from the stomach, and enables the optimal functioning of digestive enzymes in the small intestine.

Review Questions

1. What percentage of blood flow in the liver comes from the hepatic portal system?

- 33%
- 50%
- 80%

2. Which of these statements about bile is true?

- About 500 mL is secreted daily.
- Its main function is the denaturation of proteins.
- It is synthesized in the gallbladder.
- Bile salts are recycled.

3. Fill in the blanks with the following words.

central vein hepatic artery	portal vein sinusoids hepatocytes

In a liver lobule, the _____ are the main cell type of the liver. They process, store, and release nutrients into the blood. Radiating out from the _____, they are tightly packed around the hepatic _____, allowing the hepatocytes easy access to the blood flowing through. Blood enters the lobule from divisions of the smaller _____ and larger _____ of the portal triad. As the blood flows towards the central vein, the blood bathes the hepatocytes.

Answer Key

1. 80%
2. Bile salts are recycled.
3. hepatocytes, central vein, sinusoids, hepatic artery, portal vein

Adaption

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Accessory organs of the digestive **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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Gross Anatomy and Histology of Normal Liver

JENNIFER KONG

Learning Objectives

By the end of this chapter, you will be able to:

- Identify gross structures of the normal liver.
- Explain the colour and texture of the liver with the amount of blood and tissue make up.
- identify the liver lobule, sinusoids, central vein, and the components of the portal triad.

Occupying the entire upper right quadrant (and a bit of the left!) of the abdomen, the liver sits mostly behind the rib cage. However, visually, the size, colour, and shape of the liver indicates its health and function.

This video is awaiting licensing approval and will be available shortly. **Gross anatomy of normal liver with gallbladder**. Presented by Jennifer Kong using DHPLC specimen "Normal liver teaching set" and M0704 Liver with Amyloidosis, licensed under All Rights Reserved

Histologically, there is very little variation in liver tissue as the liver is made of thousands of hepatocytes (liver cells). However, these hepatocytes are organized in patterns: lobules have hepatocytes radiating from a central vein and numerous lobules are joined together to form "plates" of liver tissue separated by thin spaces known as sinusoids.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2554#h5p-136

Histology of normal liver stained with H&E. *Presented by Yimei Qin using specimen from Dr. Gang Wang's private collection*, licensed under All Rights Reserved

Section Review

The liver is well vascularized (giving a rich red-brown colour) and predominantly made of hepatocytes, organized in plates comprised of lobules (giving a smooth, homogenous texture). The posterior surface of the liver has the gallbladder and porta hepatis (comprising of hepatic artery, portal vein, and hepatic duct reside). Histologically, the liver is made of thousands of liver lobules identifiable by hepatocytes radiating out from a central vein. The outer border of the lobules are the portal triads, made of a small branch of the hepatic artery, portal vein, and bile duct.

Review Questions

1. You can determine how much blood is in the liver based on its colour.

- True
- False

2. Place the following words in the right column.

IVC Hepatis Lobules	Gallbladder Portal triad Central vein Falciform ligament

Gross structure	Histological structure

Answer Key

1. True
2.

Gross structure	Histological structure
Gallbladder IVC Hepatis Falciform ligament	Portal triad Lobules Central vein

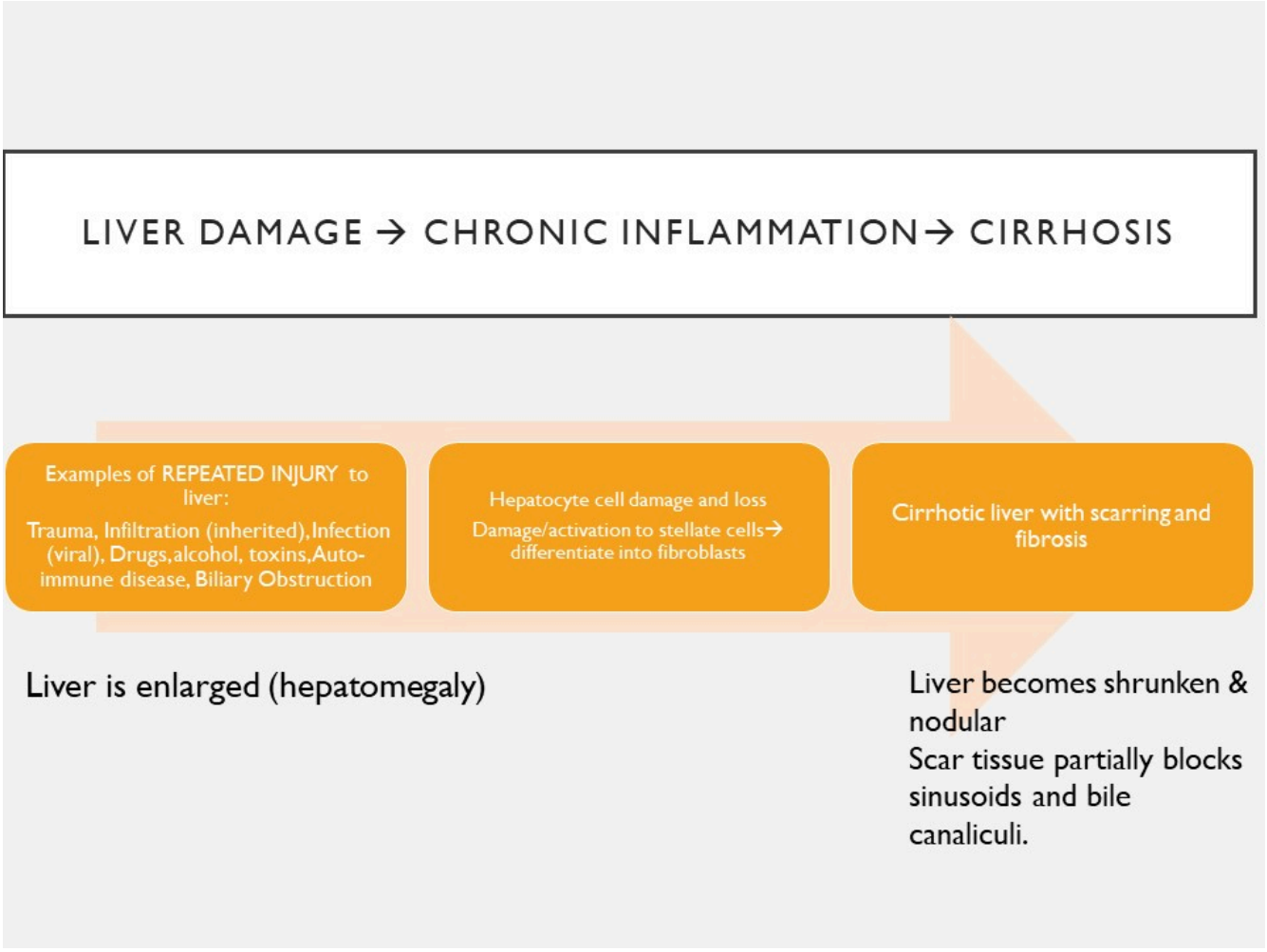
Causes and Pathophysiology of Cirrhosis

JENNIFER KONG

Learning Objectives

By the end of this chapter, you will be able to:

- Explain how repeated damage leads to physical changes in liver structure and function.
- Name possible causes of repeated liver damage that can lead to cirrhosis.



Progression of inflammatory damage to liver causing cirrhosis.

Cirrhosis develops when repeated injury to the liver causes chronic inflammation leading to loss of liver cells (hepatocyte). Hepatocytes normally have a great ability to regenerate; but the frequency of the damage exceeds the regenerative rate. As a result, liver tissue, especially stellate cells, mature and differentiate into fibroblast-like cells which lay down fibrous collagen-rich extracellular matrix. This fibrous scar tissue does not have the same properties of hepatocytes nor can it perform the actions of a hepatocyte. Thus, the liver is remodeled into an organ that has atrophied and is 'stiffer' than a healthy liver which will cause problems for blood to enter via the portal vein (portal hypertension).
Because the liver is physically well protected from repeated physical insults, repeated injury usually occurs internally within the liver itself. Possible classification of causes of liver damage are infection, volume-induced trauma, and direct hepatocyte damage.

Infection of the Liver

Like any tissue, the liver can be infected with pathogens such as viruses. There are over a dozen recognized viruses which can infect, incubate, reproduce, and cause damage within the liver. When the infected hepatocyte lyses to release the new viruses, this causes loss of liver tissue and infection of surrounding hepatocytes. Thus, this viral infection of the liver is collectively termed as viral hepatitis.
Normally, the body can get over this viral infection and retain some immunity to future infections. However, a few viruses (especially Hepatitis B, C and E) can escape detection from the immune system, thus causing a chronic hepatitis infection. This chronic infection will cause chronic inflammation which can lead to cirrhosis, and is also a risk factor for liver cancer – especially if untreated.

Volume-Induced Trauma

The liver receives and processes blood coming from the portal vein and hepatic artery, akin to acting like a big sponge. The liver empties via the hepatic vein –> IVC (blood) and hepatic ducts (bile). Any obstructions to either of these outlets will cause a volume overload in the liver which will cause damage and result in an inflammatory response. Examples of volume-induced trauma are:

- cardiac cirrhosis: right sided heart failure will cause a back up of blood into the both the superior vena cava (SVC) and IVC. Because the hepatic vein drains directly into the IVC, any excessive blood in IVC will naturally flow into the liver.
- physical obstructions within the biliary tree: bile is continuously made and drained from the liver via the biliary tree. Anything that prevents bile draining into the duodenum will essentially cause a back up of bile up into the liver. Gallstones, bile duct narrowing or congenital defects (e.g. biliary atresia) can all lead to obstructions of the biliary tree
- inheritable disease that cause ducts to plug (e.g. Cystic Fibrosis): and anything else that causes blockage of a duct or slowing down of liver drainage (e.g. fluid secretions like bile becoming thick due to cystic fibrosis) will leading to excessive volume that will harm the hepatocytes.

Direct Damage to Hepatocytes

- Inflammatory response: a healthy immune system resides in the liver (i.e. Kupffer cells/hepatic macrophages) which requires alpha-1-antitrypsin to prevent damage to normal tissue (see Emphysema chapter). Inheritable alpha-1-antitrypsin deficiency will cause unregulated inflammatory response which results in damaging normal tissue along with the intended infected/damaged liver tissue.
- Autoimmune: a healthy immune system resides in the liver (ie Kupffer cells/hepatic macrophages). And overactive immune system – such as in autoimmune diseases like lupus in which healthy tissue becomes inappropriately targeted for destruction by immune system cells that can injure and destroy functional hepatocytes, thus causing a subsequent inflammatory response which exacerbates the problem.
- Alcohol- and non-alcohol fatty liver disease: Hepatocytes store many nutrients and sometimes that storage will cause damage to the surrounding hepatocytes. Alcohol is metabolized in the liver and stored as fat. Similarly, some fat is normally stored in hepatocytes from what is absorbed in the diet. However, excessive fat storage damages the hepatocyte through formation of reactive oxygen species. In addition an excessive amount of the cytoplasm being occupied by fat droplets will impede hepatocyte function.
- Infiltrative disease: inheritable conditions sometimes cause abnormal uptake and storage of minerals (e.g. Hemochromatosis, Wilsons disease, sarcoidosis). Although the liver does store some minerals, abnormally high amounts of stored minerals, like iron become damaging to hepatocytes.
- medications/toxins: Hepatocytes detoxify substances at a phenomenal rate. However, it is possible that it can exhaust itself if required. Certain medications, chemotherapy agents, or a combination of medications may literally 'burn out' the hepatocyte as it works hard to detoxify. As well, toxins can start to accumulate in the liver causing further damage.

Section Review

Chronic, repeated damage to the liver will both damage hepatocytes and stimulate inflammation that leads to tissue changes. As a result, the liver loses function and gathers fibrotic scar tissue that does not have hepatocyte function nor the same low flow resistance properties as the original liver tissue. Causes of repeated injury to liver can be classified based on repeated infection (i.e. hepatitis), volume overload of the liver (i.e. congestion of blood as in heart failure, back up of bile as in biliary obstruction), and direct damage to hepatocytes (i.e. chemical toxins, accumulation/infiltration of damaging substances, inflammatory attack of hepatocytes)

Review Questions

1. Select the correct word for the sentence. Cirrhosis is caused by **acute OR repeated** damage to the liver. An example of an infectious cause of cirrhosis is **pneumonia OR heart failure OR chronic Hepatitis B OR acute Hepatitis A**. Repeated obstructions of the biliary tree will cause a backup of **bile OR blood OR digestive juice** into the liver causing a fluid overload that damages the liver. Hepatocytes that accumulate **iron OR copper OR fat OR starch** can cause repeated damage leading to a condition known as non-alcoholic fatty liver disease that can progress to cirrhosis.

2. Explain how autoimmune disease can possibly lead to cirrhosis.

Answer Key

1. repeated, chronic Hepatitis B, bile, fat
2. The body's immune system incorrectly recognizes something in the liver as a possible pathogen. As such, the immune system repeatedly attacks the liver, causing death of hepatocytes and deposition of scar tissue leading to cirrhosis.

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Gross Pathology of Cirrhotic Liver

JENNIFER KONG

Learning Objectives

By the end of this chapter, you will be able to:

- Describe morphological changes in liver during cirrhosis.
- Explain why there are fatty changes and nodules in liver.

Cirrhosis is classified based on morphology or cause. Morphology is not as clinically useful as classification by cause (etiology) when determining treatment options.

Morphologically, cirrhosis has bumps (nodules) which can be micronodular (<3mm), macronodular (>3mm), or mixed.

- Micronodular cirrhosis have uniform nodules less than 3 mm in diameter. Micronodular cirrhosis is most often associated with high alcohol usage, hemochromatosis, hepatic venous outflow obstruction, and chronic biliary obstruction.
- Macronodular cirrhosis have irregularly sized and shaped nodules, greater than 3 mm in diameter. Macronodular cirrhosis is most often associated with chronic hepatitis infection (e.g. hepatitis B and C), alpha-1 antitrypsin deficiency (see Emphysema chapter), and chronic inflammation of bile ducts (primary biliary cholangitis).
- Mixed cirrhosis (when features of both micronodular and macronodular cirrhosis are present): Usually, micronodular cirrhosis progresses into macronodular cirrhosis over time.

This video is awaiting licensing approval and will be available shortly. ***Cirrhotic livers*** *presented by Jennifer Kong using DHPLC specimens M0313 Liver Cirrhosis with fatty changes; M0311 – Macronodular cirrhosis (post-necrotic); and M0303 – cirrhosis and acute viral hepatitis*, licensed under All Rights Reserved

Section Review

Cirrhotic livers will have obvious morphological changes regardless of the cause. Cirrhotic livers tend to be smaller due to loss of hepatocytes and stiffer due to the presence of fibrotic scar tissue. This scar tissue is responsible for the nodular pattern seen inside and on the surface of the liver. Sometimes, cirrhotic livers have fatty accumulation which makes the liver more pale and yellow compared to the normal rich red/brown.

Review Questions

1. Select 5 correct statements from the list below.

- When a liver is first damaged, it will be larger than normal due to inflammatory swelling.
- Repeated injury to the liver will immediately make the liver turn yellow and pale.
- Chronic injury to the liver will result in loss of hepatocytes, thus making the liver larger.
- Repeated injury to the liver, faster than regeneration, will result in the net loss of hepatocytes; thus making the liver smaller.
- The liver regenerates easily after injury, often making more hepatocytes than what was lost – resulting in a larger size.
- Chronic injury to the liver leads to chronic inflammation which means permanent swelling of the hepatocytes.
- Repeated injury to the liver, faster than regeneration, will result in the net loss of hepatocytes; thus making the liver smaller.
- The liver regenerates easily after injury, often making more hepatocytes than what was lost – resulting in a larger size.
- Chronic injury to the liver leads to chronic inflammation which means permanent swelling of the hepatocytes.
- In some situations like alcohol usage or obese conditions, fat will accumulate in the liver giving it a pale appearance
- Chronic viral hepatitis is known for fat accumulation, resulting in an enlarged nodular fatty appearance
- All livers will accumulate fat during cirrhosis, giving the liver a pale yellow in appearance
- Cirrhotic livers are pale because of reduced blood flow
- Cirrhotic livers are pale due to the infiltration of pale substances such as iron
- Cirrhotic livers get darker due to the fibrotic scar tissue
- Nodules of varying size appear on cirrhotic livers due to the deposition of fibrotic tissue to replace hepatocytes
- Micronodules are >1cm and are common in all types of cirrhotic causes
- Macronodular cirrhosis is associated with periodic alcohol usage

Answer Key

1. Review the statements below:

- When a liver is first damaged, it will be larger than normal due to inflammatory swelling.
- Repeated injury to the liver, faster than regeneration, will result in the net loss of hepatocytes; thus making the liver smaller.
- In some situations like alcohol usage or obese conditions, fat will accumulate in the liver giving it a pale appearance.
- Cirrhotic livers are pale because of reduced blood flow.

- Nodules of varying size appear on cirrhotic livers due to the deposition of fibrotic tissue to replace hepatocytes.

Digestive System - Review (Zoë)

ZOË SOON

I have created this Review Practice Question Set on some of the tricky sections – feel free to give it a try. (Zoë)

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://pressbooks.bccampus.ca/pathology/?p=5826#h5p-277

This Open Education Resource is a work in progress, completed by volunteers (faculty & current students), please help out by submitting feedback in the following Quick Survey:

Quick Survey

Thank you so much for your time.

Histopathology of Cirrhosis

JENNIFER KONG AND YIMEI QIN

Learning Objectives

By the end of this section, you will be able to:

- List the effects of scar tissue on the flow of bile and blood in the liver.
- correlate the microscopic findings of cirrhosis with the nodules seen by the naked eye.

The obvious nodular pattern – seen in gross specimens – is also evident in the histology of cirrhotic livers. The deposition of stiff, fibrotic, scar tissue interrupts the normally homogenous pattern of hepatocytes organized into lobules. This scar tissue will cause resistance to both blood flowing into the liver (especially portal vein) and bile leaving the liver (i.e. bile ducts). There is a limited amount of regeneration of tissues to try to replace the damaged hepatocytes, but they are outpaced by the scar tissue deposition.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2609#h5p-137

Histopathology of liver cirrhosis *presented by Yimei Qin using specimen from Dr. Gang Wang's private collection*, licensed under All Rights Reserved

Section Review

Nodules seen in the gross specimens are a continuation of the fibrotic scar tissue that is deposited in and around liver lobules. The liver tries to regenerate the damaged liver cells, but is outpaced by the scar tissue. As a result, there is a resistance to blood flowing into the liver leading to portal hypertension AND a restriction to bile leaving the liver.

Review Questions

1. Select the correct word/phrase. Liver lobules are filled with **biliary OR fibrotic** tissue as a result of **stellate OR hepatocyte OR Kupffer cell** activation in reaction to inflammation. As a result, the normally homogenous pattern of thousands of **Kupffer cells OR macrophages OR hepatocytes** are interrupted to form visibly distinct nodules. The resulting scar tissue will prevent blood flowing from the larger **hepatic OR portal OR bile** vessel to the central vein.

Similarly, the reverse flow of **blood OR bile** will be slowed down by this scar tissue, causing an accumulation within the lobule. This explains why jaundice is often a symptom of cirrhosis.

Answer Key

1. fibrotic, stellate, hepatocytes, portal, bile

Clinical Manifestations of Cirrhosis

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Explain the clinical manifestations associated with loss of hepatocyte number and function.
- Define portal hypertension and possible consequences.

Cirrhosis causes many signs and symptoms, beyond the liver. As it all begins with liver damage, nausea and abdominal pain are often the most common complaint – particularly in the right upper quadrant.

As such, these manifestations can be classified as problems with increased liver pressure due to the fibrotic scarring (portal hypertension) and loss of hepatocyte number and function.

Manifestations Due to Loss of Hepatocyte Number and Function

- Bleeds due to inability to clot: the liver makes many of the clotting factors needed for blood clotting. It also makes the hormone thrombopoietin which stimulates the daily production of platelets – also needed for clotting. Thus, cirrhosis has easier chance to bleed and can look like small pinpoint bruises (petechiae), cm large bruises (purpura), or large areas (ecchymoses). Areas with frequent trauma may also have bleeds (e.g. bleeds within the GI tract will look like vomit that is bloody or the appearance of coffee grounds; stool that is black and tar-like or bright red)
- Swelling of all tissue (peripheral edema), especially in lower limbs: liver makes the plasma protein albumin which has many functions: one of which is being the major osmotic solute to help retain water within the blood. A lower amount of albumin in the blood means there is less osmotic pressure (i.e. less of an osmotic pull of water) from the tissues into the blood. The result is tissue swelling known as edema. Given the effects of gravity and venous return, this edema will be most noticeable in the lower limbs but will be occuring in all parts of the body during hypoalbuminemia & cirrhosis.
- Fatigue and weakness due to low storage of nutrients and vitamins: as the liver stores nutrients (e.g. starch) and minerals (e.g. iron), cirrhosis leads to poor availability of these storage items. Fatigue and weakness are common complaints – due to the anemia (low iron) and hypoglycemia (low sugar availability).
- Low blood sugar (hypoglycemia): the liver is responsible for making glucose available from its conversion of starch to glucose (glycogenolysis) or fats/proteins to glucose (gluconeogenesis). Without hepatocytes, the body may not be able to maintain a constant level of blood sugar (i.e. blood glucose). Signs of low blood sugar affect the brain as a result of neurons being poorly equipped to store glucose and heavily reliant on a constant supply of blood glucose. Symptoms therefore can include: confusion, irritability, fatigue, depressed levels of consciousness, shaking, sweating leading to cold clammy skin. Low blood glucose levels induce a sympathetic response and increased

heart and respiratory rate.
- Vitamin and hormone activation/removal: the liver activates certain hormones (e.g. Vitamin D) and removes others when in excess (e.g. estrogen). Loss of hepatocytes will manifest in deficiencies in vitamins (e.g. susceptibility to bleeding from Vit K deficiency; decreased bone density from Vit D deficiency) and possible disturbances in the balance of sex hormones. Excessive estrogen in males may manifest as gynecomastia, whereas excessive hormones in pre-menopausal females will result in disturbances to the menstrual cycle.

Another problem can occur involving bilirubin. In this case, there are sufficient hepatocytes to conjugate bilirubin but not drain it efficiently into the bile ductules, conjugated bilirubin can enter the central vein within the lobule, and eventually the hepatic vein and IVC. This conjugated bilirubin will be excreted through the kidneys – but due to the high amount of bilirubin, the urine will look dark brown akin to the colour of steeped tea.

- Jaundice: hepatocytes are responsible for elimination of the heme group when RBCs die and components are recycled. The liver performs an enzymatic modification to the hydrophobic bilirubin (unconjugated) in a process called conjugation. Conjugated bilirubin is water soluble and can now travel in the blood for elimination through the kidneys. However, with less hepatocytes, unconjugated bilirubin can't be conjugated and excreted: as such, the unconjugated bilirubin continues to circulate the bloodstream and is deposited in fat stores such as the hypodermic layer of skin (see Metastatic melanoma). As unconjugated bilirubin is a yellow pigment, the skin will appear yellow – giving rise to the term jaundice. Similarly, the bilirubin pigment has a high affinity to the elastin in the sclera of eyes – giving rise to a yellowing of the white of the eyes known as scleral icterus.
- Loss of bile production and/or impaired bile flow: hepatocytes combine cholesterol, salts, and conjugated bilirubin to form bile salts. These bile salts form bile which normally drains to the duodenum. There, the bile will emulsify fats in the GI tract, making many small lipid droplets to help provide ample surface area for lipid digestion. Loss of hepatocytes will cause less bile to be made and thus, less fat digestion. Fatty stools and diarrhea may result. Similarly, if the scar tissue within the liver fully blocks bile flow into the duodenum, the lack of bile in the GI tract will manifest as pale, grey/white stool as bilirubin in stool gives stool its distinctive colour. This can lead to malabsorption of fat-soluble vitamins (e.g. vitamins D, E, and K) as well as lipid building blocks which can affect the function of cells and tissues throughout the body.
- Confusion & changes in cognition: the liver is responsible for the breakdown of proteins which creates ammonia from the amine group of amino acids. When produced, this dangerous ammonia is converted into the safer, transportable form of urea which can then be excreted through the kidneys. Less hepatocytes mean less conversion, and ammonia can build up in the blood and irritate all tissues. The brain is particularly sensitive to ammonia and will have impaired function when ammonia levels are too high (hepatic encephalopathy). Confusion, sudden change in behaviour, decline in cognition or consciousness may result.

Manifestations Due to Portal Hypertension

Due to the fibrotic scarring, the large diameter, low pressure portal vein does not have the blood pressure to overcome the resistance caused by the scarring. As a result, flow backs up into all of the intestinal veins which normally drain into the portal vein. An example of such vessel back up are:

- Splenic vein: due to its function, the spleen has a great capacity to store blood and will do so during portal hypertension. This causes an enlarged spleen (splenomegaly). However, blood that resides the in spleen will undergo the natural function of sequestration (hoarding of blood cells, especially platelets) and removal of RBCs when they become damaged. An abnormal amount of blood staying the spleen will result in low circulating numbers of blood cells: thrombocytopenia, anemia, and possibly leukopenia.

- Superior & inferior mesenteric veins: collectively, these are the veins which drain the small and large intestine. These veins travel within the peritoneal membrane which lines the external surface along the length of the intestines. When these veins become congested with blood, it is easy for that backup pressure to push fluid out of the veins into the peritoneal space that separate the two layers of the peritoneum. There are litres worth of potential space, between these layers of peritoneal membrane: fluid accumulating in this peritoneal space is called ascites. During cirrhosis, as much as 4L of ascitic fluid can accumulate within the abdomen, causing a sudden increase in abdominal girth and weight gain, over the course of a few days. As the peritoneal space fills the abdomen, it becomes more difficult for the diaphragm to lower during inhalation – thus breathing will become more difficult.

Collateral Circulation

As the portal hypertension is preventing the drainage of intestinal venous blood into the IVC, the body takes advantage of some naturally-occurring collateral vessels to detour around the liver. There are 3 portosystemic collaterals which divert blood from portal vein to the inferior and superior vena cava. Thus, during portal hypertension, one will see dilation and tortuosity (varices) of one or more of these 3 portosystemic collaterals:

- Esophageal varices: intestinal venous blood can flow via the gastroesophageal collaterals which drain into the azygos vein and then SVC. When congested with blood, these veins can become distended and visualized with a scope as esophageal varices. Esophageal varices will make it difficult to swallow (narrowed opening) and prone to bleed since vasculature is not normally exposed in the esophagus and the swelling leads to vessel wall fragility. Rupture of these varices will cause a serious GI bleed seen as hematemesis (vomiting blood)
- Anorectal varices: intestinal venous blood can flow via collateral circulation at the rectum which drain into the iliac veins and then IVC. These varices will cause anorectal itching, discomfort and pain upon defecation. There is possibility of bleeding (hematochezia)
- Paraumbilical varices: there are vestigial umbilical veins within the abdomen, leftover from being in utero. Normally, these veins are not in use unless needed as a collateral pathway in portal hypertension. When congested with blood, these veins drain into superficial abdominal wall veins near the umbilicus. This gives the appearance of tortuous, engorged veins emanating from the navel. This feature is known as Caput Medusae (head of Medusa), named after the mythical creature which had snakes for hair.

Compensation for Perceived Low Blood Volume (Hepatorenal Syndrome)

As mentioned, fluid is shifting out of the blood into other compartments during cirrhosis (e.g. ascites, peripheral edema, splenomegaly). However, the fluid has not left the body but they are not in the blood vessels – manifesting in possible decrease to blood flow to the kidneys. In response to low blood volume, the kidneys will activate the renin-angiotensin-aldosterone system to retain Na^+ and water which acts to increase the blood volume. However, this increased blood volume will exacerbate the problem, causing more portal hypertension, and worsening of the symptoms previously listed including edema, ascites, venous distension, etc.

Section Review

Cirrhosis causes manifestations in many other body systems, classified on the 3 biggest consequences: loss of hepatocytes, portal hypertension, and renal compensation. Loss of hepatocytes will manifest as lack of bilirubin processing, evident as jaundice. Loss will also lead to decreased detoxification (leading to changes in cognition) and hormone activation/inactivation (leading to disturbances in fertility and sex characteristics). Nutrient and iron storage will be low causing possible issues with metabolism and red blood cell production. Portal hypertension involves the back up of blood to the spleen leading to many blood cells and platelets 'trapped' and removed from circulation. This trapping of platelets and RBCs will cause poor clotting, propensity to bleed, and anemia. Portal hypertension causes back up pressure in all of the intestinal veins resulting in a leakage of plasma-like fluid from the intestinal capillaries into the peritoneum (ascites) and distension of rectal, esophageal, and umbilical veins as blood tries to get back to the heart via collateral circulation. As fluid leaves the general circulation (e.g. accumulating in peritoneum, spleen), the kidneys will assume that the body is fluid deficient and activate the RAAS system – resulting in retention of more fluid which will have to pass through the cirrhotic liver (hepatorenal syndrome).

Review Questions

1. Place the following in the correct column.

Confusion & Lethargy High Peripheral Blood Pressure Laughing	Easy to Bleed Ascites Jaundice	Change of Hair Colour Breasts in Men Hemorrhoids Pregnancy

Loss of Hepatocytes	Not Associated with Cirrhosis	Portal Hypertension	Activation of RAAS

Answer Key

1.

Loss of Hepatocytes	Not Associated with Cirrhosis	Portal Hypertension	Activation of RAAS
Confusion & Lethargy Jaundice Breasts in Men	Pregnancy Laughing Change of Hair Colour	Ascites Easy to Bleed Hemorrhoids	High Peripheral Blood Pressure

Diagnosis of Cirrhosis

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- List blood tests which determine liver function.
- Describe the role of sonography in diagnosis of liver disease.
- Briefly explain the role of liver biopsy and histopathology of liver disease.

The diagnosis of cirrhosis is mostly done through medical history, blood tests, and imaging.
Medical history will examine possible causes of liver injury. A thorough history of medication/toxin exposure, liver infections, frequency of biliary obstructions, and inheritable infiltrative or autoimmune diseases will help to additionally determine the extent and frequency of liver damage.

Blood Tests

Knowing the function of the liver, blood tests are used to ensure the hepatocytes are intact and able to make its products and perform its functions such as detoxification and bilirubin conjugation
Liver function tests (LFTs) a.k.a. liver panel

- The following enzymes (GGT, AST, ALT, ALP, LDH) are in different cells in the body, but they are most concentrated inside hepatocytes. Presence of these enzymes in high levels in the blood suggest hepatocyte leakage and lysis that has lead to the release of hepatic enzymes into the bloodstream.
- Hepatic function is measured by the amount of albumin in reference to the levels of total protein consumed. This is an excellent way to measure hepatocyte function, as albumin is only made by hepatocytes, using the proteins made available from diet (measured by total protein). Hepatic function is also measured by the amount of total and conjugated bilirubin (direct bilirubin) in the blood as a functional liver will have low levels of hydrophobic unconjugated bilirubin (indirect bilirubin) in the blood.
- Hepatic function is also assessed by how well ammonia is removed. Low levels of ammonia in the blood suggests functional hepatocytes.

Coagulation Panel

As mentioned, the liver produces many of the clotting factors, stores vitamin K, and stimulates platelet synthesis.

- Platelet number – the number of platelets indicates if there is a problem with either production (i.e. lack of the liver hormone thrombopoietin), accumulation in the spleen due to splenomegaly (i.e. due to portal hypertension), or due to destruction (i.e. tortuous path of platelet flow in fibrotic liver)
- Clotting time: a deficiency in any component of coagulation will result in a prolonged clotting time (PTT/INR)

Complete Blood Count (CBC)

Cirrhosis can cause reduced production of blood cells and sequestration in the spleen. Thus complete blood count (CBC) will determine if there are any signs of anemia, leukopenia, and/or thrombocytopenia

Ultrasound

Ultrasound uses sound waves to allow for visualization of tissue density based on echogenicity. Abdominal ultrasound is used to evaluate the size and shape of the liver, as well as blood flow through the liver and surrounding abdomen. On ultrasound images, fluid accumulation in the peritoneum (ascites) can be visualized. Presence of fatty changes can be detected, in addition to scar tissue in the liver. Ultrasound can also detect blood flow, which is very useful in detecting portal hypertension.



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***Use of Ultrasound in liver** disease by Ken Marken, interviewed by Jennifer Kong*, licensed under CC-BY-NC

Liver Biopsy

The definitive diagnosis for liver disease and cirrhosis is done with a liver biopsy. Most commonly, this is a CT or ultrasound-guided procedure using a fine needle to remove a sample of liver tissue (histopathology). The sample is then examined under a microscope for signs of fatty changes, inflammation, nodules, loss of hepatocytes, and fibrosis.

Section Review

To assess the health of the liver, the liver can be both visualized and liver products & wastes measured to determine function. The liver panel are blood tests which examine the extent of hepatocyte damage by measuring the presence of intra-hepatocyte enzymes floating around in the peripheral circulation: an elevated presence of these hepatic enzymes leakiness or lysis of hepatoctyes. Hepatocyte products such as albumin can be measured in the peripheral blood to determine the liver's ability to synthesize plasma proteins. As hepatocytes are responsible for most clotting factors and starting platelet synthesis, clotting times are also useful to determine liver function. Similarly, the presence of

undesired wastes such as ammonia or unconjugated (indirect) bilirubin will determine the liver's function. Liver can be visualized by ultrasound to determine size, shape, presence of nodules, and blood/bile flow. Ultrasound is also used when obtaining a piece of liver for histopathological analysis (i.e. liver biopsy). Liver biopsy is the definitive diagnostic test for liver disease and cirrhosis.

Review Questions

1. Urinalysis that detects the presence of nitrogen in urine helps determine liver function.

- True
- False

2. Fill in the blanks.

Ultrasound uses *sound* waves to create images of the liver in real-time. Thus ultrasound is used to help guide the placement of a needle in the liver to obtain biopsy tissue. The resulting biopsy will undergo histopathological analysis looking for the presence of *fibrotic/scar* tissue and loss of functioning *hepatocytes*.

3. Which lab test determines the function of liver? Select all that apply.

- Skin test
- Serum levels of GGT
- Platelet number in blood
- Presence of nitrogen in urine (urinalysis)
- Clotting time (PTT/INR)

Answer Key

1. False
2. sound, fibrotic/scar, hepatocytes
3. Serum levels of GGT, Platelet number in blood, Clotting time (PTT/INR)

Interprofessional Collaboration During the Diagnosis and Management of Cirrhosis

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Explain the cure for cirrhosis.
- List lifestyle changes that help prevent ammonia buildup, address nutritional deficiencies, and limit further damage to the liver.
- Describe symptomatic management of portal hypertension and coagulopathies.

Due to the extent and irreversibility of the damage, the only treatment for cirrhosis is a liver transplant along with addressing the original cause of the cirrhosis. It is futile to place a new liver if the new liver will be subjected to the same kind of damage as the original. However, until a transplant can be arranged (if at all), the condition can be managed by addressing the symptoms and decreasing potential causes of damage to the liver.

Limit Damage to Liver

Patients with cirrhosis work with their health care team to consider strategies to minimize further damage to the liver. A plan is tailor-made specific for the patient's context. For example, if the patient is experiencing liver damage due to too many or toxic medications, a review of the patient's medication history with a pharmacist may lead to alternate therapies that are less hepatotoxic. Similarly, if ingestion of toxins (e.g. alcohol) is causing liver damage, a holistic plan can be created by a support team (e.g. addictions specialist, counsellor) to help limit toxin exposure. Nutritionist/ Dieticians will also be helpful with both limiting damage to the liver and ensuring an appropriate diet that provides all of the nutrients are available, even with an impaired liver.

Symptomatic Relief

As mentioned, cirrhosis causes many symptoms outside of the liver itself. Hence, multiple professionals are needed to monitor these symptoms and try to ensure relief. Medical lab technologists can conduct tests on blood to measure the amount of liver function available (i.e. liver function tests), the ability to clot blood (i.e. coagulation panel), and monitor the amount of toxins building in the blood (i.e. ammonia levels).

- **High ammonia levels (Hepatic encephalopathy)**: There are two strategies to addressing high ammonia: trap and

remove ammonia and reduce ammonia production that is outside of the liver (e.g. by bacteria within the digestive system). Dietary agents (e.g. lactulose) can be used to trap and expel excess ammonia, as ammonia is water-soluble and lactulose osmotically pulls water into GI tract for defecation. Antibiotics (in oral form) are used to reduce the number of bacteria which reside in the GI tract: by reducing their number. Therefore there will be less ammonia produced and thus less work for the liver to try to convert ammonia to urea. Similarly, a diet lower in protein will give the liver a break from having to process amino acids which generate ammonia. A dietician can recommend liver-friendly diets.

- **Portal hypertension and varices**: although the cause of portal hypertension is irreversible (fibrotic tissue is laid inside the liver), blood pressure medications can be used to help lower the pressure in the varices and portal vein. This should also reduce the risk of varices rupture. If portal hypertension can't be managed pharmacologically, a physical shunt can be surgically implanted to bypass the liver tissue by connecting the portal vein directly to the hepatic vein.
- **Swelling and ascites**: as there is excess fluid in tissues and peritoneal space, fluid needs to be removed physically or through diuretics. Diuretics are useful in promoting fluid loss from peripheral tissues – assuming that kidneys are functional. However, if ascites is severe, physical removal using a needle (paracentesis) .
- **Nutritional deficiencies**: as cirrhosis affects its storage and activation of hormones, dietary supplementation might be helpful. Iron, Vitamin D & K supplements would be helpful to address the anemia and fatigue. Consultation with a dietician would result in a dietary plan that will help give the liver a rest and address the nutritional deficiencies.
- **Poor clotting (coagulopathy)**: depending on the degree of the coagulopathy, lifestyle changes can be initiated to minimize accidental traumas. For example, using an electric razor instead of a manual razor may minimize cuts during shaving. The patient can also be educated on signs of bleeds in the GI tract from bleeding from esophageal or rectal varices. However, if the bleeding is problematic, a discussion with a health care provider about clotting factor/platelet transfusion might be helpful.

Section Review

Because the liver is irreversibly damaged in cirrhosis, the only cure is a liver transplant WITH addressing the original cause of the liver damage. Until a transplant can be arranged, symptoms of cirrhosis can be managed with lifestyle choices, medications, and if needed – medical intervention. Portal hypertension can be managed pharmacologically with select anti-hypertensives or surgically with a shunt that connects the portal vein to the hepatic vein. Ascites and swelling can be managed pharmacologically with diuretics or with physical removal of fluid with a needle (i.e. paracentesis). Patients should be educated on their likelihood to bleed and watch out for signs of GI bleed if esophageal or rectal varices rupture. A dietician should be involved in the care to address nutritional deficiencies and liver-friendly diet.

Lifestyle changes will also be encouraged to limit further damage to the cirrhotic liver. A review of toxin and medication ingestion can be done as well as dietary changes to protein intake to reduce the amount of ammonia produced.

Review Questions

1. Place the following roles and activities in the appropriate column.

Monitors liver function using the liver panel Interprofessional help in cirrhosis Measures ammonia in blood	Suggests ways to limit possible bleeds Suggest ways to address deficiencies in iron and Vit D Disepenses & Advises on Anti-hypertensives Learn about bleeds in GI tract

Nurse	Pharmacist	Dietician	Medical Lab Technologist

Answer Keys

1.

Nurse	Pharmacist	Dietician	Medical Lab Technologist
Learn about bleeds in GI tract Suggests ways to limit possible bleeds	Disepenses & Advises on Anti-hypertensives	Interprofessional help in cirrhosis Suggest ways to address deficiencies in iron and Vit D	Monitors liver function using the liver panel Measures ammonia in blood

Cirrhosis Chapter Summary and Credits

JENNIFER KONG

Chapter Summary

Cirrhosis is end stage liver disease. There are many potential causes of liver damage and disease (e.g. viral infection, toxins/medications, infiltration, fluid congestion of the liver); however repeated damage to the liver will unfortunately lead to cirrhosis.

The repeated damage to the liver despite the cause, leads to both a loss of hepatocytes (at a rate that is faster than the regenerative or mitotic rate) and the laying down of extracellular fibrous scar tissue. This scar tissue does not have the same properties nor function as hepatocytes, resulting in a firmer, less functional liver that causes resistance to blood flow. This resistance, known as portal hypertension, is great enough that the the portal vein can not deliver blood, from the intestines and spleen, to the liver. The result is a back up of the blood back into the spleen causing splenomegaly, and into the intestinal veins causing ascites. This shift in fluid will have profound changes in blood composition (i.e. anemia, thrombocytopenia, and leukopenia) and fluid levels (i.e. hepatorenal syndrome).

This repeated damage to the liver will lead to an increased loss of hepatocytes. As such, the liver can not perform its normal functions. This manifests as changes in cognition, confusion (i.e. excess ammonia irritating brain), excessive bleeding (i.e. due poor clotting abilities), swelling in all body parts (i.e. edema due to low albumin and venous congestion), signs of malnutrition (i.e. low storage of minerals and vitamins), jaundice (i.e. impaired conjugation of bilirubin, resulting in hyperbilirubinemia, and reduced elimination of bilirubin through feces).

Liver damage and cirrhosis are diagnosed through a combination of blood tests that assess liver function, as well as ultrasound imaging. The definitive diagnosis is by liver biopsy.

There is no cure for cirrhosis, other than a liver transplant. However, the disease can be managed by addressing the prementioned manifestations and implementing pharmacological & lifestyle changes in order to reduce the demands on the liver.

Credits

Author: Dr. Jennifer Kong (BCIT & UBC)

Author of questions and exercises: Yimei Qin & Andy Zhao (UBC Undergraduate students)

Gross anatomy video: Dr. Jennifer Kong (BCIT & UBC)

Histopathology video: Yimei Qin (UBC Undergraduate student) with supervision of Dr. Gang Wang (UBC, Director of DHPLC)

Sonographer: Kenneth Marken (Diagnostic Sonography, BCIT)

Videoproducer: Ian Whittlesey (BCIT)

Post-Test on Cirrhosis

JENNIFER KONG AND WILLIE WU

Branching Case study created by Willie Wu

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1. Chronic obesity is a risk factor for liver damage and possible cirrhosis

- True
- False

2. Choose the appropriate word.

When liver is damaged repeatedly, inflammation activates the **stellate OR hepatocyte OR fibroblast** to become a **hepatocyte OR stellate OR fibroblast**. As a result, fibrotic scar tissue is deposited faster than the regeneration rate of hepatocytes. The result is a loss of **bile OR blood OR hepatocytes** which means a loss of liver function. The presence of scar tissue will cause resistance for blood flowing in from the large, low-pressure portal vein which is full of **bile OR nutrients OR oxygen**. The result is portal hypertension.

3. Which are manifestations that are associated with portal hypertension? Select all that apply.

- caput medusae
- hemorrhoids
- loss of hair
- ascites
- double vision

4. Which manifestations are associated with hepatocyte loss of function? Select all the apply.

- high ammonia in blood
- nitrogen in urine
- jaundice
- confusion
- menstrual disturbances in women
- high AST and ALP in blood

5. Fill in the blanks.

Med lab technologists are helpful in determining liver function as they analyze for the presence of liver enzymes in the _____. Dieticians can help prevent hepatic encephalopathy by reducing the production of _____ by restricting protein in diet. _____ use ultrasound to measure the size of liver, ascites, and blood flow which is important to detect _____ that leads to blood backing up into the veins of the umbilicus, rectum, and _____.

6. Nodules are seen in cirrhotic livers.

- True
- False

Answer Key

1. True
2. stellate, fibroblast, hepatocytes, nutrients
3. hemorrhoids
4. high ammonia in blood, jaundice, Sonographers, confusion, menstrual disturbances in women, high AST and ALP in blood
5. blood/serum/plasma, ammonia, portal hypertension, esophagus
6. True

DIABETES MELLITUS

Diabetes Mellitus Chapter Overview

JENNIFER KONG

Chapter Learning Objectives

By the end of this section, you will be able to:

1. Define diabetes mellitus and differentiate between Type 1, Type 2, and gestational diabetes.
2. Explain the differing roles of insulin and insulin receptors in the types of diabetes.
3. Identify histological features in the pancreas associated with diabetes.
4. List the diverse clinical manifestations of the onset of diabetes and explain the pathophysiology behind each of them.
5. Correlate consequences of uncontrolled diabetes in the cardiovascular, neural, and renal systems.
6. Briefly describe how interprofessional collaboration of health care professions work towards diagnosis and management of diabetes and its consequences.

Diabetes mellitus is a dysfunction of either insulin production and secretion (Type 1) or the tissue's insensitivity to the insulin hormone (Type 2 & gestational). As a consequence, glucose can not get into most cells of the body resulting in high blood sugar and cells 'starving' for glucose. Blood sugar becomes abnormally high, regardless of when or what a person has eaten.

An increasingly common disease, diabetes mellitus is diagnosed in both adults and children; however, millions of adults have undiagnosed diabetes. In addition, the population as a whole is approaching pre-diabetic levels, a condition in which blood glucose levels are abnormally high, but not yet high enough to be classified as diabetes.

This chapter is subdivided into:

- Pre-test
- Anatomy & histology of endocrine pancreas and glucose homeostasis
- Normal gross anatomy & histology of pancreas
- Type I (1) diabetes
- Type II (2) diabetes
- Gestational diabetes
- Diagnosis of diabetes
- Consequences of chronic high sugar in other systems
- Interprofessional collaboration during care of diabetes
- Management and treatment of diabetes
- Consequences of untreated high blood sugar: diabetic ketoacidosis
- Video of patient and family's life with Type I diabetes: the McKinstry family
- Chapter summary
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

DM	Diabetes Mellitus
DKA	Diabetic Ketoacidosis
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

PDQ Videos on Diabetes Chapter

DYLAN MANN

For those readers who might not have time to read the entire chapter or wish to begin with a short overview on Diabetes, here are some “Pretty Darn Quick” summary videos which highlight the biggest take-home messages. However, we encourage you to explore this chapter fully as we explain Diabetes from the tissue level to the clinical manifestations and its impact on patients and their families.



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Pre-Test for Diabetes

JENNIFER KONG

1. If an autoimmune disorder targets the alpha cells, production of which hormone would be directly affected?

- Somatostatin
- Pancreatic polypeptide
- Glucagon
- Insulin

2. Which of the following statements about insulin is true?

- Insulin acts as a transport protein, carrying glucose across the cell membrane.
- Insulin facilitates the movement of intracellular glucose transporters to the cell membrane.
- Insulin stimulates the breakdown of stored glycogen into glucose.
- Insulin stimulates the kidneys to reabsorb glucose into the bloodstream.

3. Fill in the blanks.

In Type 1 diabetes mellitus, _____ are destroyed resulting in an inability to produce and secrete the hormone _____ which is important in the regulation of blood glucose levels. Many cells in the body are dependent on _____ binding to its receptors, resulting in that cell to take up glucose from the bloodstream. Compare that with type 2 diabetes mellitus where hormone production is fine but the tissue receptors are _____ to the hormone _____. In both types of diabetes mellitus, there would be abnormally _____ blood glucose levels.

Answer Key

1. Glucagon
2. Insulin facilitates the movement of intracellular glucose transporters to the cell membrane.
3. Beta cells, insulin, insulin, insensitive, insulin, high

Anatomy of the Pancreas and Glucose Homeostasis

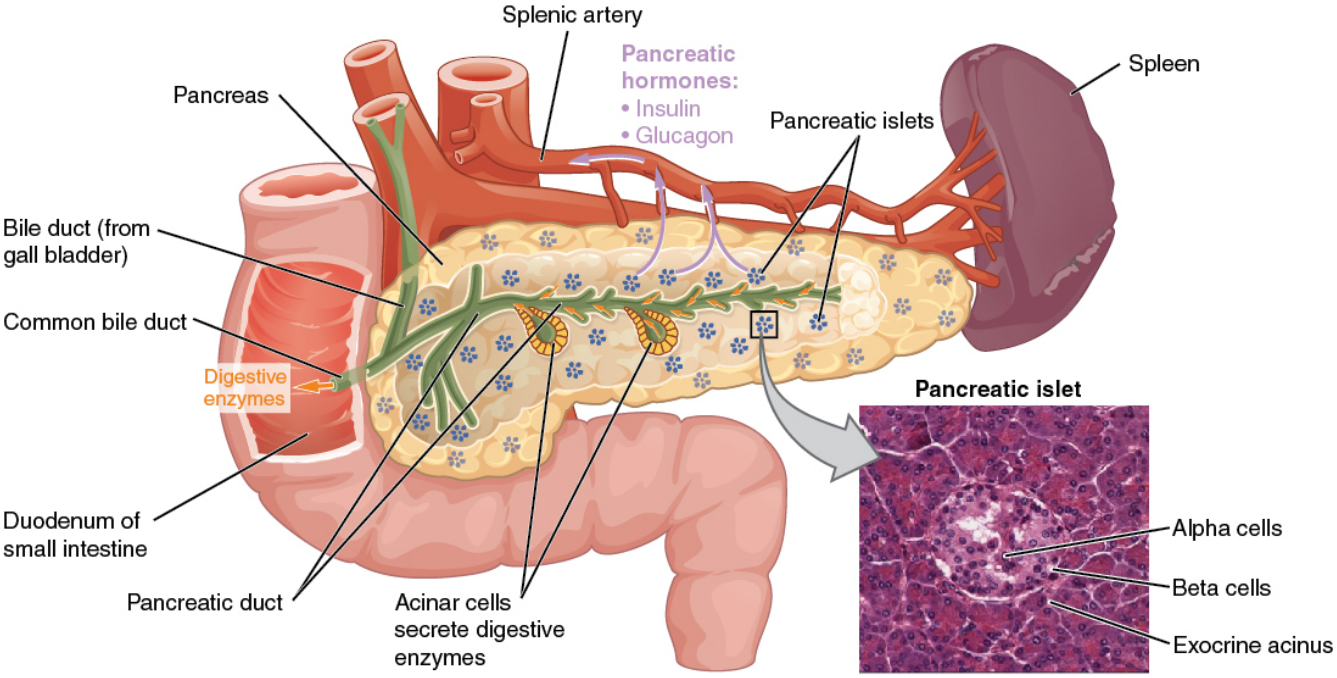
J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the location and structure of the pancreas, and the morphology and function of the pancreatic islets.
- Compare and contrast the functions of insulin and glucagon.

The **pancreas** is a long, slender organ, most of which is located posterior to the bottom half of the stomach, as shown in the figure below. Although it is primarily an exocrine gland, secreting a variety of digestive enzymes, the pancreas also has endocrine function. **Pancreatic islets**—clusters of cells formerly known as the islets of Langerhans—secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).



The Pancreas, upper duodenum, and spleen – *The pancreatic exocrine function involves the acinar cells secreting digestive enzymes that are transported into the duodenum by the pancreatic duct. Its endocrine function involves the secretion of the hormones insulin and glucagon within the pancreatic islets eventually reaching the blood circulation. These two hormones regulate the rate of glucose metabolism in the body. The micrograph reveals pancreatic islets. LM × 760. (Micrograph provided by the Regents of University of Michigan Medical School © 2012). View the University of Michigan Webscope to explore the tissue sample in greater detail.*

Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of cells:

- **Alpha (α) cell** produces the hormone glucagon and makes up approximately 20 percent of each islet. Low blood glucose levels stimulate glucagon release.
- **Beta (β) cell** produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.
- **Delta (δ) cell** accounts for four percent of the islet cells and secretes the hormone somatostatin. Recall that somatostatin is also released by the hypothalamus (as GHIH), stomach and intestines. Pancreatic somatostatin inhibits the release of both glucagon and insulin.
- **PP cell** accounts for about one percent of islet cells and secretes the pancreatic polypeptide (PP) hormone. This hormone is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. PP release following a meal may reduce further food consumption; however, it is also released in response to fasting.

Regulation of Blood Glucose Levels by Insulin and Glucagon

Glucose is required for ATP production in the process of cellular respiration and is the preferred fuel for all body cells. The body derives glucose from the breakdown of the carbohydrate-containing foods and drinks we consume. Glucose not immediately taken up by cells for fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in the adipose tissue. Hormones regulate both the storage and the utilization of glucose as required. Cells in the pancreas sense glucose levels, and subsequently secrete glucagon or insulin to maintain normal levels.

For example, it is expected that high blood glucose levels (hyperglycemia) will occur after a meal. When an influx of blood glucose occurs, specific endocrine cells in the pancreas are the first to detect excess glucose in the bloodstream. Pancreatic beta cells then respond to the increased blood glucose by releasing the peptide hormone insulin into the bloodstream. Once bound to cell surface insulin receptors, insulin stimulates cells of the body to increase the number of glucose transporters present in their plasma membranes. This allows cells to uptake more glucose. Insulin also signals skeletal muscle fibers, fat cells (adipocytes), and liver cells to take up the excess glucose, removing it from the bloodstream. As glucose concentration in the bloodstream drops, this decrease is detected by pancreatic beta cells and stimulates a negative feedback loop, inhibiting insulin production and secretion. This prevents blood sugar levels from continuing to drop below the normal range.

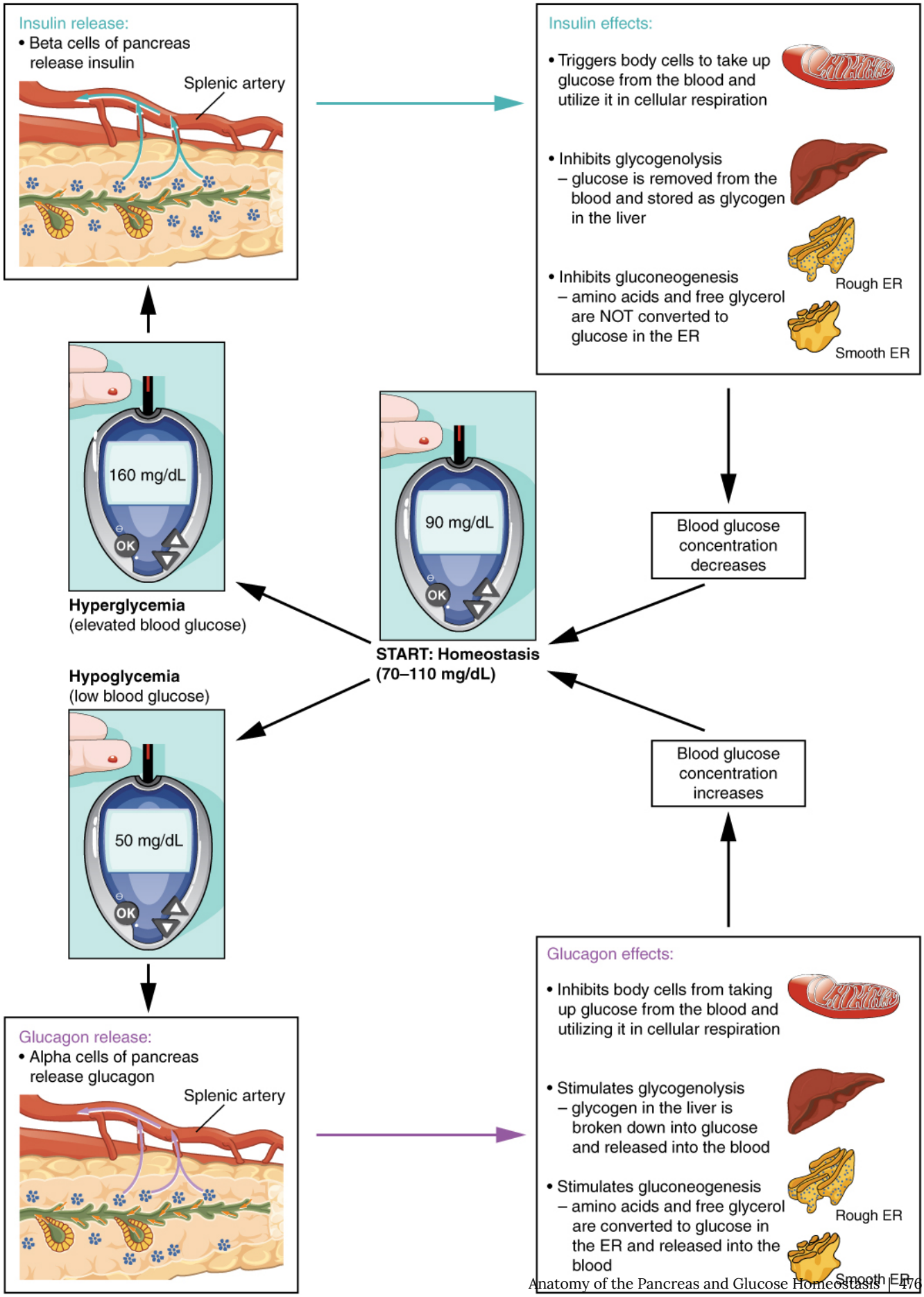
Glucagon

The cells in the pancreatic islets also sense the decrease in blood glucose levels, such as during periods of fasting or during prolonged exercise. In response, the alpha cells of the pancreas secrete the hormone **glucagon**, which has several effects:

- It stimulates the liver to convert its stores of glycogen back into glucose (glycogenolysis). The glucose is then released into the circulation for use by body cells.
- It stimulates the liver to take up amino acids from the blood and convert them into glucose (gluconeogenesis).

- It stimulates lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol. Some of the free glycerol released into the bloodstream travels to the liver, where it is converted into glucose. This is also a form of gluconeogenesis.

Together, these actions increase blood glucose levels. The activity of glucagon is regulated through a negative feedback mechanism, where rising blood glucose levels inhibit further glucagon production and secretion.


Insulin release:
• Beta cells of pancreas release insulin
Splenic artery
Insulin effects:
• Triggers body cells to take up glucose from the blood and utilize it in cellular respiration
• Inhibits glycogenolysis
– glucose is removed from the blood and stored as glycogen in the liver
• Inhibits gluconeogenesis
– amino acids and free glycerol are NOT converted to glucose in the ER
Rough ER
Smooth ER
160 mg/dL
OK
Hyperglycemia
(elevated blood glucose)
90 mg/dL
OK
START: Homeostasis
(70–110 mg/dL)
Blood glucose concentration decreases
Hypoglycemia
(low blood glucose)
50 mg/dL
OK
Blood glucose concentration increases
Glucagon release:
• Alpha cells of pancreas release glucagon
Splenic artery
Glucagon effects:
• Inhibits body cells from taking up glucose from the blood and utilizing it in cellular respiration
• Stimulates glycogenolysis
– glycogen in the liver is broken down into glucose and released into the blood
• Stimulates gluconeogenesis
– amino acids and free glycerol are converted to glucose in the ER and released into the blood
Rough ER
Smooth ER

Homeostatic Regulation of Blood Glucose Levels *– Blood glucose concentration is tightly maintained between 70 mg/dL and 110 mg/dL. If blood glucose concentration rises above this range, insulin is released, which stimulates body cells to remove glucose from the blood. If blood glucose concentration drops below this range, glucagon is released, which stimulates body cells to release glucose into the blood.*

Insulin

The primary function of **insulin** is to facilitate the uptake of glucose into body cells. Some tissues/cells, despite the presence of insulin receptors, do not require insulin to uptake glucose. This is the case of the brain, liver, kidneys and lining of small intestines. However, many body tissues require the presence of insulin to facilitate their uptake of glucose from the bloodstream. These main ones are the skeletal muscle and the adipose tissue.

The presence of food in the intestine triggers the release of gastrointestinal tract hormones such as glucose-dependent insulinotropic peptide (GIP) (previously known as gastric inhibitory peptide) and glucagon-like peptide 1 (GLP-1). This is the initial trigger for insulin production and secretion by the pancreatic beta cells. Once nutrient absorption occurs, the resulting surge in blood glucose levels further stimulates insulin secretion, as described above.

Insulin activates a tyrosine kinase receptor, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing glucose transporters to the cell membrane. Therefore, insulin triggers the rapid movement of a pool of glucose transporter vesicles to the cell membrane, where they fuse and expose the glucose transporters to the extracellular fluid. The transporters then move glucose by facilitated diffusion into the cell interior. In the absence of insulin, these transport proteins are normally recycled slowly between the cell membrane and cytoplasm.

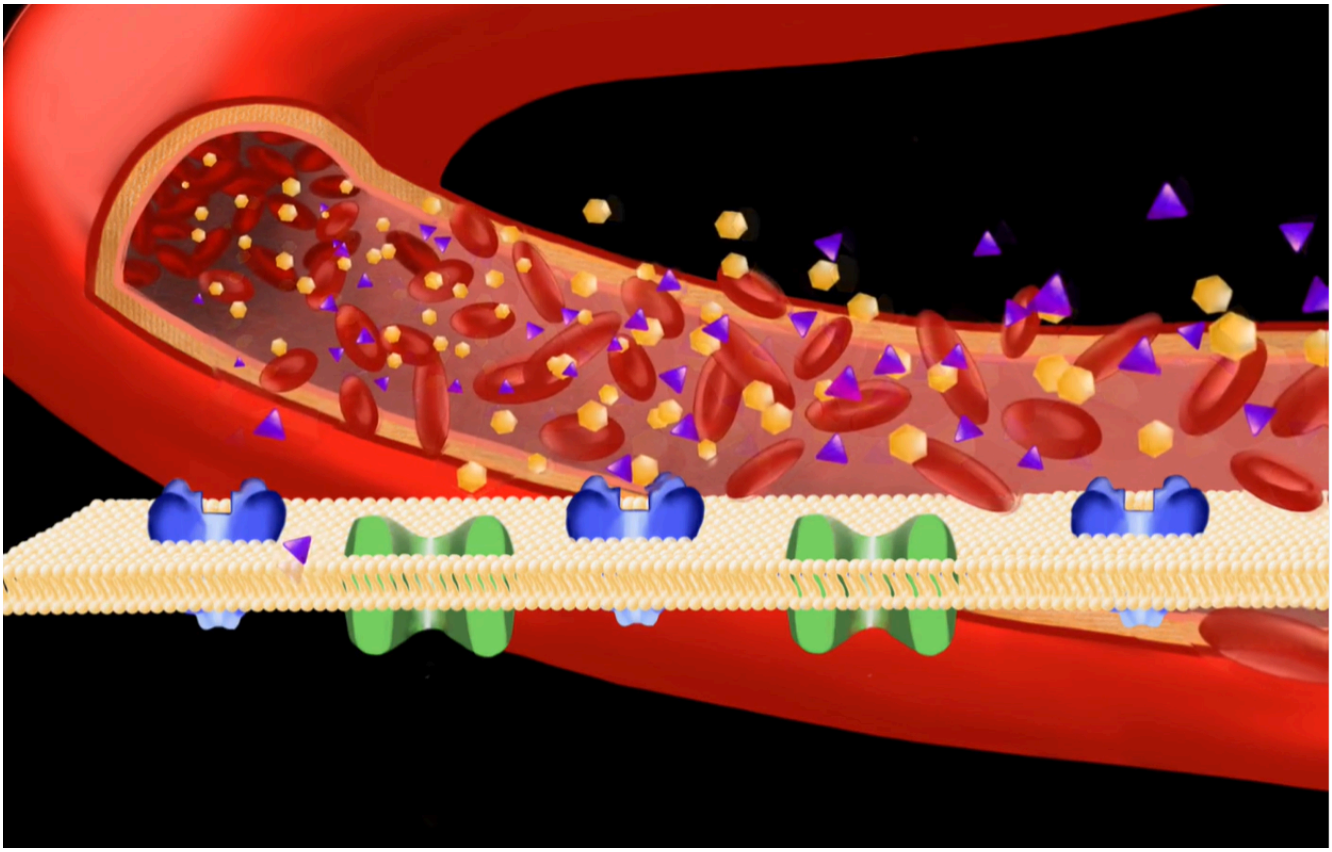


Diagram showing blood contents in contact with neighboring tissues. Circulating insulin (purple triangles) bind to the insulin receptors (blue) and stimulate glucose transporters (green) allowing glucose (gold hexagons) to enter the tissues. Images created by Sarah Perkins under a CC BY ND license

Insulin also reduces blood glucose levels by stimulating glycolysis, the metabolism of glucose for generation of ATP. Moreover, it stimulates the liver to convert excess glucose into glycogen for storage, and it inhibits enzymes involved in glycogenolysis and gluconeogenesis. Finally, insulin promotes triglyceride and protein synthesis, while inhibiting the breakdown of fat (lipolysis). The secretion of insulin is regulated through a negative feedback mechanism. As blood glucose levels decrease, insulin release is inhibited. The pancreatic hormones and their main effect in glucose homeostasis are summarized in the table below.

Hormones of the Pancreas		
Associated hormones	**Chemical class**	**Effect**
Insulin (beta cells)	Protein	Reduces blood glucose levels
Glucagon (alpha cells)	Protein	Increases blood glucose levels
Somatostatin (delta cells)	Protein	Inhibits insulin and glucagon release
Pancreatic polypeptide (PP cells)	Protein	Role in appetite

Hormones of the Pancreas

Visit this link to view an animation describing the location and function of the pancreas.

Review Questions

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2810#h5p-418

Adaptation

This chapter is adapted from the following text:

Endocrine Pancreas **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

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Normal Gross Anatomy and Histology of Pancreas

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Explain the distribution of acinar and islet cells within pancreatic tissue.
- Differentiate between acinar and islet cells during histological examination of pancreatic tissue stained with H&E.

To understand how the pancreas is both an exocrine and endocrine organ, one has to recognize that the pancreas is made out of many different cells. Each cell has a function that contributes either to the digestion of food (i.e. exocrine pancreas) or the maintenance of blood glucose (endocrine pancreas). Even though these cells have different functions, they still sit next to each other within the pancreas.

The exocrine pancreas makes up 90% of the pancreatic tissue, the acinar cells being the most numerous. Acinar cells are recognized easily as they make up most of the cells in a histological analysis of the pancreas. They are easily recognized as being the most numerous and by their cuboidal features, usually surrounding a pancreatic duct. Because acinar cells make a lot of digestive enzymes, a large nucleus is necessary and thus easily identifiable.

Conversely, the endocrine pancreas makes up <10% of the pancreatic tissue. However, the endocrine cells cluster together in 'little islands in the sea of acinar cells'. Hence, the term Islet cells. Islet cells do not stain as intensely as acinar cells, mostly because their nuclear size and lower activity compared to acinar cells. As mentioned, the islet cells are a combination of alpha, beta, gamma, and delta cells. Histologically, one can not differentiate between the cells based on shape nor nuclear size. Immunological histochemistry (i.e. using dyes attached to antibodies that are specific for each islet cell type) would be needed to identify the cells within the islets. Because islet cells must sense blood glucose levels for the purpose of releasing their hormones, islet cells are often interspersed with capillaries and are often near a blood vessel within the pancreas.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2582#h5p-158

DHPLC Specimen PATH 304-016 – Normal pancreas with H&E staining. Created by Jennifer Kong licensed under All rights reserved

Video Summary – The bulk of pancreatic tissues are made of acinar cells. Acinar cells make digestive enzymes (lots of protein synthesis) which are secreted into a central ductule. Thus giving acinar clusters staining dark pink/purple in a circular pattern: acinar nuclei on the outside border and

the ductule in the centre. In contrast, islets are clusters of cells that don't stain as dark (i.e. not as much protein present) with a central nuclei. These islet cells are interspersed with capillaries, identifiable by the spindly endothelial cells of the capillary wall and the red blood cells. Islets make up <10% of the pancreatic tissues and are often found near blood vessels.

Brief Review of Insulin Release and Glucose Entering Tissue

Revisit this link, from the "Anatomy and histology of the endocrine pancreas and glucose homeostasis" chapter to view an animation describing the role of insulin.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2582#h5p-161

Video was created by Sarah Perkins, licensed under CC-BY-NC.
Video Summary – After a meal, there is a steep rise in nutrients in the blood. These blood nutrient levels – especially glucose (gold hexagons) – will be sensed by the endocrine pancreatic islet cells. When beta cells sense high blood glucose, it releases insulin into the bloodstream.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2582#h5p-160

Video was created by Sarah Perkins, licensed under CC-BY-NC.
Video Summary – When insulin (purple triangle) reaches the tissue, it will bind to the insulin receptor (blue). Insulin receptors are on almost every cell type in the body. Upon binding with insulin, the insulin receptors activates glucose transporter (green) to allow for glucose (gold hexagons) to enter the cell via facilitated diffusion. Once inside, glucose can be immediately metabolized to produce ATP or stored as glycogen (e.g. in liver in the process known as glycogenesis)

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2582#h5p-162

Video was created by Sarah Perkins, licensed under CC-BY-NC.
Video Summary – For metabolically active tissues such as contracting skeletal muscle, insulin is needed for immediate glucose influx and metabolism within muscle cells. The resulting ATP will fuel the muscle contraction process.

Although not quite fully understood, contracting muscles can also allow for glucose entry into cells in an insulin-independent manner.[1]

Section Review

The pancreas is mostly made out of acinar cells which perform the exocrine function. Acinar cells produce digestive enzymes which drain into pancreatic ducts. Pancreatic islet cells are less numerous and are distributed infrequently within the pancreas, but are close to blood vessels. Islet cells are responsible for performing the endocrine function, constantly monitoring blood glucose levels and releasing hormones such as insulin and glucagon as necessary in order to maintain blood glucose homeostasis.

Review Questions

1. Finish the following sentence. The most numerous cell in the pancreas is the:

- Acinar cell
- Alpha cell
- Beta cell
- Delta cell

2. Finish the following sentence. Islet cells are identifiable from acinar cells based on:

- Number
- Proximity to blood vessels
- Frequency
- All of the above

3. You can identify beta cells with H&E staining.

- True
- False

Answer Key

1. Acinar cell
2. All of the above

3. False

Notes

1. Sylow, L., Kleinert, M., Richter, E. et al. Exercise-stimulated glucose uptake — regulation and implications for glycaemic control. Nat Rev Endocrinol 13, 133–148 (2017). https://doi.org/10.1038/nrendo.2016.162

Type 1 Diabetes (Insulin Dependent)

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Identify some risk factors of developing type 1 diabetes mellitus.
- Identify the manifestations of type 1 diabetes mellitus.
- Briefly describe the management of type 1 diabetes mellitus.

Type 1 diabetes mellitus (T1DM) is an autoimmune disease, making up <5% of all diabetes diagnoses. There is somewhat of a genetic component to T1DM as research has demonstrated that certain genes are recognized to increase susceptibility to the development of T1DM. Similarly, current research suggests that environmental triggers also play a role in development of T1DM alongside genetics: colder climates, preceding viral infection, and dietary patterns during infancy.

T1DM involves loss of beta cells from the pancreas resulting in no insulin production. T1DM patients have insulin receptors. A combination of genetics and environmental triggers causes the body's immune system to recognize beta cells as foreign and, as a result, the body eliminates the beta cells. This is a progressive condition, which culminates in lack of beta cells and consequently lack of insulin production. T1DM usually manifests in childhood or early adulthood, earning the alternate name "juvenille diabetes". However, adults can develop T1DM. Thus the current name "Type 1: insulin-dependent diabetes" is more accurate.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2585#h5p-165

Pathology of T1DM – *Upper panel: the immune system attacks the beta cells leading to a lack of insulin production. Lower panel: there is no insulin (purple triangles) circulating in blood. Images created by Sarah Perkins*, licensed under CC-BY-NC

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2585#h5p-163

T1DM causes hyperglycemia – Since there is no circulating insulin (purple triangles), the insulin receptors (blue) on tissues are not stimulated. Thus there is nothing to stimulate glucose receptors (green) to allow glucose (gold hexagons) to enter the tissues. As a result, the cells are deprived of glucose and glucose stays in the blood causing hyperglycemia. Images created by Sarah Perkins, licensed under CC-BY-NC

Histologically, pancreatic tissue will be affected in T1DM. Autoimmune destruction of beta cells in the islets results in hyaline tissue being laid down to replace the missing beta cells. However, all other tissues will look normal as both the insulin receptors and glucose transporters are unaffected.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2585#h5p-159

DHPLC Specimen PATH 425-125 – hyalinization of the islets of Langerhans; pancreatic tissue with H&E staining. Created by Jennifer Kong licensed under All rights reserved.

Revisit this link, from the "Anatomy and histology of the endocrine pancreas and glucose homeostasis" chapter to view an animation describing the role of insulin and the pancreas in diabetes mellitus.

Manifestations of Type 1 Diabetes

The clinical consequences are due to the lack of insulin in the blood circulation and eventually the lack of glucose uptake by the cells. The most common manifestations of T1DM are hunger, excessive urination, and thirst. This is also known as the 3P's of diabetes: polyphagia, polyuria, & polydipsia. Normally, kidneys reabsorb all of the sugar that escapes into the filtrate (see AKI chapter for review). However, in hyperglycemia, there is too much glucose in the blood already so excess glucose stays in the filtrate. Excess glucose in the filtrate will retain water in the urine: as a result a person with T1DM urinates an abnormally large and frequent quantity of 'sweet' urine. Since there is a loss of large quantities of fluid, the body becomes dehydrated and so thirst is unusually and continually present. Similarly, people with T1DM may also experience persistent hunger because the body cells are unable to access the glucose in the bloodstream due to lack of insulin (recall that the tissue's insulin receptors are present and working appropriately). This may force tissues to use fat metabolism and gluconeogenesis to meet its energy needs. As a consequence, dangerous byproducts (e.g. acidic ketones) will increase in blood and tissues.

The inability of the tissues to uptake glucose from the blood circulation cause high heart rate, fast breathing, confusion/irritability, fatigue, and cold sweat as a consequence of low glucose metabolism inside the cells. In children, the inability to bring glucose into cells alongside lack of insulin will manifest as failure to thrive (i.e. grow and develop). Insulin promotes growth through IGF-1 and GH receptors and a direct lack of insulin can lead to unintended weight loss at a time when children should grow.

Due to the high blood sugar, a person with T1DM is more susceptible to infections – particularly oral & urinary outlets as there is a higher exposure to pathogens in those areas. Thus urinary tract infections and dental/gum disease are more likely in people with T1DM.

Management of Type I Diabetes

People with T1DM do not have beta cells, thus they can not produce insulin. For this reason, synthetic insulin must be administered by injection or infusion to help regulate glucose homeostasis throughout the day.

Section Review

Regardless of the cause, T1DM results in the loss of beta cells in the pancreatic islet tissue. Thus there is no insulin released to be delivered to tissues. At the tissue level, there is no increase in the number of glucose transporters in the plasma membrane (normally, it would respond to insulin receptor binding and activation) therefore, preventing glucose to enter the cell for metabolism. The glucose stays in the blood leading to hyperglycemia, which affects all tissues in that:

- It forces tissues to use fat metabolism and gluconeogenesis to meet its energy needs. As a consequence, dangerous byproducts (e.g. acidic ketones) will increase in blood and tissues
- Hyperglycemia causes an osmotic imbalance resulting in both glucose and excessive water to be lost in urine (i.e. polyuria). As a consequence, thirst and dehydration will occur.
- As insulin is needed to build tissues, there is no opportunity to gain tissue mass. In a child, this would appear as "failure to thrive" and a slow growth rate.

Review Questions

1. Which factors are supported by research where T1DM susceptibility increases?

- Certain genes, colder climates, and previous viral infections
- Colder climates, diet during infancy, and overconsumption of sugar later in life
- Preceding viral infection, diet during infancy, and warmer climates
- Certain genes, diet during infancy, and warmer climates

2. Fill in the blanks.

T1DM is associated with a loss of pancreatic _____(alpha/beta/delta) cells and is usually diagnosed _____(earlier/later) in life. It can be identified as the body producing _____ (less/no/more) insulin compared to normal.

3. What are the 3 P's that can be used to describe the manifestations of T1DM?

4. Which of the following are NOT typically signs of a person with T1DM? Select all that apply.

- Sweet smelling urine
- Salty smelling urine
- Dehydrated body
- High heart rate
- Cold sweats
- Hot flashes

- Loss of appetite
- Increased infections

Answer Key

1. Certain genes, colder climates, and previous viral infections
2. Beta, earlier, no
3. Polyphagia (excessive hunger), Polyuria (excessive urination), and Polydipsia (excessive thirst)
4. Salty smelling urine, Hot flashes, Loss of appetite

Type 2 Diabetes (Non-Insulin Dependent)

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Identify some risk factors of developing type 2 diabetes mellitus.
- Identify the manifestations of type 2 diabetes mellitus.
- Briefly describe the management of type 2 diabetes mellitus.

Type 2 diabetes mellitus (T2DM) accounts for approximately >90% of all diagnoses of diabetes. About 80 to 90 percent of people with T2DM are overweight or obese; however, there are also genetic and lifestyle factors that cause T2DM.

In T2DM, cells become resistant to the effects of insulin: thus, tissues will not allow glucose to enter the cell and the glucose remains in the blood. In response, the pancreas will increase insulin production. Eventually the pancreas can't keep up with insulin production, resulting in elevated blood glucose. This is considered to be the pre-diabetes stage: rising blood glucose with normal or increased insulin production. However, over time, the beta cells will 'burn out' and insulin production drops and blood glucose dramatically rises.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2587#h5p-164

T2DM causes hyperglycemia – Although insulin (purple triangles) can be made and there are insulin receptors on tissues (blue), the receptors do not recognize and/or refuse to be stimulated by insulin. Thus there is nothing to stimulate glucose transporters (green) to allow glucose (gold hexagons) to enter the tissues. As a result, the cells are deprived of glucose and glucose stays in the blood causing hyperglycemia. Images created by Sarah Perkins, licensed under CC-BY-NC

Because of the gradual, yet continuous, rise of blood glucose, prediabetes and diabetes have an insidious onset. Prediabetes, although a serious health condition, will result in higher than normal blood glucose levels, but not high enough yet to be officially diagnosed as T2DM. Similarly, the signs and symptoms are easily ignored or explained since it can take years for T2DM to be diagnosed. In the developed world, it is estimated that approximately 1 in 3 adults have prediabetes. Of those with prediabetes, less than 20% of them know that they have the condition.

What makes tissue insensitive to insulin? It depends on whether it is an inheritable (genetic) cause or acquired during lifetime:

Genetic Causes

- Insulin receptors are present in all tissues but are made less effective to respond to insulin. As a result, glucose can't enter the tissues even though insulin is made in appropriate amounts. In this situation, blood glucose levels will still be high, despite exercising regularly and eating a healthy diet. Genetic cause will result in a family history of T2DM in close relatives.
- Like all organs, the pancreas will lose function as we age. The risk for pancreatic insufficiency (i.e. can't make enough insulin) increases at middle age (>45 yo).
- Some ethnicities are more at risk for T2DM – regardless of the aforementioned lifestyle causes. First Nation peoples, Asians, and African Americans are at higher risk for T2DM.

Acquired insulin resistance

- An overabundance of circulating nutrients, such when glucose and fat (e.g. overweight, physical inactivity, poor diet, exposed to gestational diabetes *in utero*) are constantly available to tissues cause continuous release of insulin. As a result, tissues will 'ignore' insulin and don't take up any more nutrients, becoming insulin resistant.
- Medications that affect glucose homeostasis (e.g. steroid treatment for inflammation), body metabolism (e.g. lipid lowering drugs), damage beta cells (e.g. certain antipsychotics, chemotherapy) or alter potassium levels that affects insulin secretion (e.g. diuretics) might produce an overabundance of circulating nutrients or reduced insulin release, both of which can contribute to decreased tissue responsiveness to insulin (insulin resistance).

Clinical Manifestations of Type 2 Diabetes

As blood glucose rise due to insulin resistance, the signs and symptoms are more insidious. T2DM can occur at any age, but is more common in adulthood. Like with T1DM, the common signs of diabetes (hunger, thirst, & frequent urination) develop gradually – such that patients might not notice as abnormal changes occur.

As you will see in a later chapter, patients with T2DM might not know they have diabetes until a diabetic complication (most often in the eye, kidney, or nerve) brings them in for health care and diagnosis.

Management of Type 2 Diabetes

In many cases, T2DM can be managed by weight loss, physical activity, and a healthy diet. However, if blood glucose levels still can not be managed with lifestyle interventions, medications can be used to improve tissue sensitivity to insulin or promote insulin release. However if the beta cells are exhausted, exogenous insulin will be required to help in managing T2DM.



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2587#h5p-166

Muscle contraction promotes glucose uptake – The action of muscle contraction and movement promotes the uptake of glucose (gold hexagons) through the glucose receptors (green) of tissues. This occurs with insulin present (purple triangles). As a result, blood sugar levels lower and the tissues get glucose. Images created by Sarah Perkins, licensed under CC-BY-NC

Section Review

T2DM is the most common form of diabetes. The pancreas can make insulin but the tissues do not respond to it. Consequently, the tissues do not take in sugar from the blood, resulting in chronic high blood glucose levels. Common manifestations are excessive thirst, hunger, and urination. T2DM is most commonly caused by lifestyle factors (e.g. overweight, medications) leading to an overabundance of nutrients; however, there are some genetic factors (e.g. ethnicity, family history) that may make T2DM more likely. T2DM can be managed with a combination of exercise, diet modifications, and medications to improve tissue sensitivity to insulin.

Review Questions

1. Which of the following is false:

- T2DM is a result of the pancreas not being able to produce insulin.
- T2DM makes up the majority of diabetes diagnoses.
- T2DM can take many years to develop.

Fill in the blanks with the following words:

glucose/sugar, higher, lower/decreased, glucose/sugar, beta

In T2DM, _____ cells in the pancreas are unable to keep up with the required insulin production since cells in the body have difficulty uptaking _____ due to _____ sensitivity to insulin. The blood _____ levels therefore remain _____ than normal.

3. In T2DM, the pancreas is still able to produce insulin, but the insulin receptors in the body are less effective. As a result, the blood glucose levels are low.

- True
- False

4. Which of the following are possible ways to help reverse T2DM? Select all that apply.

- Weight loss
- Physical activity
- Healthy diet
- Steroid treatment for inflammation
- Diuretics
- Lipid lowering drugs
- T2DM is not reversible

Answer Key

1. T2DM is a result of the pancreas not being able to produce insulin
2. beta, glucose/sugar, lower, glucose/sugar, higher
3. False
4. Weight loss, physical activity, healthy diet

Gestational Diabetes

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Identify some risk factors of developing gestational diabetes mellitus.
- Identify the manifestations of gestational mellitus.

Gestational diabetes mellitus is similar to T2DM, except that it is associated with pregnancy. As such, it often resolves shortly before or after birth. As the fetus grows, its demands for tissue growth causes a similar increased demand for both insulin and circulating nutrients. In conjunction with hormones associated with pregnancy, the mother's cells can't use its own insulin effectively causing a temporary insulin resistance. In fact, all pregnant women have some level of insulin resistance during late pregnancy, but not necessarily diagnosable gestational diabetes. Thus, many of the mother's symptoms overlap T2DM: hyperglycemia, polyuria, polydipsia (thirst), and polyphagia (hunger).

There is an association between gestational diabetes and pregnancy-induced high blood pressure (gestational hypertension). The mechanism is not well understood. However, if the mother already has diabetes-induced changes in microvasculature, the risk of developing gestational hypertension is greater.

The baby receives all of the mother's nutrients and insulin. Because insulin is an anabolic hormone (i.e. builds tissues), babies of mothers with gestational diabetes will tend to be larger than average. Because of the high amount of circulating insulin in utero, the baby may have sudden hypoglycemia upon birth as that insulin makes the tissues take up the circulating glucose even though maternal supply has been cut off.

Pregnancy is the biggest risk factor for gestational diabetes. However, if the mother has risk factors for T2DM as well, the mother is more likely to develop gestational diabetes.

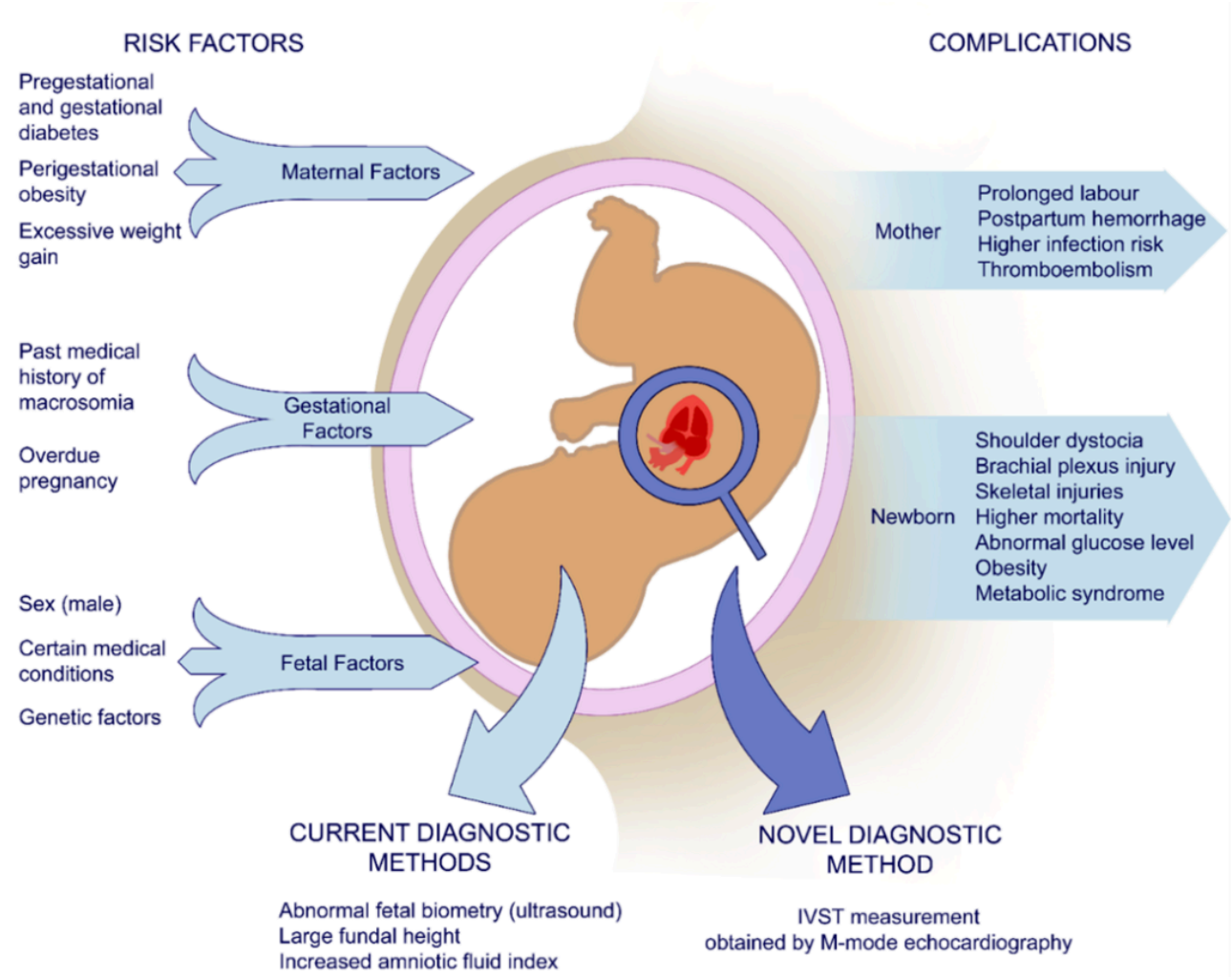


Diagram summarizing risk factors, diagnoses methods, and manifestations of gestational diabetes in both the mother and child.

Section Review

Gestational diabetes is caused by pregnancy which causes an abundance of insulin and nutrients circulating in the maternal blood. As such, maternal tissues become resistant to insulin – akin to a temporary form of T2DM which resolves in the mother upon birth. Maternal symptoms would be excessive thirst and urination. The baby exposed to high levels of nutrient and insulin may be large and have temporary hypoglycemia (due to maternal hyperinsulinemia).

Review Questions

1. Pregnancy is a risk factor for gestational diabetes mellitus and is developed in the fetus.

- True
- False

2. Fill in the blanks.
Some possible clinical manifestations for gestational diabetes mellitus are _____.

3. Which of the following can occur as a clinical manifestation of gestational diabetes mellitus?

- Baby is greater than 9 lb during delivery
- Baby is likely to develop T1DM later in life
- All of the above

Answer Key

1. False
2. Higher than normal sugar, sugar/glucose in urine, high blood pressure
3. Baby is greater than 9 lb during delivery

Media Attributions

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Diagnosis of Diabetes

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Briefly describe some of the laboratory tests of diagnosing diabetes mellitus.

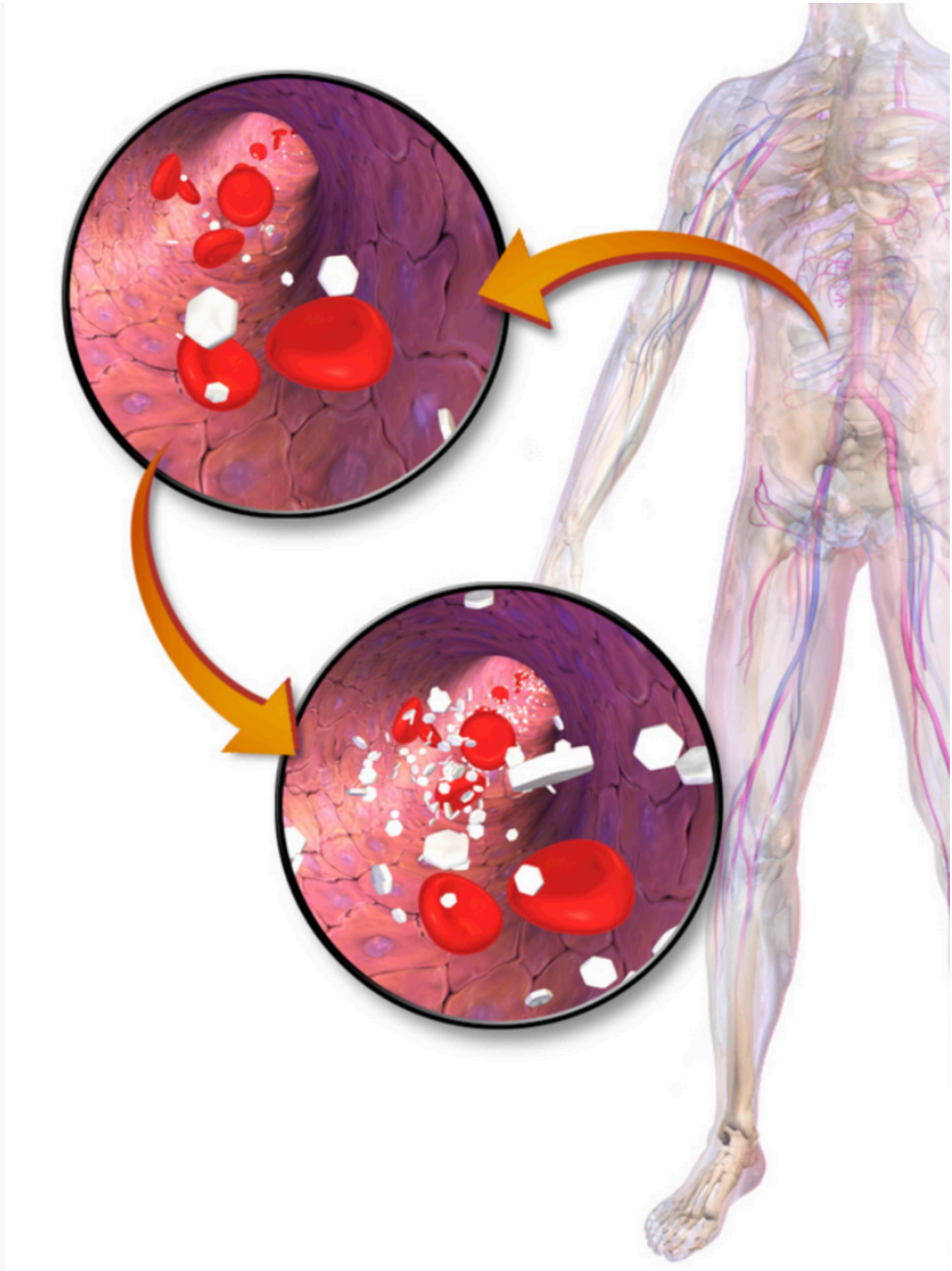
All types of diabetes mellitus are diagnosed most commonly using measurement of blood glucose levels.

In addition to taking a patient's medical history (which highlights possible risk factors), the patient does a blood test with or without fasting (normal values are different).

- Random blood glucose test = blood is taken at any time of the day, regardless of whether the patient has eaten/drunk recently
- Fasting blood glucose test = blood is taken when a patient has not eaten/drunk for at least 8 hours. In healthy fasting patients, there should be normal glucose levels with low insulin.

If high blood glucose is detected, a subsequent test is performed in case the patient failed to follow instructions.

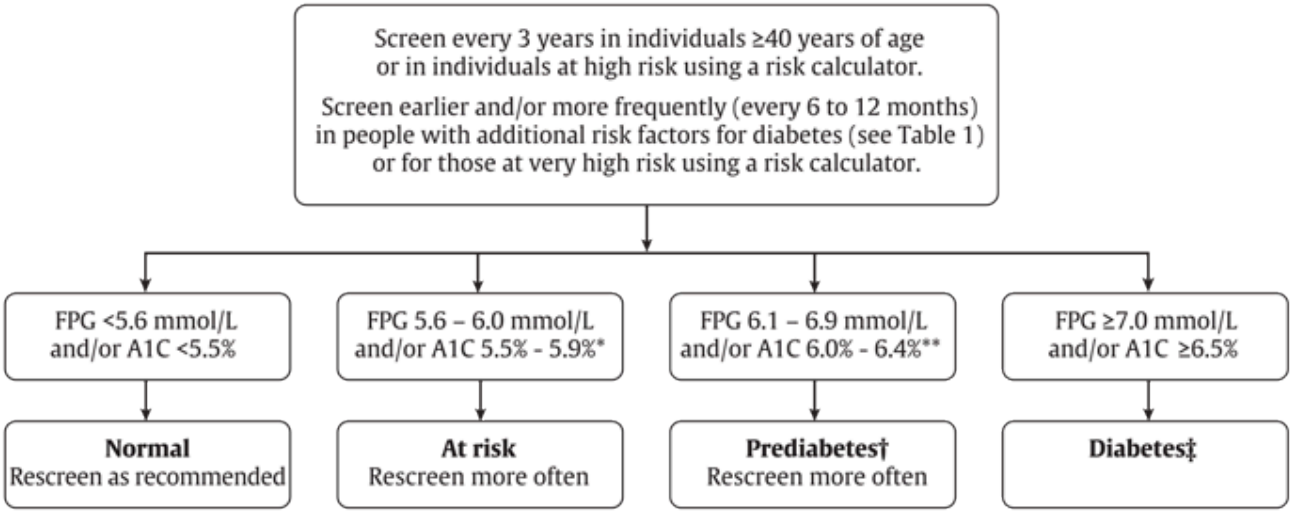
- Oral glucose tolerance test = patient is given a known amount of sugar to drink and then waits for 2h before blood sample is taken for glucose levels. In a patient without diabetes, insulin should be released to lower blood sugar levels down to normal. In a patient with diabetes, blood glucose levels will be high.
- Ketone test in blood or urine = the presence of ketones in the blood (draw blood) or urine (urine sample obtained in a cup) suggests that tissues are excessively using fat breakdown and not glucose for energy, possibly because insulin isn't available.
- Hemoglobin A1C (glycosylated hemoglobin) = this blood test examines the values of blood glucose in the last 3 months. Red blood cells take up glucose, and since red blood cells live for less than 4 months, if blood glucose was high red blood cells accumulate the excess sugar that was exposed to them during those months. Specifically, the hemoglobin molecule will bind to glucose in a process called glycosylation. The hemoglobin will be more glycosylated only if exposed to excessive sugar in the 3-4 months of the red blood cell life.



As more glucose (white) accumulates in the blood, more red blood cells have glucose attached to them forming the glycosylated hemoglobin or HbA1c. This is measured by the hemoglobin a1c test and provides an estimated information about the last 3-4 months of blood glucose levels. © Bruce Blaus is licensed under a CC BY (Attribution) license

Diagnosis of Diabetes **Meeting ANY of the following criteria confirms diagnosis when classic symptoms of hyperglycemia are present** **Absence of classic symptoms of hyperglycemia requires a repeat confirmatory test**	
FPG ≥7.0 mmol/L	• Test needs to be done after fasting (i.e., no caloric intake) for 8 hours (if fasting lipid test is ordered concurrently extend to 10 hours). • A full fasting panel rarely needed for most people with Type 1 Diabetes. • Since a number of people with Type 2 Diabetes have elevated triglycerides to the point where this affects management, a full fasting lipid panel may be needed.
A1C ≥6.5% (in adults)	• Not used for diagnosis in suspected Type 1 Diabetes, pregnant women, children, or adolescents. • Results may be inaccurate in patients with hemoglobinopathies, very low eGFR (estimated glomerular filtration rate), hematologic malignancies, anemia. See Diabetes Canada for more information.
2hPG in a 75 g OGTT ≥11.1 mmol/L	
Random PG ≥11.1 mmol/L in a patient with classic symptoms of hyperglycemia	• Random = any time of the day, regardless of the interval since the last meal

BC Guidelines on diagnosis of diabetes mellitus using blood tests.



If both FPG and A1C are available, but discordant, use the test that appears furthest to the right side of the algorithm.

*Consider 75 g OGTT if ≥1 risk factors; ** Consider 75 g OGTT (see Tables 3 and 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10 for interpretation of 75 g OGTT).

†Prediabetes = IFG or A1C 6.0 to 6.4% (see Table 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10).

‡In the presence of symptoms of hyperglycemia, a single test result in the diabetes range is sufficient to make the diagnosis of diabetes. In the absence of symptoms of hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. If results of two different tests are available and both are above the diagnostic cut points the diagnosis of diabetes is confirmed.

A1C, glycated hemoglobin; *FPG*, fasting plasma glucose; *IFG*, impaired fasting glucose

Flowchart of blood sugar and A1C test results that determine where someone is in the spectrum between normal and diabetic levels of blood sugar. Retrieved from Diabetes Canada.

Section Review

Diabetes is diagnosed through a blood test measuring glucose levels. Throughout the day, blood glucose levels fluctuate between 4-11 mmol/L depending on meals and activity. Hence, patients are instructed to not take in any nutrients (i.e. fast) for >8h to ensure – presumably – low levels of insulin with a normal range of blood glucose. If a patient's fasting plasma glucose is above normal range (i.e. hyperglycemia), this indicates a lack of insulin response: whether due to lack of circulating insulin (T1DM) or resistance to insulin at the the tissue level (i.e. T2DM or gestational). If hyperglycemia is present for more than 3 months, the excess sugar will modify the red blood cells and can be detected by measuring glycosylated hemoglobin – known as "Hemoglobin A1C". A further test for suspected diabetes is the oral glucose tolerance test (OGTT) where the patient ingests a known amount of sugar orally and their blood is measured 2h later. At this time, presumably, insulin levels will be at their highest with a decrease of blood glucose as the tissues respond to insulin. As blood high in glucose is being filtered by the kidney to produce urine, urine can be examined for the presence of glucose and/or ketones. Ketones will be present in both blood and urine if an abnormal amount of fat metabolism is occurring to compensate for the lack of glucose entering tissue for metabolism. When more than one test measures an inappropriately high amount of blood sugar/presence of ketones, diabetes mellitus is suspected and further investigations are needed to differentiate between the types of diabetes mellitus.

Optionally, check out Diabetes Canada's website where they outline screening for diabetes in adults.

Review Questions

1. Which of the following are tests taken to determine diabetes mellitus diagnoses? Select all that apply.

- Patient's medical history
- Random blood glucose test
- Oral glucose tolerance test
- Hemoglobin A1C
- Lipid urine test
- Lipid blood test
- Fasting cholesterol blood test
- Iron blood test

2. Place the tests and definitions in the correct section – Preliminary Tests or Secondary Tests.

Examining the glycosylation of sugar in red blood cells	Random Blood Glucose Test
Testing for the presence of ketones in blood or urine	Oral Glucose Tolerance Test
Blood taken at any time (regardless of most recent food/drink consumption)	Ketone Blood & Urine Test
Give known amount of sugar; wait 2 hours before taking blood sample	Fasting Blood Glucose Test
Blood taken without food/drink consumption 10 hours prior	Hemoglobin A1C

Preliminary Tests		**Secondary Tests**	
Test	**Definition**	**Test**	**Definition**

3. If a patient is suspected to have diabetes mellitus, which of the following preliminary tests should they take to determine a diagnosis? Select all the apply.

- Random blood glucose test
- Fasting blood glucose test
- Oral glucose tolerance test
- Ketone urine test
- Ketone blood test

- Hemoglobin A1C

Answer Key

1. Random blood glucose test, Oral glucose tolerance test, Ketone urine test, Hemoglobin A1C
2. Review table below.
3. Random blood glucose test, Fasting blood glucose test

Preliminary Tests		**Secondary Tests**	
Test	**Definition**	**Test**	**Definition**
Fasting Blood Glucose Test	Blood taken without food/ drink consumption 10 hours prior	Hemoglobin A1C	Examining the glycosylation of sugar in red blood cells
Random Blood Glucose Test	Blood taken at any time (regardless of most recent food/drink consumption)	Ketone Blood & Urine Test	Testing for the presence of ketones in blood or urine
		Oral Glucose Tolerance Test	Give known amount of sugar; wait 2 hours before taking blood sample

Media Attributions

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325. [Internet]. [cited 2020 Oct 16]. Available from: http://guidelines.diabetes.ca/cpg

BC Guidelines for Diabetes Care https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/diabetes#3

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- Diabetes screening-algorithm © BC Guidelines For Diabetes Care

Consequences of Chronic High Blood Glucose (Hyperglycemia) in Other Systems

JENNIFER KONG

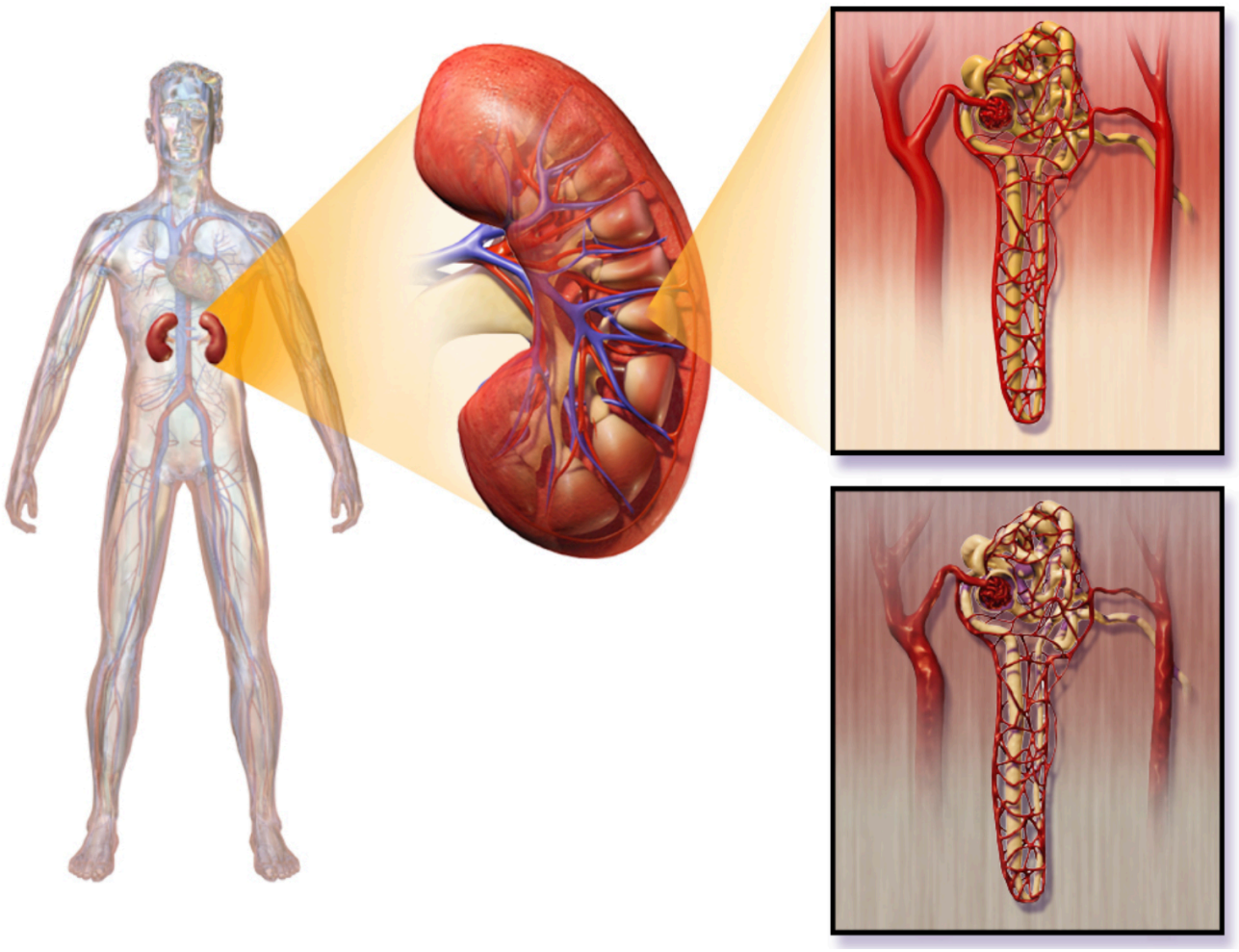
Learning Objectives

By the end of this section, you will be able to:

- Explain how manifestations of diabetes mellitus affects other organ systems in the body.
- Identify the consequences of having high blood sugar levels in the body.

All types of diabetes mellitus manifest as high blood glucose circulating in the body for a long time. Hyperglycemia damage blood vessels in the body – ESPECIALLY the very small microvasculature. Thus, the most common consequences of poorly controlled diabetes are impaired blood flow and damage in the eyes, kidneys, and nerves.

- Nerves: decreased blood flow cause loss of neural response for sensation (paresthesia) and movement (i.e. tripping while walking due to foot drop). As the nerve dies, tingling and pain develops (diabetic neuropathy). These problems can manifest in any part of the nervous system – but are more common in the hands, shins, and feet. Nerves serving the GI system will cause symptoms like gastric paralysis.
- Limbs & digits: blood vessel damage causes poor circulation to limbs and digits, which can cause tissue death. As well, hands and feet have a higher risk of injury and wound infection. In the presence of hyperglycemia and loss of neural response it might result in healing complications and the possible need of amputations.
- Eyes: damage to the retina microvasculature of the eye leads to blindness
- Blood vessels: Injury & inflammation of the lining of arteries can lead to atherosclerosis, ischemic heart disease, heart attacks and strokes (see Atherosclerosis chapter for more background).
- Kidneys: damage to microvasculature leads to a loss of the filtering ability in the kidneys resulting in renal disease and eventual renal failure.



Damage to the microvasculature is one of the most common diabetes complications. The above figure shows kidney nephrons before (above) and after (below) damage due to poor diabetes management damages the kidneys microvasculature. This may result in diabetes related nephropathy and reduced renal function. © Bruce Blaus is licensed under a CC BY (Attribution) license

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2597#h5p-167

DHPLC Specimen PATH 425-053 – Diabetic glomerulosclerosis – kidney stained with Periodic acid -Schiff stain. Created by Jennifer Kong, licensed under All rights reserved

High blood glucose in both the blood and bodily fluids (i.e. urine, saliva) creates a very favorable environment for metabolic disturbances, bacterial growth and hence infections.

- Urinary & oral infections: there are many pathogens in the genitourinary & oral cavities and high sugar in urine/saliva will encourage pathogen growth.
- Open wounds: high blood sugar promotes bacterial growth in the wound, thus delaying healing. As well, diabetes causes poor blood flow thus leading to slow or poor wound healing.

- Liver disease (non-alcoholic fatty liver disease): constantly high blood glucose wreaks havoc on nutrient processing and storage in the liver. The liver is the storage site for glucose in the form of glycogen in response to insulin. It also converts excessive nutrients like sugars into fats where it is stored locally. As a result, diabetes can lead to liver lipid accumulation and liver disease as excessive storage of these nutrients are harmful to the liver cells.

Critical thinking Exercises



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2597#h5p-89

Section Review

Diabetes involves chronic hyperglycemia and it will cause tissues to change anatomically and functionally, particularly the walls of small blood vessels. As a result, less blood is delivered to tissues. Thus, chronic hyperglycemia affects all tissues but is most noticeable in the kidneys, peripheral nervous system, eyes, and fingers/toes. As glucose metabolism is disturbed, fat metabolism is dominant causing high circulating levels of fat metabolism byproducts which will also affect the blood vessels, blood pH, and the liver.

Review Questions

1. Manifestations of diabetes mellitus can affect organ systems in the body. Fill in the blanks on the mechanism of how manifestations of diabetes mellitus affect each organ or system._____: _____ blood flow causes _____ damage resulting in tingling and/or painful sensations common in hands and feet.

Limbs & Digits: blood _____ damage causes poor circulation which can result in _____ death in limbs & digits.

_____: retinas can be damaged leading to _____.

Blood _____: _____ and _____ of the lining of arteries can lead to circulatory diseases.

_____: damaged microvasculature can lead to a loss of _____ which may lead to renal disease and renal _____.

_____: excessive storage of nutrients which is harmful to the organ.

2. High blood sugar levels in the blood and other bodily fluids may cause harm to the body since this allows a favorable environment for bacteria to growth. This may cause infections and delay healing.

- True
- False

Answer Key

1. nerves, decreased/lower, nerve, vessel, tissue, eyes, blindness, vessels, injury/injuries, inflammation, kidneys, filtering, failure, liver
2. True

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Consequences of Uncontrolled High Blood Sugar: Diabetic Ketoacidosis

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Explain a consequence of uncontrolled diabetes.
- Identify the clinical manifestations and causes of diabetic ketoacidosis.

Uncontrolled diabetes – whether due to circumstance or lack of diagnosis – can lead to a dangerous condition known as diabetic ketoacidosis (DKA). Because of a lack of glucose entering cells (regardless of whether it is due to lack of insulin or insensitivity to insulin), cells increasingly rely on fat stores for fuel. This happens despite the high amounts of circulating glucose (hyperglycemia). As a result, there is an increased production of ketones which are a byproduct of fat metabolism. Ketones are acidic and once accumulated in the blood they alter pH of the entire body causing an acidic environment in all tissues (ketoacidosis). The acidic environment forces electrolytes to be redistributed between the inside and outside of cells (i.e. blood) causing an electrolyte imbalance and disturbances. For example, DKA causes hyperkalemia because potassium (K^+) – normally in high levels within the cells – is forced out of the cell and into blood. Exiting K^+ is exchanged for incoming H^+ (acid) as the body tries to deal with the growing acidosis by storing H^+ into cells. The hyperglycemia will also cause polyuria which can quickly lead to dehydration, thus complicating the electrolyte disturbances. DKA is a serious medical condition as there are concurrent stresses on the body: electrolyte disturbances, acidic environment, and hyperglycemia with no glucose entering the cells. If DKA is left untreated, it may progress to a life-threatening "diabetic coma" as the tissues starve and continue to acidify.

DKA can occur in all the different types of diabetes – but it is more common in T1DM due to the lack of insulin.

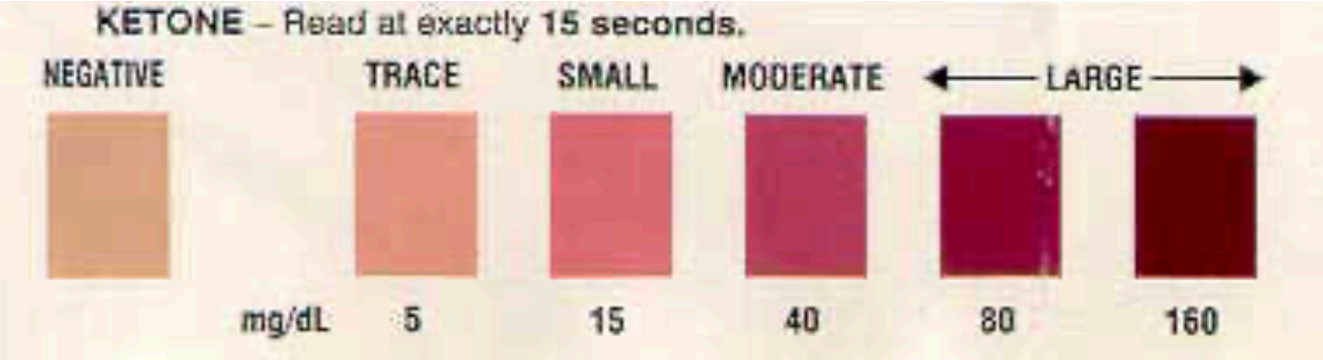
DKA can be caused by:

- Undiagnosed T1DM where lipid metabolism is needed due to the absence of insulin and ketones accumulate in the blood. DKA may develop and bring the patient for emergency care where the official diagnosis of both DKA and T1DM is made
- Insufficient insulin administration to a person with T1DM. In this case, the tissues can not get glucose into the cells and, as a result, cells turn to lipid metabolism making ketones even in the presence of hyperglycemia.
- Increased insulin demand (i.e. sudden illness or injury, alcohol/drug ingestion) in a person with T1DM leading to lipid metabolism and ketone production.

Clinical manifestations of DKA are similar to diabetes (3P's of diabetes, fatigue, dehydration) WITH the addition of:

- Fruity smelling breath (presence of ketones)
- Fast, deep breathing (breathing off the acid)

- GI upset (will complicate dehydration)
- Malaise
- Signs of Electrolyte disturbances (i.e. arrhythmia, loss of consciousness, seizures, and hyperkalemia will disrupt every tissue that is electrically excitable)



Preliminary ketone diagnosis can be done in the home through urine test. Darker colours indicate increased level of diabetic ketoacidosis in the individual. © Ketostix is licensed under a Public Domain license

Section Review

DKA is a serious condition that can result from prolonged lack of glucose intake into the cells, usually as a result of insufficient insulin production/secretion. The lack of glucose uptake into the cells induce a change in metabolism and more fat needs to be metabolized, resulting in the production of acidic ketones. High ketones cause pH changes in the body and as the body tries to compensate for this acidification, K^+ is expelled from the cells leading to hyperkalemia and electrolyte disturbances. The resulting hyperglycemia will lead to polyuria causing dehydration which further complicates the electrolyte disturbances. Electrolyte disturbances will manifest as irregular heart rhythms (arrhythmia) and neurological impairments (i.e. loss of consciousness, seizures). The high amount of circulating ketones is noticeable in a fruity breath and the acidosis causing a rapid respiratory rate. This is in conjunction with the signs of DM (i.e. polyuria, polydipsia).

Review Questions

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Interprofessional Collaboration During the Care of Diabetes

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Identify the health care professionals that take part in helping diabetic patients.
- Explain the role(s) of each health care professional in the process of caring for a patient with diabetes.

Many health care professions work collaboratively to help a patient manage diabetes. Below are examples of a few of the professionals involved in the management of diabetes:

- Medical Laboratory Technologists: test the blood and urine samples that are collected from patients.
- Electroneurophysiology Technologists: examine the extent of nerve damage caused by diabetes (neuropathy).
- Sonography Technologists: examine the changes in anatomy and function of organs damaged by diabetes. Structural changes to blood vessels or kidneys can be visualized. Heart function can be measured as diabetes can lead to cardiovascular disease (see Heart Failure chapter for an interview with a sonographer).
- Prosthetic and Orthotic Technicians: create devices to help with the mobility of a person with diabetes. Sometimes, diabetic neuropathy cause impaired sensation and/or weakness resulting in difficulty with walking and balance. If amputation is required, a prosthetic can be custom created to help the patient to regain mobility.
- Nurse educators: help people with diabetes to learn about their disease and how best to manage it. Nurses specialized in diabetic education can create customized care plans including diet recommendations, taking medication, foot care, etc.
- Dietitian: prescribe diet plan and help in managing blood glucose levels through lifestyle changes.



Example of electrophysiology test, in which the health of neurons are measured. This specific test is called electromyography, and uses a small device to stimulate electrical impulses, and measures how effectively signals travel along the arm and hand. It then indicates if the nerves are functioning properly or if there is damage to nerve conduction. *© Vaso Obradovic is licensed under a CC BY-ND (Attribution NoDerivatives) license.*



Yvonne Jeffreys a BCIT professor displaying a variety of orthotic aids. Such a variety gives insight to the necessary collaborative effort needed to provide a patient with a sufficient orthotic. *© Yvonne Jeffreys is licensed under a CC BY-ND (Attribution NoDerivatives) license.*

Section Review

Patients living with DM will need to take their disease into consideration when they go through their daily activities and long term plans. To help patients live a healthy life, many health care professionals will interact with the patient to help them manage normal blood sugar levels, dietary choices , and management. Health care professionals will also help monitor for possible effects on nerves, kidneys, and eyes. If a limb loses function or if amputation is necessary, a prosthetic/orthotic technologist can help the patient regain mobility and function.

Review Questions

1. Match the professional with the responsibility.

Medical Laboratory Technologists	Help patients create customized care plans
Sonography Technologists	Examine nerve damage
Nurses	Create devices to help with patient mobility
Electroneurophysiology Technologists	Test blood and urine samples
Prosthetic & Orthotic Technicians	Examine changes in anatomy and function of organs

Answer Key

1. **Medical Laboratory Technologists:** Test blood and urine samples
   Sonography Technologists: Examine changes in anatomy and function of organs
   Nurses: Help patients create customized care plans
   Electroneurophysiology Technologists: Examine nerve damage
   Prosthetic & Orthotic Clinicians: Create devices to help with patient mobility

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- Orthotics and their varieties © Yvonne Jeffreys is licensed under a CC BY-ND (Attribution NoDerivatives) license

Management and Treatment of Diabetes

JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Compare and contrast the management and treatment in type 1, type 2, and gestational diabetes mellitus.

Management of diabetes depends on the type, the severity of the condition, and the ability of the patient to make lifestyle changes. Below is a summary of some of the management strategies and treatment options for each type of DM discussed in this chapter.

Type 1 Diabetes

As people with T1DM do not make insulin, daily blood glucose monitoring, insulin injections and thoughtful consideration of diet and activity are necessary to manage their condition. There are many versions of injectable insulin based on onset of action and duration. There has also been progress on different modes of delivery of insulin and blood glucose monitoring.

The only long term cure for T1DM is a pancreatic transplant. Meet Sally Patient Narrative on Type 1 Diabetes: Sally who describes her life before and after her pancreatic and kidney transplant for T1DM.



T1DM is treated through a combination of blood glucose tests and injectable artificial insulin.

Classical Type 2 & Gestational Management

As T2DM & gestational diabetes involves tissues being insulin resistant, management focusses on tissues becoming more sensitive to insulin. This can be achieved through lifestyle changes or through pharmacotherapy.

Lifestyle changes:

- Exercise: physical movement encourages nutrients to be taken into the tissues – independent of insulin – thus reducing blood sugar.
- Weight loss: decrease in body weight is associated with an improvement in tissues response to insulin.
- Nutrition: food is digested and releases glucose and nutrients at different rates. Foods that are high in sugars will lead to a boost of insulin release in a short period of time, if chronic, it may lead to insensitivity to insulin. Therefore, a diet that can limit high insulin release (i.e. whole foods instead of ultra processed foods) will help in preventing peaks of insulin release.
- In gestational diabetes, birth of the child will often lead to the resolution of diabetes. However, there is an increased chance for the mother to develop T2DM later in life.

Some patients with T2DM/gestational diabetes may be unable to control their disease with these lifestyle changes, and will require medication. These medications work to:

a) Improve tissue insulin sensitivity

b) Promote insulin release from the pancreas

c) Decrease the amount of sugar coming from liver storage or being absorbed in the gut/reabsorbed in the kidney



The most popular GLP-1 receptor agonists include semaglutide, which mimic the structure of the natural hormone GLP-1. The above image is an example of an injectable semaglutide called Ozempic which is administered subcutaneously.

Section Review

Management of diabetes depends on the type. Because T1DM is characterized by insufficient insulin production, the only treatment possible is insulin injections and strategies that help maintain steady blood sugar levels throughout the day. T2DM and gestational involve tissues not responding to circulating insulin. Hence management of T2DM/gestational are strategies to improve tissue sensitivity to insulin and maintenance of a steady blood sugar level throughout the day. Pharmacologic management of T2DM/gestation aims to encourage tissues to respond to insulin and limit sugar coming from stored sources. Gestational diabetes is often resolved upon birth.

Review Questions

1. Match the methods for managing diabetes to the type of diabetes that it will likely benefit.

Blood glucose monitoring Consideration of activity/exercise Pancreatic transplant Weight loss	Insulin injections Weight loss Medication Consideration of diet Lifestyle changes

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus	Gestational Diabetes Mellitus

2. Which of the following are classifications of medications that help patients with T2DM or gestational diabetes mellitus to control their disease? Select all the apply.

- Medications that promote insulin sensitivity
- Medications that promote insulin release
- Medications that decrease circulating sugar from storage in the liver, gut or kidneys
- Medications that replace insulin
- Insulin injections

Answer Key

1.

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus	Gestational Diabetes Mellitus
Blood glucose monitoring Insulin injections Consideration of activity/exercise Pancreatic transplant Weight loss Medication Consideration of diet	Consideration of activity/exercise Weight loss Lifestyle change Medication Consideration of diet	Consideration of activity/exercise Weight loss Lifestyle change Medication Consideration of diet

2. Medications that promote insulin sensitivity, Medications that promote insulin release, Medications that decrease circulating sugar from storage in the liver, gut or kidneys

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- Ozempic © Haulin is licensed under a CC BY-SA (Attribution ShareAlike) license

Diabetes Mellitus Pharmacology

Diabetes Mellitus Pharmacology

DYLAN MANN AND STEPHENY ZANI

Learning Objectives

By the end of this section, you will be able to:

- Classify the major drugs used to manage type 2 diabetes mellitus into groups
- Associate the groups of drugs with their unique mechanisms

Introduction

In general, T2DM pharmacotherapy is aimed at reducing hyperglycemia through increasing tissue sensitivity to insulin, increasing insulin production, or decreasing glucose production and absorption. Additionally, as much as the North American population approaches pre-diabetic levels or has developed T2DM, the management and treatment options continue to grow alongside them. The class of drugs that we will focus in this chapter include GLP-1 receptor agonists, insulin sensitizers, insulin secretagogues, SLGT-2 inhibitors, DPP4 inhibitors, and alpha-glucosidase inhibitors.

GLP-1 Receptor Agonists

The most popular of new T2DM drugs can be grouped as GLP-1 receptor agonists (or GLP-1 analogs). These act by mimicking the effect of the natural hormone GLP-1, and activating GLP-1 receptors. The combined effects of activating GLP-1 receptors exogenously include increased insulin production, decreased glucagon production, slowed gastric emptying, and decreased appetite. All of these effects contribute to stabilizing blood glucose levels in a person with T2DM, and are particularly potent in causing weight loss. However, although touted as miracle drugs by many, there are multiple side effects that persist in the widely available drugs. These include general nausea, stomach pain, and vomiting, primarily due to effects of slowed gastric emptying. Additionally, due to such strong appetite suppression and rapid weight loss, patients often lose significant muscle mass alongside fat loss, especially if insignificant protein and exercise is paired with the medication.**It is worth to keep in mind, that GLP-1 receptor agonists are not the first group of drugs prescribed to manage T2DM and that they should be used cautiously and as an add on therapy.**



The most popular GLP-1 receptor agonists include semaglutide, which mimic the structure of the natural hormone GLP-1. The above image is an example of an injectable semaglutide called Ozempic.

Insulin Sensitizers

Insulin sensitizing drugs have historically been the **first class of drugs given to a person with T2DM** once diet and exercise are no longer sufficient in managing blood glucose levels. Their main mechanism of action is to reduce the production of new glucose from the liver (reduce gluconeogenesis). Additionally, these drugs cause more glucose transporter proteins such as GLUT4 to embed themselves in the plasma membrane of muscle and adipose tissue, allowing glucose to enter cells at a higher rate. Furthermore, such drugs can decrease glucose absorption in the intestines, resulting in less glucose in the bloodstream. By reducing gluconeogenesis in the liver, increasing insulin sensitivity in the muscle and adipose tissue, and decreasing glucose absorption in the intestines, this class of drugs greatly reduces overall glucose level in the blood. Most common side effects of such drugs include gastrointestinal disturbances such diarrhea, nausea, and abdominal cramps.



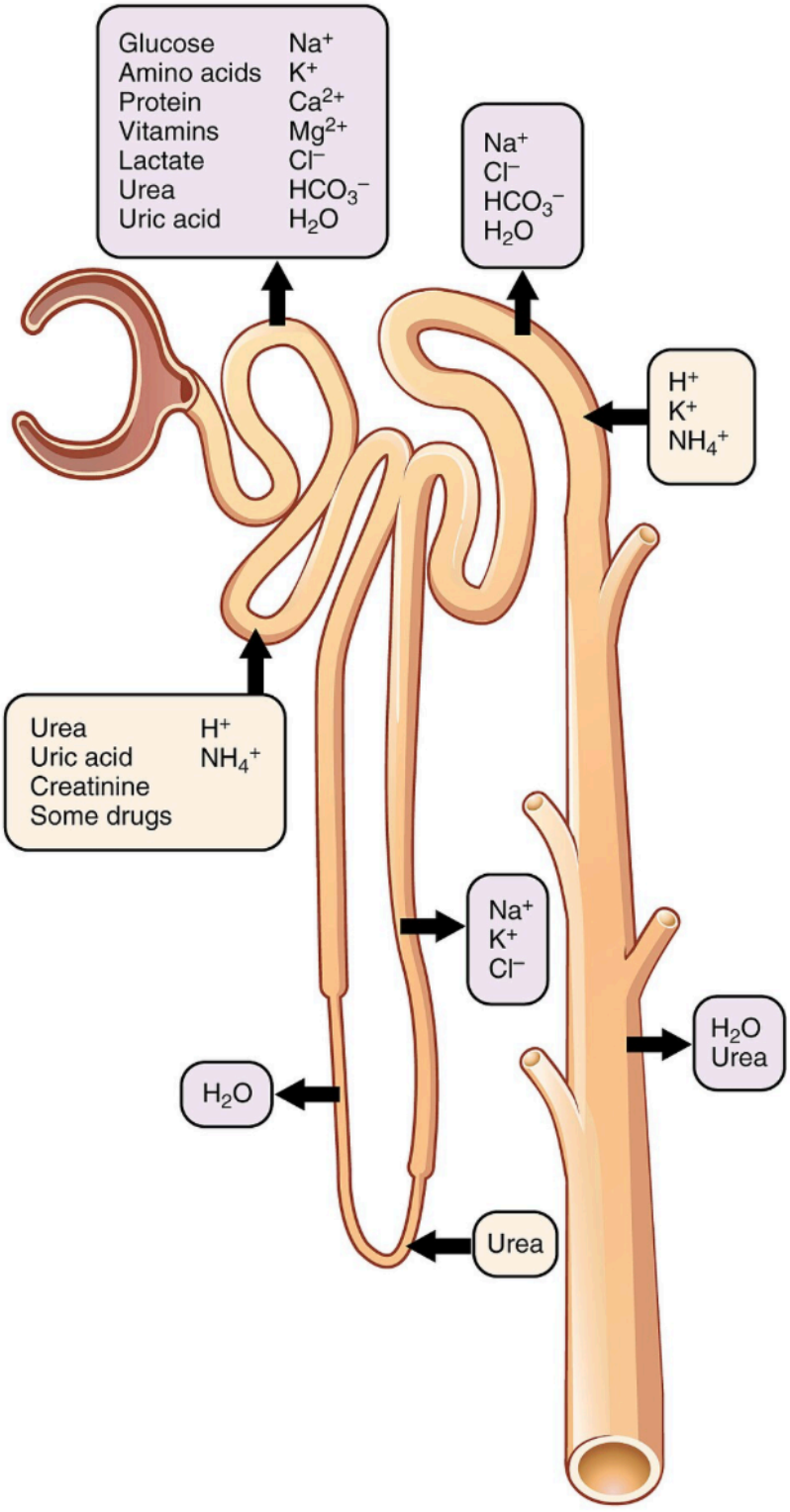
Metformin is a common insulin sensitizer that is administered orally. Often the first class of drug prescribed to a person with T2DM.

Insulin Secretagogues (Sulfonylureas)

Insulin secretagogues or the sulfonylureas class of T2DM drugs act by stimulating the release of insulin from pancreatic beta cells. They work by binding to specific receptors on pancreatic beta cells, and blocking potassium channels. The blocking of potassium channels causes depolarization of the cells, allowing calcium to enter and trigger the release of insulin. The increased release of insulin facilitates the uptake of glucose into tissues and cells, and in turn reduces the amount of glucose in the blood. Because of sulfonylureas direct increase in insulin production, patients must monitor blood glucose levels frequently, and avoid skipping meals to avoid hypoglycemia.

SGLT-2 Inhibitors

SGLT-2 inhibitors act by inhibiting sodium glucose transport protein 2 (SGLT-2) in the kidneys, which accounts for over 90% of the total renal reabsorption of glucose. When SGLT-2 is inhibited, the kidneys ability to reabsorb glucose back into the blood is greatly limited, and instead glucose is excreted out into the urine. When people with T2DM use SGLT-2 inhibitors, it is hugely important that they consume enough water and nutrients, as common side effects include urinary tract infections, and dehydration. For this class of drugs to work efficiently, renal filtration must be occurring normally, therefore, patients with impaired kidney function might not benefit from this therapy.



Kidney nephrons have the transporter SGLT-2 on the plasma membrane of cells in the proximal tubule. These transporters accounts for the majority of glucose reabsorption. When inhibited, reabsorption is greatly decreased.

DDP-4 Inhibitors

DDP-4 inhibitors are a class of oral T2DM drugs that act by blocking the enzyme dipeptidyl peptidase-4 (DPP-4). Under normal action, DDP-4 breaks down incretin hormones such as GLP-1 and GIP. By inhibiting DDP-4, these hormones are able to circulate the body for extended periods of time. When incretin hormones circulate for longer periods, insulin release is stimulated and glucagon release is reduced for a longer time, both of which contribute to decreasing blood glucose levels.

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors are a class of T2DM drug that inhibits the enzyme alpha-glucosidase. Under normal conditions, alpha-glucosidase aids in the breakdown of complex carbs into simple carbs such as glucose that the body can easily absorb. If alpha-glucosidase is inhibited, complex carbohydrates are broken down at a slower rate, and glucose absorption is thus slowed down. Overall, alpha-glucosidase slows down digestion, and creates a more gradual onset of glucose after a meal opposed to an otherwise rapid spike.

Section Review

There are many T2DM pharmaceutical therapies, and they all operate under different mechanisms. However, all of such drugs aim to do one thing: reduce blood glucose levels. This may be achieved through multiple mechanisms such as by increasing insulin production, increasing insulin sensitivity, slowing digestion, or inhibiting the breakdown of glucose. With the advancement of knowledge about T2DM and scientific research, more and more options are to become available in the future.

Review Questions

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- Metformin is a common insulin sensitizer that is administered orally. Often the class of drug first prescribed to person with T2DM. © Life of a Diabetic is licensed under a CC BY (Attribution) license
- Kidney nephron which which includes the receptor SGLT-2 which accounts for the majority of glucose reabsorption. When inhibited, reabsorption is greatly decreased. © OpenStax College is licensed under a CC BY (Attribution) license

Patient Narrative on Type 1 Diabetes: Sally

Diabetes affects both the patient and their entire family – including their plans for a future family! Meet Sally McKinstry as she describes what living with Type I diabetes has been like since her diagnosis at the age of 16 y.o.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=2602#h5p-154

This patient interview with Sally was conducted by Lorraine Gilman & Dr. David Kojwang, BCIT Basic Health Sciences Dept. Licensed under All rights reserved

Sally describes the effects of "brittle diabetes" (i.e. difficult to control Type I diabetes due to the huge swings in blood sugar) on her body and her transplant which gave her a new view on life.

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This patient interview with Sally was conducted by Lorraine Gilman & Dr. David Kojwang, BCIT Basic Health Sciences Dept. Licensed under All rights reserved. Please note that the dialysis machines depicted are examples of machinery found in health care settings at the time of Sally's need for peritoneal dialysis.

Meet Sally's family as they describe how Sally's diabetes influenced their lives.

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These patient interviews with Bill and Katie were conducted by Dr. Jennifer Kong in 2022, BCIT Basic Health Sciences Dept. Licensed under All rights reserved

In 2019, Sally developed an aggressive cancer – unrelated to diabetes – which she and her family lived with during the COVID lockdown. Sally McKinstry died of this cancer in 2021. The McKinstry family strives to continue telling her story for the benefit of those living with diabetes and those who care for them.



Bill McKinstry shares his knowledge with BCIT students Adam Vuong (Med Rad), Sahib (Bachelors of Nursing, and Madeline Angus (Medical Radiography)

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Diabetes Chapter Summary and Credits

JENNIFER KONG

Chapter Summary

The endocrine pancreas is primarily comprised of the pancreatic islet cells: alpha (glucagon) and beta (insulin) cells. Insulin and glucagon are involved in glucose homeostasis: maintaining a consistent blood sugar level regardless of whether one has eaten or not. In response to high blood glucose levels (i.e. after a meal), insulin is produced by the beta cells to encourage glucose uptake and utilization by tissues. As well, insulin release promotes storage of excess glucose in the form of glycogen or lipids, available for later use (i.e. fasting).

DM is characterized by high blood glucose levels (hyperglycemia). The cause of the hyperglycemia could be due to either a problem with the production and release of insulin (T1DM) or the loss of sensitivity to insulin in the tissues (T2DM and gestational). The common manifestations of DM, regardless of the type, are high blood glucose, excessive thirst and urination, fatigue, confusion/irritability, and high heart rate.

The cause and risk factors of diabetes are based on the type. Genetics and environmental triggers are thought to be the cause of T1DM, leading to the destruction of insulin-producing beta cells by autoantibodies. T2DM also has a genetic component, but risk factors such as an overabundance of circulating nutrients can lead to tissue insensitivity to insulin. In gestational diabetes, pregnancy is the cause as well as the risk factors of having pre-diabetes before pregnancy.

Diagnosis is based on tests for blood glucose – whether amount circulating when fasting (fasting blood glucose), after a glucose challenge (oral glucose tolerance test), or after months of high circulating sugars (glycosylated hemoglobin A1C). Urine can also be tested for the presence of glucose which is suggestive of diabetes, but not definitively as diet and kidney disease can also yield urine with sugar. The presence of ketones – common during diabetic ketoacidosis – can also be measured in both the blood and urine.

Treatment and management of diabetes depends on the type. T1DM requires injectable insulin, daily blood glucose checks, and thoughtful consideration of diet and physical activities. T2DM and gestational diabetes can be managed with lifestyle changes to promote insulin sensitivity (i.e. exercise and dietary modifications). Medications can also be used in T2DM/gestational if lifestyle changes are insufficient.

Credits

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Post-Test for Diabetes

JENNIFER KONG

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1. Place each descriptor under the correct heading.

Beta cells functional	Beta cells unable to produce insulin	Likely diagnosed later in life	Greater than 90% of diabetes diagnoses
Associated with pregnancy	Insulin dependent	Likely diagnosed in early childhood	Non-insulin dependant
Less than 5% of diabetes diagnoses	Temporary insulin resistance	Likely developed after giving birth	Requires synthetic insulin for survival

T1DM	T2DM	Gestational DM

Answer Key

T1DM	T2DM	Gestational DM
Beta cells unable to produce insulin Insulin dependent Less than 5% of diabetes diagnoses Likely diagnosed in early childhood Requires synthetic insulin for survival	Beta cells functional Likely diagnosed later in life Greater than 90% of diabetes diagnoses Non-insulin dependent Likely developed after giving birth	Associated with pregnancy Temporary insulin resistance

BLOOD, ANEMIA, LEUKEMIA, AND BLOOD TESTS

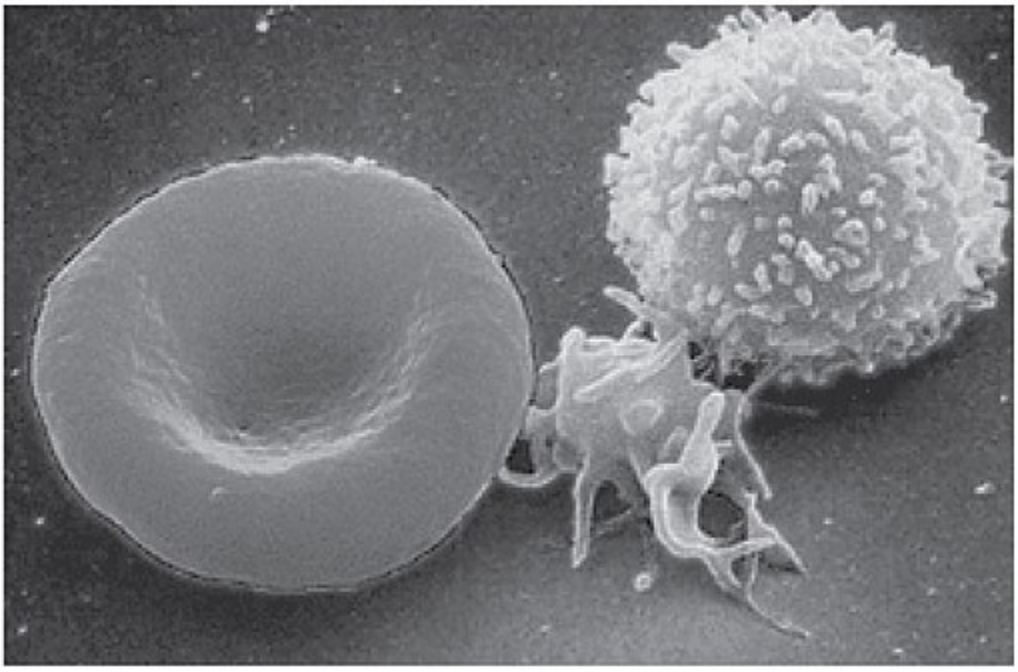
Blood, Anemia, Leukemia & Blood Tests Chapter Overview

WILLIAM WANG AND JENNIFER KONG

Chapter Learning Objectives

By the end of this chapter, you will be able to:

- Identify the primary functions of blood in transportation, defense, and maintenance of homeostasis.
- Name the fluid and cellular components of blood and identify their relative proportions in a blood sample.
- Identify the composition of blood plasma, including its most important solutes and plasma proteins.
- Describe how anemia can develop, its classification, appearance in peripheral blood smears, and treatment.
- Briefly explain how leukemia can develop, its classification, appearance in peripheral blood smears and bone marrow biopsies, and treatment.
- Compare and contrast the signs and symptoms of anemia and leukemia.
- List the specialties of medical laboratory sciences and the tests they do with blood.
- Explain the blood test iron studies and how it is related to the diagnosis of anemia.
- Briefly describe the journey a blood sample takes in LifeLabs, when being analyzed for hematology and blood chemistry test.



Blood Cells – *A single drop of blood contains millions of red blood cells, white blood cells, and platelets. One of each type is shown here, isolated from a scanning electron micrograph.*

Blood is essential for life: it delivers all the oxygen and nutrients the tissues need and removes their wastes. The cellular components of blood—referred to as the formed elements—include red blood cells (RBCs), white blood cells (WBCs), and cell fragments called platelets. Plasma, which is mostly water, suspends the formed elements and carries within it everything that is water soluble (e.g., nutrients and electrolytes). Together, the plasma and formed elements circulate throughout the body as part of the cardiovascular system.

Blood disorders are often associated with disorders of the formed elements. Anemia is a blood disorder involving the abnormal synthesis of RBCs and/or hemoglobin. Anemia is quite common in the population due to a variety of causes.

In contrast, blood cancers – called leukemias – involve an inability to produce mature blood cells from the bone marrow. Leukemias involve the overproduction of abnormal, immature blood cells – called blasts – which crowd out and replace the growth an maturation of blood cells. Leukemias can be subclassified based on the blood stem cell that is abnormally proliferating (lymphoid vs myeloid stem cell) and whether the leukemia develops suddenly (i.e. acute) or long term (i.e. chronic)

From a health care perspective, blood tests are a common part of investigations. However, 'blood tests' are actually subdivided (like blood itself) into tests for either the number/quality of mature blood cells (e.g. hematology test will look at the number of RBC, WBC, and platelets) or tests for the content within plasma (E.g. chemistry test will look at amount of glucose and electrolytes within the plasma part of blood). Taken together, these test results can give signs of organ dysfunction, along with a snapshot of a person's ability to carry oxygen, nutrients, electrolytes.

This chapter is subdivided into:

- Pre-test
- Normal blood production and function (including histology of normal bone marrow & peripheral blood)
- Classification of anemia and leukemia
- Pathophysiology and hematopathology of anemia and acute leukemia

- Interviews with health care professionals diagnosing/treating those with leukemia and discussions its complications
    - Hematopathologist
    - Medical laboratory science technologists (hematology & clinical chemistry)
- Video tour of LifeLabs facility: the largest processor of blood tests in Western Canada.
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

ALL	Acute Lymphoblastic Leukemia
Fe	Iron
Hb	Hemoglobin
Hct	Hematocrit
LIS	Laboratory Info System
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MLA	Medical Lab Assistant
MLT	Medical Lab Technologist
MI	Myocardial Infarction
O2	Oxygen
PCR	Polymerase Chain Reaction
ROI	Region of Interest
RBC	Red Blood Cell
TIBC	Total Iron Binding Capacity
WBC	White Blood Cell

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Pre-Test

WILLIAM WANG



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Normal Blood Composition

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Identify the primary functions of blood in transportation, defense, and maintenance of homeostasis.
- Name the fluid component of blood and the three major types of formed elements, and identify their relative proportions in a blood sample.
- Discuss the unique physical characteristics of blood.
- Identify the composition of blood plasma, including its most important solutes and plasma proteins.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body. Moreover, endocrine glands scattered throughout the body release their products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body. Various waste products are also transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the

bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Recall that body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

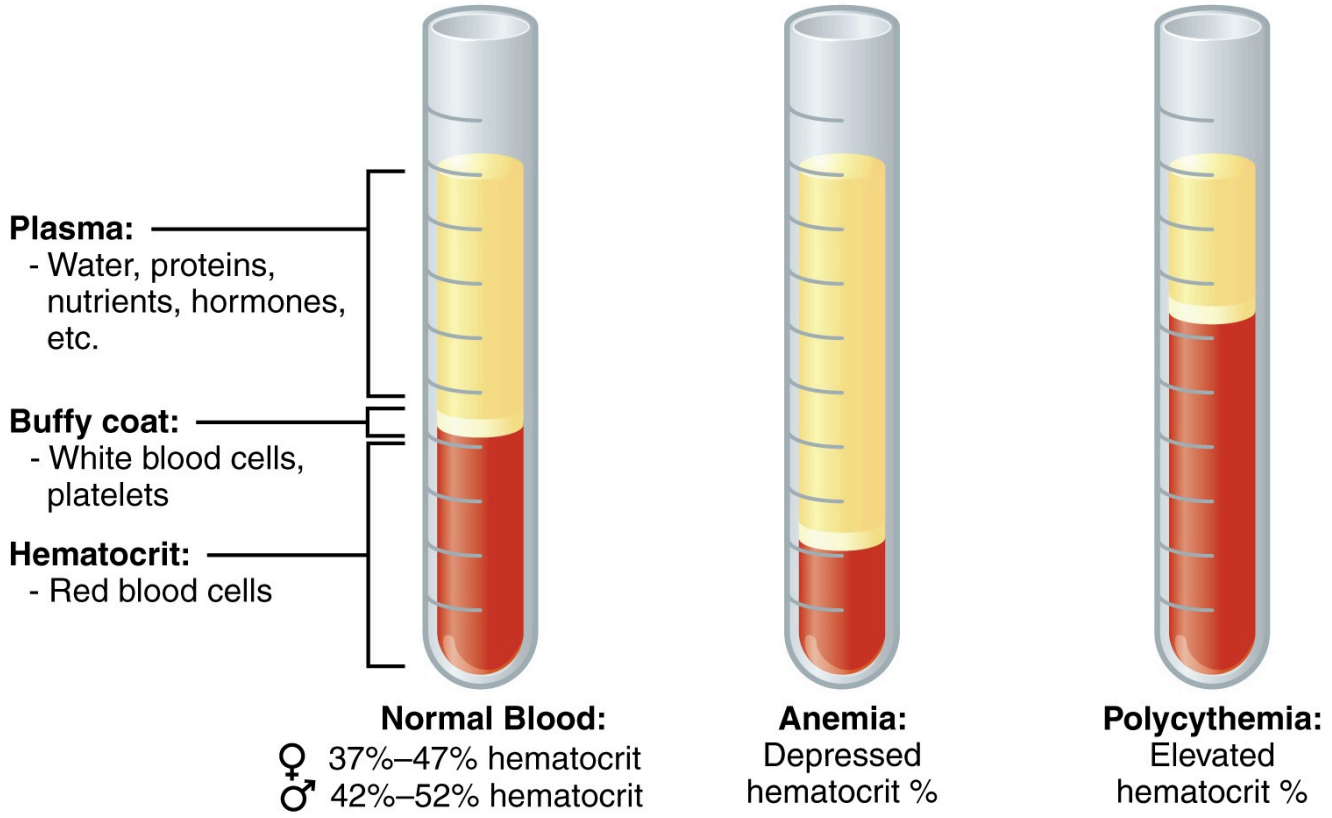
Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in the blood act as buffers, which thereby help to regulate the pH of body tissues. Blood also helps to regulate the water content of body cells.

Composition of Blood

You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements. This figure below shows the three components of blood in different conditions.

One such test, called a hematocrit, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma. Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the WBCs, clinically known as leukocytes, and the platelets, cell fragments also called thrombocytes. This layer is referred to as the buffy coat because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

The volume of erythrocytes after centrifugation is also commonly referred to as packed cell volume (PCV). In normal blood, about 45 percent of a sample is erythrocytes. The hematocrit of any one sample can vary significantly, however, about 36–50 percent, according to gender and other factors. Normal hematocrit values for females range from 37 to 47, with a mean value of 41; for males, hematocrit ranges from 42 to 52, with a mean of 47. The percentage of other formed elements, the WBCs and platelets, is extremely small so it is not normally considered with the hematocrit. So the mean plasma percentage is the percent of blood that is not erythrocytes: for females, it is approximately 59 (or 100 minus 41), and for males, it is approximately 53 (or 100 minus 47).



Blood Viscosity – *The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison.*

Characteristics of Blood

When you think about blood, the first characteristic that probably comes to mind is its color. Blood that has just taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a more dusky red. This is because hemoglobin is a pigment that changes color, depending upon the degree of oxygen saturation.

Blood is viscous and somewhat sticky to the touch. It has a viscosity approximately five times greater than water. Viscosity is a measure of a fluid's thickness or resistance to flow, and is influenced by the presence of the plasma proteins and formed elements within the blood. The viscosity of blood has a dramatic impact on blood pressure and flow. Consider the difference in flow between water and honey. The more viscous honey would demonstrate a greater resistance to flow than the less viscous water. The same principle applies to blood.

The normal temperature of blood is slightly higher than normal body temperature—about 38 °C (or 100.4 °F), compared to 37 °C (or 98.6 °F) for an internal body temperature reading, although daily variations of 0.5 °C are normal. Although the surface of blood vessels is relatively smooth, as blood flows through them, it experiences some friction and resistance, especially as vessels age and lose their elasticity, thereby producing heat. This accounts for its slightly higher temperature.

The pH of blood averages about 7.4; however, it can range from 7.35 to 7.45 in a healthy person. Blood is therefore

somewhat more basic (alkaline) on a chemical scale than pure water, which has a pH of 7.0. Blood contains numerous buffers that actually help to regulate pH.

Blood constitutes approximately 8 percent of adult body weight. Adult males typically have an average about 5 to 6 liters of blood. Females typically have an average 4 to 5 liters.

Blood Plasma

Like other fluids in the body, plasma is composed primarily of water. In fact, it is about 92 percent water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, although many of them are found only in very small quantities.

Visit Laboratory Reference Values for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed.

Reference ranges, also called normal ranges, are established by testing a large population of healthy individuals for their laboratory values. Patient values that fall outside of this established range are considered to be abnormal and may indicate that the patient is in need of medical treatment, whether or not they are showing symptoms.

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones. The major components of plasma are summarized in the following table.

The three major groups of plasma proteins are as follows:

- Albumin is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL of blood.
- The second most common plasma proteins are the globulins. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells. Like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as antibodies or immunoglobulins. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL of blood.
- Fibrinogen is the third of the three major groups of plasma proteins. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL of blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes (e.g., sodium, potassium, and calcium ions), dissolved gases (e.g., oxygen, carbon dioxide, and nitrogen), organic nutrients (e.g., vitamins, lipids, glucose, and amino acids), and metabolic wastes. All of these non-protein solutes together contribute approximately 1 percent to the total volume of plasma.

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46-63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54-60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35-38 percent	Alpha globulins-liver	Transport, maintain osmotic concentration
			Beta globulins-liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins)-plasma cells	Immune responses
		Fibrinogen 4-7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1 percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37-54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils, eosinophils, basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes, monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Career Connection

Phlebotomy and Medical Lab Technology

Phlebotomists are professionals trained to draw blood (phleb- = "a blood vessel"; -tomy = "to cut"). When more than a few drops of blood are required, phlebotomists perform a venipuncture, typically of a surface vein in the arm. They perform a capillary stick on a finger, an earlobe, or the heel of an infant when only a small quantity of blood is required. An arterial stick is collected from an artery and used to analyze blood gases. After collection, the blood may be analyzed by medical laboratories or perhaps used for transfusions, donations, or research. While many allied health professionals practice phlebotomy, the American Society of Phlebotomy Technicians issues certificates to individuals passing a national examination, and some large labs and hospitals hire individuals expressly for their skill in phlebotomy.

Medical or clinical laboratories employ a variety of individuals in technical positions:

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor's degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT) typically have an associate's degree but may perform duties similar to those of an MT.
- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

In Canada, the distinction is only between MLT & MLA. Medical Laboratory Technologists hold a certification with CSMLS. It is not necessary to have a bachelor's with this certification, although many do. In BC, there's not a distinction between MT and MLT – they're all considered MLTs. Other provinces I'm not sure about. Medical Laboratory Assistants may perform a very, very limited range of simple tests but may not work doing complex testing in a clinical lab. They're usually tasked with doing things like phelebotomy and accessioning samples.

It's a little different in the US. There the distinction is between a Medical Laboratory Scientist (previously Medical Laboratory Technologist) who has passed the ASCP certifying exam and a Medical Laboratory Technician who has not. There was a LOT of confusion between Technologist/Technician which is why the Technologist name changed recently. The MLS does work similar to that of an MLT in Canada while the MLT does work similar to that of an MLA. There is a sub-category of people who have completed a Med Lab Sciences program (degree/diploma/certification) of some kind but who have not passed the ASCP – they're not common and can do certain limited kinds of complex lab testing but must be supervised by someone with ASCP certification and can't release results. They're considered to be MLSs.

Simple vs. complex testing is defined by CLSI standards.

Section Review

Blood is a fluid connective tissue critical to the transportation of nutrients, gases, and wastes throughout the body;

to defend the body against infection and other threats; and to the homeostatic regulation of pH, temperature, and other internal conditions. Blood is composed of formed elements—erythrocytes, leukocytes, and cell fragments called platelets—and a fluid extracellular matrix called plasma. More than 90 percent of plasma is water. The remainder is mostly plasma proteins—mainly albumin, globulins, and fibrinogen—and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases. Because of the formed elements and the plasma proteins and other solutes, blood is sticky and more viscous than water. It is also slightly alkaline, and its temperature is slightly higher than normal body temperature.

Review Questions

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Adaption

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Production of the Mature Blood Cells (Formed Elements)

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Trace the generation of the formed elements of blood from bone marrow stem cells.
- Discuss the role of hemopoietic growth factors in promoting the production of the formed elements.

The lifespan of the formed elements is very brief. Although one type of leukocyte called memory cells can survive for years, most erythrocytes, leukocytes, and platelets normally live only a few hours to a few weeks. Thus, the body must form new blood cells and platelets quickly and continuously. When you donate a unit of blood during a blood drive (approximately 475 mL, or about 1 pint), your body typically replaces the donated plasma within 24 hours, but it takes about 4 to 6 weeks to replace the blood cells. This restricts the frequency with which donors can contribute their blood. The process by which this replacement occurs is called hemopoiesis, or hematopoiesis (from the Greek root haima- = "blood"; -poiesis = "production").

Sites of Hemopoiesis

Prior to birth, hemopoiesis occurs in a number of tissues, beginning with the yolk sac of the developing embryo, and continuing in the fetal liver, spleen, lymphatic tissue, and eventually the red bone marrow. Following birth, most hemopoiesis occurs in the red marrow, a connective tissue within the spaces of spongy (cancellous) bone tissue. In children, hemopoiesis can occur in the medullary cavity of long bones; in adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

The end product of hemopoiesis are mature blood cells: red blood cells (erythrocytes), white blood cells (leukocytes), and thrombocytes (platelets). Because platelets are actually pieces of cellular material (lacking nuclei and organelles), it technically isn't a cell. Hence, some refer to mature blood cells as 'formed elements' which helps reflect platelets can't be classified as a cell.

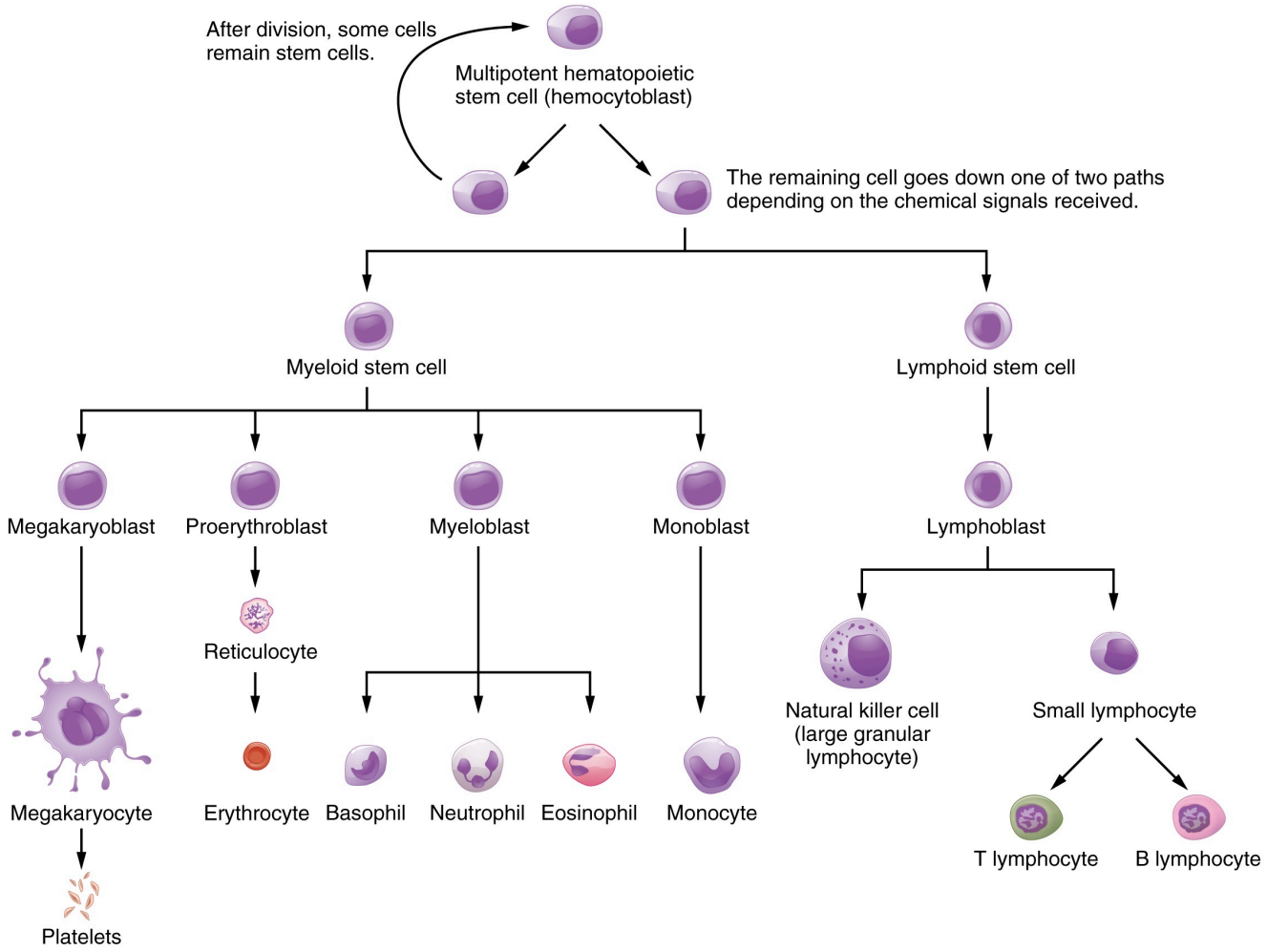
Throughout adulthood, the liver and spleen maintain their ability to generate mature blood cells. This process is referred to as extramedullary hemopoiesis (meaning hemopoiesis outside the medullary cavity of adult bones). When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

Differentiation of Mature Blood Cells (Formed Elements) from Stem Cells

All mature blood cells (formed elements) arise from stem cells of the red bone marrow. Recall that stem cells undergo mitosis plus cytokinesis (cellular division) to give rise to new daughter cells: One of these remains a stem cell and the other differentiates into one of any number of diverse cell types. Stem cells may be viewed as occupying a hierarchal system, with some loss of the ability to diversify at each step. The totipotent stem cell is the zygote, or fertilized egg. The totipotent (toti- = "all") stem cell gives rise to all cells of the human body. The next level is the pluripotent stem cell, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes. Beneath this level, the mesenchymal cell is a stem cell that develops only into types of connective tissue, including fibrous connective tissue, bone, cartilage, and blood, but not epithelium, muscle, and nervous tissue. One step lower on the hierarchy of stem cells is the hematopoietic stem cell, or hemocytoblast. All of the mature blood cells (formed elements) of blood originate from this specific type of cell.

Hemopoiesis begins when the hematopoietic stem cell is exposed to appropriate chemical stimuli collectively called hemopoietic growth factors, which prompt it to divide and differentiate. One daughter cell remains a hematopoietic stem cell, allowing hemopoiesis to continue. The other daughter cell becomes either of two types of more specialized stem cells, shown in this figure:

- Lymphoid stem cells give rise to a class of leukocytes known as lymphocytes, which include the various T cells, B cells, and natural killer (NK) cells, all of which function in immunity. However, hemopoiesis of lymphocytes progresses somewhat differently from the process for the other formed elements. In brief, lymphoid stem cells quickly migrate from the bone marrow to lymphatic tissues, including the lymph nodes, spleen, and thymus, where their production and differentiation continues. B cells are so named since they mature in the bone marrow, while T cells mature in the thymus.
- Myeloid stem cells give rise to all the other formed elements, including the erythrocytes; megakaryocytes that produce platelets; and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes: neutrophils, eosinophils, and basophils.



Hematopoietic System of Bone Marrow – *Hemopoiesis is the proliferation and differentiation of the formed elements of blood.*

Lymphoid and myeloid stem cells do not immediately divide and differentiate into mature formed elements. As you can see in the figure above, there are several intermediate stages of precursor cells (literally, forerunner cells), many of which can be recognized by their names, which have the suffix -blast. For instance, megakaryoblasts are the precursors of megakaryocytes, and proerythroblasts become reticulocytes, which eject their nucleus and most other organelles before maturing into erythrocytes.

Hemopoietic Growth Factors

Development from stem cells to precursor cells to mature cells is again initiated by hemopoietic growth factors. These include the following:

- Erythropoietin (EPO) is a glycoprotein hormone secreted by the interstitial fibroblast cells of the kidneys in response to low oxygen levels. It prompts the production of erythrocytes. Some athletes use synthetic EPO as a performance-enhancing drug (called blood doping) to increase RBC counts and subsequently increase oxygen delivery to tissues throughout the body. EPO is a banned substance in most organized sports, but it is also used

medically in the treatment of certain anemia, specifically those triggered by certain types of cancer, and other disorders in which increased erythrocyte counts and oxygen levels are desirable.

- Thrombopoietin, another glycoprotein hormone, is produced by the liver and kidneys. It triggers the development of megakaryocytes into platelets.
- Cytokines are glycoproteins secreted by a wide variety of cells, including red bone marrow, leukocytes, macrophages, fibroblasts, and endothelial cells. They act locally as autocrine or paracrine factors, stimulating the proliferation of progenitor cells and helping to stimulate both nonspecific and specific resistance to disease. There are two major subtypes of cytokines known as colony-stimulating factors and interleukins.
    - Colony-stimulating factors (CSFs) are glycoproteins that act locally, as autocrine or paracrine factors. Some trigger the differentiation of myeloblasts into granular leukocytes, namely, neutrophils, eosinophils, and basophils. These are referred to as granulocyte CSFs. A different CSF induces the production of monocytes, called monocyte CSFs. Both granulocytes and monocytes are stimulated by GM-CSF; granulocytes, monocytes, platelets, and erythrocytes are stimulated by multi-CSF. Synthetic forms of these hormones are often administered to patients with various forms of cancer who are receiving chemotherapy to revive their WBC counts.
    - Interleukins are another class of cytokine signaling molecules important in hemopoiesis. They were initially thought to be secreted uniquely by leukocytes and to communicate only with other leukocytes, and were named accordingly, but are now known to be produced by a variety of cells including those from the bone marrow and the endothelium. Researchers now suspect that interleukins may play other roles in body functioning, including the differentiation and maturation of cells, along with the production of immunity and inflammation. To date, more than a dozen interleukins have been identified, with others likely to follow. They are generally numbered IL-1, IL-2, IL-3, etc.

Bone Marrow Sampling and Transplants

Sometimes, a healthcare provider will order a bone marrow biopsy, a diagnostic test of a sample of red bone marrow, or a bone marrow transplant, a treatment in which a donor's healthy bone marrow—and its stem cells—replaces the faulty bone marrow of a patient. These tests and procedures are often used to assist in the diagnosis and treatment of various severe forms of anemia, such as thalassemia major and sickle cell anemia, as well as some types of cancer, specifically leukemia.

In the past, when a bone marrow sample or transplant was necessary, the procedure would have required inserting a large-bore needle into the region near the iliac crest of the pelvic bones (os coxae). This location was preferred, since its location close to the body surface makes it more accessible, and it is relatively isolated from most vital organs. Unfortunately, the procedure is quite painful.

Now, direct sampling of bone marrow can often be avoided. In many cases, stem cells can be isolated in just a few hours from a sample of a patient's blood. The isolated stem cells are then grown in culture using the appropriate hemopoietic growth factors, and analyzed or sometimes frozen for later use.

For an individual requiring a transplant, a matching donor is essential to prevent the immune system from destroying the donor cells—a phenomenon known as tissue rejection. To treat patients with bone marrow transplants, it is first necessary to destroy the patient's own diseased marrow through radiation and/or chemotherapy. Donor bone marrow stem cells are then intravenously infused. From the bloodstream, they establish themselves in the recipient's bone marrow.

Everyday connection

Blood Doping

In its original intent, the term blood doping was used to describe the practice of injecting by transfusion supplemental RBCs into an individual, typically to enhance performance in a sport. Additional RBCs would deliver more oxygen to the tissues, providing extra aerobic capacity, clinically referred to as VO_2 max. The source of the cells was either from the recipient (autologous) or from a donor with compatible blood (homologous). This practice was aided by the well-developed techniques of harvesting, concentrating, and freezing of the RBCs that could be later thawed and injected, yet still retain their functionality. These practices are considered illegal in virtually all sports and run the risk of infection, significantly increasing the viscosity of the blood and the potential for transmission of blood-borne pathogens if the blood was collected from another individual.

With the development of synthetic EPO in the 1980s, it became possible to provide additional RBCs by artificially stimulating RBC production in the bone marrow. Originally developed to treat patients suffering from anemia, renal failure, or cancer treatment, large quantities of EPO can be generated by recombinant DNA technology. Synthetic EPO is injected under the skin and can increase hematocrit for many weeks. It may also induce polycythemia and raise hematocrit to 70 or greater. This increased viscosity raises the resistance of the blood and forces the heart to pump more powerfully; in extreme cases, it has resulted in death. Other drugs such as cobalt II chloride have been shown to increase natural EPO gene expression. Blood doping has become problematic in many sports, especially cycling. Lance Armstrong, winner of seven Tour de France and many other cycling titles, was stripped of his victories and admitted to blood doping in 2013.

Section Review

Through the process of hemopoiesis, the mature blood cells (formed elements) are continually produced, replacing the relatively short-lived erythrocytes, leukocytes, and platelets. Hemopoiesis begins in the red bone marrow, with hematopoietic stem cells that differentiate into myeloid and lymphoid lineages. Myeloid stem cells give rise to most of the formed elements. Lymphoid stem cells give rise only to the various lymphocytes designated as B and T cells, and NK cells. Hemopoietic growth factors, including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins, promote the proliferation and differentiation of mature blood cells (formed elements).

Review Questions

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Erythrocytes

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the anatomy of erythrocytes.
- Discuss the various steps in the lifecycle of an erythrocyte.
- Explain the composition and function of hemoglobin.

The erythrocyte, commonly known as a red blood cell (or RBC), is by far the most common mature blood cell: A single drop of blood contains millions of erythrocytes and just thousands of leukocytes. Specifically, males have about 5.4 million erythrocytes per microliter (μL) of blood, and females have approximately 4.8 million per μL. In fact, erythrocytes are estimated to make up about 25 percent of the total cells in the body. As you can imagine, they are quite small cells, with a mean diameter of only about 7–8 micrometers (μm). The primary functions of erythrocytes are to pick up inhaled oxygen from the lungs and transport it to the body's tissues, and to pick up some (about 24 percent) carbon dioxide waste at the tissues and transport it to the lungs for exhalation. Erythrocytes remain within the vascular network. Although leukocytes typically leave the blood vessels to perform their defensive functions, movement of erythrocytes from the blood vessels is abnormal.

Mature blood cell (Formed element)	Major subtypes	Numbers present per microliter (uL) and mean (range)	Appearance in a standard blood smear	Summary of functions	Comments
Erythrocytes (red blood cells)		5.2 million (4.4-6.0 million)	Flattened biconcave disk; no nucleus; pale red color	Transport oxygen and some carbon dioxide between tissues and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)		7000 (5000-10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes including neutrophils, eosinophils, and basophils	4360 (1800-9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils	4150 (1800-7300)	Nuclear lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
	Eosinophils	165 (0-700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen-antibody complexes. Release antihistamines. Increase in allergies and parasitic infections	Lifespan of minutes to days
	Basophils	44 (0-150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Promotes inflammation	Least common leukocyte; lifespan unknown
	Agranulocytes including lymphocytes and monocytes	2640 (1700-4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes	2185 (1500-4000)	Spherical cells with a single often large nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes	455 (200-950)	Largest leukocyte with an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system	Produced in red bone marrow; referred to as macrophages after leaving circulation

Thrombocytes (platelets)	350,000 (150,000-500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; purple stain	Hemostasis plus release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

Summary of Mature Blood Cells (Formed Elements)

Shape and Structure of Erythrocytes

As an erythrocyte matures in the red bone marrow, it extrudes its nucleus and most of its other organelles. Because it is missing a nucleus and organelles, some do not consider erythrocytes a cell and refer to them being "formed elements of the blood".

During the first day or two that it is in the circulation, an immature erythrocyte, known as a reticulocyte, will still typically contain remnants of organelles. Reticulocytes should comprise approximately 1–2 percent of the erythrocyte count and provide a rough estimate of the rate of RBC production, with abnormally low or high rates indicating deviations in the production of these cells. However, these remnants (primarily of networks, or reticula, of ribosomes) are quickly shed. Mature, circulating erythrocytes have few internal cellular structural components. Lacking mitochondria, for example, they rely on anaerobic respiration. This means that they do not utilize any of the oxygen they are transporting, so they can deliver it all to the tissues. They also lack endoplasmic reticula and do not synthesize proteins. Erythrocytes do, however, contain some structural proteins that help the blood cells maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

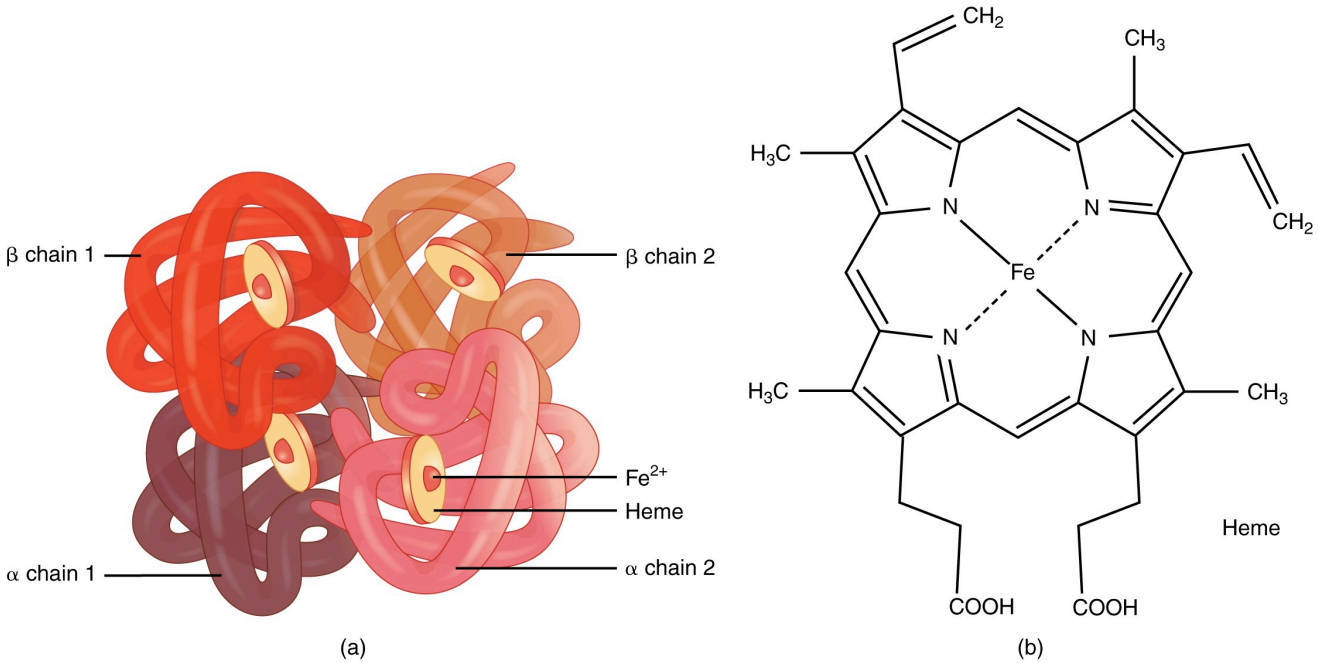
Erythrocytes are biconcave disks; that is, they are plump at their periphery and very thin in the center, as shown in this image. Since they lack most organelles, there is more interior space for the presence of the hemoglobin molecules that, as you will see shortly, transport gases. The biconcave shape also provides a greater surface area across which gas exchange can occur, relative to its volume; a sphere of a similar diameter would have a lower surface area-to-volume ratio. In the capillaries, the oxygen carried by the erythrocytes can diffuse into the plasma and then through the capillary walls to reach the cells, whereas some of the carbon dioxide produced by the cells as a waste product diffuses into the capillaries to be picked up by the erythrocytes. Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur. However, the space within capillaries can be so minute that, despite their own small size, erythrocytes may have to fold in on themselves if they are to make their way through. Fortunately, their structural proteins like spectrin are flexible, allowing them to bend over themselves to a surprising degree, then spring back again when they enter a wider vessel. In wider vessels, erythrocytes may stack up much like a roll of coins, forming a rouleaux (French word for "roll").



Shape of Red Blood Cells *Erythrocytes are biconcave discs with very shallow centers. This shape optimizes the ratio of surface area to volume, facilitating gas exchange. It also enables them to fold up as they move through narrow blood vessels.*

Hemoglobin

Hemoglobin is a large molecule made up of proteins and iron. It consists of four folded chains of a protein called globin, designated alpha 1 and 2, and beta 1 and 2 (diagram on the left). Each of these globin molecules is bound to a red pigment molecule called heme, which contains an ion of iron (Fe^{2+}) (compound structure on the right).



Hemoglobin *(a) A molecule of hemoglobin contains four globin proteins, each of which is bound to one molecule of the iron-containing pigment heme. (b) A single erythrocyte can contain 300 million hemoglobin molecules, and thus more than 1 billion oxygen molecules.*

Each iron ion in the heme can bind to one oxygen molecule; therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and therefore can bind to and transport up to 1.2 billion oxygen molecules.

In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming oxyhemoglobin. The bright red, oxygenated hemoglobin travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red deoxyhemoglobin, sometimes referred to as reduced hemoglobin. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely if ever leaves all of its oxygen behind. In the capillaries, carbon dioxide enters the bloodstream. About 76 percent dissolves in the plasma, some of it remaining as dissolved CO_2, and the remainder forming bicarbonate ion. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as carbaminohemoglobin. From the capillaries, the hemoglobin carries carbon dioxide back to the lungs, where it releases it for exchange of oxygen.

Changes in the levels of RBCs can have significant effects on the body's ability to effectively deliver oxygen to the tissues. Ineffective hematopoiesis results in insufficient numbers of RBCs and results in one of several forms of anemia. An overproduction of RBCs produces a condition called polycythemia. The primary drawback with polycythemia is not a failure to directly deliver enough oxygen to the tissues, but rather the increased viscosity of the blood, which makes it more difficult for the heart to circulate the blood.

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen, resulting in another form of anemia. In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of hemoglobin sites occupied by oxygen in a patient's blood. Clinically this value is commonly referred to simply as "percent sat."

Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient's finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect hypoxemia, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply P_{O2} or PO2 and is typically recorded in units of millimeters of mercury, mm Hg.

The kidneys filter about 180 liters (~380 pints) of blood in an average adult each day, or about 20 percent of the total resting volume, and thus serve as ideal sites for receptors that determine oxygen saturation. In response to hypoxemia, less oxygen will exit the vessels supplying the kidney, resulting in hypoxia (low oxygen concentration) in the tissue fluid of the kidney where oxygen concentration is actually monitored. Interstitial fibroblasts within the kidney secrete EPO, thereby increasing erythrocyte production and restoring oxygen levels. In a classic negative-feedback loop, as oxygen saturation rises, EPO secretion falls, and vice versa, thereby maintaining homeostasis. Populations dwelling at high elevations, with inherently lower levels of oxygen in the atmosphere, naturally maintain a hematocrit higher than people living at sea level. Consequently, people traveling to high elevations may experience symptoms of hypoxemia, such as fatigue, headache, and shortness of breath, for a few days after their arrival. In response to the hypoxemia, the kidneys secrete EPO to step up the production of erythrocytes until homeostasis is achieved once again. To avoid the symptoms of hypoxemia, or altitude sickness, mountain climbers typically rest for several days to a week or more at a series of camps situated at increasing elevations to allow EPO levels and, consequently, erythrocyte counts to rise. When climbing the tallest peaks, such as Mt. Everest and K2 in the Himalayas, many mountain climbers rely upon bottled oxygen as they near the summit.

Lifecycle of Erythrocytes

Production of erythrocytes in the marrow occurs at the staggering rate of more than 2 million cells per second. For this production to occur, a number of raw materials must be present in adequate amounts. These include the same nutrients that are essential to the production and maintenance of any cell, such as glucose, lipids, and amino acids. However, erythrocyte production also requires several trace elements:

- Iron. We have said that each heme group in a hemoglobin molecule contains an ion of the trace mineral iron. On average, less than 20 percent of the iron we consume is absorbed. Heme iron, from animal foods such as meat, poultry, and fish, is absorbed more efficiently than non-heme iron from plant foods. Upon absorption, iron becomes part of the body's total iron pool. The bone marrow, liver, and spleen can store iron in the protein compounds ferritin and hemosiderin. Ferroportin transports the iron across the intestinal cell plasma membranes and from its storage sites into tissue fluid where it enters the blood. When EPO stimulates the production of erythrocytes, iron is released from storage, bound to transferrin, and carried to the red marrow where it attaches to erythrocyte precursors.
- Copper. A trace mineral, copper is a component of two plasma proteins, hephaestin and ceruloplasmin. Without these, hemoglobin could not be adequately produced. Located in intestinal villi, hephaestin enables iron to be absorbed by intestinal cells. Ceruloplasmin transports copper. Both enable the oxidation of iron from Fe^{2+} to Fe^{3+}, a form in which it can be bound to its transport protein, transferrin, for transport to body cells. In a state of copper deficiency, the transport of iron for heme synthesis decreases, and iron can accumulate in tissues, where it can eventually lead to organ damage.
- Zinc. The trace mineral zinc functions as a co-enzyme that facilitates the synthesis of the heme portion of hemoglobin.
- B vitamins. The B vitamins folate and vitamin B_{12} function as co-enzymes that facilitate DNA synthesis. Thus, both are critical for the synthesis of new cells, including erythrocytes.

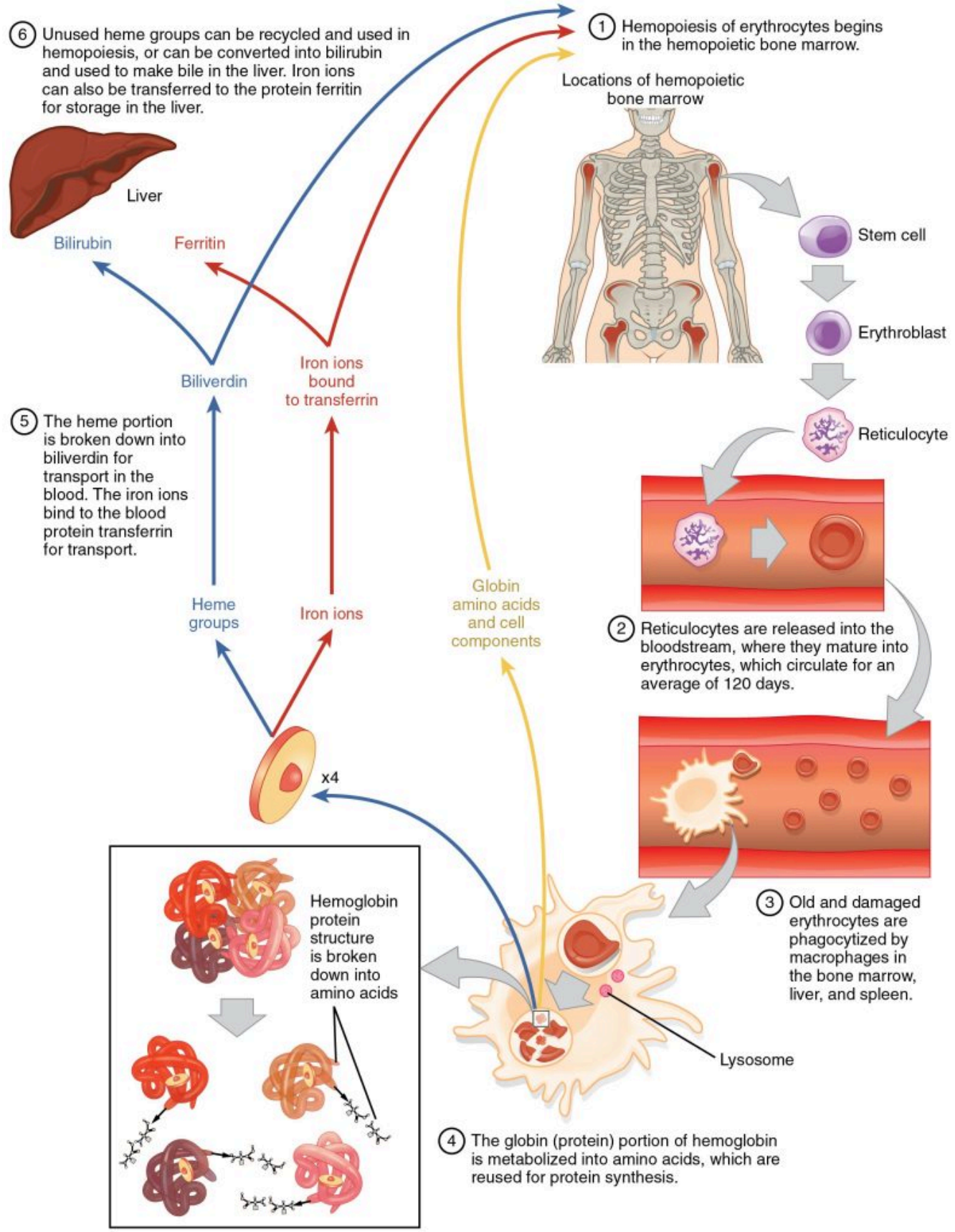
Erythrocytes live up to 120 days in the circulation, after which the worn-out cells are removed by a type of myeloid phagocytic cell called a macrophage, located primarily within the bone marrow, liver, and spleen. The components of the degraded erythrocytes' hemoglobin are further processed as follows:

- Globin, the protein portion of hemoglobin, is broken down into amino acids, which can be sent back to the bone marrow to be used in the production of new erythrocytes. Hemoglobin that is not phagocytized is broken down in the circulation, releasing alpha and beta chains that are removed from circulation by the kidneys.
- The iron contained in the heme portion of hemoglobin may be stored in the liver or spleen, primarily in the form of ferritin or hemosiderin, or carried through the bloodstream by transferrin to the red bone marrow for recycling into new erythrocytes.
- The non-iron portion of heme is degraded into the waste product biliverdin, a green pigment, and then into another waste product, bilirubin, a yellow pigment. Bilirubin binds to albumin and travels in the blood to the liver, which uses it in the manufacture of bile, a compound released into the intestines to help emulsify dietary fats. In the large intestine, bacteria breaks the bilirubin apart from the bile and converts it to urobilinogen and then into stercobilin. It is then eliminated from the body in the feces. Broad-spectrum antibiotics typically eliminate these bacteria as well and may alter the color of feces. The kidneys also remove any circulating bilirubin and other related metabolic byproducts such as urobilins and secrete them into the urine.

The breakdown pigments formed from the destruction of hemoglobin can be seen in a variety of situations. At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colors associated with a bruise. With a failing liver, bilirubin cannot be removed effectively from circulation and causes the body to assume a yellowish tinge

associated with jaundice. Stercobilins within the feces produce the typical brown color associated with this waste. And the yellow of urine is associated with the urobilins.

The erythrocyte lifecycle is summarized here.



Erythrocyte Lifecycle – *Erythrocytes are produced in the bone marrow and sent into the circulation. At the end of their lifecycle, they are destroyed by macrophages, and their components are recycled.*

Disorders of Erythrocytes

The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person's health. When the number of RBCs or hemoglobin is deficient, the general condition is called anemia. There are more than 400 types of anemia and more than 3.5 million Americans suffering from this condition. Anemia can be broken down into three major groups: those caused by blood loss, those caused by faulty or decreased RBC production, and those caused by excessive destruction of RBCs. Clinicians often use two groupings in diagnosis: the kinetic approach focuses on evaluating the production, destruction, and removal of RBCs, whereas the morphological approach examines the RBCs themselves, paying particular emphasis to their size. A common test is the mean corpuscle volume (MCV), which measures size. Normal-sized cells are referred to as normocytic, smaller-than-normal cells are referred to as microcytic, and larger-than-normal cells are referred to as macrocytic. Reticulocyte counts are also important and may reveal inadequate production of RBCs. The effects of the various anemias are widespread, because reduced numbers of RBCs or hemoglobin will result in lower levels of oxygen being delivered to body tissues. Since oxygen is required for tissue functioning, anemia produces fatigue, lethargy, and an increased risk for infection. An oxygen deficit in the brain impairs the ability to think clearly, and may prompt headaches and irritability. Lack of oxygen leaves the patient short of breath, even as the heart and lungs work harder in response to the deficit.

Blood loss anemias are fairly straightforward. In addition to bleeding from wounds or other lesions, these forms of anemia may be due to ulcers, hemorrhoids, inflammation of the stomach (gastritis), and some cancers of the gastrointestinal tract. The excessive use of aspirin or other nonsteroidal anti-inflammatory drugs such as ibuprofen can trigger ulceration and gastritis. Excessive menstruation and loss of blood during childbirth are also potential causes.

Anemias caused by faulty or decreased RBC production include sickle cell anemia, iron deficiency anemia, vitamin deficiency anemia, and diseases of the bone marrow and stem cells.

- A characteristic change in the shape of erythrocytes is seen in sickle cell disease (also referred to as sickle cell anemia). A genetic disorder, it is caused by production of an abnormal type of hemoglobin, called hemoglobin S, which delivers less oxygen to tissues and causes erythrocytes to assume a sickle (or crescent) shape, especially at low oxygen concentrations (see the image below). These abnormally shaped cells can then become lodged in narrow capillaries because they are unable to fold in on themselves to squeeze through, blocking blood flow to tissues and causing a variety of serious problems from painful joints to delayed growth and even blindness and cerebrovascular accidents (strokes). Sickle cell anemia is a genetic condition particularly found in individuals of African descent.



Sickle Cells *– Sickle cell anemia is caused by a mutation in one of the hemoglobin genes. Erythrocytes produce an abnormal type of hemoglobin, which causes the cell to take on a sickle or crescent shape. (credit: Janice Haney Carr)*

- Iron deficiency anemia is the most common type and results when the amount of available iron is insufficient to allow production of sufficient heme. This condition can occur in individuals with a deficiency of iron in the diet and is especially common in teens and children as well as in vegans and vegetarians. Additionally, iron deficiency anemia may be caused by either an inability to absorb and transport iron or slow, chronic bleeding.
- Vitamin-deficient anemias generally involve insufficient vitamin B12 and folate.

    - Megaloblastic anemia involves a deficiency of vitamin B12 and/or folate, and often involves diets deficient in these essential nutrients. Lack of meat or a viable alternate source, and overcooking or eating insufficient amounts of vegetables may lead to a lack of folate.
    - Pernicious anemia is caused by poor absorption of vitamin B12 and is often seen in patients with Crohn's disease (a severe intestinal disorder often treated by surgery), surgical removal of the intestines or stomach (common in some weight loss surgeries), intestinal parasites, and AIDS.
    - Pregnancies, certain medications, excessive alcohol consumption, and some diseases such as celiac disease are also associated with vitamin deficiencies. It is essential to provide sufficient folic acid during the early stages of pregnancy to reduce the risk of neurological defects, including spina bifida, a failure of the neural tube to close.

- Assorted disease processes can also interfere with the production and formation of RBCs and hemoglobin. If myeloid stem cells are defective or replaced by cancer cells, there will be insufficient quantities of RBCs produced.

    - Aplastic anemia is the condition in which there are deficient numbers of RBC stem cells. Aplastic anemia is often inherited, or it may be triggered by radiation, medication, chemotherapy, or infection.
    - Thalassemia is an inherited condition typically occurring in individuals from the Middle East, the Mediterranean, African, and Southeast Asia, in which maturation of the RBCs does not proceed normally. The most severe form is called Cooley's anemia.
    - Lead exposure from industrial sources or even dust from paint chips of iron-containing paints or pottery that has not been properly glazed may also lead to destruction of the red marrow.

- Various disease processes also can lead to anemias. These include chronic kidney diseases often associated with a decreased production of EPO, hypothyroidism, certain cancers, lupus, and rheumatoid arthritis.

In contrast to anemia, an elevated RBC count is called polycythemia and is detected in a patient's elevated hematocrit. It can occur transiently in a person who is dehydrated; when water intake is inadequate or water losses are excessive, the plasma volume falls. As a result, the hematocrit rises. For reasons mentioned earlier, a mild form of polycythemia is chronic but normal in people living at high altitudes. Some elite athletes train at high elevations specifically to induce this phenomenon. Finally, a type of bone marrow disease called polycythemia vera (from the Greek vera = "true") causes an excessive production of immature erythrocytes. Polycythemia vera can dangerously elevate the viscosity of blood, raising blood pressure and making it more difficult for the heart to pump blood throughout the body. It is a relatively rare disease that occurs more often in men than women, and is more likely to be present in elderly patients over 60 years of age.

Section Review

The most abundant mature blood cell (formed elements), erythrocytes are red, biconcave disks packed with an oxygen-carrying compound called hemoglobin. The hemoglobin molecule contains four globin proteins bound to a pigment molecule called heme, which contains an ion of iron. In the bloodstream, iron picks up oxygen in the lungs and drops it off in the tissues; the amino acids in hemoglobin then transport carbon dioxide from the tissues back to the lungs. Erythrocytes live only 120 days on average, and thus must be continually replaced. Worn-out erythrocytes are phagocytized by macrophages and their hemoglobin is broken down. The breakdown products are recycled or removed as wastes: Globin is broken down into amino acids for synthesis of new proteins; iron is stored in the liver or spleen or

used by the bone marrow for production of new erythrocytes; and the remnants of heme are converted into bilirubin, or other waste products that are taken up by the liver and excreted in the bile or removed by the kidneys. Anemia is a deficiency of RBCs or hemoglobin, whereas polycythemia is an excess of RBCs.

Review Questions

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Leukocytes (White Blood Cells) and Platelets (Thrombocytes)

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the general characteristics of leukocytes.
- Classify leukocytes according to their lineage, main structural features, and primary functions.
- Discuss the most common malignancies involving leukocytes.
- Identify the lineage, basic structure, and function of platelets.

The leukocyte, commonly known as a white blood cell (or WBC), is a major component of the body's defenses against disease. Leukocytes protect the body against invading microorganisms and body cells with mutated DNA. They also clean up debris. Platelets are essential for the repair of blood vessels when damage to them has occurred; they also provide growth factors for healing and repair.

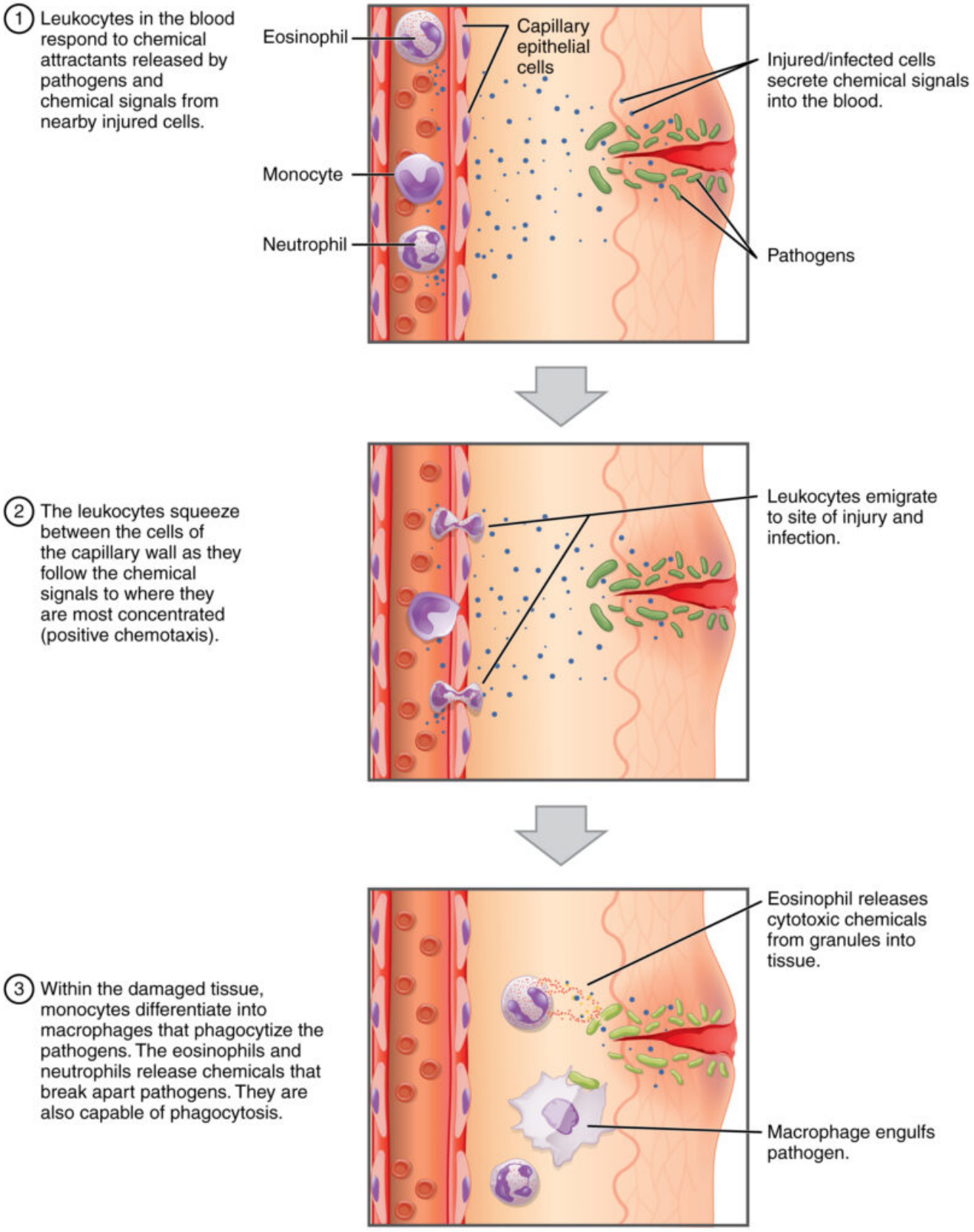
Characteristics of Leukocytes

Although leukocytes and erythrocytes both originate from hematopoietic stem cells in the bone marrow, they are very different from each other in many significant ways. For instance, leukocytes are far less numerous than erythrocytes: Typically there are only 5000 to 10,000 per μL. They are also larger than erythrocytes and are the only mature blood cell (formed elements) that are complete cells, possessing a nucleus and organelles. And although there is just one type of erythrocyte, there are many types of leukocytes. Most of these types have a much shorter lifespan than that of erythrocytes, some as short as a few hours or even a few minutes in the case of acute infection.

One of the most distinctive characteristics of leukocytes is their movement. Whereas erythrocytes spend their days circulating within the blood vessels, leukocytes routinely leave the bloodstream to perform their defensive functions in the body's tissues. For leukocytes, the vascular network is simply a highway they travel and soon exit to reach their true destination. When they arrive, they are often given distinct names, such as macrophage or microglia, depending on their function. As shown in the figure below, they leave the capillaries—the smallest blood vessels—or other small vessels through a process known as emigration (from the Latin for "removal") or diapedesis (dia- = "through"; -pedan = "to leap") in which they squeeze through adjacent cells in a blood vessel wall.

Once they have exited the capillaries, some leukocytes will take up fixed positions in lymphatic tissue, bone marrow, the spleen, the thymus, or other organs. Others will move about through the tissue spaces very much like amoebas, continuously extending their plasma membranes, sometimes wandering freely, and sometimes moving toward the

direction in which they are drawn by chemical signals. This attracting of leukocytes occurs because of positive chemotaxis (literally "movement in response to chemicals"), a phenomenon in which injured or infected cells and nearby leukocytes emit the equivalent of a chemical "911" call, attracting more leukocytes to the site. In clinical medicine, the differential counts of the types and percentages of leukocytes present are often key indicators in making a diagnosis and selecting a treatment.



Emigration – *Leukocytes exit the blood vessel and then move through the connective tissue of the dermis toward the site of a wound. Some leukocytes, such as the eosinophil and neutrophil, are characterized as granular leukocytes. They release chemicals from their granules that destroy pathogens; they are also capable of phagocytosis. The monocyte, an agranular leukocyte, differentiates into a macrophage that then phagocytizes the pathogens.*

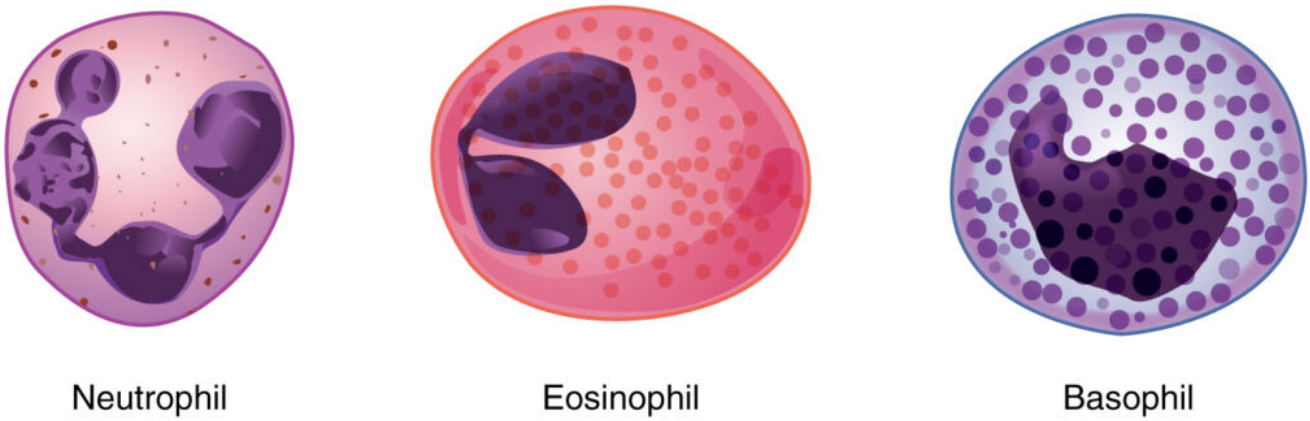
Classification of Leukocytes

When scientists first began to observe stained blood slides, it quickly became evident that leukocytes could be divided into two groups, according to whether their cytoplasm contained highly visible granules:

- Granular leukocytes contain abundant granules within the cytoplasm. They include neutrophils, eosinophils, and basophils (you can view their lineage from myeloid stem cells in here).
- While granules are not totally lacking in agranular leukocytes, they are far fewer and less obvious. Agranular leukocytes include monocytes, which mature into macrophages that are phagocytic, and lymphocytes, which arise from the lymphoid stem cell line.

Granular Leukocytes

We will consider the granular leukocytes in order from most common to least common. All of these are produced in the red bone marrow and have a short lifespan of hours to days. They typically have a lobed nucleus and are classified according to which type of stain best highlights their granules shown below.



Granular Leukocytes – *A neutrophil has small granules that stain light lilac and a nucleus with two to five lobes. An eosinophil's granules are slightly larger and stain reddish-orange, and its nucleus has two to three lobes. A basophil has large granules that stain dark blue to purple and a two-lobed nucleus.*

The most common of all the leukocytes, neutrophils will normally comprise 50–70 percent of total leukocyte count. They are 10–12 μm in diameter, significantly larger than erythrocytes. They are called neutrophils because their granules show up most clearly with stains that are chemically neutral (neither acidic nor basic). The granules are numerous but quite fine and normally appear light lilac. The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell. Older neutrophils have increasing numbers of lobes and are often referred to as polymorphonuclear (a nucleus with many forms), or simply "polys." Younger and immature neutrophils begin to develop lobes and are known as "bands."

Neutrophils are rapid responders to the site of infection and are efficient phagocytes with a preference for bacteria. Their granules include lysozyme, an enzyme capable of lysing, or breaking down, bacterial cell walls; oxidants such as hydrogen peroxide; and defensins, proteins that bind to and puncture bacterial and fungal plasma membranes, so that the cell contents leak out. Abnormally high counts of neutrophils indicate infection and/or inflammation, particularly

triggered by bacteria, but are also found in burn patients and others experiencing unusual stress. A burn injury increases the proliferation of neutrophils in order to fight off infection that can result from the destruction of the barrier of the skin. Low counts may be caused by drug toxicity and other disorders, and may increase an individual's susceptibility to infection.

Eosinophils typically represent 2–4 percent of total leukocyte count. They are also 10–12 μm in diameter. The granules of eosinophils stain best with an acidic stain known as eosin. The nucleus of the eosinophil will typically have two to three lobes and, if stained properly, the granules will have a distinct red to orange color.

The granules of eosinophils include antihistamine molecules, which counteract the activities of histamines, inflammatory chemicals produced by basophils and mast cells. Some eosinophil granules contain molecules toxic to parasitic worms, which can enter the body through the integument, or when an individual consumes raw or undercooked fish or meat. Eosinophils are also capable of phagocytosis and are particularly effective when antibodies bind to the target and form an antigen-antibody complex. High counts of eosinophils are typical of patients experiencing allergies, parasitic worm infestations, and some autoimmune diseases. Low counts may be due to drug toxicity and stress.

Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They are slightly smaller than neutrophils and eosinophils at 8–10 μm in diameter. The granules of basophils stain best with basic (alkaline) stains. Basophils contain large granules that pick up a dark blue stain and are so common they may make it difficult to see the two-lobed nucleus.

In general, basophils intensify the inflammatory response. They share this trait with mast cells. In the past, mast cells were considered to be basophils that left the circulation. However, this appears not to be the case, as the two cell types develop from different lineages.

The granules of basophils release histamines, which contribute to inflammation, and heparin, which opposes blood clotting. High counts of basophils are associated with allergies, parasitic infections, and hypothyroidism. Low counts are associated with pregnancy, stress, and hyperthyroidism.

Agranular Leukocytes

Agranular leukocytes contain smaller, less-visible granules in their cytoplasm than do granular leukocytes. The nucleus is simple in shape, sometimes with an indentation but without distinct lobes. There are two major types of agranulocytes: lymphocytes and monocytes (see this figure).

Lymphocytes are the only mature blood cell that arises from lymphoid stem cells. Although they form initially in the bone marrow, much of their subsequent development and reproduction occurs in the lymphatic tissues. Lymphocytes are the second most common type of leukocyte, accounting for about 20–30 percent of all leukocytes, and are essential for the immune response. The size range of lymphocytes is quite extensive, with some authorities recognizing two size classes and others three. Typically, the large cells are 10–14 μm and have a smaller nucleus-to-cytoplasm ratio and more granules. The smaller cells are typically 6–9 μm with a larger volume of nucleus to cytoplasm, creating a "halo" effect. A few cells may fall outside these ranges, at 14–17 μm. This finding has led to the three size range classification.

The three major groups of lymphocytes include natural killer cells, B cells, and T cells. Natural killer (NK) cells are capable of recognizing cells that do not express "self" proteins on their plasma membrane or that contain foreign or abnormal markers. These "non-self" cells include cancer cells, cells infected with a virus, and other cells with atypical surface proteins. Thus, they provide generalized, nonspecific immunity. The larger lymphocytes are typically NK cells.

B cells and T cells, also called B lymphocytes and T lymphocytes, play prominent roles in defending the body against specific pathogens (disease-causing microorganisms) and are involved in specific immunity. One form of B cells (plasma cells) produces the antibodies or immunoglobulins that bind to specific foreign or abnormal components of plasma membranes. This is also referred to as humoral (body fluid) immunity. T cells provide cellular-level immunity by physically attacking foreign or diseased cells. A memory cell is a variety of both B and T cells that forms after exposure to a pathogen and mounts rapid responses upon subsequent exposures. Unlike other leukocytes, memory cells live for many years. B cells undergo a maturation process in the bone marrow, whereas T cells undergo maturation in the thymus. This site of the maturation process gives rise to the name B and T cells. The functions of lymphocytes are complex and will be covered in detail in the chapter covering the lymphatic system and immunity. Smaller lymphocytes are either B or T cells, although they cannot be differentiated in a normal blood smear.

Abnormally high lymphocyte counts are characteristic of viral infections as well as some types of cancer. Abnormally low lymphocyte counts are characteristic of prolonged (chronic) illness or immunosuppression, including that caused by HIV infection and drug therapies that often involve steroids.

Monocytes originate from myeloid stem cells. They normally represent 2–8 percent of the total leukocyte count. They are typically easily recognized by their large size of 12–20 μm and indented or horseshoe-shaped nuclei. Macrophages are monocytes that have left the circulation. They phagocytize debris, foreign pathogens, worn-out erythrocytes, and many other dead, worn out, or damaged cells. Macrophages also release antimicrobial defensins and chemotactic chemicals that attract other leukocytes to the site of an infection. Some macrophages occupy fixed locations, whereas others wander through the tissue fluid.

Abnormally high counts of monocytes are associated with viral or fungal infections, tuberculosis, and some forms of leukemia and other chronic diseases. Abnormally low counts are typically caused by suppression of the bone marrow.

Lifecycle of Leukocytes

Most leukocytes have a relatively short lifespan, typically measured in hours or days. Production of all leukocytes begins in the bone marrow under the influence of CSFs and interleukins. Secondary production and maturation of lymphocytes occurs in specific regions of lymphatic tissue known as germinal centers. Lymphocytes are fully capable of mitosis and may produce clones of cells with identical properties. This capacity enables an individual to maintain immunity throughout life to many threats that have been encountered in the past.

Disorders of Leukocytes

Leukopenia is a condition in which too few leukocytes are produced. If this condition is pronounced, the individual may be unable to ward off disease. Excessive leukocyte proliferation is known as leukocytosis. Although leukocyte counts are high, the cells themselves are often nonfunctional, leaving the individual at increased risk for disease.

Leukemia is a cancer involving an abundance of leukocytes. It may involve only one specific type of leukocyte from either the myeloid line (myelocytic leukemia) or the lymphoid line (lymphocytic leukemia). In chronic leukemia, mature leukocytes accumulate and fail to die. In acute leukemia, there is an overproduction of young, immature leukocytes. In both conditions the cells do not function properly.

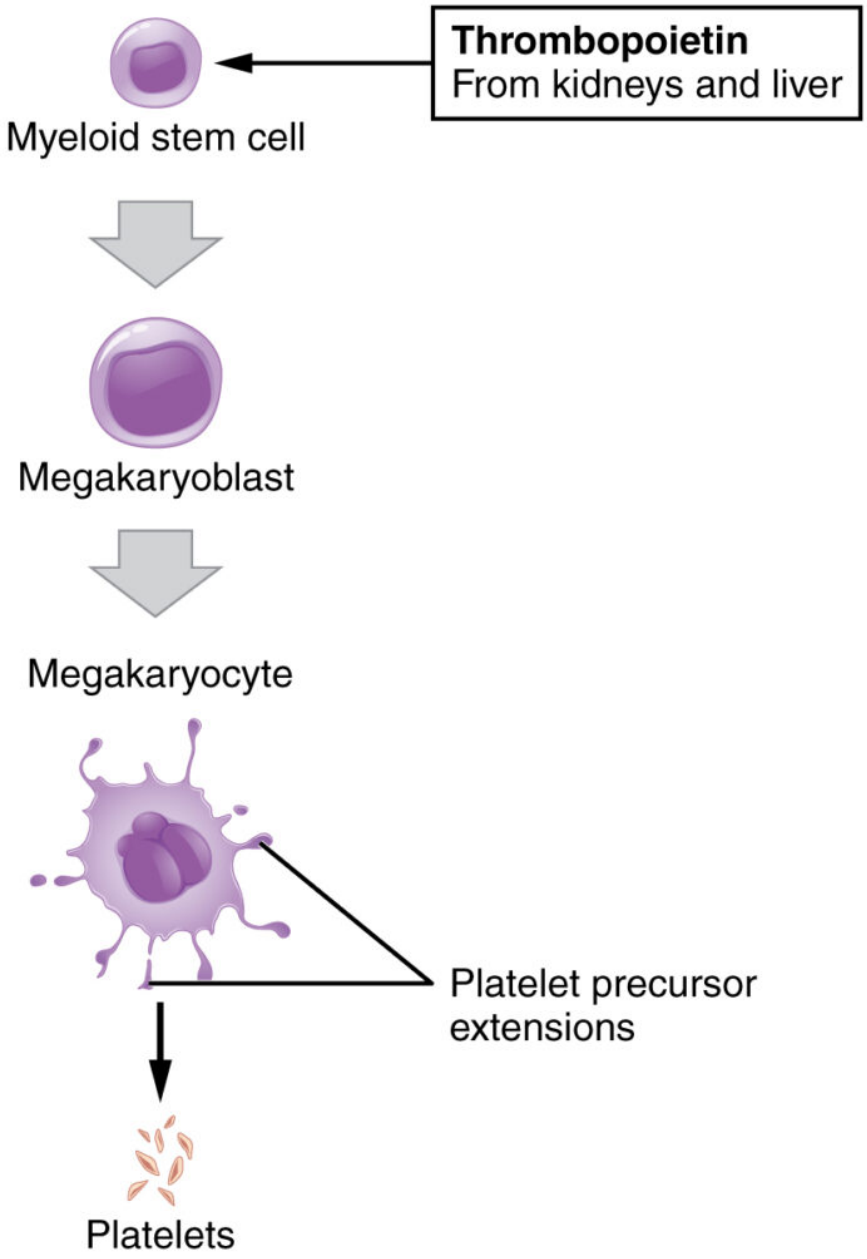
Lymphoma is a form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues. As in leukemia, the malignant leukocytes do not function properly, and the patient is vulnerable to infection. Some forms of lymphoma tend to progress slowly and respond well to treatment. Others tend to progress quickly and require aggressive treatment, without which they are rapidly fatal.

Platelets (Thrombocytes)

You may occasionally see platelets referred to as thrombocytes, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a megakaryocyte that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see this figure) and are large, typically 50–100 μm in diameter, and contain an enlarged, lobed nucleus. As noted earlier, thrombopoietin, a glycoprotein secreted by the kidneys and liver, stimulates the proliferation of megakaryoblasts, which mature into megakaryocytes. These remain within bone marrow tissue and ultimately form platelet-precursor extensions that extend through the walls of bone marrow capillaries to release into the circulation thousands of cytoplasmic fragments, each enclosed by a bit of plasma membrane. These enclosed fragments are platelets. Each megakarocyte releases 2000–3000 platelets during its lifespan. Following platelet release, megakaryocyte remnants, which are little more than a cell nucleus, are consumed by macrophages. This illustration shows the overall platelet maturation steps.

Platelets are relatively small, 2–4 μm in diameter, but numerous, with typically 150,000–160,000 per μL of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.



Platelets – *Platelets are derived from cells called megakaryocytes.*

Disorders of Platelets

Thrombocytosis is a condition in which there are too many platelets. This may trigger formation of unwanted

blood clots (thrombosis), a potentially fatal disorder. If there is an insufficient number of platelets, called thrombocytopenia, blood may not clot properly, and excessive bleeding may result.

Section Review

Leukocytes function in body defenses. They squeeze out of the walls of blood vessels through emigration or diapedesis, then may move through tissue fluid or become attached to various organs where they fight against pathogenic organisms, diseased cells, or other threats to health. Granular leukocytes, which include neutrophils, eosinophils, and basophils, originate with myeloid stem cells, as do the agranular monocytes. The other agranular leukocytes, NK cells, B cells, and T cells, arise from the lymphoid stem cell line. The most abundant leukocytes are the neutrophils, which are first responders to infections, especially with bacteria. About 20–30 percent of all leukocytes are lymphocytes, which are critical to the body's defense against specific threats. Leukemia and lymphoma are malignancies involving leukocytes. Platelets are fragments of cells known as megakaryocytes that dwell within the bone marrow. While many platelets are stored in the spleen, others enter the circulation and are essential for hemostasis; they also produce several growth factors important for repair and healing.

Review Questions



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Adaption

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Normal Histology of Blood

SHING TAT THEODORE LAM AND WILLIAM WANG

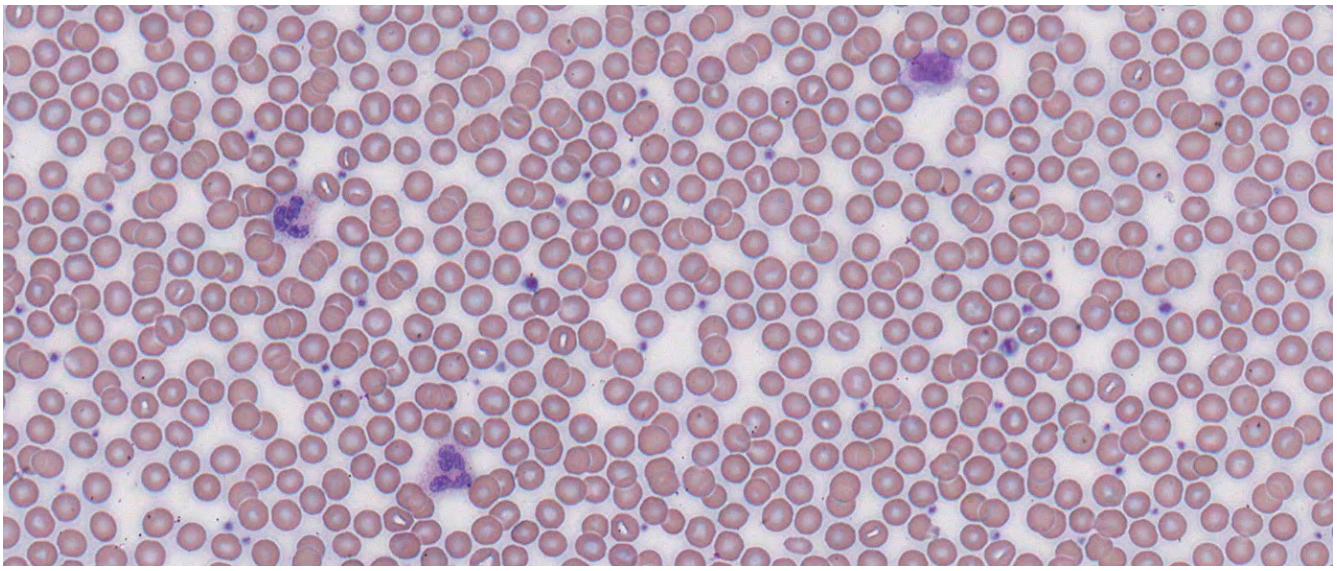
Learning Objectives

By the end of this section, you will be able to

- Rank the relative sizes of red blood cells, platelets, and granulocytes in the peripheral blood.
- Relate the appearance of red blood cells and neutrophils to their morphology and composition.
- Identify the three distinct features in the bone marrow core: trabecular bone, blood cells, adipocytes.
- Define and estimate cellularity based on one's age.
- State the difference between blasts and cytes.
- State key features of the blood cells in the bone marrow: stem cells, blasts, reticulocytes.

The diversity of normal blood cell physiology and anatomy is reflected through microscope images of histological samples from multiple different areas of the human body. This section will introduce said diversity with the assistance of histological images from three regions of interest (ROIs).

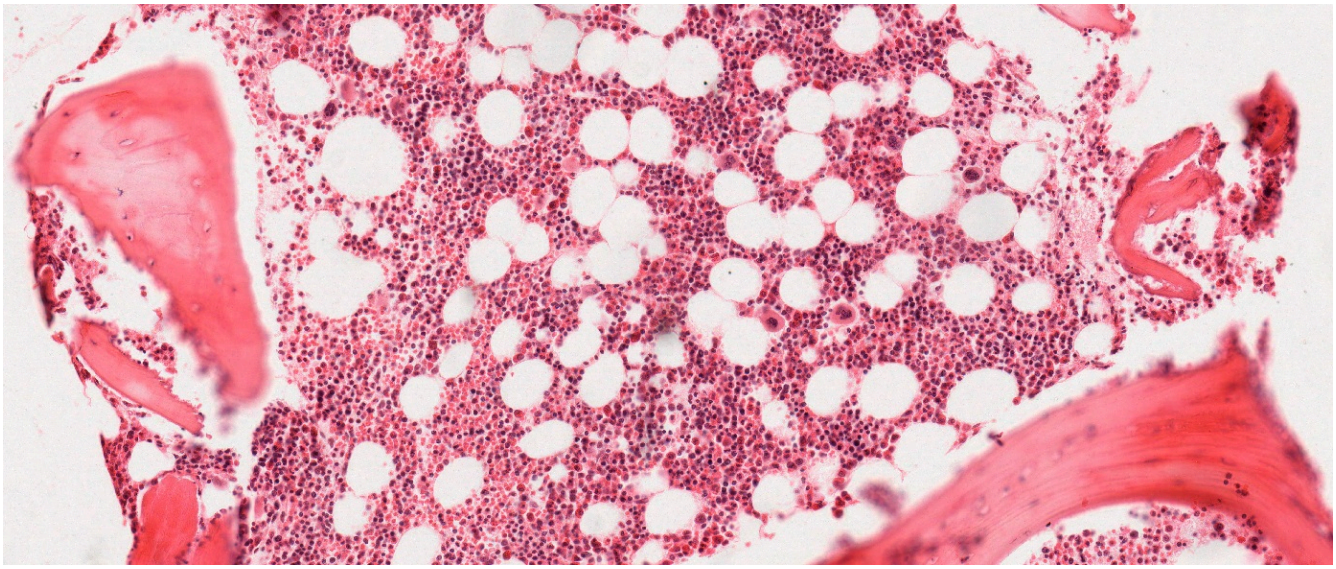
ROI 1 – Peripheral Blood Smear



DHPLC specimen PATH 304-061 *Normal Peripheral Blood Smear at 10x magnification. All rights reserved.*

The image above is derived from a thin peripheral blood smear with normal histology. Contrasting the white background is an overwhelming majority of red blood cells. Mainly responsible for gas exchange, they appear as round red donuts with a white center. This is a reflection of their natural shape: the biconcave disk. Occasionally, the background would be interrupted by purple specks that are much smaller than the red blood cells. Those are platelets, a major component of hemostasis and coagulation. The purple cells that are much larger than the red blood cells are neutrophils, which are characterized by their light purple cytoplasm and dark purple, multi-segmented nuclei. Amongst the leukocytes, cells part of the immune system, neutrophils are present in the blood with the highest concentration, far outnumbering their fellow granulocytes (eosinophils and basophils).

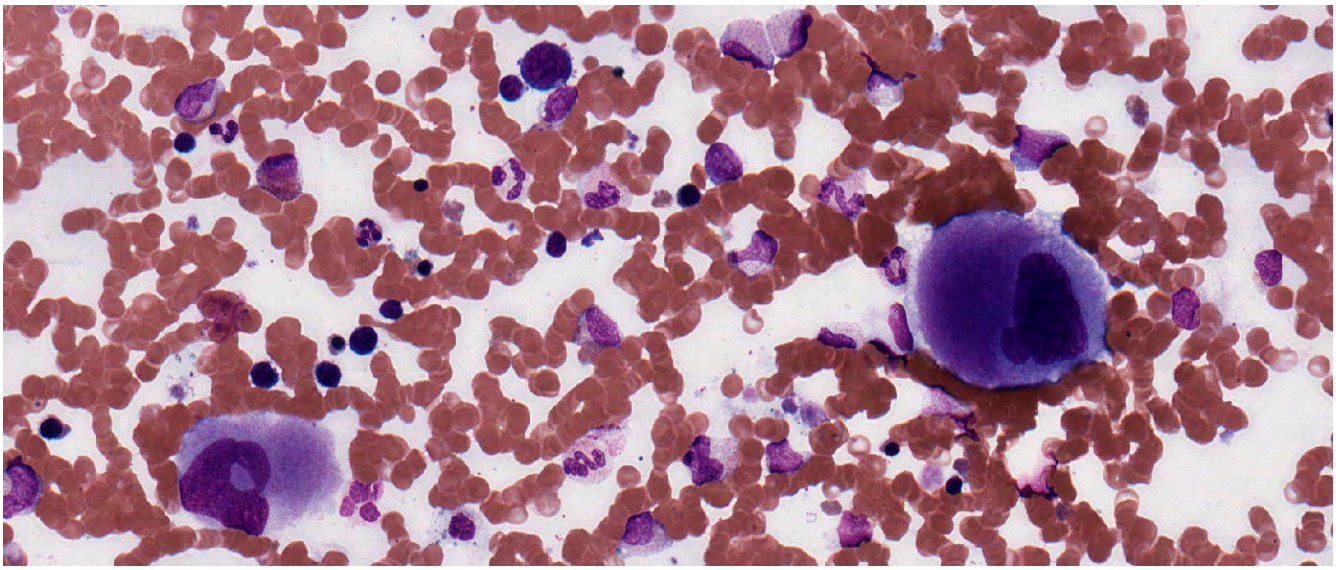
ROI 2- Bone Marrow Core



***DHPLC specimen* PATH 304-207** *Normal Bone Marrow Core. All rights reserved*

Bone marrow biopsies can yield normal histological images of the bone marrow core just like the one above. The trabecular bone is visualized as large, smooth, red patches interwoven amongst the rest of the tissue. In between the trabecular bone is a myriad of light and dark red dots of different sizes and intensities. These are the bone marrow blood stem cells and blasts (young blood cells in earlier stages of development). Dotting these cells are adipocytes (fat storing cells), which appear as large, round patches of emptiness. As one ages, the percentage of cells (also called cellularity) in the bone marrow core decreases and the amount of adipocytes increases. Changes in cellularity can be indicative of many different blood disorders.

ROI 3 – Bone Marrow Smear



DHPLC Specimen PATH 304 207 *Bone Marrow Smear*

In addition to biopsies, smears of bone marrow aspirate (example above) can also provide insight into the normal cellular ecosystem of the bone marrow. Most cells in the bone marrow are blasts (immature cells) as opposed to cytes (mature cells). The small, dark purple cells are the stem cells and the blasts of various leukocytic lineages. They are characterized by their high nucleus/cytoplasm (N/C) ratio as well as their smaller size compared to their mature counterparts. Between the stem cells and the blasts, the blasts are usually larger with a lower N/C ratio. Reticulocytes, immature red blood cells, are also present in abundance in the bone marrow. They are multi-lobular, irregularly shaped red cells that are larger than their mature counterparts. Under a microscope, the most distinctive feature of reticulocytes is the residual cytoplasmic RNA. This gives some reticulocytes dark granules that clearly separates them from the clear center of healthy, mature red blood cells.

Watch the following video lessons of author Theodore Lam looking at normal and peripheral blood smear and bone marrow biopsy.

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Section Review

Circulating blood – or peripheral blood -consists predominantly is full of RBCs, which are easily identified by its biconcave (donut) shape disk with a pale centre. The next most common cell are the larger leukocytes which is easily identified by the dominant purple nucleus with varying amounts of cytoplasm. Periodically, a very small dense purple speck – lacking recognizable organelle or nucleus – are platelets.

Mature blood cells (formed elements) are made in the bone marrow in a healthy adult. An aspirate or bone marrow core biopsy will reveal a mixture of fat cells (adipocytes) and hemopoietic stem cells in varying levels of differentiation, known as blasts. There would be few mature blood cells in marrow as they would normally leave the bone and enter the peripheral circulation. However, early red blood cells (reticulocytes) can be seen but they lack the characteristic biconcave disk with pale centre

Review Questions

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Pathophysiology of Anemia

GHAZAL SOKHANRAN

Learning Objectives

By the end of this section, you will be able to:

- Define anemia and be able to describe the general classification of anemia.
- describe the basic characteristics of anemia.
- Name some signs and symptoms of anemia and be able to explain why they occur.

Anemia is one of the most common hematological diseases, affecting up to 33% of the global population. It is described as a decrease in hemoglobin (Hb) concentration in the blood, below the standard value (i.e. population-based 'normal' range of values) based on the age and gender of an individual. As hemoglobin is transported only in RBCs, a decrease in hemoglobin may also reflect the number of RBCs in circulation.

The Hb concentration is determined by both changes in total circulating plasma volume and total circulating Hb mass. Reduced plasma volume (as in dehydration) may conceal anemia or even induce an abnormally high number of RBCs in the blood (i.e. relative polycythemia); on the other hand, increased plasma volume (as in pregnancy or fluid excess) may cause anemia despite normal total circulating RBC and Hb mass (i.e. dilutional anemia).

Anemia caused by a decrease in circulating Hb – with or without an associated drop in RBC number – will be the focus of this chapter.

General Classification of Anemia

There are two ways to classify anemia: by etiology (i.e. what has caused the anemia) and by morphology of the RBC.

By determining what has caused it (Etiology):

- *Decreased hematopoiesis*. This could be due to:
  - Nutritional deficiencies affecting DNA synthesis or Hb production
  - Bone marrow failure
- *Abnormal hematopoiesis*. Due to errors in progenitor cell formation.
- *Increased loss of* RBCs. Generally, because of a bleeding problem, which could be acute (e.g., trauma) or chronic (e.g., Gastrointestinal bleeding).
  - Keep in mind that anemia does not appear immediately after acute major blood loss because the total blood

volume is reduced. It takes some time (about a day) for plasma volume to be replenished, then the degree of anemia can be assessed. Regeneration of RBCs and Hb mass takes much longer (approximately a week). Therefore, the initial clinical features of major blood loss are a result of the reduction in blood volume rather than of anemia.

- *Increased destruction of* RBCs.
  - Destruction of abnormal RBCs can be due to:
    - Inherited disorders
      - RBC cell membrane disorders, for example, cause the formation of spherocytes (round like a sphere instead of normally donut-shaped RBC), which leads to autoimmune hemolysis
      - Enzyme deficiencies, for example, G6PD deficiency
      - Abnormal Hb production, for example, sickle cell disease
    - Acquired disorders, for instance, with PNH (paroxysmal nocturnal hemoglobinuria)
  - Destruction of normal RBCs can be caused by
    - Immune-mediated, as in immune hemolytic anemia
    - Mechanical problems, for example, with repetitive trauma (hand drummers, marathon runners)
    - Infections such as Malaria
    - Chemical or toxic injury, for example, lead poisoning or snake venom

By morphology and structure:

This is done by assessing the size and shape of erythrocytes (by doing peripheral blood smears) and chemically analyzing Hb and other major constituent proteins of RBCs (through antibody-mediated tests or PCR).

- Upon assessment of the RBC size in the sample, it is then categorized as microcytic (small), normocytic (normal), macrocytic (large)
- Depending on the amount of Hb content which determines the 'colour of RBCs', the sample can be categorized as hypochromic (pale) or normochromic (normal)

Another chapter (Diagnosis of Anemia & Leukemia) will discuss the quantitative measurements of blood components.

Clinical Characteristics of Anemia

Surprisingly, there may be no symptoms nor signs in some patients with relatively severe anemia; whereas, in contrast, others with milder anemia may experience severe effects. To address the anemia, the body compensates for the decreased hemoglobin, and thus decrease oxygen carrying capabilities, by influencing the cardiovascular system: most commonly by increasing stroke volume and **tachycardia**. As well, the body can compensate by shifting the Hb-O2 dissociation curve (i.e. factors that influence how well oxygen can bind to and release from Hb). Thus, the body's ability to compensate for anemia – whether through cardiovascular or Hb-O2 binding adaptation – determines how symptomatic a patient may feel.

Other clinical characteristics can be considered and classified as follows:

1. ***Speed of onset***: As evident as it can be, fast and rapidly progressive anemia leads to more symptoms than anemia of

slow onset because there is less time for changes in the body to occur.

2. ***Severity***: Mild anemia often produces no symptoms or signs, but these are usually present when the Hb is less than 90g/L. Even severe anemia may produce remarkably few symptoms when there is a very gradual onset in a young subject who is otherwise healthy.
3. ***Age***: Young patients can tolerate anemia much better than the elderly because cardiovascular compensation is better in younger patients.

Section Review

Anemia is a common problem worldwide and involves an abnormally low amount of hemoglobin. The cause of the anemia can be classified with problems with hemoglobin or RBC production (e.g. iron or Vit B12 deficiency, problems with erythropoiesis) or with loss of red blood cells. Loss can be subclassified as pure loss of blood (e.g. bleed) or abnormal destruction of the RBCs (e.g. autoimmune, RBC fragility).

Anemia can also be described by how the RBCs look, based on size and colour, and how quickly the symptoms of anemia appear.

Review Questions



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Hematopathology of Leukemia

SHING TAT THEODORE LAM AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Define leukemia and be able to differentiate between acute and chronic.
- Explain the basic pathophysiology of leukemia and distinguish between myelogenous vs lymphoblastic.
- Name some signs and symptoms of leukemia and provide rationale.
- Describe the basic features of lymphoblastic and myelogenous leukemia in a peripheral blood smear.
- Describe the basic features of leukemia in a bone marrow aspirate and a bone marrow biopsy.

All blood cells are made in the bone marrow, arising from stem cells. There are two types of stem cells, based on the blood cells they differentiate into: myeloid and lymphoid. Myeloid stem cells differentiate into RBCs, monocytes or platelets. Lymphoid stem cells differentiate into specialized white blood cells known as lymphocytes: T, B, and natural killer (NK) cells.

While in bone marrow, stem cells respond to various chemical factors which determine which mature blood cell it is to become. For example the hormone erythropoietin will act on a myeloid stem cell to develop first into a blast and, with further exposure to erythropoietin, will develop into the mature red blood cell. Further chemical stimulation will then force those blasts to differentiate into the mature form of blood cell.

Leukemia is a cancer of blood stem cells and are named based on the affected stem cell: myeloid or lymphoid leukemia. Leukemia involves a genetic mutation that promotes overproduction of blasts such that they don't fully differentiate into mature blood cells. Over time, they will out-number the normal stem cells and replace mature blood cells within the bone marrow. As such, the bone marrow becomes overcrowded with abnormal blasts and the end result is a reduced number of normal mature blood cells in the peripheral blood. It's this replacement and low counts of mature cells that often causes the patient's clinical manifestations.

Lymphocytic leukemia (a.k.a. lymphoblastic leukemia) is caused by abnormal lymphoid stem cells leading to abnormally made T or B cells. Conversely, myelogenous leukemias are a result of abnormal myeloid stem cells, resulting in abnormal RBCs, granulocytes (e.g. neutrophils, monocytes), and/or platelets.

Leukemia can then be further subdivided into how quickly the cancer develops. Signs and symptoms of acute leukemias start suddenly – within days or weeks. Chronic leukemias slow manifest, sometimes insidiously, over months or even years.

Acute Lymphoblastic Leukemia (ALL)

For reasons not yet determined, Acute lymphoblastic leukemia (ALL) is the most common cancer in childhood.[1] ALL involves an excess production of immature blasts that matches most closely to lymphocytes (i.e. lymphoblasts). The production of these leukemic lymphoblasts is so excessive that it physically takes up all of the room within the bone marrow, and the nutrients needed, causing a decreased hematopoiesis. As a result, bone marrow is replaced with these leukemic lymphoblasts and eventually spill out into the peripheral blood.

Normally, ALL patients present with symptoms associated with the loss of normal formed elements (ie erythrocytes, leukocytes, or platelets), and not due to the excessive lymphoblasts. For example, an ALL patient may present to a health care provider for severe anemia. The anemia is due to loss of erythrocytes since ALL has taken over the bone marrow such that proper erythropoiesis isn't possible. An ALL patient with low blood cells counts is described as being pancytopenic (pan-= all, cyto = cells, penia = lack of within the blood). Pancytopenic patients are very vulnerable to low oxygen carrying (no RBCs), infections (no WBCs), and bleeding (no platelets) and can thus, present with any one or all of these.

Watch this video lesson of author Theodore Lam looking at peripheral blood smears of an acute lymphoblastic leukemia and chronic myelogenous leukemia.

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Section Review

Leukemia is a cancer involving an overproduction of abnormal blood cells called blasts in the bone marrow. These immature blasts don't function properly and replace normal hemopoiesis within the bone marrow. Leukemia involve a mutation of a hematopoietic stem cell either from the myeloid or lymphoid lines, thus creating multiple copies of leukemic blasts. The most common manifestation of leukemia is the lack of one or more mature blood cells (formed elements) in the peripheral circulation, resulting in problems with bleeding, anemia, and/or infection. Leukemia can be further classified by how quickly it develops: acute vs chronic.

Review Questions



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Notes

1. https://www150.statcan.gc.ca/n1/pub/82-003-x/2021002/article/00001-eng.htm "Trends in paediatric cancer survival in Canada, 1992 to 2017"by Larry F. Ellison, Lin Xie and Lillian Sung. Statistics Canada

Clinical Manifestations of Anemia & Leukemia

SAMUEL LAM; GHAZAL SOKHANRAN; AND KRISTEN DANIELLE GO

Learning Objectives

By the end of this section, you will be able to:

- Explain the role of red blood cells and hemoglobin in oxygen transport and how their deficiency leads to various symptoms of anemia.
- Identify the clinical manifestations of anemia.
- Differentiate between the manifestations of anemia caused by reduced RBC production and blood loss.
- Describe the physiological basis for sympathetic nervous system activation in response to blood loss and its associated symptoms.
- Describe how leukemia disrupts normal hematopoiesis and leads to a deficiency in red blood cells, white blood cells, and platelets.
- Distinguish between general symptoms common to both anemia and leukemia, and those specific to leukemia's malignant pathophysiology.

As you can imagine, there is significant overlap of clinical manifestations between anemia and leukemia since they both involve the impaired synthesis and distribution of red blood cells. Thus, we present clinical manifestations to anemia first as it represents the signs and symptoms of decreased RBCs which can also be seen in leukemia – whether the leukemia targets the erythrocyte stem cell (i.e. myeloid) or the leukemia significantly decreases normal hematopoiesis as leukemic cells replace normal mature blood cells within the bone marrow.

Clinical Manifestation of Anemia

Red blood cells are responsible for carrying oxygen from the lungs to all over the body, where the oxygen is used in energy metabolism and various cellular processes. In anemia, the number of hemoglobin within functional red blood cells is decreased, resulting in clinical manifestations related to the decreased distribution of oxygen throughout the body – typically tiredness, shortness of breath, and pale appearance. However, as anemia may arise from a number of underlying causes, there are several other signs and symptoms that may accompany the classic manifestations depending on the source of the red blood cell deficiency.

Generally, anemia is caused by lack of production (e.g. deficiencies of iron, certain vitamins/nutrients, or erythropoietin), loss (i.e. bleeding), or destruction (i.e. something is targeting the RBCs and removing them from circulation). A full discussion of the manifestations for each cause of anemia is beyond the scope of this book, we will focus on the most common causes of poor RBC production (i.e. iron deficiency) and RBC loss (i.e. hemorrhage)

Manifestations Due to Reduced Oxygen Distribution (e.g. Iron Deficiency)

Red blood cells contain hemoglobin, a red iron-containing protein unit which binds oxygen, giving red blood cells their colour and allowing the red blood cells to carry oxygen to distribute throughout the body. In iron-deficiency anemia, red blood cells have low amount of hemoglobin, thus reducing their oxygen-carrying capacity and resulting in a pale appearance. Oxygen is used for cellular respiration, the metabolic pathway that produces energy in the form of ATP. With anemia, the reduced number of red blood cells leads to a reduction in the amount of oxygen that reaches cells to be used in cellular respiration, and there is a resulting decrease in the amount of energy being produced by cells. This manifests as tiredness and shortness of breath in the individual. A pale appearance may also be observed due to reduced blood cells flowing to the skin. Since low red blood cells are the defining characteristic of anemia, these clinical manifestations can be seen in all types of anemia

Manifestations Due to Blood Loss

The most common cause of anemia in North America is bleeding. Blood loss can occur in a number of ways such as hemorrhage, trauma, menstrual bleeding, or blood donation. Anemia due to blood loss exhibits classic clinical manifestations of anemia – paleness, tiredness, shortness of breath – in addition to several other clinical manifestations related to sympathetic nervous system activation. Bleeding activates the sympathetic nervous system, triggering a fight-or-flight response. This has several effects:

- **Heart rate increases.** The sympathetic nervous system activates beta-1 receptors on the heart which raises heart rate to more efficiently transport the reduced volume of blood throughout the body.

- **Respiratory rate increases.** The sympathetic nervous system activates beta-2 receptors in the smooth muscles of the respiratory system, causing them to relax and open up airways to deliver more oxygen to cells.

- **Diaphoresis.** Also known as a 'cold sweat' which occurs regardless of warm environment. Chemical messengers released by the sympathetic nervous system activate sweat glands to cool down the body when under stress, perhaps in anticipation to cool down the muscles needed for "fight or flight".

General symptoms	Why they occur
Weakness Fatigue Drowsiness	Patients feel these, particularly upon exertion, since insufficient oxygen is carried in their bodies. Hence, their organs and tissues can't function at 100% capacity.
Shortness of breath	This is because of the reduction of Hb, and the tissues do not receive enough oxygen, and symptoms of hypoxia develop. This stimulates the chemoreceptors in blood vessels that measure O2 levels. The result is fast breathing with the sensation of "short of breath" since the increased respiratory rate can't compensate for the poor oxygen carrying capabilities of anemia
Chest pain	The heart tissue is not getting sufficient oxygenated while it works much harder and pumps faster to compensate for the low blood oxygen levels and blood volume. This puts a lot of metabolic demand on the heart, which causes it to beat faster leading to possible irregular rhythm and/or chest pain. Furthermore, it can create observable cardiovascular changes (e.g. murmurs)
Unusual cravings	Abnormal desire to eat clay (termed as pica) to ingest the iron needed for hemoglobin synthesis
Headaches Light-headedness Dizziness	When the brain doesn't receive enough blood and oxygen supply, the blood vessels in the brain dilate and cause pressure that sets off a headache. The decrease in blood volume perfusion will cause the sensation of dizziness & light-headedness due to decreased perfusion of brain tissue
Visual disturbances Retinal hypoxia	If the retina does not receive adequate oxygen, the blood vessels behind the eye and the retina itself might become damaged, resulting in vision problems. Retinal hypoxia also leads to vascular changes, loss of retinal tissue, increased transmural pressure, and microtrauma to the vessel walls, resulting in retinal edema and hemorrhages.
General Signs	
Paleness of mucosae (e.g. inside mouth, conjunctiva of the eyes)	Less hemoglobin means less redness of the blood causing pallor. However, color is unreliable in areas with temperature change (e.g., fingertips or skin color). But, internal structures like oral mucosa (i.e., inside the mouth) and conjunctiva (i.e., inside the eyelid) are areas where healthcare professionals look for pallor.
Palpitation Tachycardia	Aka. Fast heart rate and/or rhythm There is less Hb carrying oxygen, so the heart needs to pump much faster and harder
Poor growth/wound repair	Oxygen is needed for cellular growth and maintenance. Low oxygen leads to less cellular growth during healing of wounded tissue due leading to slow wound repair or tissue growth.
Koilonychia	Aka. Spoon nails or brittle nails The nail has raised ridges and is thin and curved inward. This disorder is associated with iron deficiency anemia. Research shows that lack of blood flow in anemic patients causes the weakening and depression of underlying nail-connective tissue.

Summary of clinical manifestations of anemia

Clinical Manifestations of Leukemia

Leukemia can generally be divided into four different types – Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia. While the four have varying characteristics under the microscope and pathophysiology, they can share similar manifestations. With leukemia being a blood disease, most of these symptoms can be understood by investigating leukemia's effect on our blood cells.

Manifestations Due to Missing Blood Cells

Hematopoietic stem cells in bone marrow are multipotent cells, meaning that they differentiate into a variety of cells: red blood cells, platelets and granulocytes are derived from the common myeloid progenitor whereas lymphocytes are derived from the common lymphoid progenitor cells.

Clinical manifestation of leukemias are more about the lack of mature blood cells in circulation due to it's 'replacement' by leukemic blast cells which crowd out normal hematopoiesis. Regardless of the lineage the leukemia is affecting (i.e. myelogenous vs lymphoid), signs and symptoms will relate to lack of one or more mature blood cell. Thus, symptoms can vary.

Anemia

- As discussed above, low red blood cell count will result in fatigue, pallor, and cardiovascular adaptations to the reduced oxygen carrying capability of the blood.

Leukopenia

- A decrease in white blood cells is known as leukopenia. White blood cells protect against infection and leukopenia will results in reduced immune function, manifesting as fever, cough, persisting sores/ulcerations, and concurrent infections.

Thrombocytopenia

- Platelets are derived from fragments of megakaryocytes and are responsible for clotting. When a blood vessel is damaged, platelets are activated and clump together to form a blood clot to cover the hole and control bleeding. With thrombocytopenia, there is reduced clotting ability due to the platelet deficiency, which can lead to bleeds to ordinary traumas (e.g. nosebleeds when sneezing, bleeding gums from brushing teeth, bruising) and wounds that keep re-opening leading to prolonged periods of bleeding.
- Tiny multiple bleeds, known as petechiae and purpura, can occur as tiny blood vessels have torn or experienced a burst, leaking within the skin while platelet cells are unable to effectively clot and stop bleeding. Hence, tiny red pinpoint spots (**petechiae**) or <1cm bruises (**purpura**) are visible on the skin. **Ecchymoses**, on the other hand, are bruises due to larger rupture in blood vessels, they tend to be visibly larger, greater than 1 cm.

Persistent fatigue, weakness

- Most cancer patients – including leukemic patients – experience fatigue and weakness of varying degree, known as cancer-related-fatigue. In the case of leukemia, it can be the direct result of reduced RBC number and hence, reduced oxygen carrying capacity; thus, a lowered amount of red blood cells, and hence oxygen, leads to decreased energy production for cellular processes. Hence, fatigue is a very common symptom for cancer.

Swollen lymph nodes, enlarged liver or spleen (hepatosplenomegaly)

- Swollen lymph nodes usually appear around neck and armpit area. Sometimes, these swelling are just indications that one's body is actively fighting against infections. With leukemia/lymphoma have swollen lymph nodes that are mainly caused by the replacement of abnormal malignant cells. As liver and spleen are also lymphatic organs, they can also enlarge and cause discomfort and dysfunction.

Losing weight without trying

- Unintentional weight loss can be observed in chronic leukemias patients regardless of whether one is eating sufficiently, as their energy storage gets consumed by cancer. On the other hand, enlarged liver and or spleen can sometimes occur and places limit of stomach expansion, leading to possible lower appetite. Tumor cells take a lot of nutrients to feed its metabolism leaving the body with little nutrients.

Bone pain or tenderness at area of bone pain

- It is speculated that the massive accumulation of malignant leukemia cells causes an expansion of cellular marrow space that may cause the bone pain.

Section Review

- The clinical manifestations of anemia can vary depending on the underlying cause of the decrease in red blood cell levels.
- Tiredness, and shortness of breath are classic clinical manifestations of anemia due to reduced delivery of the oxygen necessary for cells to generate ATP through cellular respiration. Anemia patients may also appear pale due to reduced blood flow to the surface of the skin.
- Red blood cells in iron-deficiency anemia lack hemoglobin, which leads to the individual being pale and tired.
- Anemia due to blood loss may cause several clinical manifestations from the activation of the sympathetic nervous system such as increased heart rate, increased respiratory rate, and diaphoresis
- If the red blood cell deficiency is accompanied by deficiencies of other blood cell types, manifestations related to the missing blood cells may be seen
- Leukemia will manifest as reduced number of mature red blood cells. Thus clinical manifestations will appear as anemia (lack of RBCs), frequent severe infections (lack of white blood cells), and/or abnormal bleeding (lack of platelets).
- Being a cancer, leukemia will manifest with common cancer manifestations such as fatigue, unintentional loss of

weight, decreased appetite, and swollen lymph nodes and organs. Bone pain is sometimes associated with leuekmia.

Review Questions

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Blood Tests

EMILY FRAWLEY

Learning Objectives

By the end of this section, you will be able to:

- Describe the general process of blood collection, labeling, and transportation to the laboratory.
- List possible reasons for blood sample rejection, and explain the implications of sample rejection for patient care.
- Compare and contrast the core functions of key laboratory departments (Chemistry, Hematology, Microbiology, and Transfusion medicine), and explain the types of tests and biological samples each department typically handles.

At some point in one's life, blood testing will become necessary – whether at a health care provider's office, lab testing facility in the community, or while in a hospital. But how a tiny 5 ml vial of blood tell so much about one's state of health?

Ordering and Collection of Blood for Testing

Clinical laboratories process, test, and obtain results from hundreds to tens of thousands of samples a day, depending on the size of the lab.

When samples arrive in the laboratory, they must be received into the lab's Laboratory Information System (LIS). A staff person, usually a Medical Laboratory Assistant (MLA), will confirm the patient's identification. They will also ensure that all samples and requisitions contain at least two unique identifiers and check that the ordering requisition's information matches with the sample unequivocally. A bar-coded label may be applied at this time or it may have already been applied by the phlebotomist that drew the sample. The received samples are then checked to confirm the expected number and type of samples and for proper centrifugation and sample stability.

If there is an error in any of the previous steps, it may cause the sample to be rejected. It cannot be tested and the ordering physician will be notified so that the sample may be recollected. If a given clinical lab is does not run the test required by the physician, the sample will be "sent out" to another location or reference laboratory that does perform the test.

Scanning the barcode into the LIS alerts the laboratory that the sample is available in the laboratory and ready to be tested. The Chemistry department typically uses gold-topped SST tubes while the Hematology department uses lavender-topped EDTA tubes. Microbiology and Molecular samples are usually more varied and include things such as throat swabs, urine, stool, human tissue, and other sterile body fluids.

Blood Chemistry (Serum/Plasma/Urine)

The Chemistry department primarily uses serum or urine as the sample type for testing. Serum is the clear, pale yellow liquid component of blood that remains after the blood cells and clotting factors have been removed. It makes up about 55% of the total blood volume. Plasma can also be used for some chemistry tests.

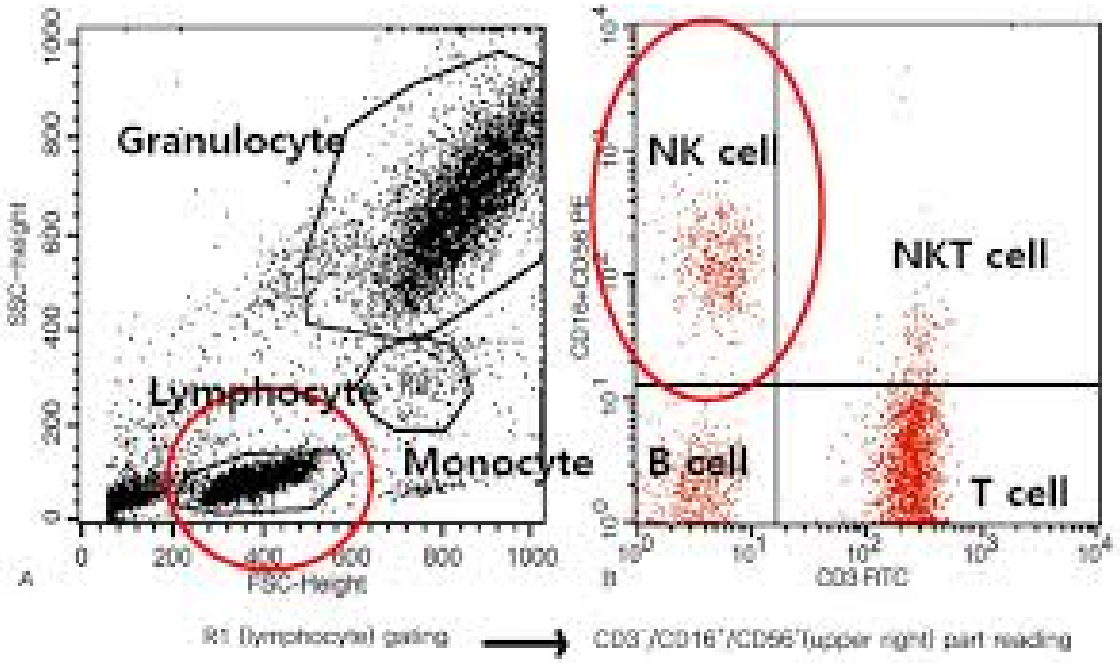
While Medical Laboratory Technologists (MLTs) in the department often test samples for electrolytes such as sodium and potassium, many other tests can be run on serum samples. These may include tests for cardiac markers, pregnancy and reproductive hormones, cancer markers, drug screening, sexually transmitted infections, and liver or kidney hormones. Chemistry test methods include immunoassay to detect and quantify specific molecules, ion-selective electrodes analysis for electrolytes, and enzymatic reaction assays. More specialized Chemistry testing may be done to identify allergies and food sensitivities or to analyze the levels of certain harmful or therapeutic drugs.



Empty Vials for blood samples. Each tube top indicates the desired blood test. The most commonly used tubes are gold tops, Serum Separation Tubes (SST), red tops, and green grey tops.

Hematology (Complete Blood Count)

The Hematology department is responsible for analyzing whole blood samples. These tests use un-centrifuged blood to diagnose and monitor medical conditions relating to the function of a patient's red cells, white cells, and platelets. One of the most commonly requested tests is the complete blood count (CBC) test, generally run by MLTs on an automated hematology analyzer. The size, complexity, and number of a patient's cells are measured to provide important information about a patient's health.



Scattergram or Flow Cytometry chart of white blood cells. *The picture on the left shows the full Flow Cytometry chart with all of the white blood cells listed and the lymphocytes (lymphoid cells) are highlighted. The chart to the right shows a zoomed picture of each type of the lymphocytes. If one were to see a deficiency of one type of cell, that would lead to a leukemia. The flow cytometer is used to count and visualize the amount of white blood cells that cannot be deciphered under a microscope.*

The size and shape of red blood cells can help diagnose different types of anemia, while white blood cell differentiation is crucial in identifying blood cancers and current infections in the body. Platelets are also measured to determine a patient's risk for bleeding or clotting disorders. Samples with abnormal parameters are further analyzed by an MLT looking directly at a stained blood smear on a slide to help identify and characterize abnormal cells. That slide may be sent on to a pathologist for further interpretation before a final result is determined. The Hematology department is also responsible for testing samples for clotting disorders.

Microbiology

The Microbiology Department tests a wide variety of bodily substances for bacterial, viral, parasitic, or fungal infections. Samples from patients with suspected pneumonia, sepsis, food poisoning, and urinary tract infections get spread onto an agar gel infused with nutrients or placed in a nutrient broth. These plates or tubes are then incubated aerobically or anaerobically at the suspected organism's optimal growth temperature.

Once the organism has grown to a detectable level, MLTs isolate it and determine if it's normal flora or a pathogen. Biochemical analysis and an algorithmic system of confirmation testing is used to identify isolated pathogenic bacteria. Molecular testing and immunological methods can be used for the rapid diagnosis of common pathogens by identifying specific molecules unique to a given organism. The Microbiology Department also identifies bacteria with antibiotic resistance and can recommend the most effect antibiotic or antibiotic combination for that bacteria.

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Medical Laboratory Sciences (Microbiology) and Pneumonia created by Marion Regan & Jennifer Kong, licensed under a CC-BY-NC

Transfusion Medicine

Transfusion Medicine or Blood Banking is another department within the Medical Laboratory Sciences but it is generally a self-contained unit typically located within a hospital. This department plays a critical role in ensuring the safe and effective use of blood products for transfusion. Blood samples are kept onsite for analysis or sent to a group such as Canadian Blood Services for testing and storage.

Patient samples must be carefully matched with donor units to prevent rejection by the body's immune system. The Transfusion Medicine Department will also maintain and issue plasma, platelets, and other products to enhance or enable clotting in deficient patients, RhoGAM to prevent hemolytic disease of the newborn (HDN) during pregnancy, and some intravenous immunoglobulins (IVIg).

Storage of Blood Samples for Future Tests or Disposal

Once the sample has undergone all the necessary tests, the samples are stored in a refrigerator or freezer. They may be kept for 3 to 7 days, depending on the laboratory's storage protocols. This allows healthcare providers the opportunity to add-on or follow-up on any previously ordered tests. It not only reduces the need for additional blood draws from the patient but also allows for a more comprehensive evaluation of the patient's condition. If no additional testing or follow-up is required, the tubes are disposed of into biohazardous containers, which are then transported to a waste facility for proper incineration.

Section Review

Blood tests are an essential part of health care. Health care providers can order tests, performed by medical lab technologists, to examine for components in blood (both blood cells and plasma), urine, sputum, and more!

A blood test involves blood being taken from a patient and the blood separated into either the plasma (for chemistry analysis) or blood cells (Hematology). These tests often determine the health of a patients organs or blood based on the presence (or absence) of components in the plasma and/or changes in blood cell number or shape.

Infections can occur in patients which require identification of the organism to prescribe antimicrobial treatment. Microbiology tests of bodily fluids (e.g. urine, saliva, discharge from an infection) are performed to first identify the microbe and then determine which antimicrobial agent/treatment is appropriate.

Transfusion science is a separate branch of medical laboratory sciences, focusing on the banking and storage of blood

and blood products. They ensure the quality and safety of the blood and blood products, prior to distribution to patients in need.

When the blood test result is sent to the health care practitioner, the remaining blood samples are refrigerated and kept for days up to a week to allow for re-testing, if requested.

Review Questions



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Diagnosis of Anemia & Leukemia

EMILY FRAWLEY AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Compare and interpret key hematologic parameters used in diagnosing iron deficiency anemia, including hemoglobin, hematocrit, MCV, MCH, and MCHC.
- Identify and interpret typical morphological changes seen in peripheral blood smears in iron deficiency anemia (e.g. microcytosis, hypochromia, presence of pencil cells).
- Describe the role of peripheral blood smear in identifying immature blast cells and distinguishing between different hematopoietic lineages.
- Differentiate between bone marrow aspirate and biopsy, and their respective diagnostic contributions in leukemia.

As mentioned earlier, anemia would have first been detected as part of the hematology test which calculates number and size of RBCs, alongside WBC and platelets. As the health ca

re team explores the cause of the anemia, particularly anemia due to iron deficiency, iron studies will be conducted.

Diagnosis of Iron Deficiency Anemia

Meat in the diet is the primary source of bodily iron (Fe^{2+} or Fe^{3+}). Hemoglobin and myoglobin are absorbed as heme or inorganic Fe^{2+} by ferritin and transferrin in the intestinal duodenum. When erythrocytes are destroyed, their iron is recycled in the bone marrow and eventually re-incorporated into forming reticulocytes.

Deficiency disorders arise from two broad categories:

- Increased requirements: infants, children, and pregnant women require more iron in their daily lives
- Increased loss or decreased intake: menstruation in females and bleeding into the GI tract for males can create an iron deficient state, as can nutritional or absorption deficiencies.

Overload disorders are much less common. Hemosiderosis and hemochromatosis are both disorders characterized by increased serum iron, sideroblastic anemia causes iron to accumulate in the mitochondria, and repeated transfusions may cause iron overload.



Different coloured vials for blood collection, based on the intended blood test

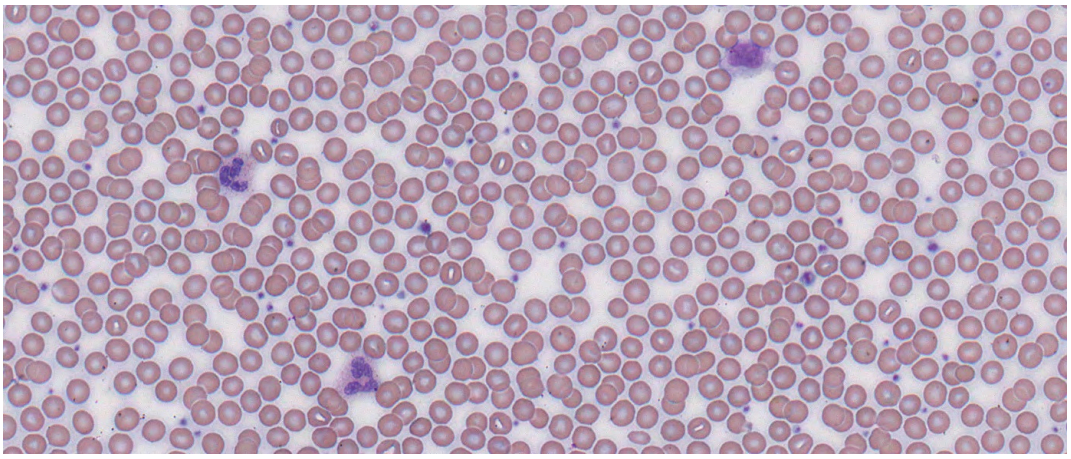


Clinical Chemistry analyzer

Two departments in the pathology lab are primarily responsible for assisting in a diagnosis of anemia:

- The Immunochemistry department tests patient serum to directly determine levels of circulating and stored iron present. Serum Iron, Ferritin, and Transferrin are tests commonly used for this purpose.

- Hematology indirectly determines the levels of iron present by evaluating the status of circulating erythrocytes. Hemoglobin levels, Hematocrit, and Red Cell Indices (MCV, MCH, & MCHC) are tests commonly used for this purpose.



DHPLC specimen PATH 304-061 Normal Peripheral Blood Smear at 10x magnification

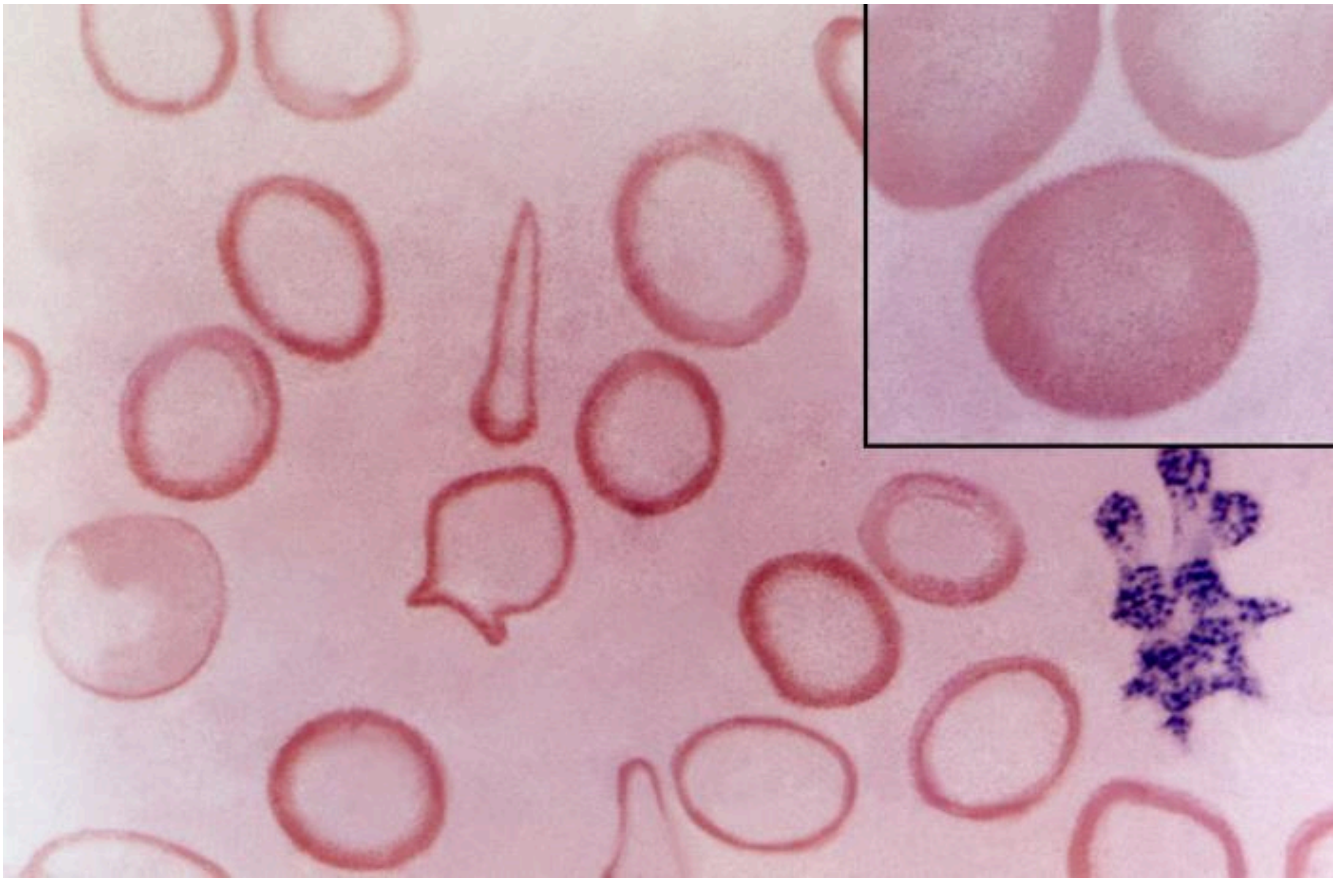
Serum iron is found in the ferric (Fe^{3+}) ion form and is bound to transferrin rather than found as free hemoglobin. There is a strong diurnal variation in serum iron so results for this test must be interpreted with caution. Levels are high in the morning, decrease over the course of the afternoon, and are the lowest in the evening. In addition, a patient with iron deficiency may have a normal serum iron and TIBC. (Note: if a sample has marked hemolysis, it must be rejected because a significant free iron is released when a large number of RBCs are damaged. Mild hemolysis has no effect on serum iron testing.)

Ferritin is the major storage form of the ferrous (Fe^{2+}) ion form and is primarily found in hepatocytes and tissue macrophages. It serves as a reserve for the formation of hemoglobin and other proteins. Ferritin levels are a more reliable way of monitoring a patient's iron status than serum iron as it is not subject to diurnal variation. Ferritin levels will decrease before serum iron levels in iron deficiency scenarios as iron is removed from storage for active use and not replaced.

Transferrin is the transport form of the ferric (Fe^{3+}) ion. It moves iron from it's storage form of ferritin in hepatocytes and tissue macrophages into the bone marrow where it becomes available for the formation of new erythrocytes. Inflammation or liver damage may cause a reduction in transferrin values.

Transferrin levels may be tested and reported as Total Iron Binding Capacity. TIBC is an indirect measure of how much transferrin is available to carry iron. An increased TIBC indicates more space to take up iron and as such indicates decreased iron levels.

Transferrin saturation is another indirect measure of transferrin and expresses the ratio of serum iron to TIBC. Low saturation indicates decreased iron levels.



A blood smear of very hollow, red rimmed erthyrocytes that are small and hypochromic, indicative of iron deficiency anemia. Center of the image is a 'pencil cell' which is commonly seen in this type of anemia. The inset has normal RBCs to compare for size and colour

Anemia states will be reflected in the size, shape, and color of red cells. A Complete Blood Count will evaluate these indices as a routine and standard part of hematology testing to determine a patient's Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC). In addition, a Hematocrit test will evaluate the ratio of plasma volume to red cells.

MCV is an indication of the size of erythrocytes. Microcytes occur when there is not enough iron present in the bone marrow to form full sized erythrocytes. Macrocytes occur due to ineffective erythropoiesis in the bone marrow and are usually due to a deficiency in Vitamin B12, folic acid, and/or folate.

MCH is an indication of how much hemoglobin is contained in the erythrocytes and is expressed in the relative color of the red cell. Hypochromic erythrocytes carry a decreased amount of hemoglobin that can be visualized on the blood smear as a larger than normal center clear area on the red cells. Hyperchromic erythrocytes have a reduced or missing center clear area and are an indication of some form of iron overload.

MCHC is an indication of the concentration of hemoglobin in the erythrocyte relative to its size. It is calculated by dividing the hemoglobin concentration by the hematocrit (MCHC = hgb ÷hct). A decreased MCHC indicates hypochromic erythrocytes are present.

Hematocrit is an indication of the ratio of plasma volume to red cells. A decreased hematocrit indicates a reduction in the number of erythrocytes present in a patient's blood and is usually due to an anemic state. Note: a relative anemia may occur due to an increase in plasma volume with a normal amount erythrocytes causing a relative decrease in hematocrit.

Diagnosis of Leukemia

As mentioned earlier, the signs and symptoms of leukemia may be manifestations of anemia, leukopenia, and/or thrombocytopenia. Hence the first step in diagnosis is often the patient undergoing a blood test after a visit to their health care provider with complaints of fatigue, pallor, abnormal bleeding or bruising, and/or infection. A blood test would be ordered to examine the mature blood cells in peripheral blood where numbers & types of blood cells are calculated. If these results come back with abnormal values (e.g. abnormally low number of mature RBC, WBC, and/or platelets), a peripheral blood smear will be prepared for examination by a hematopathologist.

Using the peripheral blood smear, the hematopathologist will look at any abnormal cells present that are suggestive of immature, undifferentiated blood cells known as blasts. The hematopathologist will also look for all cell lines to get a sense of which cell lineage is impacted (i.e. myeloid vs lymphoid). At this point, the peripheral blood smear can give results highly suggestive of leukemia but a definite diagnosis can't be made until cells from the bone marrow can be analyzed.

Bone Marrow Aspirate and Biopsy in Leukemia

The process of bone marrow aspirate vs biopsy is beyond the scope of this text. However, each test gives important information when investigating leukemia. Bone marrow aspiration uses a surgical needle to remove a small amount of fluid and cells from the bone marrow whereas a bone marrow biopsy removes a small piece of bone containing marrow and cells. The advantage of a bone marrow biopsy is that it demonstrates the architecture of bone including marrow cells and possibly infiltration by leukemic cells. Both bone marrow aspirates and biopsy specimens are examined under a microscope.

After examination of the bone marrow, the hematopathologist can give a definitive diagnosis of leukemia and classification. ALL is diagnosed with a bone marrow aspirate of >20% of cells present are lymphoblasts. There will be numerous lymphoblasts with characteristics such as a high Nuclear:Cytoplasm ratio, fine chromatin seen within the nucleus, and numerous vacuolations within the cytoplasm. Ancillary testing, including flow cytometry, and immunohistochemical stains on the biopsy, and cytogenetics/molecular studies may also help with the diagnosis and prognosis.

Upon diagnosis, approximately 90% of children with ALL will be cured with proper treatment[1].

Section Review

To diagnose anemia, a condition of low hemoglobin, iron studies must be undertaken. Iron content in RBCs can be measured either in hematology. The number of red blood cells (hematocrit) and Red Cell Indices (MCV, MCH, & MCHC) are used to determine the amount of iron-containing hemoglobin is present in RBC and how much RBC is present in circulating blood. The amount of iron available – whether as plasma iron, ferritin, or transferrin – is determined using immunochemistry.

To diagnose leukemia, the patients blood sample would have had abnormalities in the hematology tests. When that patient's sample is identified as such, a blood smear is prepared and human analysis by a medical lab technologist or hematopathologist. If the hematopathologist identifies the presence of numerous blasts in the circulating blood, they will refer the patient to a bone marrow aspirate or biopsy. These tests will analyze the number and type of cells within

bone marrow which the presence (or absence) of blasts will help with the diagnosis of leukemia and its classification of lymphoid or myeloid.

Review Questions

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Notes

1. https://www150.statcan.gc.ca/n1/pub/82-003-x/2021002/article/00001-eng.htm “Trends in paediatric cancer survival in Canada, 1992 to 2017”by Larry F. Ellison, Lin Xie and Lillian Sung. Statistics Canada

Treatment of Anemia & Leukemia

KRISTEN DANIELLE GO AND SAMUEL LAM

Learning Objectives

By the end of this section, you will be able to:

- List common nutritional treatments for anemia.
- Identify appropriate treatments depending on the severity of anemia.
- Briefly describe the treatment for leukemia with respects to eradication of leukemic cells.

Treatment for Anemia

Anemia is caused when hemoglobin drops, and its symptoms are a result of the decreased delivery of oxygen and other vital materials carried by blood. Treatments focus on correcting this hemoglobin and red blood cell deficiency by addressing the underlying cause. Recall the main types of anemia from the previous chapter "Pathophysiology of Anemia". If the anemia is non-urgent (ie not causing significant impact on tissue oxygenation), the treatment is to increase the body's natural production of red blood cells. If the anemia is causing complications in other organs, more serious interventions will be considered.

Collaboration with multiple health care providers is key to a patient's recover (e.g. medical lab technologist, nutritionist, pharmacist, hematologist, transfusion technologist).

Treatment for Anemia due to Impaired Hb or RBC Synthesis

Treatments address the decreased number of hemoglobin and/or red blood cells in a number of ways:

- Directly – by providing the patient with a blood transfusion to raise their blood cell and hemoglobin levels, or
- Indirectly – by administering nutrition and medications to stimulate synthesis of new hemoglobin and blood cells within the patient.

Below are methods used to indirectly increase hemoglobin and/or RBC synthesis

Treatment for Iron Deficiency Anemia: Supplementation with Iron, Vitamin B12, and Folate

In patients with anemia due to insufficient blood production, the underlying cause is often due to a deficiency in a component needed in the assembly of new blood cells. Treatment for this can involve treating the deficiency by supplementing the insufficient component.

Iron-deficiency anemia can be treated with iron supplements, which can be obtained over the counter in tablet form or liquid form for children. Iron is incorporated into **hemoglobin** — the functional unit of a red blood cell that is responsible for carrying oxygen. In iron-deficiency anemia, red blood cells are underfilled with hemoglobin, resulting in smaller than normal red blood cells with diminished oxygen-carrying capacity. As non-heme iron (i.e. iron that isn't already part of hemoglobin as in meat products with blood) can be difficult to absorb, it can be recommended to combine the intake of iron supplements with vitamin C.

Vitamin B12 and Vitamin B9 (also known as folate or folic acid), are both also components needed for DNA and cell synthesis to make healthy, functioning red blood cells. Sufficient amounts prompt normal hematopoiesis and the complete development into fully functional mature blood cells. Without Vitamin B12 and folate, all blood cells, especially RBCs, remain undivided and large, resulting in premature destruction in the spleen.

Diet is a major source of the components needed to build new red blood cells. Dietary changes to increase intake of the missing vitamins may also contribute to treating anemia. Food sources rich in iron include red meat, spinach, and beans. Vitamin B12 can be found in seafood, dairy, and other animal derived products, meaning that individuals with vegan diets often have minimal sources of Vitamin B12. Folate can be obtained from food sources such as broccoli and bananas, and is also commonly added to enriched breads, cereals, and pastas. A referral to a dietitian for a consult may be provided to aid in ensuring that dietary needs are met.

Vitamin B12 and folate may also be prescribed in tablet form. If dietary sources of Vit B12 is insufficient and/or there are issues with gastrointestinal absorption, Vitamin B12 can be administered by injections. In many cases, vitamin B12 shots are needed as a regular, lifelong treatment if the underlying cause of the deficiency cannot be cured.

Treatment for Anemia due to Lack of Erythropoiesis

If all key red blood cell building blocks are present in sufficient amounts AND the bone marrow is functional, anemia can be addressed by administering the hormone erythropoietin, which stimulates erythropoiesis to increase the patient's red blood cell count. Erythropoietin is normally made in the kidneys (see Acute Kidney Injury Chapter for review) and kidney disease can cause anemia due to decreased erythropoiesis.

Treatment for Anemia due to RBC Loss or Destruction

If the anemia were due to blood loss or destruction, the treatment would be to stop that loss/destruction AND promote increased synthesis of hemoglobin as previously stated. As the causes for blood loss are many (e.g. trauma, occult bleed in GI system), this text can not comment on treatment, other than stopping the bleed. Similarly, there are many causes for RBC destruction (e.g. autoimmune, infectious, RBC structural defects, vascular defects) which discussion about treatments are beyond the scope of this book.

Blood Transfusions

Regardless of the cause, if the anemia is severe enough to impact organ function and below a certain threshold for hemoglobin amount, anemic patients can receive additional blood in the form of red blood cell transfusions. Prior to transfusion, the patient's blood type will need to be determined and matched to a donor blood type to prevent hemolytic reactions. Packed red blood cells are obtained by removing plasma, white blood cells, and other blood components from whole blood. Packed red blood cells are usually used in transfusions for anemia patients to minimize risks associated with fluid overload or hemolytic reactions in the recipient.

However, blood transfusions are more invasive compared to the previously mentioned anemia treatments, and are associated with more possible complications. Because of this, blood transfusions for deficiency related anemias are only administered in more severe cases.

Treatment of Leukemia

The goal of leukemia treatment is to stop and eradicate the leukemic blasts within the bone marrow AND encourage the synthesis and function of the normal blood cells. Thus, in addition to the cancer treatments listed below, treatment will also include supportive therapy (i.e.. transfusion of RBCs and/or platelets or drugs to augment the white blood cell count.

As bone marrow is the site of pathology, treatment of leukemia is focused here. However, because bone marrow is in many bones, a localized target for eradication, as with radiation therapy focused on a single spot in bone, isn't likely. Thus, eradication must be done throughout the entire body via chemotherapy.

Chemotherapy

- Chemotherapy uses drugs to kill leukemia cells, it can consist of one of multiple types of chemicals. Chemotherapy drugs are often injected into bloodstream, and travels along body to kill malignant cells. These drugs could also affect some normal cells and cause many side effects such as hair loss, fatigue, nausea. With recent advances, we have more targeted therapy to the malignant cancer cells that may harbour certain chromosomal abnormalities or mutations.

Bone Marrow or Stem Cell Transplant

- Bone marrow transplant can be used on acute leukemia patients via donation of healthy hemtaopoietic stem cells. High doses of chemotherapy are often performed to kill leukemia cells and marrow before patients are infused with donor hematopoietic stem cells via intravenous (IV) catheter.

Immunotherapy

- Recent developments of targeted therapy by using monoclonal antibodies to target specific cell surface markers which are exhibited on the leukemic cell line.

Section Review

- Anemia treatments all increase red blood cell counts, although the means will vary depending on the specific type of anemia the patient has. The treatments will aim to address the underlying cause of the low level of red blood cells that may have been caused by decreased blood cell production, increased blood cell destruction, or blood loss.
- Insufficient red blood cell constituents — such as iron, Vitamin B12, and folate — can be corrected by administering the missing nutrients or by increasing dietary intake.
- In cases that cannot be corrected by administering drugs, red blood cell counts can be increased via a blood transfusion of packed red blood cells.
- The hormone erythropoietin may also be administered to stimulate synthesis of new red blood cells in the individual.
- The goal of leukemia treatment is to stop the proliferation of the leukemic blasts within the bone marrow by localized (radiotherapy), systemic (chemotherapy), and immunologic methods.
- After eradication of leukemic blasts, bone marrow transplants encourage the synthesis and function of the normal blood cells.

Review Questions



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Interprofessional Collaboration: the Journey a Blood Test Takes in LifeLabs

JENNIFER KONG AND EMILY FRAWLEY

Learning Objectives

By the end of this section, you will be able to:

- Describe how a blood sample is taken from a patient, prepared and delivered to LifeLabs for specialty laboratory testing service.
- Trace the steps a hematology blood sample takes upon receipt of sample to microscopic analysis by a hematopathologist.
- Trace the steps a plasma chemistry sample takes upon receipt of sample, reporting of results, and eventual disposal.

It takes many health care professionals to help a client navigate through their health journey. Blood tests will play a major component in determining a patient's diagnosis and monitoring their health while on treatment.

Watch the process of how blood tests are collected, tested, interpreted and reported in BC at the LifeLabs facility in Burnaby BC.

Blood Collection & Receipt

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=4403#h5p-337

Blood collection recorded at BCIT campus by Lindsay Belloc, Heather McMullen, Emily Frawley, & Jennifer Kong. Video tour of LifeLabs facility in Burnaby BC conducted by Lindsay Belloc, Emily Frawley, & Jennifer Kong. Narration by Riley Belloc. Licensed under All Rights Reserved

Blood Tests: Hematology

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Blood Tests: Chemistry

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Video tour of LifeLabs facility in Burnaby BC conducted by Lindsay Belloc, Emily Frawley, & Jennifer Kong. Licensed under All Rights Reserved

Section Review

For two common blood tests (hematology and chemistry), blood is collected from the patient in tubes with colour coded tops that designate the type of blood test. In the case of the chemistry test, the blood has to be spun down to separate the plasma/serum from the blood cells.

The blood vials are delivered to Lifelabs, the largest specialty laboratory testing facility in Western Canada. The blood vials are registered (accessioned) and sent to the respective testing area within Lifelabs.

Chemistry tests are examined in the chemistry analyzer machine which measures components in the plasma/serum such as electrolytes (e.g. Na^+, K^+), nutrients (e.g. glucose), enzymes (e.g. liver function test) and much more – depending on the tests requisitioned for the patient. After the test results are obtained and sent electronically to the health care provider, the blood tubes are refrigerated and stored for up to 7 days in the likelihood that the provider would like further testing and avoiding the patient having to give blood again.

Hematology tests are examined by the hematology analyzer which can separate and calculate the different types and number of blood cells/formed elements based on their size. If a sample yields an abnormal result, it is diverted to have a peripheral blood smear prepared for microscopic analysis. A MLT will first look at the peripheral blood smear and determine whether it needs further analysis by the hematopathologist. Using special computer analysis and personal viewing of the blood cells, the hematopathologist can determine whether urgent communication of these results to the patient and health care provider are needed.

Review Questions



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Blood Chapter Summary and Credits

JENNIFER KONG

Chapter Summary

Our body relies on the blood to deliver its life-essential oxygen and nutrients to all of the tissues and organs. The mature blood cells (formed elements) are responsible for delivery of oxygen (RBCs), clotting (platelets), and immunological defence (WBCs). The watery part of blood, the plasma, carries the nutrients, plasma proteins, electrolytes, and wastes.

The mature blood cells are created in the bone marrow with chemical stimulation of their respective hemopoietic stem cell. Blood cells/formed elements leave the bone marrow when mature: RBCs and platelets lack organelles and nuclei and are hence, not cells. Hence, some refer to circulating mature blood cells as formed elements rather than blood cells.

Anemia is the most common disorder in the world. It's defined as an abnormally low amount of hemoglobin, the iron-containing protein molecule that binds O_2 and RBCs. The cause of anemia can be organized as due to lack of synthesis (i.e. RBCs and/or hemoglobin), loss of whole blood (i.e. bleed), or destruction of RBCs (i.e. RBCs are fragile or something is destroying RBCs). As there is reduced O_2 carrying capability, anemia manifests as a global lack of energy production since O_2 is preferred to to generate ATP in all cells. Anemia often manifests as appearing pale, tired, with weakness. Cardiovascular adaptations such as high heart rate and blood pressure may also be seen. Diagnosis of anemia is performed with hematological analysis to determine the number of mature RBCs and iron studies. Treatment of anemia is to address the underlying cause: whether with nutritional/hormonal supplementation if causes are due to poor synthesis or identifying and stopping the bleed if the cause is due to loss or limiting the RBC destruction if it all possible.

Leukemia is a blood cancer where there is abnormal development and proliferation of a hemopoietic cell line: either myeloid or lymphoid. As a result, the bone marrow will be overcrowded with these abnormal, non-functional leukemic blasts, which replace the normal hemopoiesis that occurs in the bone barrow. The numerous leukemic blasts may leave the bone and enter the peripheral circulation. At the same time, there is a severe reduction in mature blood cells being generated and enter the circulation. Thus, leukemia manifests as signs of the lack of those blood cells moreso than the presence of the leukemic blasts: signs of anemia (lack of RBCs), abnormal bleeding (lack of platelets), and infections (lack of white blood cells). Diagnosis of leukemia first requires hematologic analysis of circulating blood for the presence of blasts and a reduction in blood cells. This can then be followed up by samples of bone marrow (whether through aspiration or core biopsy) to assess the degree of blast formation and the stem cell affected. Treatment of leukemia focuses on eradicating the abnormal stem cell and blasts – often by chemotherapy or targeted immunotherapy.

Credits

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Post Test: Blood Function, Composition Hematopoiesis and Hemostasis

ZOË SOON



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Review Crossword: Blood Function and Composition

ZOË SOON



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AUTOIMMUNITY

Autoimmunity Chapter Overview

Autoimmunity Chapter Overview

MORGAN ALFORD AND DYLAN MANN

Chapter Learning Objectives

By the end of this chapter, you will be able to:

- Describe the mechanisms and components of the immune system and differentiate between innate and adaptive immune responses.
- Explain the structure, function, and classes of antibodies and how these features effect antibody affinity, avidity, and cross reactivity.
- Discuss disruptions in the immune systems and differentiate between hypersensitivities and autoimmune reactions.
- Highlight key mechanisms and manifestations of common autoimmune conditions such as Celiac Disease, Graves' Disease, Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Vitiligo.

Autoimmunity is a condition in which the body's immune system mistakenly attacks its own cells, tissues, or organs. A combination of genetic and environmental factors influence the development of autoimmunity. Autoimmune processes may manifest as one of many diseases, some of which are discussed in this chapter.

This chapter is subdivided into the following sections:

- Pre-test
- Immunity Overview
- Innate Immune Responses
- Adaptive Immune Responses
- Antibodies
- Disruptions in the Immune System
- Celiac Disease
- Rheumatoid Arthritis
- Vitiligo
- Graves' Disease
- Systemic Lupus Eryhematosus
- Post-test

Abbreviations

PAMPs	Pathogen associated molecular patterns
TLRs	Toll like receptors
PRRs	Pattern recognition receptors
NK cells	Natural killer cells
MHC	Major histocompatibility complex
APC	Antigen presenting cell
CTLs	Cytotoxic T lymphocytes
TCRs	T cell receptors
TH lymphocytes	T helper lymphocytes
BCR	B cell receptor
MALT	Mucosa associated lymphoid tissue
Treg	T regulatory
Ig	Immunoglobulin
SLE	Systemic lupus Eryhematosus
SCID	Severe combined immunodeficiency
HLA	Human leukocyte antigen
GFD	Gluten free diet
anti-CPP	Anti-cyclic citrullinated peptide
NSAIDs	Non-steroidal anti-inflammatory agents
RA	Rheumatoid arthritis
UV	Ultraviolet
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
ANAs	Anti nucleic antibodies

Pre-Test for Autoimmunity

Pre-Test for Autoimmunity

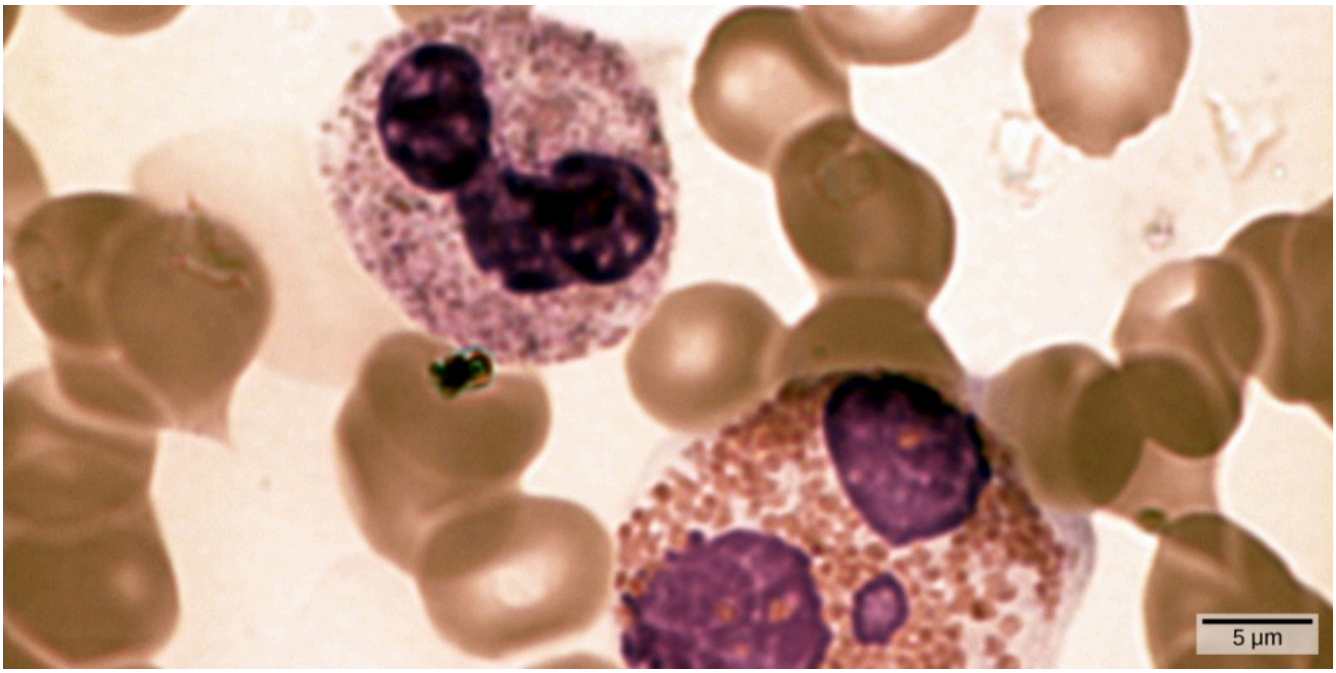
DYLAN MANN AND MORGAN ALFORD



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Immunity Overview

MORGAN ALFORD; CHARLES MOLNAR; AND JANE GAIR



In this compound light micrograph purple-stained neutrophil (upper left) and eosinophil (lower right) are white blood cells that float among red blood cells in this blood smear. Neutrophils provide an early, rapid, and nonspecific defense against invading pathogens. Eosinophils play a variety of roles in the immune response. Red blood cells are about 7–8 µm in diameter, and a neutrophil is about 10–12µm. (Credit: modification of work by Dr. David Csaba)

The environment consists of numerous **pathogens**, which are agents, usually microorganisms, that cause diseases in their hosts. A **host** is the organism that is invaded and often harmed by a pathogen. Pathogens include bacteria, protists, fungi and other infectious organisms. We are constantly exposed to pathogens in food and water, on surfaces, and in the air. Mammalian immune systems evolved for protection from such pathogens; they are composed of an extremely diverse array of specialized cells and soluble molecules that coordinate a rapid and flexible defense system capable of providing protection from a majority of these disease agents.

Components of the immune system constantly search the body for signs of pathogens. When pathogens are found, immune factors are mobilized to the site of an infection. The immune factors identify the nature of the pathogen, strengthen the corresponding cells and molecules to combat it efficiently, and then halt the immune response after the infection is cleared to avoid unnecessary host cell damage. The immune system can remember pathogens to which it has been exposed to create a more efficient response upon re-exposure. This memory can last several decades. Features of the immune system, such as pathogen identification, specific response, amplification, retreat, and remembrance are essential for survival against pathogens. The immune response can be classified as either innate or active. The innate immune response is always present and attempts to defend against all pathogens rather than focusing on specific ones. Conversely, the adaptive immune response stores information about past infections and mounts pathogen-specific defenses.

Adaption

This chapter is adapted by Morgan Alford from the following text:

The Immune System in Concepts of Biology, First Canadian Edition by Drs. Jane Gair and Charles Molnar is licensed under a Creative Commons Attribution 4.0 International License.

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Innate Immune Responses

CHARLES MOLNAR; JANE GAIR; AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

- Describe physical and chemical immune barriers.
- Explain immediate and induced innate immune responses.
- Discuss natural killer cells.
- Describe major histocompatibility class I molecules.
- Summarize how the proteins in a complement system function to destroy extracellular pathogens.

The immune system comprises both innate and adaptive immune responses. **Innate immunity** occurs naturally because of genetic factors or physiology; it is not induced by infection or vaccination but works to reduce the workload for the adaptive immune response. Both the innate and adaptive levels of the immune response involve secreted proteins, receptor-mediated signaling, and intricate cell-to-cell communication. The innate immune system developed early in animal evolution, roughly a billion years ago, as an essential response to infection. Innate immunity has a limited number of specific targets: any pathogenic threat triggers a consistent sequence of events that can identify the type of pathogen and either clear the infection independently or mobilize a highly specialized adaptive immune response. For example, tears and mucus secretions contain microbicidal factors.

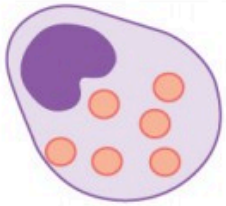
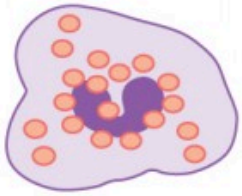
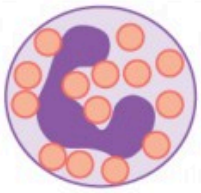
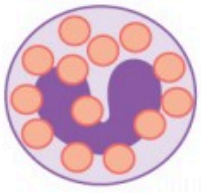
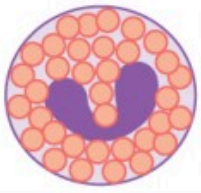
Physical and Chemical Barriers

Before any immune factors are triggered, the skin functions as a continuous, impassable barrier to potentially infectious pathogens. Pathogens are killed or inactivated on the skin by desiccation (drying out) and by the skin's acidity. In addition, beneficial microorganisms that coexist on the skin compete with invading pathogens, preventing infection. Regions of the body that are not protected by skin (such as the eyes and mucus membranes) have alternative methods of defense, such as tears and mucus secretions that trap and rinse away pathogens, and cilia in the nasal passages and respiratory tract that push the mucus with the pathogens out of the body. Throughout the body are other defenses, such as the low pH of the stomach (which inhibits the growth of pathogens), blood proteins that bind and disrupt bacterial cell membranes, and the process of urination (which flushes pathogens from the urinary tract).

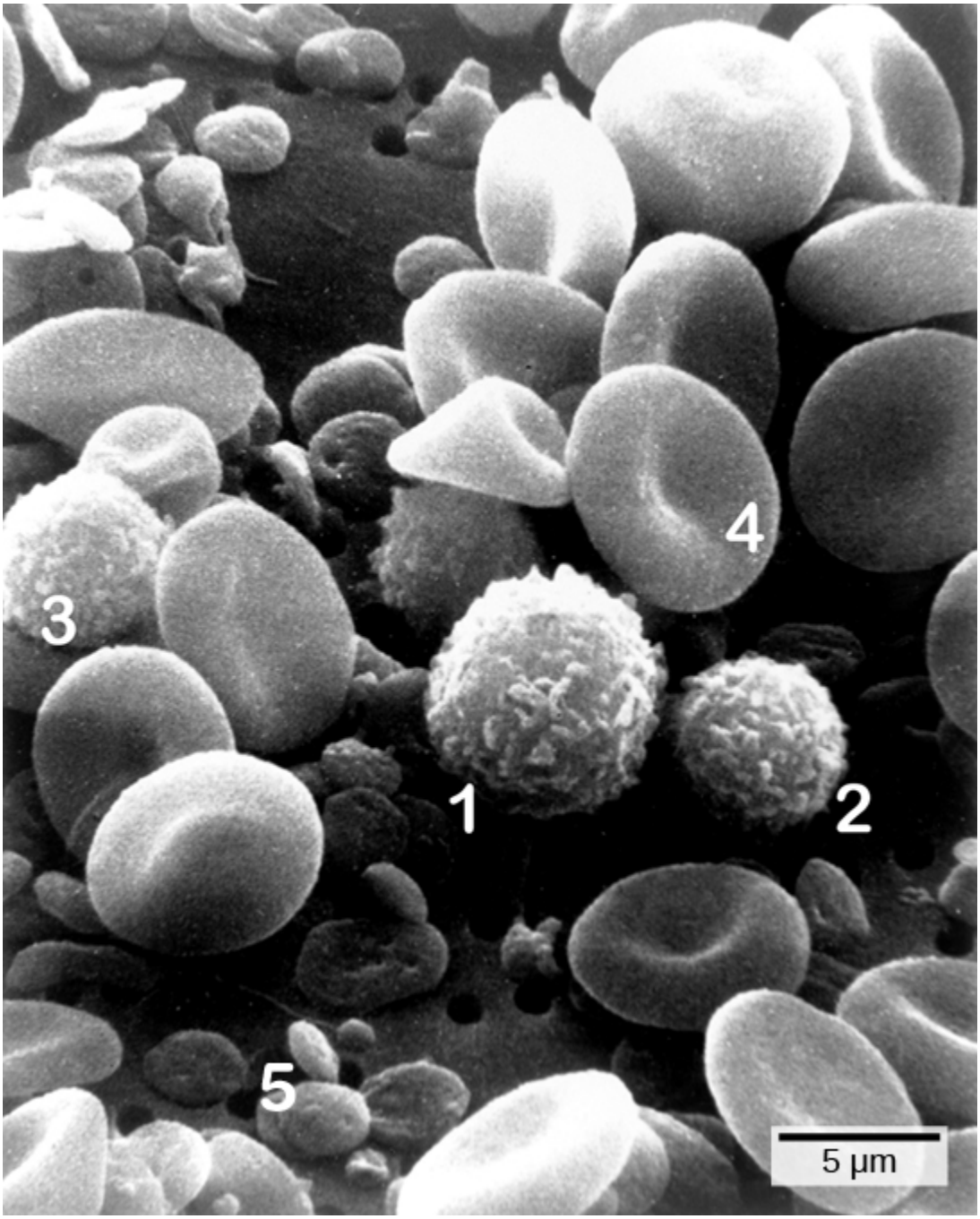
Despite these barriers, pathogens may enter the body through skin abrasions or punctures, or by collecting on mucosal surfaces in large numbers that overcome the mucus or cilia. Some pathogens have evolved specific mechanisms that allow them to overcome physical and chemical barriers. When pathogens do enter the body, the innate immune system responds with inflammation, pathogen engulfment, and secretion of immune factors and proteins.

Pathogen Recognition

An infection may be intracellular or extracellular, depending on the pathogen. All viruses infect cells and replicate within those cells (intracellularly), whereas bacteria and other parasites may replicate intracellularly or extracellularly, depending on the species. The innate immune system must respond accordingly: by identifying the extracellular pathogen and/or by identifying host cells that have already been infected. When a pathogen enters the body, cells in the blood and lymph detect the specific **pathogen-associated molecular patterns** (PAMPS) on the pathogen's surface. PAMPs are carbohydrate, polypeptide, and nucleic acid "signatures" that are expressed by viruses, bacteria, and parasites but which differ from molecules on host cells. The immune system has specific cells with receptors that recognize these PAMPs. A **macrophage** is a large phagocytic cell that engulfs foreign particles and pathogens. Macrophages recognize PAMPs via complementary **pattern recognition receptors** (PRRs). PRRs are molecules on macrophages and dendritic cells which are in contact with the external environment. A **monocyte** is a type of white blood cell that circulates in the blood and lymph and differentiates into macrophages after it moves into infected tissue. Dendritic cells bind molecular signatures of pathogens and promote pathogen engulfment and destruction. Toll-like receptors (TLRs) are a type of PRR that recognizes molecules that are shared by pathogens but distinguishable from host molecules). TLRs are present in invertebrates as well as vertebrates, and appear to be one of the most ancient components of the immune system. TLRs have also been identified in the mammalian nervous system.

Cell type	Characteristics	Location	Image
Mast cell	Dilates blood vessels and induces inflammation through release of histamines and heparin. Recruits macrophages and neutrophils. Involved in wound healing and defense against pathogens but can also be responsible for allergic reactions.	Connective tissues, mucous membranes	
Macrophage	Phagocytic cell that consumes foreign pathogens and cancer cells. Stimulates response of other immune cells.	Migrates from blood vessels into tissues.	
Natural killer cell	Kills tumor cells and virus-infected cells.	Circulates in blood and migrates into tissues.	
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	
Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	

The characteristics and location of cells involved in the innate immune system are described.



Cells of the blood include (1) monocytes, (2) lymphocytes, (3) neutrophils, (4) red blood cells, and (5) platelets. Note the very similar morphologies of the leukocytes (1, 2, 3).

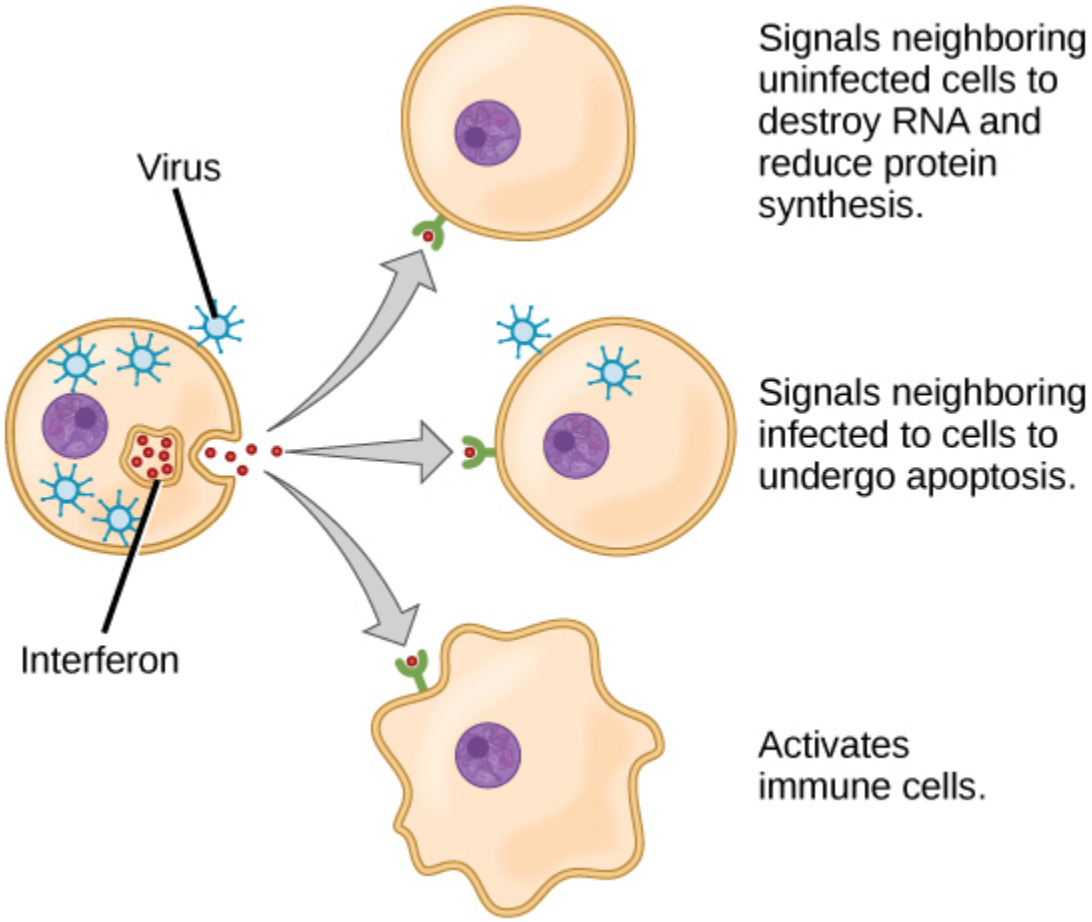
Cytokine Release Affect

The binding of PRRs with PAMPs triggers the release of cytokines, which signal that a pathogen is present and needs to be destroyed along with any infected cells. A **cytokine** is a chemical messenger that regulates cell differentiation (form and function), proliferation (production), and gene expression to affect immune responses. At least 40 types of cytokines

exist in humans that differ in terms of the cell type that produces them, the cell type that responds to them, and the changes they produce.

One subclass of cytokines is the interleukin (IL), so named because they mediate interactions between leukocytes (white blood cells). Interleukins are involved in bridging the innate and adaptive immune responses. In addition to being released from cells after PAMP recognition, cytokines are released by the infected cells which bind to nearby uninfected cells and induce those cells to release cytokines, which results in a cytokine burst.

A second class of early-acting cytokines is interferons, which are released by infected cells as a warning to nearby uninfected cells. One of the functions of an **interferon** is to inhibit viral replication. They also have other important functions, such as tumor surveillance. Interferons work by signaling neighboring uninfected cells to destroy RNA and reduce protein synthesis, signaling neighboring infected cells to undergo apoptosis (programmed cell death), and activating immune cells.



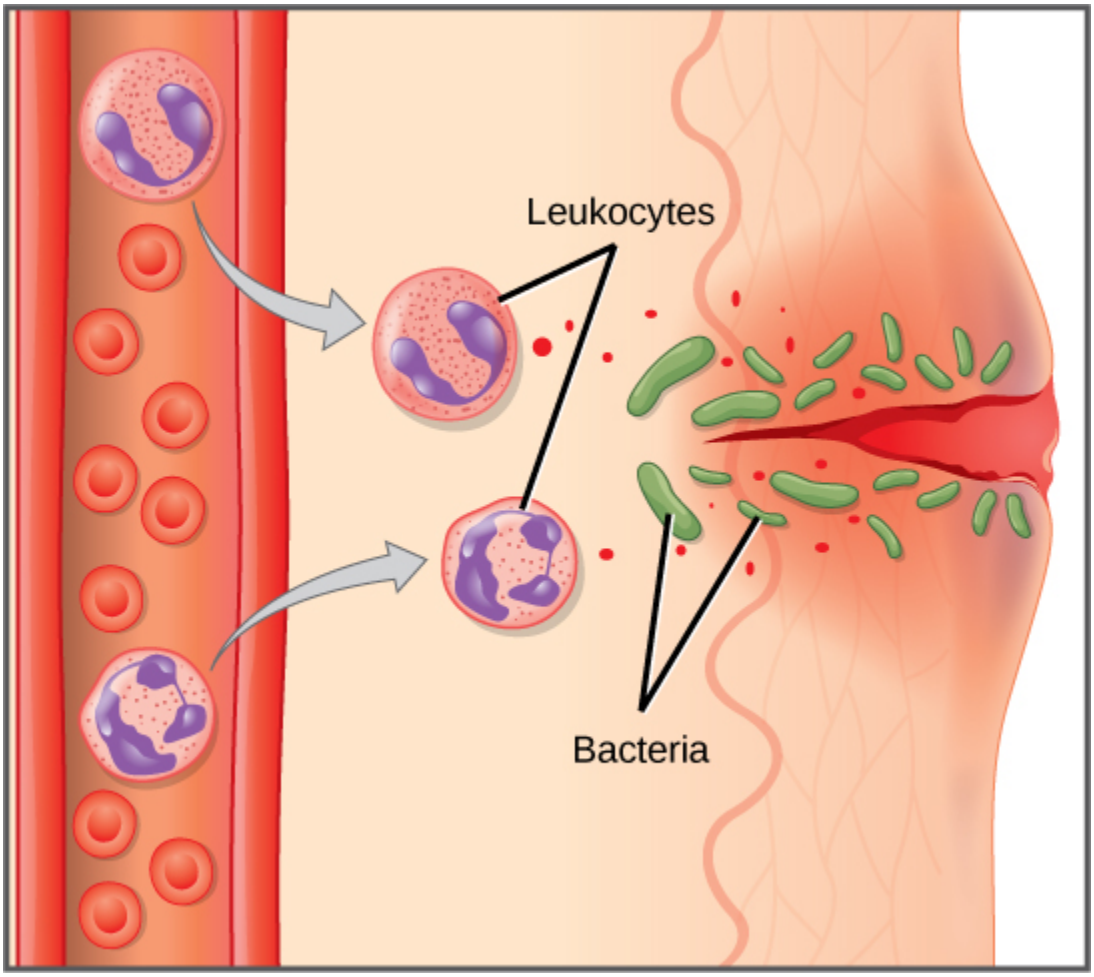
Interferons are cytokines that are released by a cell infected with a virus. Response of neighboring cells to interferon helps stem the infection.

In response to interferons, uninfected cells alter their gene expression, which increases the cells' resistance to infection. One effect of interferon-induced gene expression is a sharply reduced cellular protein synthesis. Virally infected cells produce more viruses by synthesizing large quantities of viral proteins. Thus, by reducing protein synthesis, a cell becomes resistant to viral infection.

Phagocytosis and Inflammation

The first cytokines to be produced are pro-inflammatory; that is, they encourage **inflammation**, the localized redness, swelling, heat, and pain that result from the movement of leukocytes and fluid through increasingly permeable capillaries to a site of infection. The population of leukocytes that arrives at an infection site depends on the nature of the infecting pathogen. Both macrophages and dendritic cells engulf pathogens and cellular debris through phagocytosis. A **neutrophil** is also a phagocytic leukocyte that engulfs and digests pathogens. Neutrophils are the most abundant leukocytes of the immune system. Neutrophils have a nucleus with two to five lobes, and they contain organelles, called lysosomes, that digest engulfed pathogens. An **eosinophil** is a leukocyte that works with other eosinophils to surround a parasite; it is involved in the allergic response and in protection against helminthes (parasitic worms).

Neutrophils and eosinophils are particularly important leukocytes that engulf large pathogens, such as bacteria and fungi. A **mast cell** is a leukocyte that produces inflammatory molecules, such as histamine, in response to large pathogens. A basophil is a leukocyte that, like a neutrophil, releases chemicals to stimulate the inflammatory response. Basophils are also involved in allergy and hypersensitivity responses and induce specific types of inflammatory responses. Eosinophils and basophils produce additional inflammatory mediators to recruit more leukocytes. A hypersensitive immune response to harmless antigens, such as in pollen, often involves the release of histamine by basophils and mast cells.



In response to a cut, mast cells secrete histamines that cause nearby capillaries to dilate. Neutrophils and monocytes leave the capillaries. Monocytes mature into macrophages. Neutrophils, dendritic cells and macrophages release chemicals to stimulate the inflammatory response. Neutrophils and macrophages also consume invading bacteria by phagocytosis.

Cytokines also send feedback to cells of the nervous system to bring about the overall symptoms of feeling sick, which include lethargy, muscle pain, and nausea. These effects may have evolved because the symptoms encourage the individual to rest and prevent them from spreading the infection to others. Cytokines also increase the core body temperature, causing a fever, which causes the liver to withhold iron from the blood. Without iron, certain pathogens, such as some bacteria, are unable to replicate; this is called nutritional immunity.

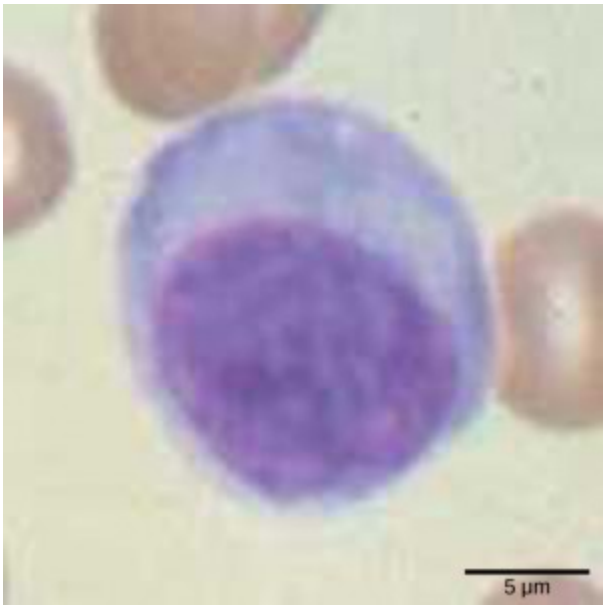
Concept in Action



Watch this 23-second stop-motion video showing a neutrophil that searches for and engulfs fungus spores during an elapsed time of about 79 minutes.

Natural Killer Cells

Lymphocytes are leukocytes that are histologically identifiable by their large, darkly staining nuclei; they are small cells with very little cytoplasm. Infected cells are identified and destroyed by **natural killer cells** (NK cells), lymphocytes that can kill cells infected with viruses or tumour cells (abnormal cells that uncontrollably divide and invade other tissue). T cells and B cells of the adaptive immune system also are classified as lymphocytes. **T cells** are lymphocytes that mature in the thymus gland, and **B cells** are lymphocytes that mature in the bone marrow. NK cells identify intracellular infections, especially from viruses, by the altered expression of major histocompatibility class (MHC) I molecules on the surface of infected cells. **MHC I** molecules are proteins on the surfaces of all nucleated cells, thus they are scarce on red blood cells and platelets which are non-nucleated. The function of MHC I molecules is to display fragments of proteins from the infectious agents within the cell to T-cells; healthy cells will be ignored, while "non-self" or foreign proteins will be attacked by the immune system. **MHC II** molecules are found mainly on cells containing antigens ("non-self proteins") and on lymphocytes. MHC II molecules interact with helper T-cells to trigger the appropriate immune response, which may include the inflammatory response.



Lymphocytes, such as NK cells, are characterized by their large nuclei that actively absorb Wright stain and therefore appear dark colored under a microscope.

An infected cell (or a tumor cell) is usually incapable of synthesizing and displaying MHC I molecules appropriately. The metabolic resources of cells infected by some viruses produce proteins that interfere with MHC I processing and/or trafficking to the cell surface. The reduced MHC I on host cells varies from virus to virus and results from active inhibitors being produced by the viruses. This process can deplete host MHC I molecules on the cell surface, which NK cells detect as "unhealthy" or "abnormal" while searching for cellular MHC I molecules. Similarly, the dramatically altered gene expression of tumor cells leads to expression of extremely deformed or absent MHC I molecules that also signal "unhealthy" or "abnormal."

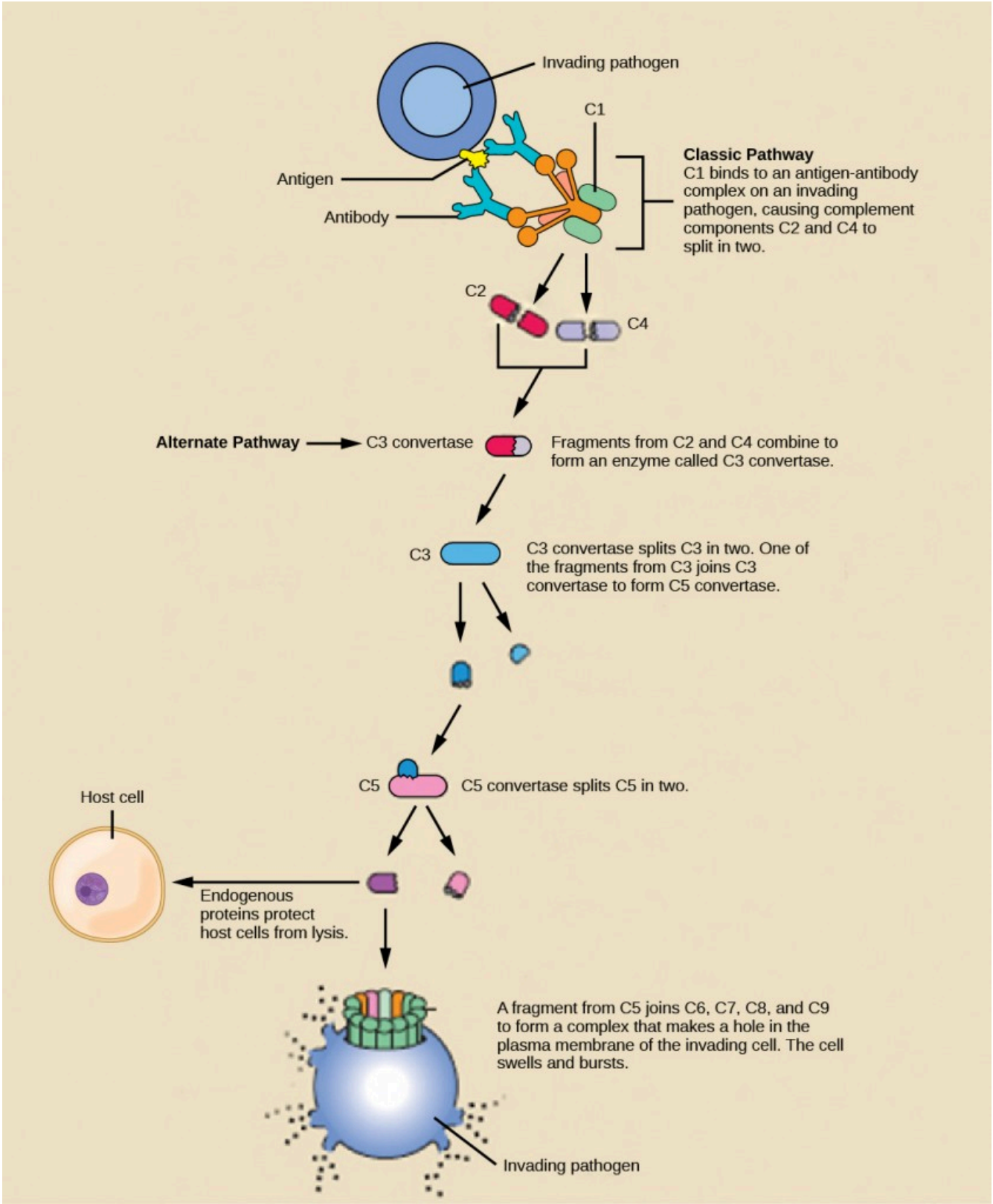
NK cells are always active; an interaction with normal, intact MHC I molecules on a healthy cell disables the killing sequence, and the NK cell moves on. After the NK cell detects an infected or tumor cell, its cytoplasm secretes granules comprised of **perforin**, a destructive protein that creates a pore in the target cell. Granzymes are released along with the perforin in the immunological synapse. A **granzyme** granzyme is a protease that digests cellular proteins and induces the target cell to undergo programmed cell death, or apoptosis. Phagocytic cells then digest the cell debris left behind. NK cells are constantly patrolling the body and are an effective mechanism for controlling potential infections and preventing cancer progression.

Complement

An array of approximately 20 types of soluble proteins, called a **complement system**, functions to destroy extracellular pathogens. Cells of the liver and macrophages synthesize complement proteins continuously; these proteins are abundant in the blood serum and are capable of responding immediately to infecting microorganisms. The complement system is so named because it is complementary to the antibody response of the adaptive immune system. Complement proteins bind to the surfaces of microorganisms and are particularly attracted to pathogens that are already bound by antibodies. Binding of complement proteins occurs in a specific and highly regulated sequence, with each successive protein being activated by cleavage and/or structural changes induced upon binding of the preceding protein(s). After

the first few complement proteins bind, a cascade of sequential binding events follows in which the pathogen rapidly becomes coated in complement proteins.

Complement proteins perform several functions. The proteins serve as a marker to indicate the presence of a pathogen to phagocytic cells, such as macrophages and B cells, and enhance engulfment; this process is called **opsonization**. Certain complement proteins can combine to form attack complexes that open pores in microbial cell membranes. These structures destroy pathogens by causing their contents to leak, as illustrated in figure below.



The classic pathway for the complement cascade involves the attachment of several initial complement proteins to an antibody-bound pathogen followed by rapid activation and binding of many more complement proteins and the creation of destructive pores in the microbial cell envelope and cell wall. The alternate pathway does not involve antibody activation. Rather, C3 convertase spontaneously breaks down C3. Endogenous regulatory proteins prevent the complement complex from binding to host cells. Pathogens lacking these regulatory proteins are lysed.

Section Review

The innate immune system serves as a first responder to pathogenic threats that bypass natural physical and chemical barriers of the body. Using a combination of cellular and molecular attacks, the innate immune system identifies the nature of a pathogen and responds with inflammation, phagocytosis, cytokine release, destruction by NK cells, and/or a complement system. When innate mechanisms are insufficient to clear an infection, the adaptive immune response is informed and mobilized.

Exercises

1. Which of the following is a barrier against pathogens provided by the skin?

    1. high pH
    2. mucus
    3. tears
    4. desiccation

2. Although interferons have several effects, they are particularly useful against infections with which type of pathogen?

    1. bacteria
    2. viruses
    3. fungi
    4. helminths

3. Which organelle do phagocytes use to digest engulfed particles?

    1. lysosome
    2. nucleus
    3. endoplasmic reticulum
    4. mitochondria

4. Which innate immune system component uses MHC I molecules directly in its defense strategy?

    1. macrophages
    2. neutrophils
    3. NK cells
    4. interferon

5. Different MHC I molecules between donor and recipient cells can lead to rejection of a transplanted organ or tissue. Suggest a reason for this.
6. If a series of genetic mutations prevented some, but not all, of the complement proteins from binding antibodies or pathogens, would the entire complement system be compromised?

Answers

1. D
2. B

3. A
4. C
5. If the MHC I molecules expressed on donor cells differ from the MHC I molecules expressed on recipient cells, NK cells may identify the donor cells as “non-self” and produce perforin and granzymes to induce the donor cells to undergo apoptosis, which would destroy the transplanted organ.
6. The entire complement system would probably be affected even when only a few members were mutated such that they could no longer bind. Because the complement involves the binding of activated proteins in a specific sequence, when one or more proteins in the sequence are absent, the subsequent proteins would be incapable of binding to elicit the complement’s pathogen-destructive effects.

Adaptation

This chapter was adapted by Morgan Alford from the following text:

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Adaptive Immune Responses

CHARLES MOLNAR; JANE GAIR; AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

- Explain adaptive immunity.
- Compare and contrast adaptive and innate immunity.
- Describe cell-mediated immune response and humoral immune response.
- Describe immune tolerance.

The adaptive, or acquired, immune response takes days or even weeks to become established—much longer than the innate response; however, adaptive immunity is more specific to pathogens and has memory. **Adaptive immunity** is an immunity that occurs after exposure to an antigen either from a pathogen or a vaccination. This part of the immune system is activated when the innate immune response is insufficient to control an infection. In fact, without information from the innate immune system, the adaptive response could not be mobilized. There are two types of adaptive responses: the **cell-mediated immune response**, which is carried out by T cells, and the **humoral immune response**, which is controlled by activated B cells and antibodies. Activated T cells and B cells that are specific to molecular structures on the pathogen proliferate and attack the invading pathogen. Their attack can kill pathogens directly or secrete antibodies that enhance the phagocytosis of pathogens and disrupt the infection. Adaptive immunity also involves a memory to provide the host with long-term protection from reinfection with the same type of pathogen; on re-exposure, this memory will facilitate an efficient and quick response.

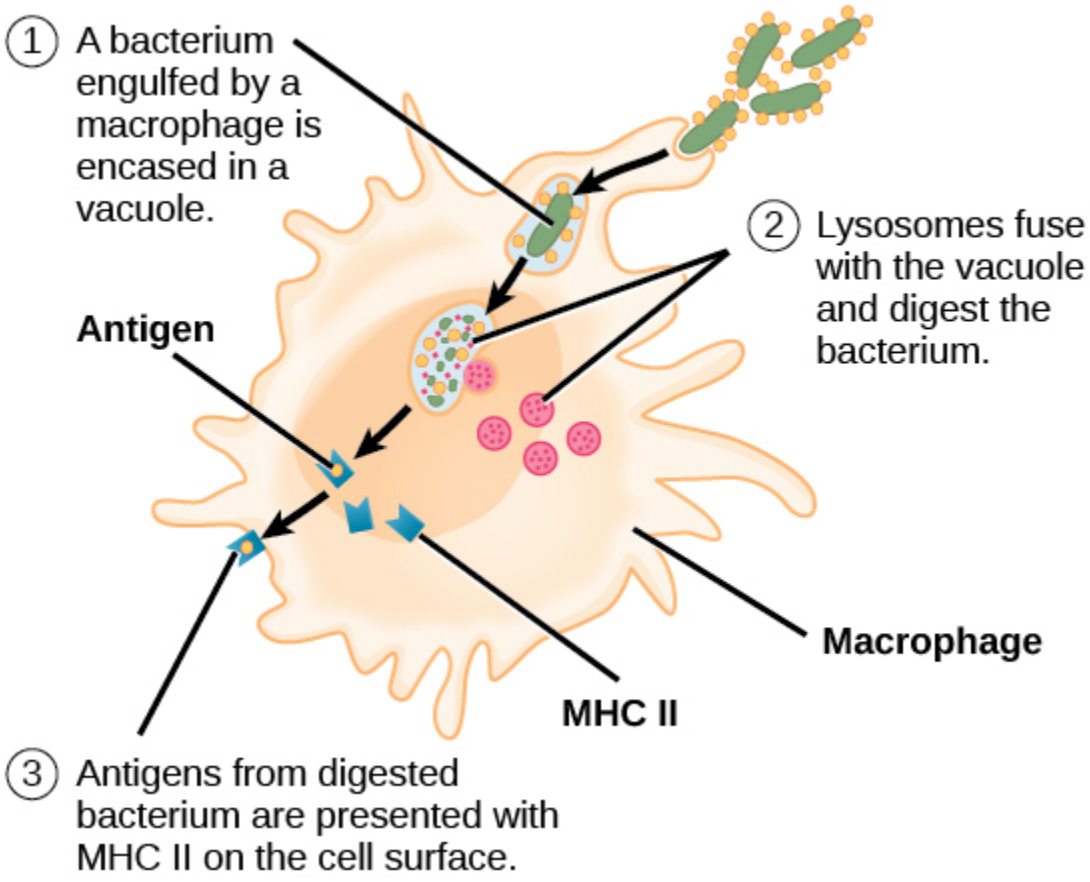
Antigen-Presenting Cells

Unlike NK cells of the innate immune system, B cells (B lymphocytes) are a type of white blood cell that gives rise to antibodies, whereas T cells (T lymphocytes) are a type of white blood cell that plays an important role in the immune response. T cells are a key component in the cell-mediated response—the specific immune response that utilizes T cells to neutralize cells that have been infected with viruses and certain bacteria. There are three types of T cells: cytotoxic, helper, and suppressor T cells. Cytotoxic T cells destroy virus-infected cells in the cell-mediated immune response, and helper T cells play a part in activating both the antibody and the cell-mediated immune responses. Suppressor T cells deactivate T cells and B cells when needed, and thus prevent the immune response from becoming too intense.

An **antigen** is a foreign or "non-self" macromolecule that reacts with cells of the immune system. Not all antigens will provoke a response. For instance, individuals produce innumerable "self" antigens and are constantly exposed to harmless foreign antigens, such as food proteins, pollen, or dust components. The suppression of immune responses to harmless macromolecules is highly regulated and typically prevents processes that could be damaging to the host, known as tolerance.

The innate immune system contains cells that detect potentially harmful antigens, and then inform the adaptive immune response about the presence of these antigens. An **antigen-presenting cell** (APC) is an immune cell that detects, engulfs, and informs the adaptive immune response about an infection. When a pathogen is detected, these APCs will phagocytose the pathogen and digest it to form many different fragments of the antigen. Antigen fragments will then be transported to the surface of the APC, where they will serve as an indicator to other immune cells. **Dendritic cells** are immune cells that process antigen material; they are present in the skin (Langerhans cells) and the lining of the nose, lungs, stomach, and intestines. Sometimes a dendritic cell presents on the surface of other cells to induce an immune response, thus functioning as an antigen-presenting cell. Macrophages also function as APCs. Before activation and differentiation, B cells can also function as APCs.

After phagocytosis by APCs, the phagocytic vesicle fuses with an intracellular lysosome forming phagolysosome. Within the phagolysosome, the components are broken down into fragments; the fragments are then loaded onto MHC class I or MHC class II molecules and are transported to the cell surface for antigen presentation. Note that T lymphocytes cannot properly respond to the antigen unless it is processed and embedded in an MHC II molecule. APCs express MHC on their surfaces, and when combined with a foreign antigen, these complexes signal a "non-self" invader. Once the fragment of antigen is embedded in the MHC II molecule, the immune cell can respond. Helper T cells are one of the main lymphocytes that respond to antigen-presenting cells. Recall that all other nucleated cells of the body expressed MHC I molecules, which signal "healthy" or "normal."



An APC, such as a macrophage, engulfs and digests a foreign bacterium. An antigen from the bacterium is presented on the cell surface in conjunction with an MHC II molecule Lymphocytes of the adaptive immune response interact with antigen-embedded MHC II molecules to mature into functional immune cells.

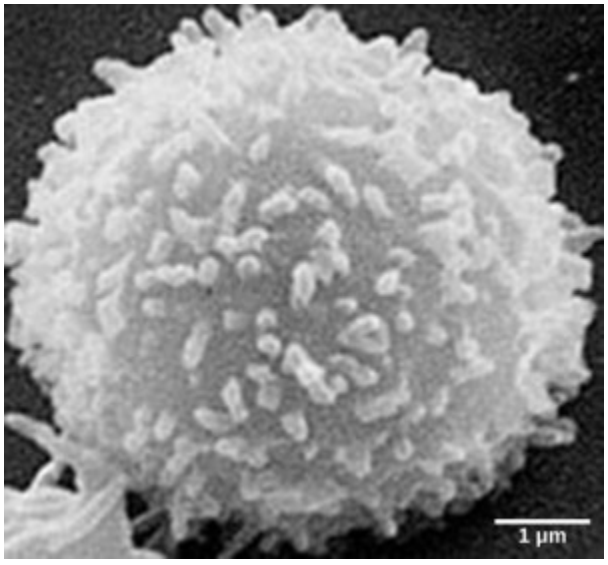
Concept in Action

This animation from Rockefeller University shows how dendritic cells act as sentinels in the body's immune system.

T and B Lymphocytes

Lymphocytes in human circulating blood are approximately 80 to 90 percent T cells and 10 to 20 percent B cells. Recall that the T cells are involved in the cell-mediated immune response, whereas B cells are part of the humoral immune response.

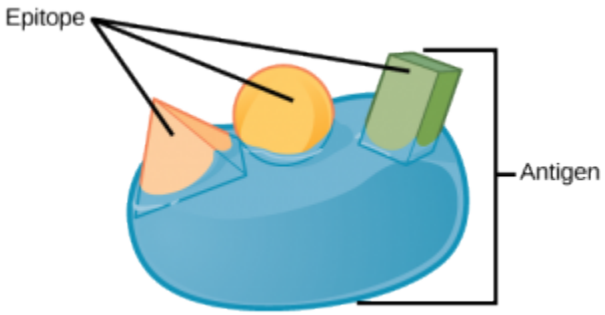
T cells encompass a heterogeneous population of cells with extremely diverse functions. Some T cells respond to APCs of the innate immune system, and indirectly induce immune responses by releasing cytokines. Other T cells stimulate B cells to prepare their own response. Another population of T cells detects APC signals and directly kills the infected cells. Other T cells are involved in suppressing inappropriate immune reactions to harmless or "self" antigens.



This scanning electron micrograph shows a T lymphocyte, which is responsible for the cell-mediated immune response. T cells are able to recognize antigens.

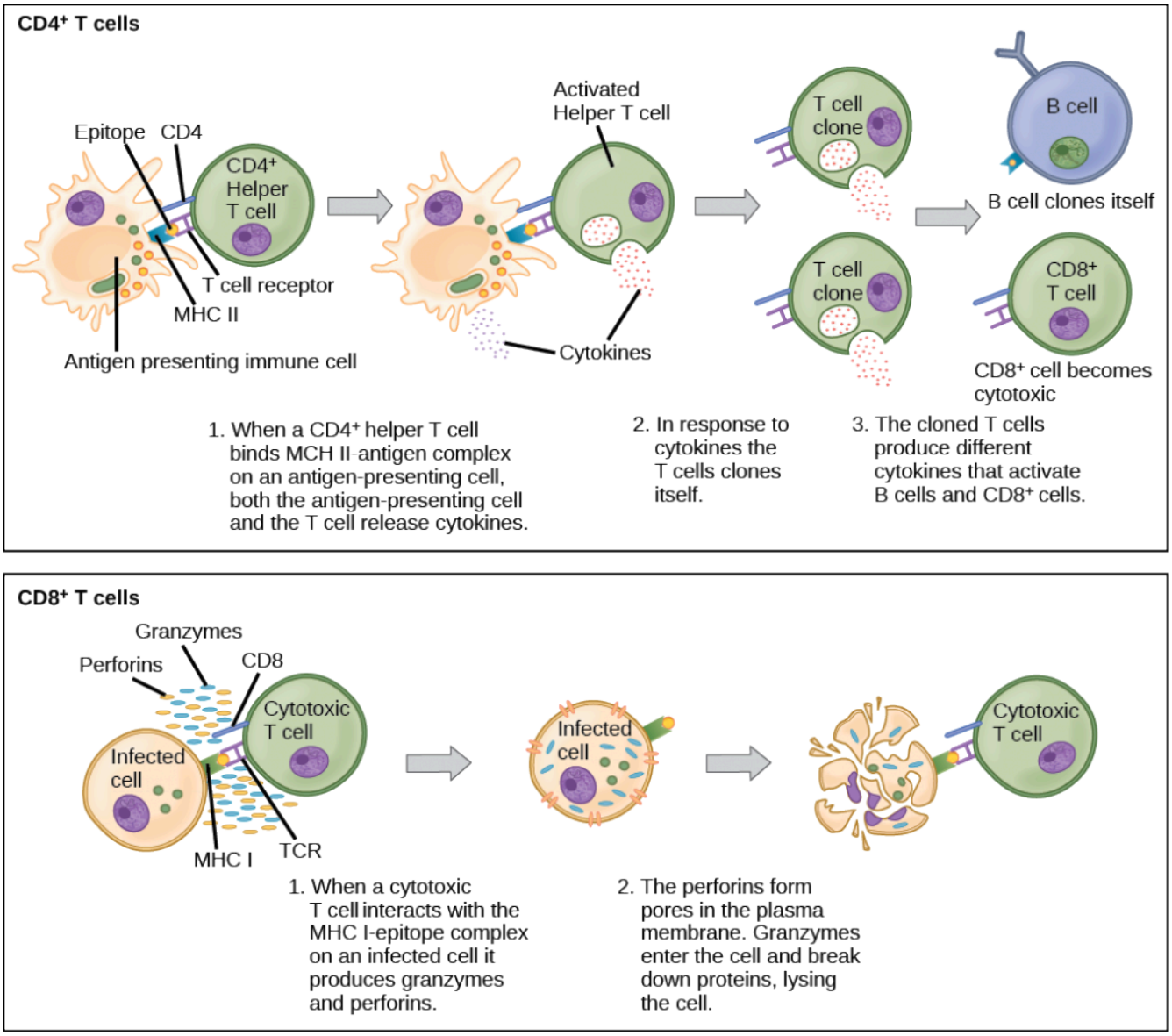
T and B cells exhibit a common theme of recognition/binding of specific antigens via a complementary receptor, followed by activation and self-amplification/maturation to specifically bind to the particular antigen of the infecting

pathogen. T and B lymphocytes are also similar in that each cell only expresses one type of antigen receptor. Any individual may possess a population of T and B cells that together express a near limitless variety of antigen receptors that are capable of recognizing virtually any infecting pathogen. T and B cells are activated when they recognize small components of antigens, called **epitopes**, presented by APCs. Note that recognition occurs at a specific epitope rather than on the entire antigen; for this reason, epitopes are known as "antigenic determinants." In the absence of information from APCs, T and B cells remain inactive, or naïve, and are unable to prepare an immune response. The requirement for information from the APCs of innate immunity to trigger B cell or T cell activation illustrates the essential nature of the innate immune response to the functioning of the entire immune system.



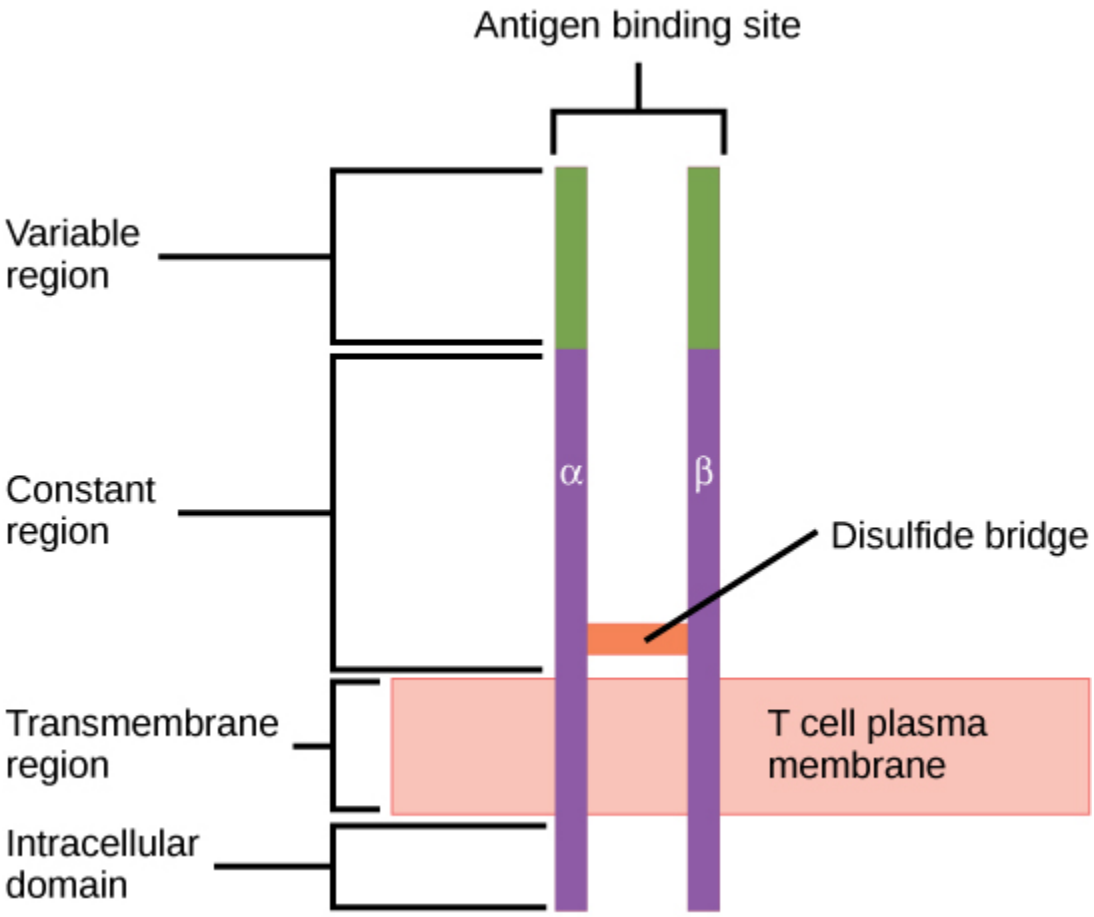
An antigen is a macromolecule that reacts with components of the immune system. A given antigen may contain several motifs that are recognized by immune cells. Each motif is an epitope. In this figure, the entire structure is an antigen, and the orange, salmon and green components projecting from it represent potential epitopes.

Naïve T cells can express one of two different molecules, CD4 or CD8, on their surface and are accordingly classified as $CD4^+$ or $CD8^+$ cells. These molecules are important because they regulate how a T cell will interact with and respond to an APC. Naïve $CD4^+$ cells bind APCs via their antigen-embedded MHC II molecules and are stimulated to become **helper T (T_H) lymphocytes**, cells that go on to stimulate B cells (or cytotoxic T cells) directly or secrete cytokines to inform more and various target cells about the pathogenic threat. In contrast, $CD8^+$ cells engage antigen-embedded MHC I molecules on APCs and are stimulated to become **cytotoxic T lymphocytes** (CTLs), which directly kill infected cells by apoptosis and emit cytokines to amplify the immune response. The two populations of T cells have different mechanisms of immune protection, but both bind MHC molecules via their antigen receptors called T cell receptors (TCRs). The CD4 or CD8 surface molecules differentiate whether the TCR will engage an MHC II or an MHC I molecule. Because they assist in binding specificity, the CD4 and CD8 molecules are described as coreceptors.



Naïve CD4+ T cells engage MHC II molecules on antigen-presenting cells (APCs) and become activated. Clones of the activated helper T cell, in turn, activate B cells and CD8+ T cells, which become cytotoxic T cells. Cytotoxic T cells kill infected cells.

Consider the innumerable possible antigens that an individual will be exposed to during a lifetime. The mammalian adaptive immune system is adept in responding appropriately to each antigen. Mammals have an enormous diversity of T cell populations, resulting from the diversity of TCRs. Each TCR consists of two polypeptide chains that span the T cell membrane; the chains are linked by a disulfide bridge. Each polypeptide chain is comprised of a constant domain and a variable domain: a domain, in this sense, is a specific region of a protein that may be regulatory or structural. The intracellular domain is involved in intracellular signaling. A single T cell will express thousands of identical copies of one specific TCR variant on its cell surface. The specificity of the adaptive immune system occurs because it synthesizes millions of different T cell populations, each expressing a TCR that differs in its variable domain. This TCR diversity is achieved by the mutation and recombination of genes that encode these receptors in stem cell precursors of T cells. The binding between an antigen-displaying MHC molecule and a complementary TCR "match" indicates that the adaptive immune system needs to activate and produce that specific T cell because its structure is appropriate to recognize and destroy the invading pathogen.



A T cell receptor spans the membrane and projects variable binding regions into the extracellular space to bind processed antigens via MHC molecules on APCs.

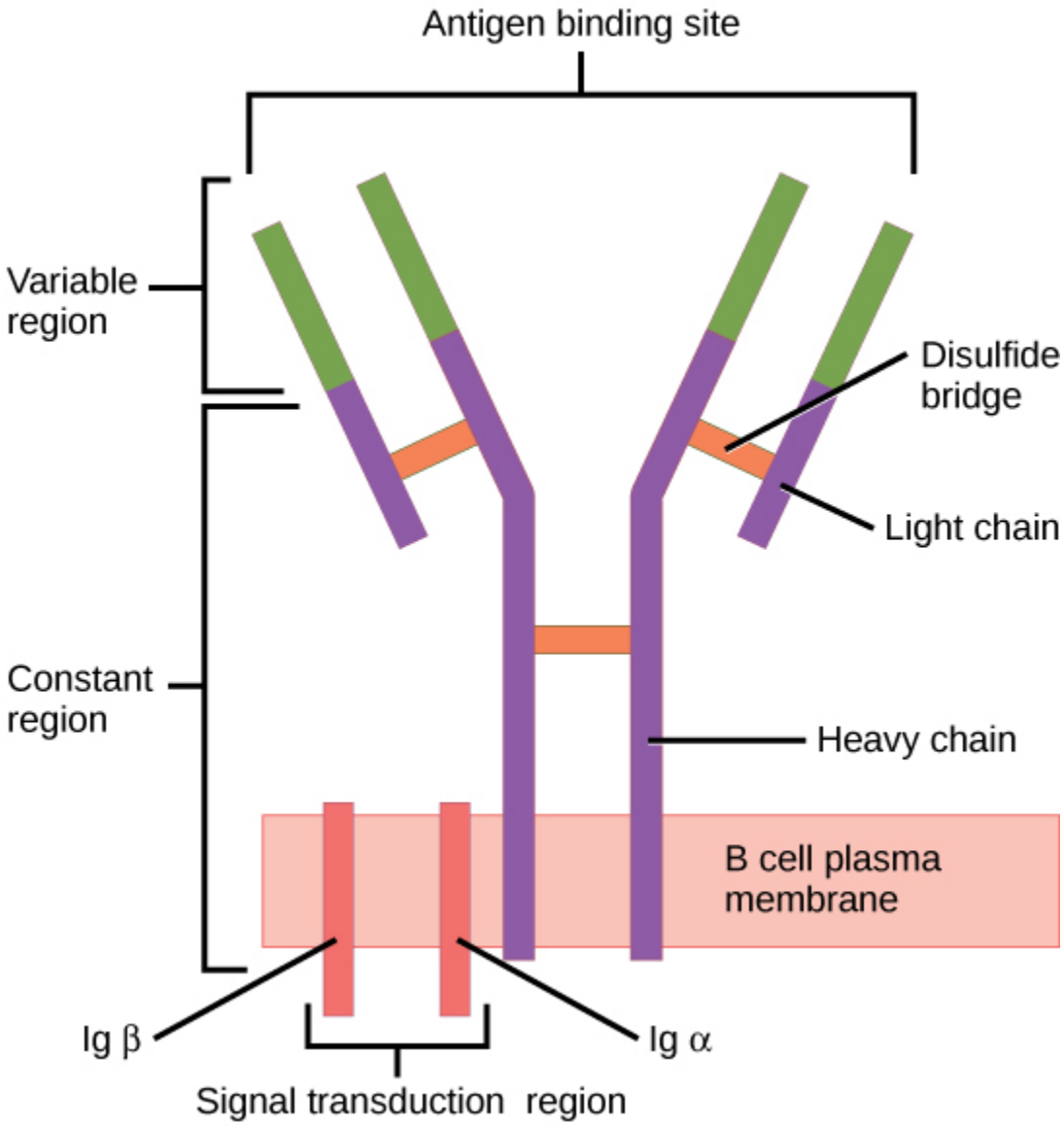
Helper T Lymphocytes

The T_H lymphocytes function indirectly to identify potential pathogens for other cells of the immune system. These cells are important for extracellular infections, such as those caused by certain bacteria, helminths, and protozoa. T_H lymphocytes recognize specific antigens displayed in the MHC II complexes of APCs. There are two major populations of T_H cells: T_H1 and T_H2. T_H1 cells secrete cytokines to enhance the activities of macrophages and other T cells. T_H1 cells activate the action of cyotoxic T cells, as well as macrophages. T_H2 cells stimulate naïve B cells to destroy foreign invaders via antibody secretion. Whether a T_H1 or a T_H2 immune response develops depends on the specific types of cytokines secreted by cells of the innate immune system, which in turn depends on the nature of the invading pathogen.

The T_H1-mediated response involves macrophages and is associated with inflammation. Recall the frontline defenses of macrophages involved in the innate immune response. Some intracellular bacteria, such as *Mycobacterium tuberculosis*, have evolved to multiply in macrophages after they have been engulfed. These pathogens evade attempts by macrophages to destroy and digest the pathogen. When *M. tuberculosis* infection occurs, macrophages can stimulate naïve T cells to become T_H1 cells. These stimulated T cells secrete specific cytokines that send feedback to the macrophage to stimulate its digestive capabilities and allow it to destroy the colonizing *M. tuberculosis*. In the same manner, T_H1-activated macrophages also become better suited to ingest and kill tumor cells. In summary; T_H1 responses are directed toward intracellular invaders while T_H2 responses are aimed at those that are extracellular.

B Lymphocytes

When stimulated by the T_H2 pathway, naïve B cells differentiate into antibody-secreting plasma cells. A **plasma cell** is an immune cell that secrets antibodies; these cells arise from B cells that were stimulated by antigens. Similar to T cells, naïve B cells initially are coated in thousands of B cell receptors (BCRs), which are membrane-bound forms of Ig (immunoglobulin, or an antibody). The B cell receptor has two heavy chains and two light chains connected by disulfide linkages. Each chain has a constant and a variable region; the latter is involved in antigen binding. Two other membrane proteins, Ig alpha and Ig beta, are involved in signaling. The receptors of any particular B cell are all the same, but the hundreds of millions of different B cells in an individual have distinct recognition domains that contribute to extensive diversity in the types of molecular structures to which they can bind. In this state, B cells function as APCs. They bind and engulf foreign antigens via their BCRs and then display processed antigens in the context of MHC II molecules to T_H2 cells. When a T_H2 cell detects that a B cell is bound to a relevant antigen, it secretes specific cytokines that induce the B cell to proliferate rapidly, which makes thousands of identical (clonal) copies of it, and then it synthesizes and secretes antibodies with the same antigen recognition pattern as the BCRs. The activation of B cells corresponding to one specific BCR variant and the dramatic proliferation of that variant is known as **clonal selection**. This phenomenon drastically, but briefly, changes the proportions of BCR variants expressed by the immune system, and shifts the balance toward BCRs specific to the infecting pathogen.



B cell receptors are embedded in the membranes of B cells and bind a variety of antigens through their variable regions. The signal transduction region transfers the signal into the cell.

T and B cells differ in one fundamental way: whereas T cells bind antigens that have been digested and embedded in MHC molecules by APCs, B cells function as APCs that bind intact antigens that have not been processed. Although T and B cells both react with molecules that are termed "antigens," these lymphocytes actually respond to very different types of molecules. B cells must be able to bind intact antigens because they secrete antibodies that must recognize the pathogen directly, rather than digested remnants of the pathogen. Bacterial carbohydrate and lipid molecules can activate B cells independently from the T cells.

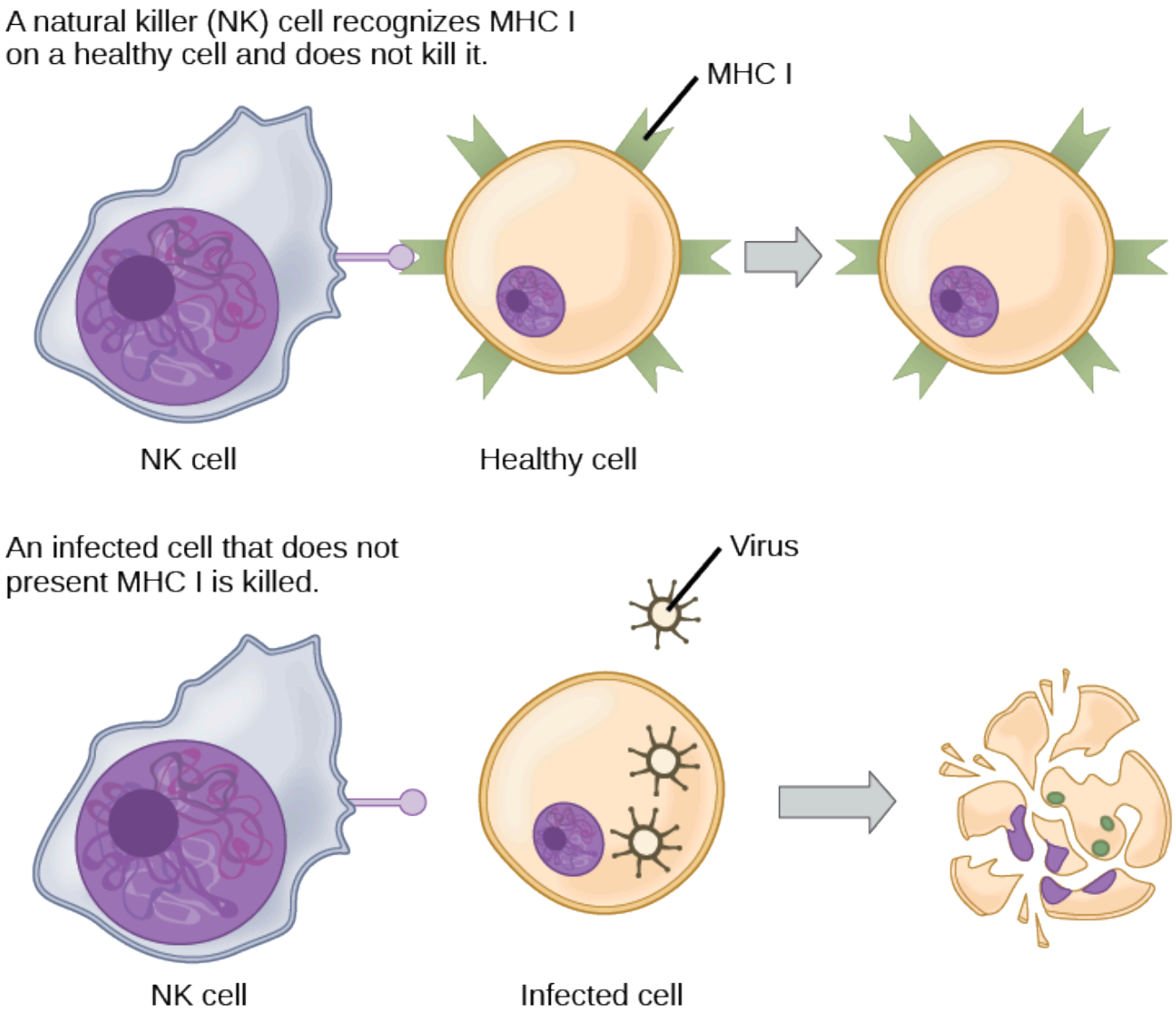
Cytotoxic T Lymphocytes

CTLs, a subclass of T cells, function to clear infections directly. The cell-mediated part of the adaptive immune

system consists of CTLs that attack and destroy infected cells. CTLs are particularly important in protecting against viral infections; this is because viruses replicate within cells where they are shielded from extracellular contact with circulating antibodies. When APCs phagocytize pathogens and present MHC I-embedded antigens to naïve $CD8^+$ T cells that express complementary TCRs, the $CD8^+$ T cells become activated to proliferate according to clonal selection. These resulting CTLs then identify non-APCs displaying the same MHC I-embedded antigens (for example, viral proteins)—for example, the CTLs identify infected host cells.

Intracellularly, infected cells typically die after the infecting pathogen replicates to a sufficient concentration and lyses the cell, as many viruses do. CTLs attempt to identify and destroy infected cells before the pathogen can replicate and escape, thereby halting the progression of intracellular infections. CTLs also support NK lymphocytes to destroy early cancers. Cytokines secreted by the T_H1 response that stimulates macrophages also stimulate CTLs and enhance their ability to identify and destroy infected cells and tumors.

CTLs sense MHC I-embedded antigens by directly interacting with infected cells via their TCRs. Binding of TCRs with antigens activates CTLs to release perforin and granzyme, degradative enzymes that will induce apoptosis of the infected cell. Recall that this is a similar destruction mechanism to that used by NK cells. In this process, the CTL does not become infected and is not harmed by the secretion of perforin and granzymes. In fact, the functions of NK cells and CTLs are complementary and maximize the removal of infected cells. If the NK cell cannot identify the "missing self" pattern of down-regulated MHC I molecules, then the CTL can identify it by the complex of MHC I with foreign antigens, which signals "altered self." Similarly, if the CTL cannot detect antigen-embedded MHC I because the receptors are depleted from the cell surface, NK cells will destroy the cell instead. CTLs also emit cytokines, such as interferons, that alter surface protein expression in other infected cells, such that the infected cells can be easily identified and destroyed. Moreover, these interferons can also prevent virally infected cells from releasing virus particles.



Natural killer (NK) cells recognize the MHC I receptor on healthy cells. If MHC I is absent, the cell is lysed.

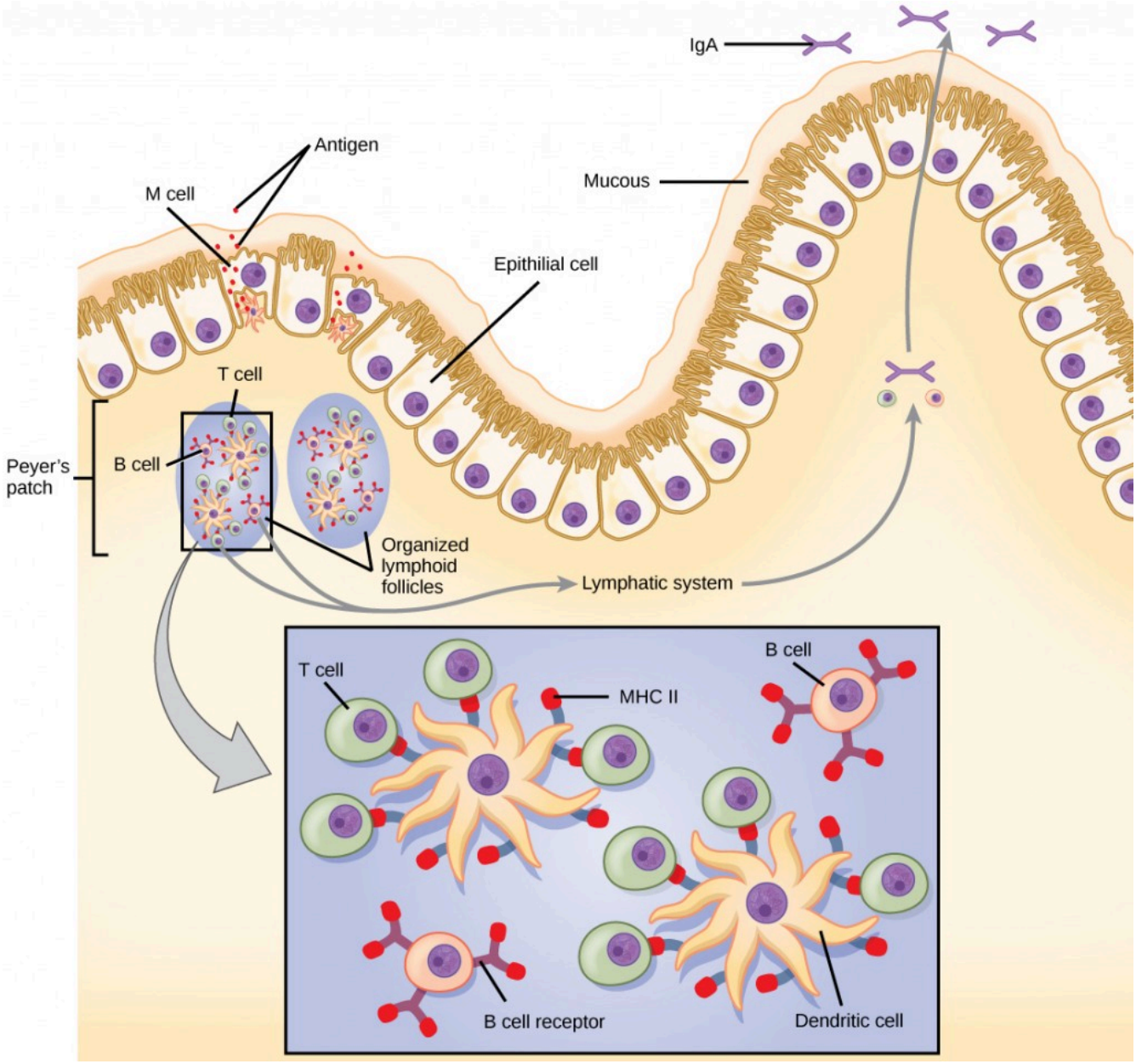
Based on what you know about MHC receptors, why do you think an organ transplanted from an incompatible donor to a recipient will be rejected?

Plasma cells and CTLs are collectively called **effector cells**: they represent differentiated versions of their naïve counterparts, and they are involved in bringing about the immune defense of killing pathogens and infected host cells.

Mucosal Surfaces and Immune Tolerance

The innate and adaptive immune responses discussed thus far comprise the systemic immune system (affecting the whole body), which is distinct from the mucosal immune system. Mucosal immunity is formed by mucosa-associated lymphoid tissue, which functions independently of the systemic immune system, and which has its own innate and adaptive components. **Mucosa-associated lymphoid tissue** (MALT), is a collection of lymphatic tissue that combines

with epithelial tissue lining the mucosa throughout the body. This tissue functions as the immune barrier and response in areas of the body with direct contact to the external environment. The systemic and mucosal immune systems use many of the same cell types. Foreign particles that make their way to MALT are taken up by absorptive epithelial cells called M cells and delivered to APCs located directly below the mucosal tissue. M cells function in the transport described, and are located in the Peyer's patch, a lymphoid nodule. APCs of the mucosal immune system are primarily dendritic cells, with B cells and macrophages having minor roles. Processed antigens displayed on APCs are detected by T cells in the MALT and at various mucosal induction sites, such as the tonsils, adenoids, appendix, or the mesenteric lymph nodes of the intestine. Activated T cells then migrate through the lymphatic system and into the circulatory system to mucosal sites of infection.



The topology and function of intestinal MALT is shown. Pathogens are taken up by M cells in the intestinal epithelium and excreted into a pocket formed by the inner surface of the cell. The pocket contains antigen-presenting cells such as dendritic cells, which engulf the antigens, then present them with MHC II molecules on the cell surface. The dendritic cells migrate to an underlying tissue called a Peyer's patch. Antigen-presenting cells, T cells, and B cells aggregate within the Peyer's patch, forming organized lymphoid follicles. There, some T cells and B cells are activated. Other antigen-loaded dendritic cells migrate through the lymphatic system where they activate B cells, T cells, and plasma cells in the lymph nodes. The activated cells then return to MALT tissue effector sites. IgA and other antibodies are secreted into the intestinal lumen.

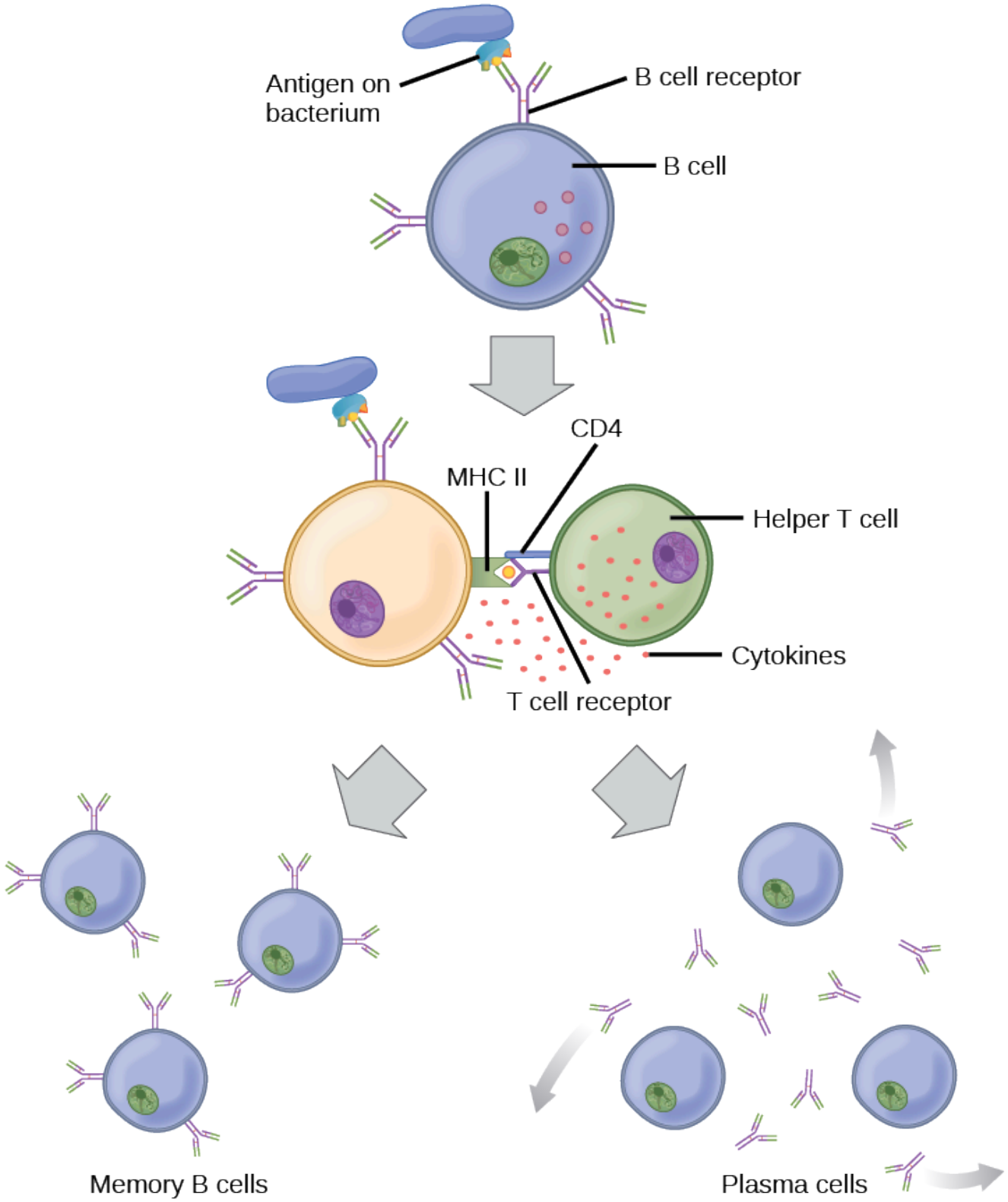
MALT is a crucial component of a functional immune system because mucosal surfaces, such as the nasal passages, are the first tissues onto which inhaled or ingested pathogens are deposited. The mucosal tissue includes the mouth, pharynx, and esophagus, and the gastrointestinal, respiratory, and urogenital tracts.

The immune system has to be regulated to prevent wasteful, unnecessary responses to harmless substances, and more importantly so that it does not attack "self." The acquired ability to prevent an unnecessary or harmful immune response to a detected foreign substance known not to cause disease is described as **immune tolerance**. Immune tolerance is crucial for maintaining mucosal homeostasis given the tremendous number of foreign substances (such as food proteins) that APCs of the oral cavity, pharynx, and gastrointestinal mucosa encounter. Immune tolerance is brought about by specialized APCs in the liver, lymph nodes, small intestine, and lung that present harmless antigens to an exceptionally diverse population of regulatory T (T**regulatory T (T_{reg}) cells**) cells, specialized lymphocytes that suppress local inflammation and inhibit the secretion of stimulatory immune factors. The combined result of T_{reg} cells is to prevent immunologic activation and inflammation in undesired tissue compartments and to allow the immune system to focus on pathogens instead. In addition to promoting immune tolerance of harmless antigens, other subsets of T_{reg} cells are involved in the prevention of the **autoimmune response**, which is an inappropriate immune response to host cells or self-antigens. Another T_{reg} class suppresses immune responses to harmful pathogens after the infection has cleared to minimize host cell damage induced by inflammation and cell lysis.

Immunological Memory

The adaptive immune system possesses a memory component that allows for an efficient and dramatic response upon reinvasion of the same pathogen. Memory is handled by the adaptive immune system with little reliance on cues from the innate response. During the adaptive immune response to a pathogen that has not been encountered before, called a primary response, plasma cells secreting antibodies and differentiated T cells increase, then plateau over time. As B and T cells mature into effector cells, a subset of the naïve populations differentiates into B and T memory cells with the same antigen specificities.

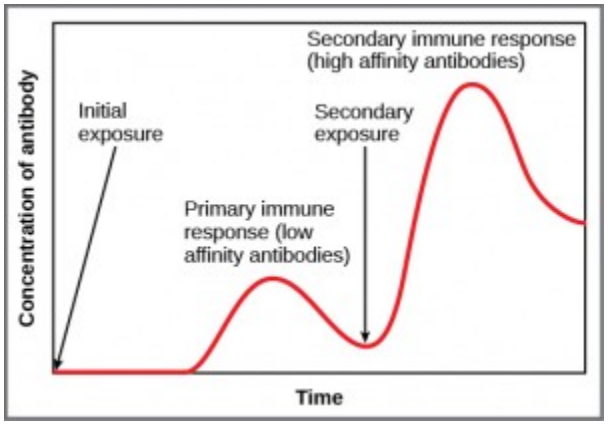
A **memory cell** is an antigen-specific B or T lymphocyte that does not differentiate into effector cells during the primary immune response, but that can immediately become effector cells upon re-exposure to the same pathogen. During the primary immune response, memory cells do not respond to antigens and do not contribute to host defenses. As the infection is cleared and pathogenic stimuli subside, the effectors are no longer needed, and they undergo apoptosis. In contrast, the memory cells persist in the circulation.



After initially binding an antigen to the B cell receptor (BCR), a B cell internalizes the antigen and presents it on MHC II. A helper T cell recognizes the MHC II–antigen complex and activates the B cell. As a result, memory B cells and plasma cells are made.

The Rh antigen is found on Rh-positive red blood cells. An Rh-negative female can usually carry an Rh-positive fetus

to term without difficulty. However, if she has a second Rh-positive fetus, her body may launch an immune attack that causes hemolytic disease of the newborn. Why do you think hemolytic disease is only a problem during the second or subsequent pregnancies? If the pathogen is never encountered again during the individual's lifetime, B and T memory cells will circulate for a few years or even several decades and will gradually die off, having never functioned as effector cells. However, if the host is re-exposed to the same pathogen type, circulating memory cells will immediately differentiate into plasma cells and CTLs without input from APCs or T_H cells. One reason the adaptive immune response is delayed is because it takes time for naïve B and T cells with the appropriate antigen specificities to be identified and activated. Upon reinfection, this step is skipped, and the result is a more rapid production of immune defenses. Memory B cells that differentiate into plasma cells output tens to hundreds-fold greater antibody amounts than were secreted during the primary response, as the graph below illustrates. This rapid and dramatic antibody response may stop the infection before it can even become established, and the individual may not realize they had been exposed.



In the primary response to infection, antibodies are secreted first from plasma cells. Upon re-exposure to the same pathogen, memory cells differentiate into antibody-secreting plasma cells that output a greater amount of antibody for a longer period of time.

Vaccination is based on the knowledge that exposure to noninfectious antigens, derived from known pathogens, generates a mild primary immune response. The immune response to vaccination may not be perceived by the host as illness but still confers immune memory. When exposed to the corresponding pathogen to which an individual was vaccinated, the reaction is similar to a secondary exposure. Because each reinfection generates more memory cells and increased resistance to the pathogen, and because some memory cells die, certain vaccine courses involve one or more booster vaccinations to mimic repeat exposures: for instance, tetanus boosters are necessary every ten years because the memory cells only live that long.

Mucosal Immune Memory

A subset of T and B cells of the mucosal immune system differentiates into memory cells just as in the systemic immune system. Upon reinvasion of the same pathogen type, a pronounced immune response occurs at the mucosal site where the original pathogen deposited, but a collective defense is also organized within interconnected or adjacent mucosal tissue. For instance, the immune memory of an infection in the oral cavity would also elicit a response in the pharynx if the oral cavity was exposed to the same pathogen.

Vaccination

Vaccination (or immunization) involves the delivery, usually by injection, of noninfectious antigen(s) derived from known pathogens. Other components, called adjuvants, are delivered in parallel to help stimulate the immune response. Immunological memory is the reason vaccines work. Ideally, the effect of vaccination is to elicit immunological memory, and thus resistance to specific pathogens without the individual having to experience an infection.



A Hepatitis-B vaccine is administered to a Sailor aboard the Nimitz class aircraft carrier USS Ronald Reagan (CVN 76). Reagan is currently underway conducting routine carrier operations. U.S. Navy photo by Photographer's Mate Airman Apprentice Christopher D. Blachly.

Vaccinologists are involved in the process of vaccine development from the initial idea to the availability of the completed vaccine. This process can take decades, can cost millions of dollars, and can involve many obstacles along the way. For instance, injected vaccines stimulate the systemic immune system, eliciting humoral and cell-mediated immunity, but have little effect on the mucosal response, which presents a challenge because many pathogens are deposited and replicate in mucosal compartments, and the injection does not provide the most efficient immune memory for these disease agents. For this reason, vaccinologists are actively involved in developing new vaccines that are applied via intranasal, aerosol, oral, or transcutaneous (absorbed through the skin) delivery methods. Importantly, mucosal-administered vaccines elicit both mucosal and systemic immunity and produce the same level of disease resistance as injected vaccines.

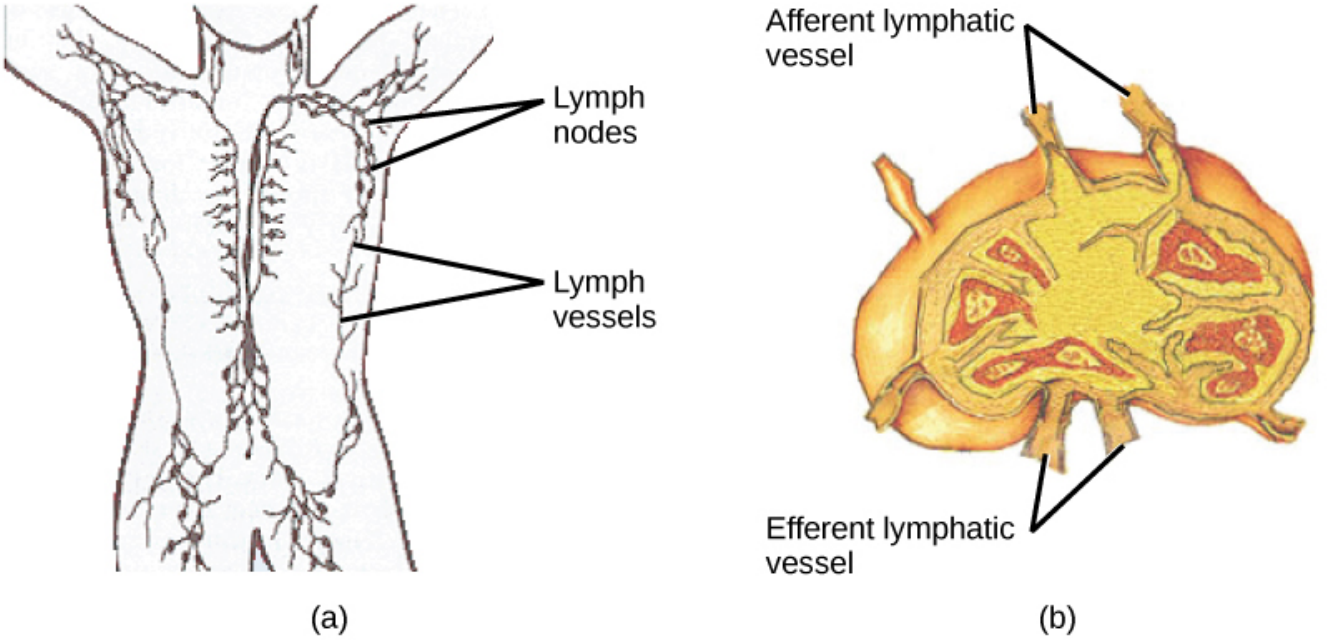
Primary Centers of the Immune System

Although the immune system is characterized by circulating cells throughout the body, the regulation, maturation,

and intercommunication of immune factors occur at specific sites. The blood circulates immune cells, proteins, and other factors through the body. Approximately 0.1 percent of all cells in the blood are leukocytes, which encompass monocytes (the precursor of macrophages) and lymphocytes. The majority of cells in the blood are erythrocytes (red blood cells). **Lymph** is a watery fluid that bathes tissues and organs with protective white blood cells and does not contain erythrocytes. Cells of the immune system can travel between the distinct lymphatic and blood circulatory systems, which are separated by interstitial space, by a process called extravasation (passing through to surrounding tissue).

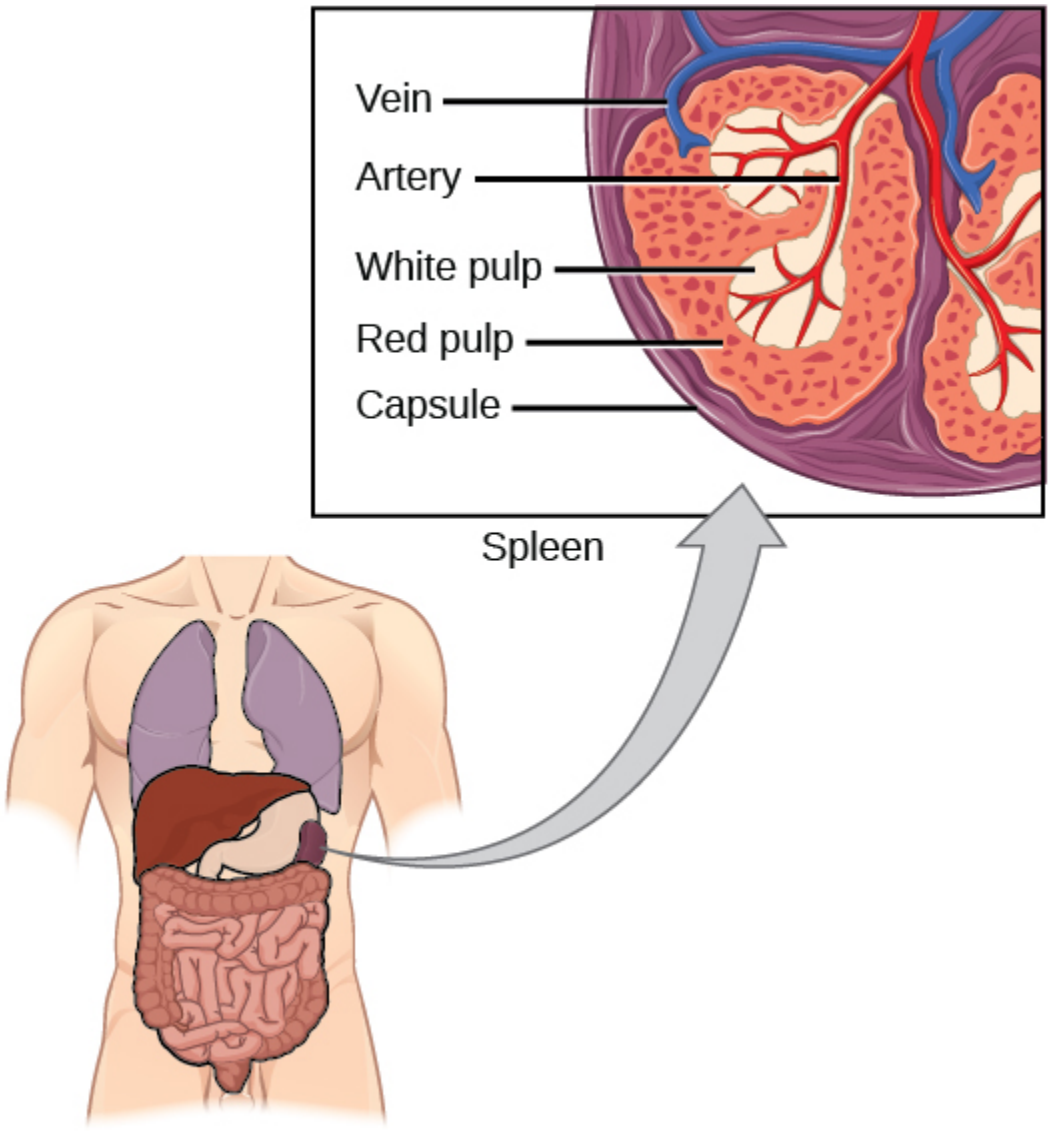
The cells of the immune system originate from hematopoietic stem cells in the bone marrow. Cytokines stimulate these stem cells to differentiate into immune cells. B cell maturation occurs in the bone marrow, whereas naïve T cells transit from the bone marrow to the thymus for maturation. In the thymus, immature T cells that express TCRs complementary to self-antigens are destroyed. This process helps prevent autoimmune responses.

On maturation, T and B lymphocytes circulate to various destinations. Lymph nodes scattered throughout the body house large populations of T and B cells, dendritic cells, and macrophages. Lymph gathers antigens as it drains from tissues. These antigens then are filtered through lymph nodes before the lymph is returned to circulation. APCs in the lymph nodes capture and process antigens and inform nearby lymphocytes about potential pathogens.



(a) Lymphatic vessels carry a clear fluid called lymph throughout the body. The liquid enters (b) lymph nodes through afferent vessels. Lymph nodes are filled with lymphocytes that purge infecting cells. The lymph then exits through efferent vessels. (Credit: modification of work by NIH, NCI)

The spleen houses B and T cells, macrophages, dendritic cells, and NK cells. The spleen is the site where APCs that have trapped foreign particles in the blood can communicate with lymphocytes. Antibodies are synthesized and secreted by activated plasma cells in the spleen, and the spleen filters foreign substances and antibody-complexed pathogens from the blood. Functionally, the spleen is to the blood as lymph nodes are to the lymph.



The spleen is similar to a lymph node but is much larger and filters blood instead of lymph. Blood enters the spleen through arteries and exits through veins. The spleen contains two types of tissue: red pulp and white pulp. Red pulp consists of cavities that store blood. Within the red pulp, damaged red blood cells are removed and replaced by new ones. White pulp is rich in lymphocytes that remove antigen-coated bacteria from the blood. (Credit: modification of work by NCI)

Section Review

The adaptive immune response is a slower-acting, longer-lasting, and more specific response than the innate response. However, the adaptive response requires information from the innate immune system to function. APCs display antigens via MHC molecules to complementary naïve T cells. In response, the T cells differentiate and proliferate, becoming T_H cells or CTLs. T_H cells stimulate B cells that have engulfed and presented pathogen-derived antigens. B cells differentiate into plasma cells that secrete antibodies, whereas CTLs induce apoptosis in intracellularly infected or cancerous cells. Memory cells persist after a primary exposure to a pathogen. If re-exposure occurs, memory cells differentiate into

effector cells without input from the innate immune system. The mucosal immune system is largely independent from the systemic immune system but functions in a parallel fashion to protect the extensive mucosal surfaces of the body.

Exercises

1. Which of the following statements about T cells is false?

    1. Helper T cells release cytokines while cytotoxic T cells kill the infected cell.
    2. Helper T cells are CD4+, while cytotoxic T cells are $CD8^{+}$.
    3. MHC II is a receptor found on most body cells, while MHC I is a receptor found on immune cells only.
    4. The T cell receptor is found on both $CD4^{+}$ and $CD8^{+}$ T cells.

2. Based on what you know about MHC receptors, why do you think an organ transplanted from an incompatible donor to a recipient will be rejected?
3. The Rh antigen is found on Rh-positive red blood cells. An Rh-negative female can usually carry an Rh-positive fetus to term without difficulty. However, if she has a second Rh-positive fetus, her body may launch an immune attack that causes hemolytic disease of the newborn. Why do you think hemolytic disease is only a problem during the second or subsequent pregnancies?
4. Which of the following is both a phagocyte and an antigen-presenting cell?

    1. NK cell
    2. eosinophil
    3. neutrophil
    4. macrophage

5. Which immune cells bind MHC molecules on APCs via CD8 coreceptors on their cell surfaces?

    1. T_H cells
    2. CTLs
    3. mast cells
    4. basophils

6. What "self" pattern is identified by NK cells?

    1. altered self
    2. missing self
    3. normal self
    4. non-self

7. The acquired ability to prevent an unnecessary or destructive immune reaction to a harmless foreign particle, such as a food protein, is called _____.

    1. the T_H2 response
    2. allergy
    3. immune tolerance
    4. autoimmunity

8. A memory B cell can differentiate upon re-exposure to a pathogen of which cell type?

1. CTL
2. naïve B cell
3. memory T cell
4. plasma cell

9. Foreign particles circulating in the blood are filtered by the _____.

    1. spleen
    2. lymph nodes
    3. MALT
    4. lymph

10. Explain the difference between an epitope and an antigen.
11. What is a naïve B or T cell?
12. How does the T_H1 response differ from the T_H2 response?
13. In mammalian adaptive immune systems, T cell receptors are extraordinarily diverse. What function of the immune system results from this diversity, and how is this diversity achieved?
14. How do B and T cells differ with respect to antigens that they bind?
15. Why is the immune response after reinfection much faster than the adaptive immune response after the initial infection?

Answers

1. C
2. MHC receptors differ from person to person. Thus, MHC receptors on an incompatible donor are considered "non-self" and are rejected by the immune system.
3. If the blood of the mother and fetus mixes, memory cells that recognize the Rh antigen can form late in the first pregnancy. During subsequent pregnancies, these memory cells launch an immune attack on the fetal blood cells. Injection of anti-Rh antibody during the first pregnancy prevents the immune response from occurring.
4. D
5. B
6. B
7. C
8. D
9. A
10. An antigen is a molecule that reacts with some component of the immune response (antibody, B cell receptor, T cell receptor). An epitope is the region on the antigen through which binding with the immune component actually occurs.
11. A naïve T or B cell is one that has not been activated by binding to the appropriate epitope. Naïve T and B cells cannot produce responses.
12. The T_H1 response involves the secretion of cytokines to stimulate macrophages and CTLs and improve their destruction of intracellular pathogens and tumor cells. It is associated with inflammation. The T_H2 response is involved in the stimulation of B cells into plasma cells that synthesize and secrete antibodies.
13. The diversity of TCRs allows the immune system to have millions of different T cells, and thereby to be specific in distinguishing antigens. This diversity arises from mutation and recombination in the genes that encode the variable regions of TCRs.
14. T cells bind antigens that have been digested and embedded in MHC molecules by APCs. In contrast, B cells function themselves as APCs to bind intact, unprocessed antigens.

15. Upon reinfection, the memory cells will immediately differentiate into plasma cells and CTLs without input from APCs or T_H cells. In contrast, the adaptive immune response to the initial infection requires time for naïve B and T cells with the appropriate antigen specificities to be identified and activated.

Adaptation

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Antibodies

CHARLES MOLNAR; JANE GAIR; AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

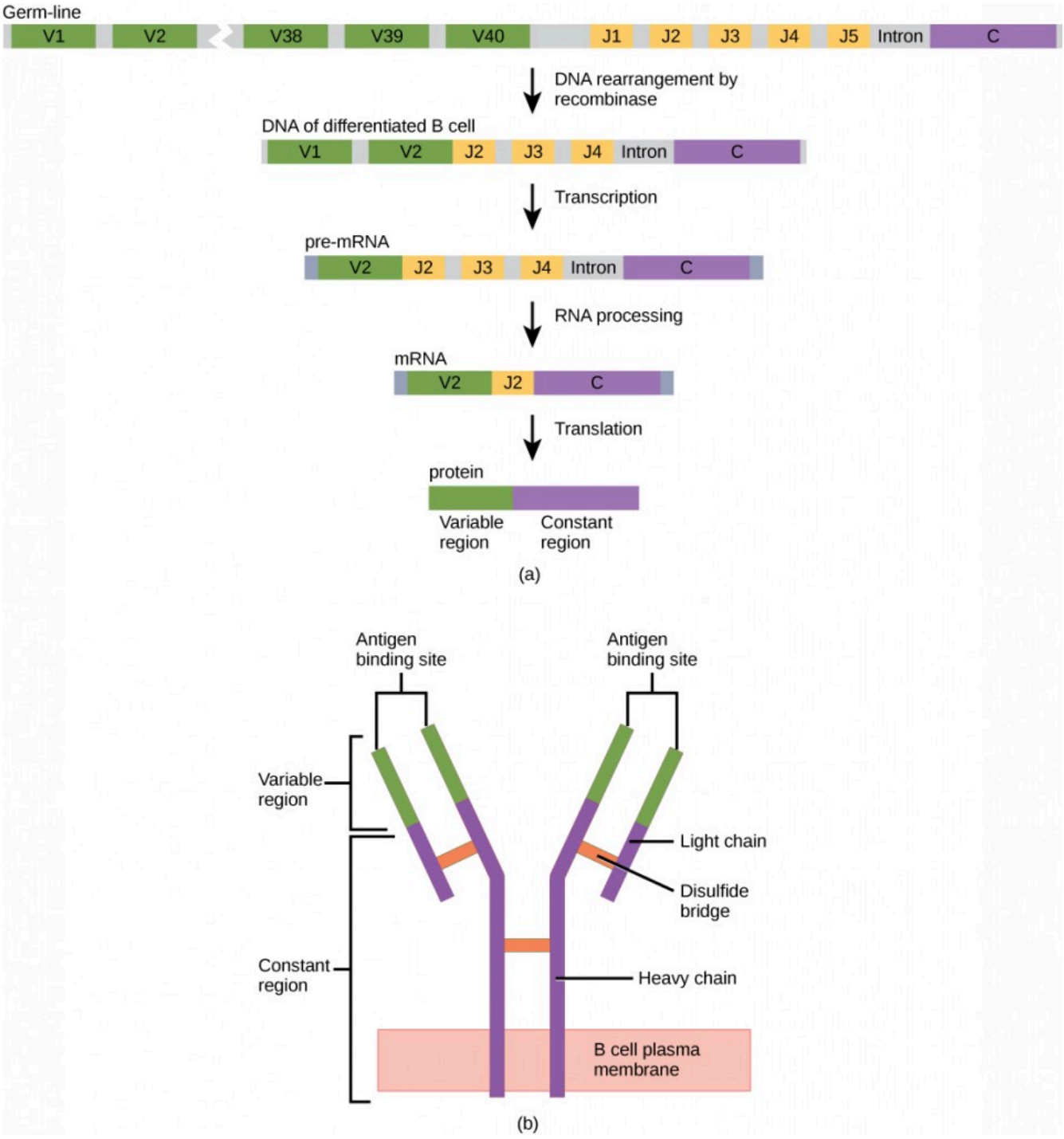
- Explain cross-reactivity.
- Describe the structure and function of antibodies.
- Discuss antibody production.

An **antibody**, also known as an immunoglobulin (Ig), is a protein that is produced by plasma cells after stimulation by an antigen. Antibodies are the functional basis of humoral immunity. Antibodies occur in the blood, in gastric and mucus secretions, and in breast milk. Antibodies in these bodily fluids can bind pathogens and mark them for destruction by phagocytes before they can infect cells.

Antibody Structure

An antibody molecule is comprised of four polypeptides: two identical heavy chains (large peptide units) that are partially bound to each other in a "Y" formation, which are flanked by two identical light chains (small peptide units). Bonds between the cysteine amino acids in the antibody molecule attach the polypeptides to each other. The areas where the antigen is recognized on the antibody are variable domains and the antibody base is composed of constant domains.

In germ-line B cells, the variable region of the light chain gene has 40 variable (V) and five joining (J) segments. An enzyme called DNA recombinase randomly excises most of these segments out of the gene, and splices one V segment to one J segment. During RNA processing, all but one V and J segment are spliced out. Recombination and splicing may result in over 10^6 possible VJ combinations. As a result, each differentiated B cell in the human body typically has a unique variable chain. The constant domain, which does not bind antibody, is the same for all antibodies.



(a) As a germ-line B cell matures, an enzyme called DNA recombinase randomly excises V and J segments from the light chain gene. Splicing at the mRNA level results in further gene rearrangement. As a result, (b) each antibody has a unique variable region capable of binding a different antigen.

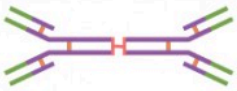
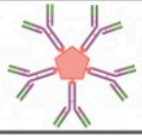
Similar to TCRs and BCRs, antibody diversity is produced by the mutation and recombination of approximately 300 different gene segments encoding the light and heavy chain variable domains in precursor cells that are destined to become B cells. The variable domains from the heavy and light chains interact to form the binding site through which an antibody can bind a specific epitope on an antigen. The numbers of repeated constant domains in Ig classes are the same

for all antibodies corresponding to a specific class. Antibodies are structurally similar to the extracellular component of the BCRs, and B cell maturation to plasma cells can be visualized in simple terms as the cell acquires the ability to secrete the extracellular portion of its BCR in large quantities.

Antibody Classes

Antibodies can be divided into five classes—IgM, IgG, IgA, IgD, IgE—based on their physiochemical, structural, and immunological properties. IgGs, which make up about 80 percent of all antibodies, have heavy chains that consist of one variable domain and three identical constant domains. IgA and IgD also have three constant domains per heavy chain, whereas IgM and IgE each have four constant domains per heavy chain. The variable domain determines binding specificity and the constant domain of the heavy chain determines the immunological mechanism of action of the corresponding antibody class. It is possible for two antibodies to have the same binding specificities but be in different classes and, therefore, to be involved in different functions.

After an adaptive defense is produced against a pathogen, typically plasma cells first secrete IgM into the blood. BCRs on naïve B cells are of the IgM class and occasionally IgD class. IgM molecules make up approximately ten percent of all antibodies. Prior to antibody secretion, plasma cells assemble IgM molecules into pentamers (five individual antibodies) linked by a joining (J) chain. The pentamer arrangement means that these macromolecules can bind ten identical antigens. However, IgM molecules released early in the adaptive immune response do not bind to antigens as stably as IgGs, which are one of the possible types of antibodies secreted in large quantities upon re-exposure to the same pathogen.

Name	Properties	Structure
IgA	Found in mucous, saliva, tears, and breast milk. Protects against pathogens.	
IgD	Part of the B cell receptor. Activates basophils and mast cells.	
IgE	Protects against parasitic worms. Responsible for allergic reactions.	
IgG	Secreted by plasma cells in the blood. Able to cross the placenta into the fetus.	
IgM	May be attached to the surface of a B cell or secreted into the blood. Responsible for early stages of immunity.	

Immunoglobulins have different functions, but all are composed of light and heavy chains that form a Y*-shaped structure.*

IgAs populate the saliva, tears, breast milk, and mucus secretions of the gastrointestinal, respiratory, and genitourinary tracts. Collectively, these bodily fluids coat and protect the extensive mucosa (4000 square feet in humans). The total

number of IgA molecules in these bodily secretions is greater than the number of IgG molecules in the blood serum. A small amount of IgA is also secreted into the serum in monomeric form. Conversely, some IgM is secreted into bodily fluids of the mucosa. Similar to IgM, IgA molecules are secreted as polymeric structures linked with a J chain. However, IgAs are secreted mostly as dimeric molecules, not pentamers.

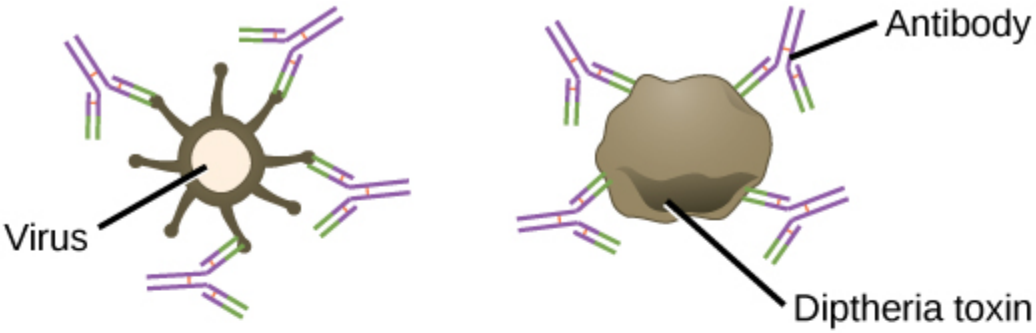
IgE is present in the serum in small quantities and is best characterized in its role as an allergy mediator. IgD is also present in small quantities. Similar to IgM, BCRs of the IgD class are found on the surface of naïve B cells. This class supports antigen recognition and maturation of B cells to plasma cells.

Antibody Functions

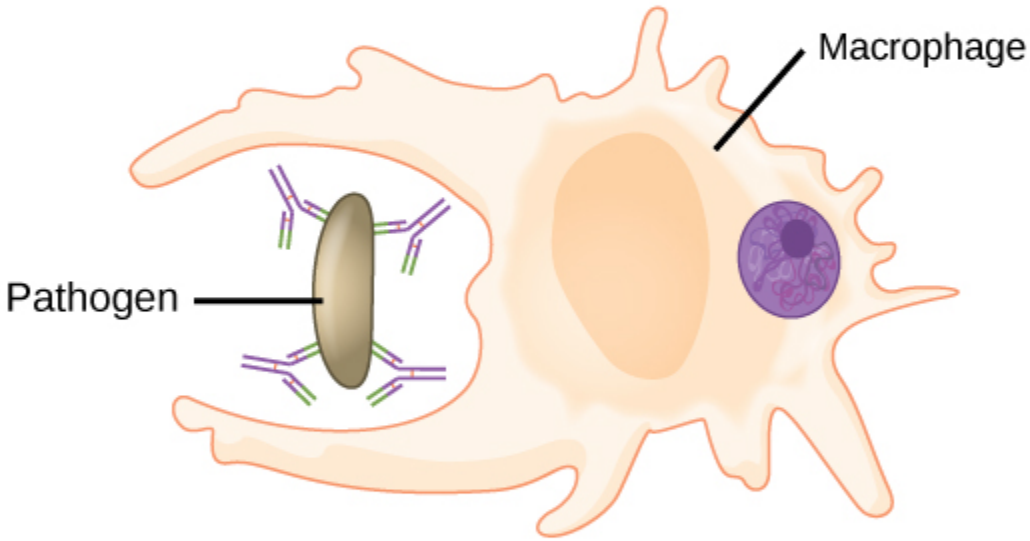
Differentiated plasma cells are crucial players in the humoral response, and the antibodies they secrete are particularly significant against extracellular pathogens and toxins. Antibodies circulate freely and act independently of plasma cells. Antibodies can be transferred from one individual to another to temporarily protect against infectious disease. For instance, a person who has recently produced a successful immune response against a particular disease agent can donate blood to a nonimmune recipient and confer temporary immunity through antibodies in the donor's blood serum. This phenomenon is called **passive immunity**; it also occurs naturally during breastfeeding, which makes breastfed infants highly resistant to infections during the first few months of life.

Antibodies coat extracellular pathogens and neutralize them by blocking key sites on the pathogen that enhance their infectivity (such as receptors that "dock" pathogens on host cells). Antibody neutralization can prevent pathogens from entering and infecting host cells, as opposed to the CTL-mediated approach of killing cells that are already infected to prevent progression of an established infection. The neutralized antibody-coated pathogens can then be filtered by the spleen and eliminated in urine or feces.

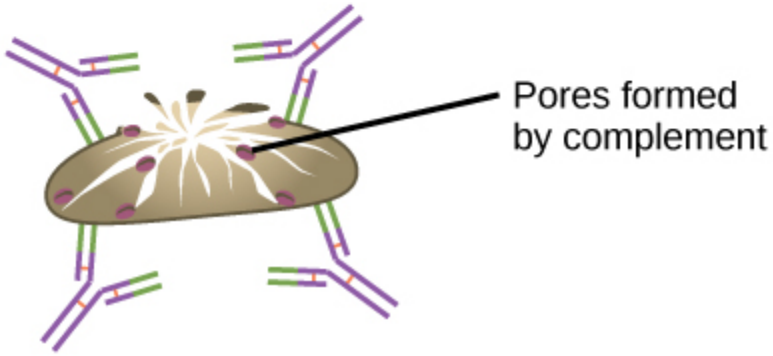
(a) Neutralization Antibodies prevent a virus or toxic protein from binding their target.



(b) Opsonization A pathogen tagged by antibodies is consumed by a macrophage or neutrophil.



(c) Complement activation Antibodies attached to the surface of a pathogen cell activate the complement system.



Antibodies may inhibit infection by (a) preventing the antigen from binding its target, (b) tagging a pathogen for

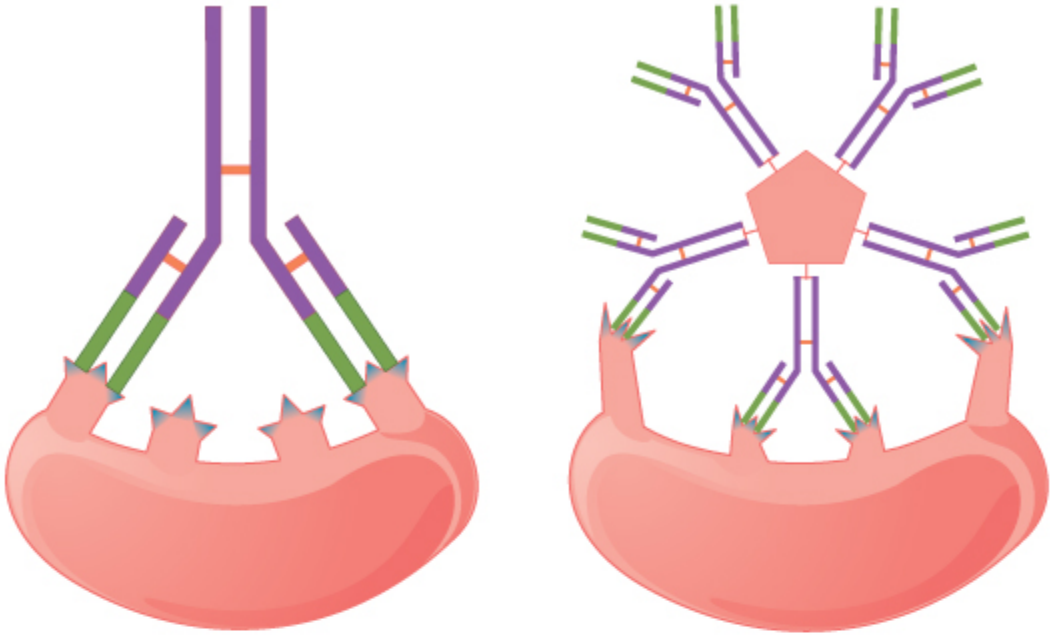
destruction by macrophages or neutrophils, or (c) activating the complement cascade.

Antibodies also mark pathogens for destruction by phagocytic cells, such as macrophages or neutrophils, because phagocytic cells are highly attracted to macromolecules complexed with antibodies. Phagocytic enhancement by antibodies is called opsonization. In a process called complement fixation, IgM and IgG in serum bind to antigens and provide docking sites onto which sequential complement proteins can bind. The combination of antibodies and complement enhances opsonization even further and promotes rapid clearing of pathogens.

Affinity, Avidity, and Cross Reactivity

Not all antibodies bind with the same strength, specificity, and stability. In fact, antibodies exhibit different **affinities** (attraction) depending on the molecular complementarity between antigen and antibody molecules. An antibody with a higher affinity for a particular antigen would bind more strongly and stably, and thus would be expected to present a more challenging defense against the pathogen corresponding to the specific antigen.

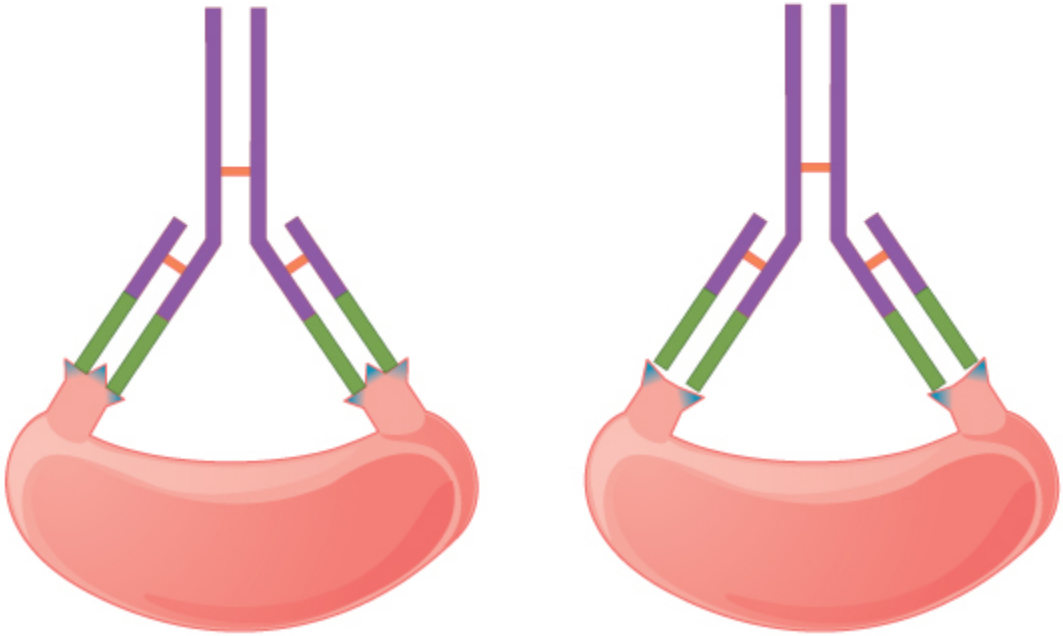
(a) Affinity versus avidity



Affinity refers to the strength of a single antibody–antigen interaction. Each IgG antigen binding site typically has high affinity for its target.

Avidity refers to the strength of all interactions combined. IgM typically has low affinity antigen binding sites, but there are ten of them, so avidity is high.

(b) Cross reactivity



An antibody may react with two different epitopes.

(a) Affinity refers to the strength of single interaction between antigen and antibody, while avidity refers to the strength of all interactions combined. (b) An antibody may cross react with different epitopes.

The term **avidity** describes binding by antibody classes that are secreted as joined, multivalent structures (such as IgM and IgA). Although avidity measures the strength of binding, just as affinity does, the avidity is not simply the sum of the affinities of the antibodies in a multimeric structure. The avidity depends on the number of identical binding sites on the antigen being detected, as well as other physical and chemical factors. Typically, multimeric antibodies, such as pentameric IgM, are classified as having lower affinity than monomeric antibodies, but high avidity. Essentially, the fact that multimeric antibodies can bind many antigens simultaneously balances their slightly lower binding strength for each antibody/antigen interaction.

Antibodies secreted after binding to one epitope on an antigen may exhibit cross reactivity for the same or similar epitopes on different antigens. Because an epitope corresponds to such a small region (the surface area of about four to six amino acids), it is possible for different macromolecules to exhibit the same molecular identities and orientations over short regions. **Cross reactivity** describes when an antibody binds not to the antigen that elicited its synthesis and secretion, but to a different antigen.

Cross reactivity can be beneficial if an individual develops immunity to several related pathogens despite having only been exposed to or vaccinated against one of them. For instance, antibody cross reactivity may occur against the similar surface structures of various Gram-negative bacteria. Conversely, antibodies raised against pathogenic molecular components that resemble self molecules may incorrectly mark host cells for destruction and cause autoimmune damage. Patients who develop systemic lupus erythematosus (SLE) commonly exhibit antibodies that react with their own DNA. These antibodies may have been initially raised against the nucleic acid of microorganisms but later cross-reacted with self-antigens. This phenomenon is also called molecular mimicry.

Antibodies of the Mucosal Immune System

Antibodies synthesized by the mucosal immune system include IgA and IgM. Activated B cells differentiate into mucosal plasma cells that synthesize and secrete dimeric IgA, and to a lesser extent, pentameric IgM. Secreted IgA is abundant in tears, saliva, breast milk, and in secretions of the gastrointestinal and respiratory tracts. Antibody secretion results in a local humoral response at epithelial surfaces and prevents infection of the mucosa by binding and neutralizing pathogens.

Review Section

Antibodies (immunoglobulins) are the molecules secreted from plasma cells that mediate the humoral immune response. There are five antibody classes; an antibody's class determines its mechanism of action and production site but does not control its binding specificity. Antibodies bind antigens via variable domains and can either neutralize pathogens or mark them for phagocytosis or activate the complement cascade.

Exercises

1. The structure of an antibody is similar to the extracellular component of which receptor?

    1. MHC I
    2. MHC II
    3. BCR
    4. none of the above

2. The first antibody class to appear in the serum in response to a newly encountered pathogen is _____.

    1. IgM
    2. IgA
    3. IgG
    4. IgE

3. What is the most abundant antibody class detected in the serum upon reexposure to a pathogen or in reaction to a vaccine?

    1. IgM
    2. IgA
    3. IgG
    4. IgE

4. Breastfed infants typically are resistant to disease because of _____.

    1. active immunity
    2. passive immunity
    3. immune tolerance
    4. immune memory

5. What are the benefits and costs of antibody cross reactivity?

Answers

1. C
2. A
3. C
4. B
5. Cross reactivity of antibodies can be beneficial when it allows an individual's immune system to respond to an array of similar pathogens after being exposed to just one of them. A potential cost of cross reactivity is an antibody response to parts of the body (self) in addition to the appropriate antigen.

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Disruptions in the Immune System

CHARLES MOLNAR; JANE GAIR; AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

- Describe hypersensitivity.
- Define autoimmunity.

A functioning immune system is essential for survival, but even the sophisticated cellular and molecular defenses of the mammalian immune response can be defeated by pathogens at virtually every step. In the competition between immune protection and pathogen evasion, pathogens have the advantage of more rapid evolution because of their shorter generation time and other characteristics. For instance, *Streptococcus pneumoniae* (bacterium that cause pneumonia and meningitis) surrounds itself with a capsule that inhibits phagocytes from engulfing it and displaying antigens to the adaptive immune system. *Staphylococcus aureus* (bacterium that can cause skin infections, abscesses, and meningitis) synthesizes a toxin called leukocidin that kills phagocytes after they engulf the bacterium. Other pathogens can also hinder the adaptive immune system. HIV infects T_H cells via their CD4 surface molecules, gradually depleting the number of T_H cells in the body; this inhibits the adaptive immune system's capacity to generate sufficient responses to infection or tumors. As a result, HIV-infected individuals often suffer from infections that would not cause illness in people with healthy immune systems but which can cause devastating illness to immune-compromised individuals. Maladaptive responses of immune cells and molecules themselves can also disrupt the proper functioning of the entire system, leading to host cell damage that could become fatal.

Immunodeficiency

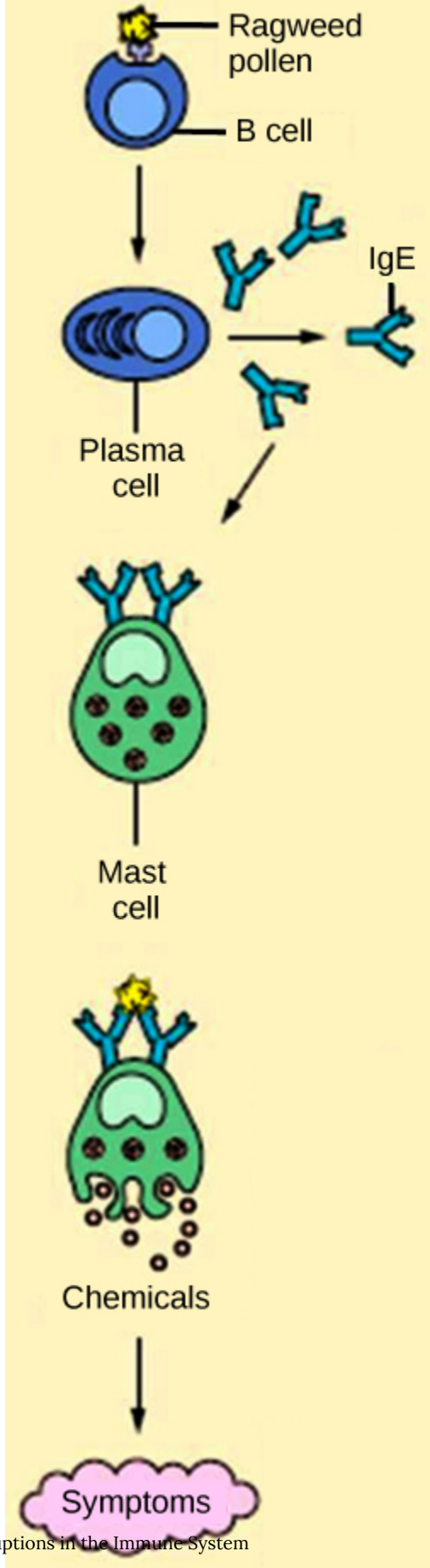
Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold and replicate or proliferate to high enough levels that the immune system becomes overwhelmed. **Immunodeficiency** can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or possibly by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes and elevate an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), Bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

Hypersensitivities

Maladaptive immune responses toward harmless foreign substances or self antigens that occur after tissue sensitization are termed **hypersensitivities**. The types of hypersensitivities include immediate, delayed, and autoimmune. A large proportion of the population is affected by one or more types of hypersensitivity.

Allergies

The immune reaction that results from immediate hypersensitivities in which an antibody-mediated immune response occurs within minutes of exposure to a harmless antigen is called an **allergy**. In the United States, 20 percent of the population exhibits symptoms of allergy or asthma, whereas 55 percent test positive against one or more allergens. Upon initial exposure to a potential allergen, an allergic individual synthesizes antibodies of the IgE class via the typical process of APCs presenting processed antigen to TH cells that stimulate B cells to produce IgE. This class of antibodies also mediates the immune response to parasitic worms. The constant domain of the IgE molecules interact with mast cells embedded in connective tissues. This process primes, or sensitizes, the tissue. Upon subsequent exposure to the same allergen, IgE molecules on mast cells bind the antigen via their variable domains and stimulate the mast cell to release the modified amino acids histamine and serotonin; these chemical mediators then recruit eosinophils which mediate allergic responses. The effects of an allergic reaction range from mild symptoms like sneezing and itchy, watery eyes to more severe or even life-threatening reactions involving intensely itchy welts or hives, airway contraction with severe respiratory distress, and plummeting blood pressure. This extreme reaction is known as anaphylactic shock. If not treated with epinephrine to counter the blood pressure and breathing effects, this condition can be fatal.



Upon initial exposure to the antigen, IgE antibody is produced and attached to mast cells.

Upon a second exposure, binding of the antigen to the IgE-primed mast cells causes the release of chemical mediators that elicit an allergic reaction.

On first exposure to an allergen, an IgE antibody is synthesized by plasma cells in response to a harmless antigen. The IgE molecules bind to mast cells, and on secondary exposure, the mast cells release histamines and other modulators that affect the symptoms of allergy. (credit: modification of work by NIH)

Delayed hypersensitivity is a cell-mediated immune response that takes approximately one to two days after secondary exposure for a maximal reaction to be observed. This type of hypersensitivity involves the T_H1 cytokine-mediated inflammatory response and may manifest as local tissue lesions or contact dermatitis (rash or skin irritation). Delayed hypersensitivity occurs in some individuals in response to contact with certain types of jewelry or cosmetics. Delayed hypersensitivity facilitates the immune response to poison ivy and is also the reason why the skin test for tuberculosis results in a small region of inflammation on individuals who were previously exposed to *Mycobacterium tuberculosis*. That is also why cortisone is used to treat such responses: it will inhibit cytokine production.

Autoimmunity

Autoimmunity is a type of hypersensitivity to self antigens that affects approximately five percent of the population. Most types of autoimmunity involve the humoral immune response. Antibodies that inappropriately mark self components as foreign are termed **autoantibodies**. Certain autoimmune diseases have a hereditary (genetic) component. The MHC II molecules expressed on the surface of antigen presenting cells such as macrophages are encoded by human leukocyte antigen (HLA) genes. Certain alleles of this gene, namely HLA-DQ2 and HLA-DQ8, are associated with increased incidence of autoimmune disorders.

There have been simultaneous "epidemics" of autoimmune disorders in certain parts of the world, including North America. This has led some to postulate that environmental factors such as diet and lifestyle can also have a profound influence on autoimmunity. For instance, the hygiene hypothesis suggests that reduced exposure to environmental and/or commensal microbes may be associated with increased risk of autoimmune conditions, though the mechanism by which that occurs remains unclear. Further, individuals who were not fed breastmilk during their infancy are at increased risk of developing some autoimmune conditions that we expand on in the following chapters or elsewhere, including celiac disease and Type I diabetes mellitus.

Section Review

Immune disruptions may involve insufficient immune responses or inappropriate immune targets. Immunodeficiency increases an individual's susceptibility to infections and cancers. Hypersensitivities are misdirected responses either to harmless foreign particles, as in the case of allergies, or to host factors, as in the case of autoimmunity. Reactions to self components may be the result of molecular mimicry.

Exercises

1. Allergy to pollen is classified as:

    1. an autoimmune reaction
    2. immunodeficiency
    3. delayed hypersensitivity
    4. immediate hypersensitivity

2. A potential cause of acquired autoimmunity is _____.

    1. tissue hypersensitivity
    2. molecular mimicry
    3. histamine release
    4. radiation exposure

3. Autoantibodies are probably involved in:

    1. reactions to poison ivy
    2. pollen allergies
    3. systemic lupus erythematosus
    4. HIV/AIDS

4. Which of the following diseases is not due to autoimmunity?

    1. rheumatic fever
    2. systemic lupus erythematosus
    3. diabetes mellitus
    4. HIV/AIDS

Answers

1. D
2. B
3. C
4. D

Adaptation

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Celiac Disease

Celiac Disease

DYLAN MANN AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

- Define Celiac disease.
- Describe autoimmune processes underlying Celiac disease.
- Explain how genetic and environmental factors impact on the pathogenesis of Celiac disease.
- Distinguish between Celiac disease and other autoimmune diseases of the gut.

Introduction

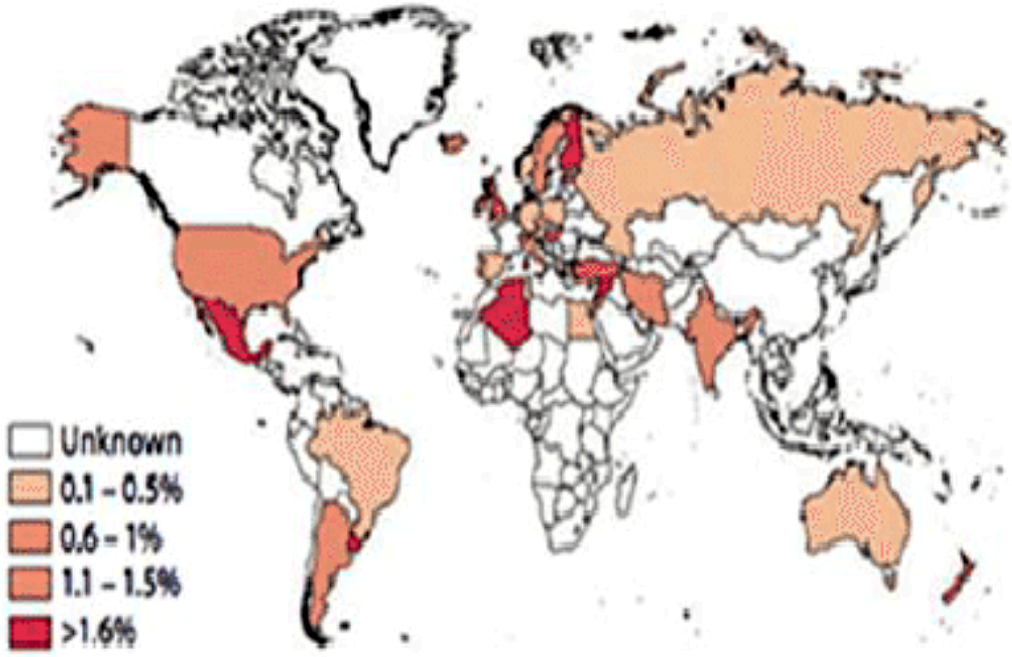
Celiac disease is a common autoimmune condition, affecting approximately 1 in 100 people worldwide. It is characterized by an **autoimmune response** triggered by consumption of gluten, a protein that is in food products containing wheat, barley, and rye.

Mechanism

Gluten is one of the few chronically consumed proteins that is digested incompletely. Gliadin, a metabolic byproduct of gluten digestion, is bound by secretory **IgA**in the small intestine. Under normal conditions, IgA protects gut **epithelial** cells from pathogens by marking the pathogens for destruction by the immune system. However, in the case of celiac disease, IgA facilitates the transport of gliadin into the **lamina propria** . There, gliadin is deaminated by tissue transglutaminase (ttg). Then, deaminated gliadin is phagocytosed by intestinal **macrophages**, broken down into small peptides and presented on **MHC II**. When presented on MHC II, **helper T cells**(CD4+ T cells) can bind and be activated by deaminated gliadin epitopes, resulting in the production of inflammatory **cytokines**. The resulting inflammation can damage the epithelium of the small intestine. Simultaneously, **B cells** may be stimulated to produce anti-gliadin IgA and anti-endomysial IgA, or endomysial antibodies (EMAs), which can interfere with the activity of transglutaminase. The cytokines produced by helper (CD4+) T cells can also recruit **cytotoxic (CD8+) T cells** , which can worsen epithelial cell damage. As epithelium is destroyed, it becomes possible for more gliadin to enter the lamina propria, propagating the autoimmune process.

Genetic Predisposition and the Environment

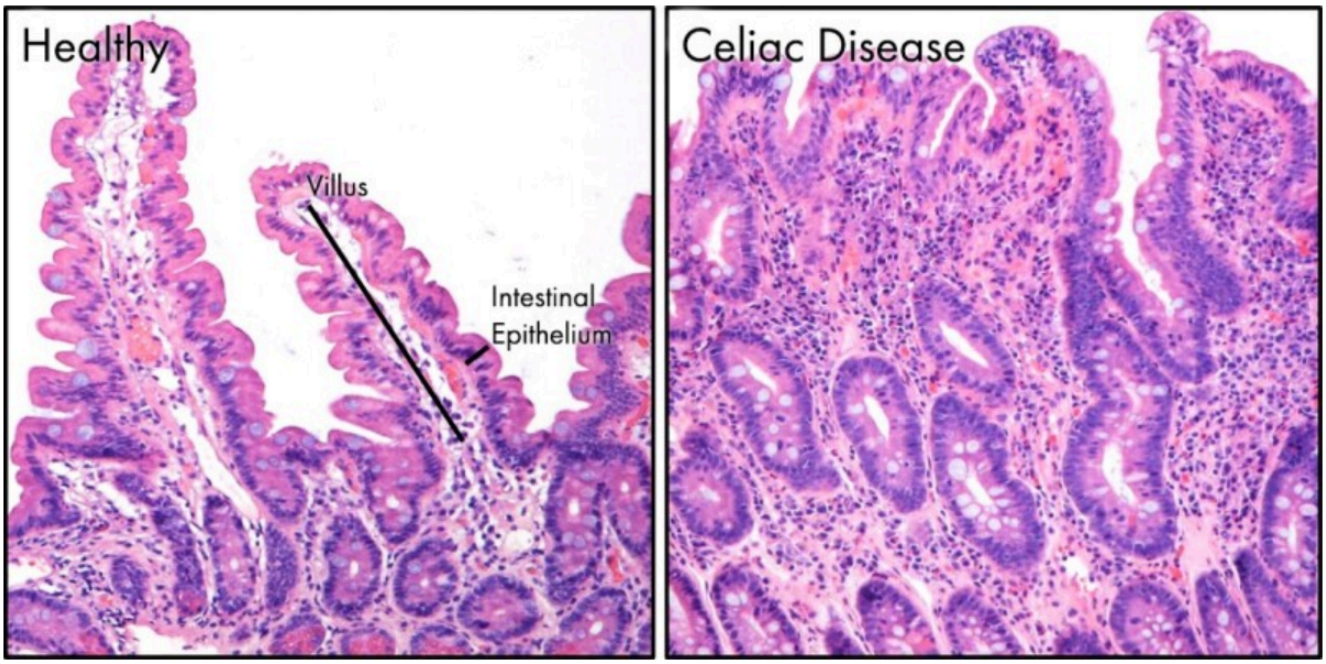
Although Celiac disease, like most autoimmune diseases, is influenced by environmental factors there are genes that are associated with the condition. For example, certain alleles of the **human leukocyte antigen** (HLA) gene, which encodes MHC proteins, are common in patients with celiac disease. More specifically, HLA-DQ2 and HLA-DQ8 are risk factors for celiac disease. Interestingly, the extent to which other genes are expressed can influence celiac pathology. For example, the receptor TFR, which is necessary for transporting gliadin complexes across the intestinal epithelium, is overexpressed in people with celiac disease. Numerous environmental factors influence celiac pathology as well, as demonstrated by uneven geographic distribution of the disease, which implies that different lifestyles and climates may impact manifestation. For example, the hygiene hypothesis proposes that decreased exposure to bacterial antigens as an infant may trigger future autoimmunity. In the case of celiacs, the prevalence of **H. pylori** is found to be significantly less than the rest of the population. Current data implies that Celiac disease is most prevalent in Europe and Oceania, and least prevalent in South America. While the unequal distribution of celiac disease of ongoing debate, it may be caused by any combination of weather, bacterial populations, hygiene standards, and diet.



Map showing difference in Celiac Disease prevalence across the world where data is available. © Mohammadi et al. is licensed under a CC BY (Attribution) license

Diagnoses

A non-invasive way to screen for Celiac disease is to perform **serology** to determine titres of anti-gliadin IgA and EMA. However, because anti-gliadin IgA is not uniformly expressed in celiacs or non-celiacs, this test lacks specificity. It can be used as a tool to suggest Celiac disease prevalence or rule out other autoimmune diseases. A definitive diagnosis can be made following **biopsy** of the duodenum; the first part of the small intestine. A biopsy of a person with celiac disease would show a damaged duodenum, with destroyed villi, and abnormally long crypts.



High magnification samples of intestinal villi with H&E stain from healthy and Celiac patients. Image from: Daley SF & Haseeb M. Celiac Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441900/ (CC BY-NC-ND 4.0)

Symptoms and Treatment

The symptoms of celiac disease vary among children and adults. In children, symptoms include abdominal distension and pain, failure to thrive, and diarrhea. In adults, though symptoms are more variable, they commonly include bloating, chronic diarrhea, joint pain, and fatigue. The current recommendation for celiac disease treatment is following a strict gluten free diet (GFD), which in most cases removes all symptoms. However, due to cross contamination in factories, restaurants, and even the home, it is extremely difficult for Celiacs to avoid gluten exposure completely. This helps to explain the higher-than-normal incidence rates of secondary diseases in celiac patients, even with adherence to a GFD. This is due to increased inflammation associated with gluten exposure, as well as malnutrition due to poor absorption caused by intestinal damage.

Review Questions

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Rheumatoid Arthritis

Rheumatoid Arthritis

MORGAN ALFORD AND DYLAN MANN

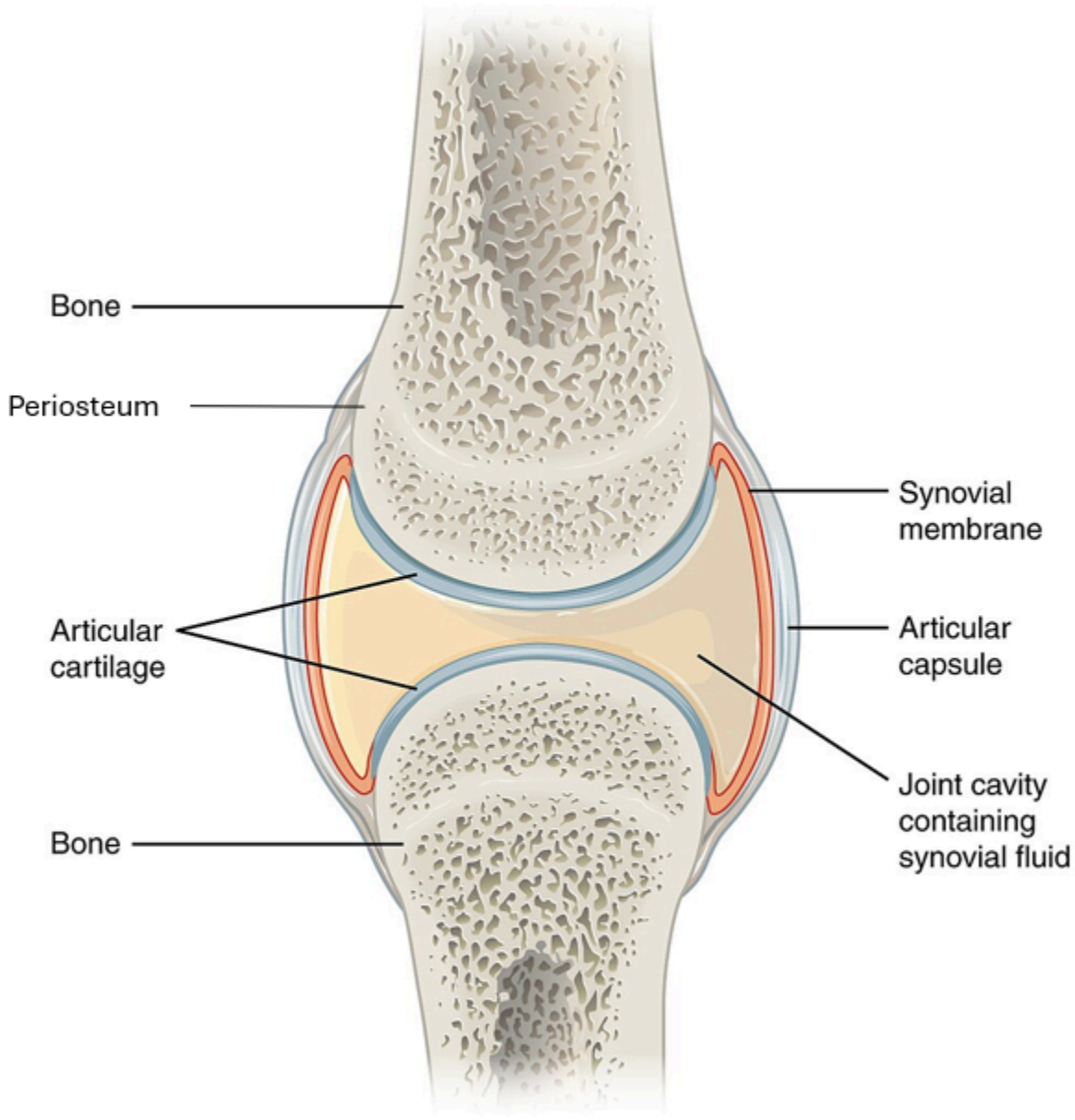
Learning Objectives

By the end of this section, you will be able to:

- Describe the basic anatomy of a synovial joint.
- Explain the autoimmune mechanism underlying rheumatoid arthritis.
- List extra-articular manifestations of rheumatoid arthritis.
- Identify an appropriate therapeutic regimen for a person with advanced rheumatoid arthritis.

Introduction

Rheumatoid arthritis is a chronic inflammatory disorder mostly affecting the joints. It is progressive, and can also affect the skin, lungs, and other organ systems. The type of joints that are primarily affected are the synovial joints. Synovial joints include fibrous joint capsules that are continuous with the **periosteum** . They are also lined with synovial membrane which contains synovial cells that produce lubricating fluid and remove debris. To meet functional and metabolic needs, the synovial membrane has many blood vessels and lymphatics running through them.

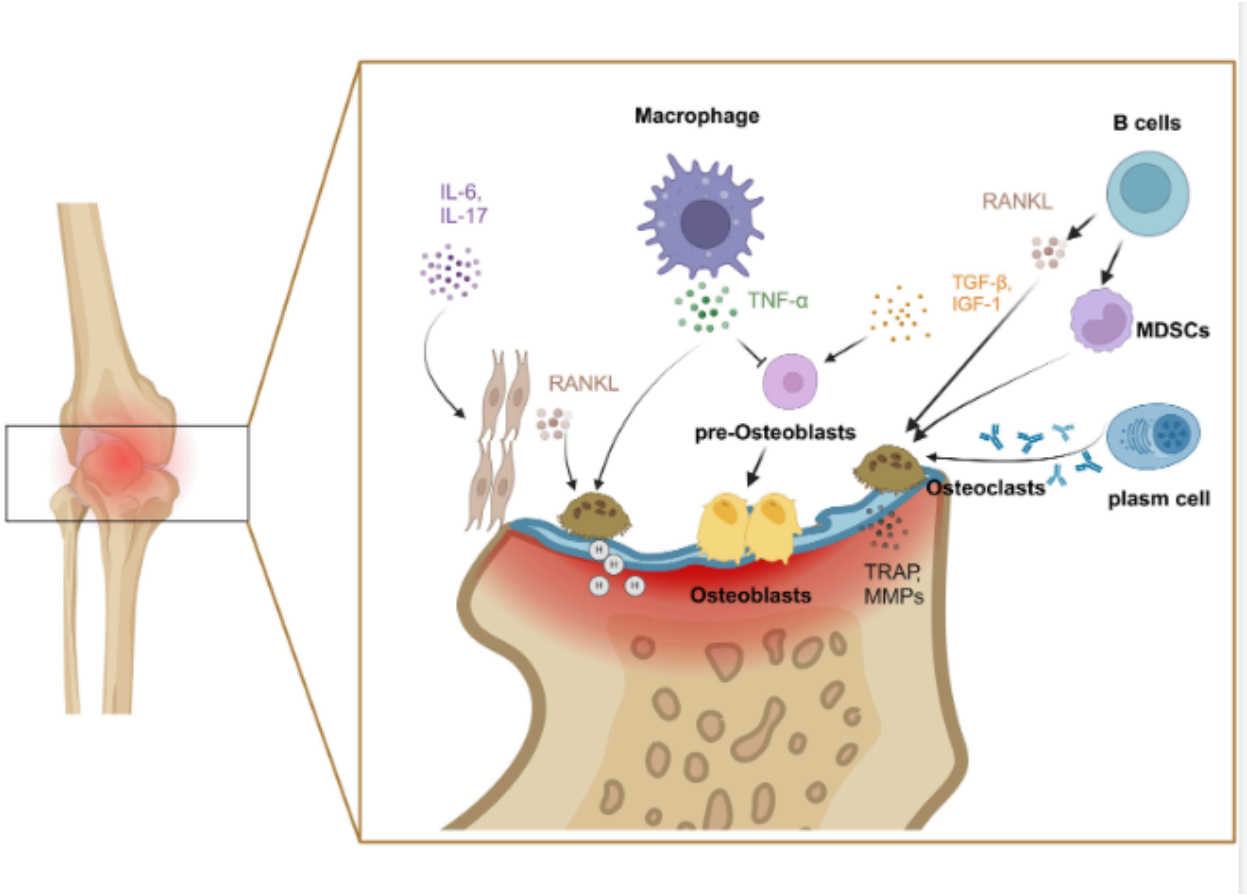


Labelled diagram of healthy synovial joint. © OpenStax College adapted by Dylan Mann is licensed under a CC BY (Attribution) license

Citrullinated Proteins Trigger Inflammation

Genetic factors can predispose individuals to developing rheumatoid arthritis, though environmental factors such as infection and exposure to certain chemicals can influence disease pathogenesis. The **human leukocyte antigen** (HLA) genes that are commonly found in people with rheumatoid arthritis include HLA-DR1 and HLA-DR4. Rheumatoid arthritis can be triggered by modification of type II collagen and vimentin. Type II collagen provides structural support and vimentin influences filament cell migration and deposition in the joint space. Conversion of arginine to citrulline

produces modified type II collagen and vimentin which is recognized by immune cells (**macrophages**and **dendritic cells**) as foreign. Then, citrullinated protein antigens are engulfed, processed and presented by **antigen-presenting cells** that travel to the lymph nodes, where they can activate CD4+ T helper cells. Activated T helper cells may go on to stimulate B cells, which would subsequently differentiate into plasma cells that produce autoantibodies against the self-antigens. Activated T helper cells and antibodies enter circulation and travel to the joints where they may release pro-inflammatory cytokines such as interferon-γ and interleukin-17. Localized macrophages may also contribute to the inflammatory response by producing cytokines such as TNF-α, interleukin-1, and interleukin-6.



Autoimmune pathway triggering rheumatoid arthritis inflammation. © Han et al. is licensed under a CC BY (Attribution) license

Pannus Formation

Cytokines raised by immune cells can stimulate synovial cell proliferation in the joints, leading to **pannus** formation. Over time, the inflamed pannus can damage cartilage and other soft tissues in the joint space since activated synovial cells produce proteases that target articular cartilage. This may cause bony erosions since cartilage loss causes bones to be exposed to each other, which may rub together painfully. Inflammatory cytokines also increase T-cell surface expression of **Rank-Ligand** , allowing osteoclast activation which would further damage the bones.

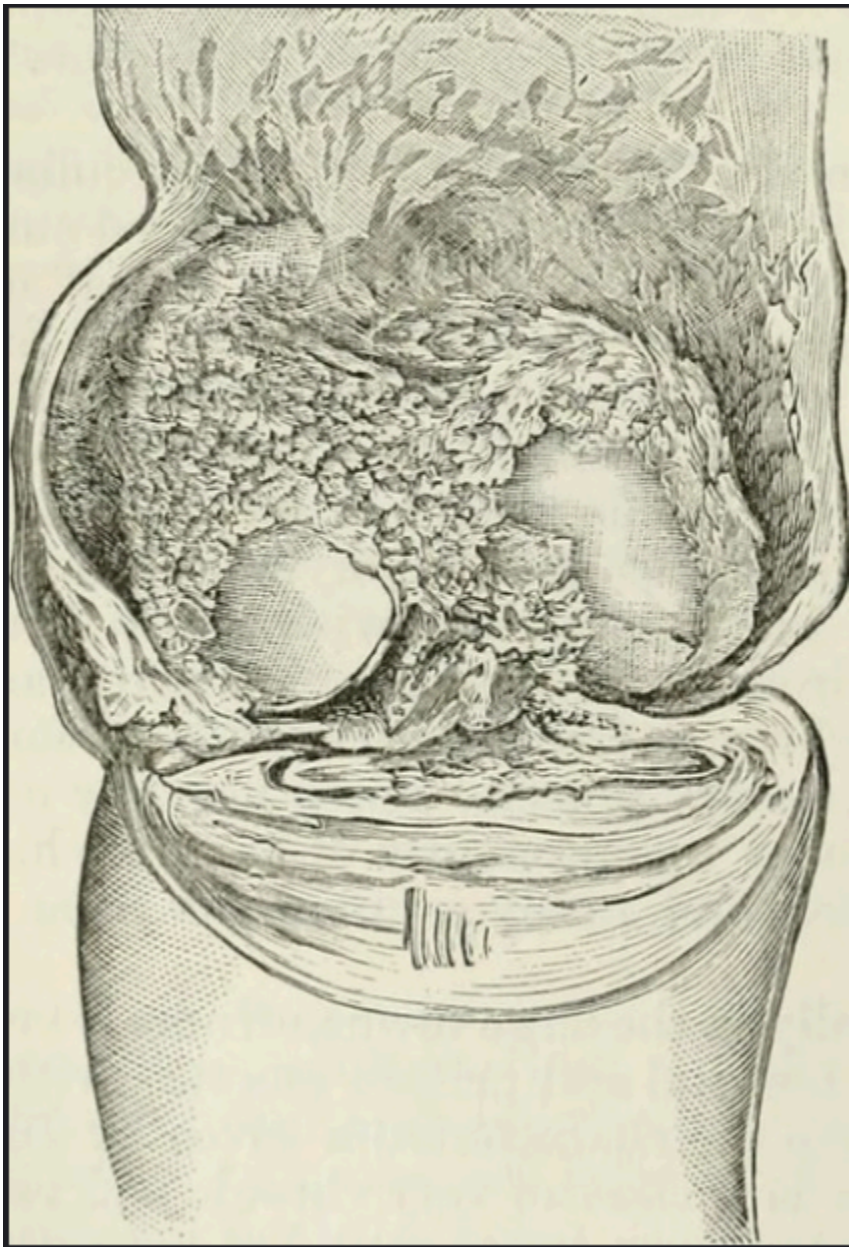


Illustration of pannus formation, showing extreme damage and inflammation of joint.
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Complement Activation Contributes to Disease Progression

As antibodies accumulate in the joint space, a staggering amount of immune complexes form. In the case of rheumatoid arthritis, anti-cyclic citrullinated peptide (anti-CPP) targets citrullinated proteins and forms immune complexes that accumulate in the synovial fluid. Immune complex deposition activates the **complement system**. The ensuing chronic inflammation causes **angiogenesis** around the joint, which propagates further inflammation by vascularizing the joint space. Disease progression is characterized by prolonged, extensive inflammation through multiple joints on both sides of the body, which can be destroyed without medical intervention.

Joint Damage

Joints are affected symmetrically, meaning joints on both sides of the body are impacted approximately equally. Initially, rheumatoid arthritis impacts the smaller joints of the hands and feet. These include the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hand, as well as the metatarsophalangeal (MTP) joints of the feet. Eventually, the disease may spread to large joints such as the shoulders, elbows, knees, and ankles. Flares involve swelling, warmth, redness, and pain in the affected joints. People with rheumatoid arthritis complain of prolonged stiffness after periods of inactivity, especially in the morning. Joint damage may be observed in the hands of people with rheumatoid arthritis patients' through various signs, including ulnar deviation, buttonhole deformity, extensor tendon splits, hyperextension, and swan neck deformity. Identification of these deformities is important in aiding medical professionals' treatment and monitoring of disease progression.



Severely swanneck deformed hand of 65 year old rheumatoid arthritis patient. © User:Phoenix119 is licensed under a CC BY-SA (Attribution ShareAlike) license

Extra-articular Impacts

Inflammatory cytokines can have long-ranging extra-articular impacts on the body. These signaling molecules can travel via the circulatory system to wreak havoc in multiple organ systems. For example, Interleukin-1 and interleukin-6 can cross the blood-brain barrier and induce fever. In the skin, rheumatoid nodules arise from **granuloma** formation. In blood vessels, inflammation promotes deposition of atheromatous plaques, increasing an individual's risk of heart attack. In the liver, hepcidin may sequester iron and lead to anemia. In the lungs, activated

fibroblasts may contribute to formation of scar tissue, making gas exchange more difficult. The pleural cavity may also fill with fluid, which would decrease lung capacity. It is important to acknowledge that RA symptoms are not limited to the joints, and thus crucial to consider when treating and monitoring the disease.

Diagnosis and Treatment

Clinicians will test for rheumatic diseases when patients present with symptomology consistent with the clinical picture of rheumatoid arthritis. Clinicians may test for rheumatoid factor and anti-citrullinated peptide (anti-CCP) antibody titres. While rheumatoid factor remains a useful biomarker, anti-CCP reliably differentiates rheumatoid arthritis from other rheumatic diseases. Another important diagnostic tool is X-ray imaging, which may reveal decreased bone density around affected joints, soft tissue swelling, narrowing of the joint space, and bony erosions. Long-term treatments for RA are classified as follows. Disease modifying anti-rheumatic medications (DMARDs) include the drugs methotrexate, hydroxychloroquine and sulfasalazine, which are anti-inflammatory therapeutic agents. Biologics, which act to block or suppress specific proteins or cells, include abatacept (T cell suppressor), Rituximab (B cell suppressor), and others that block chemokines, immunoglobulins and interleukins. Acute flares can be treated using non-steroidal anti-inflammatory agents (NSAIDs) and glucocorticoids. NSAIDs include over the counter drugs such as Ibuprofen and aspirin, which act by blocking enzymes that elicit pain and inflammation. Glucocorticoids similarly act by blocking production of inflammatory cells, however, are typically more potent then NSAIDs and require prescription.



X-ray showing deformed hand of rheumatoid arthritis patient. © HellerHoff is licensed under a CC BY-SA (Attribution ShareAlike) license

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Vitiligo

Vitiligo

DYLAN MANN AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

- Describe the basics of skin anatomy and the key players in the melanin production pathway.
- Distinguish between segmental and non-segmental vitiligo based on mechanism and incidence rate.
- Describe the autoimmune aspect of vitiligo development and action.
- Explain vitiligo diagnoses, treatment options and their mechanisms of action.

Introduction and Classification

Vitiligo is a skin condition defined by localized patches of depigmentation of the skin, irises, and hair. Although it is more noticeable in individuals with darker skin, it can occur in people of all races and ethnicities, with a global incidence rate between 0.5-1.5%. This disease is comprised of two main types: non-segmental and segmental vitiligo. Non-segmental vitiligo is more common, affecting ~0.5% of the Canadian population and makes up ~85% of all vitiligo cases. In this sub-type, hypopigmentation may be observed across the body, most often affecting the hands, forearms, neck, scalp, feet, and face. Segmental vitiligo occurs mostly in children, asymmetrically along single spinal nerves. In both cases, depigmented areas vary greatly in size and can expand or merge over time. Since segmental vitiligo does not have an autoimmune component, it will not be the focus of this chapter.



Example non-segmental vitiligo in a patient hands © Tor Langeland is licensed under a CC BY-NC (Attribution NonCommercial) license

Skin Anatomy

The main site of vitiligo is the skin, which can be divided into three layers. The innermost layer is hypodermis, which contains fat and connective tissue. The middle layer is the dermis, and contains hair follicles, nerves, and blood vessels. The outermost layer is the epidermis, which contains many cell types, and is the site of vitiligo development. The main cell type in the epidermis is the keratinocytes, which contain and produce protein keratin. Keratin is a strong fibrous protein, which protects skin cells from being destroyed by rough materials.

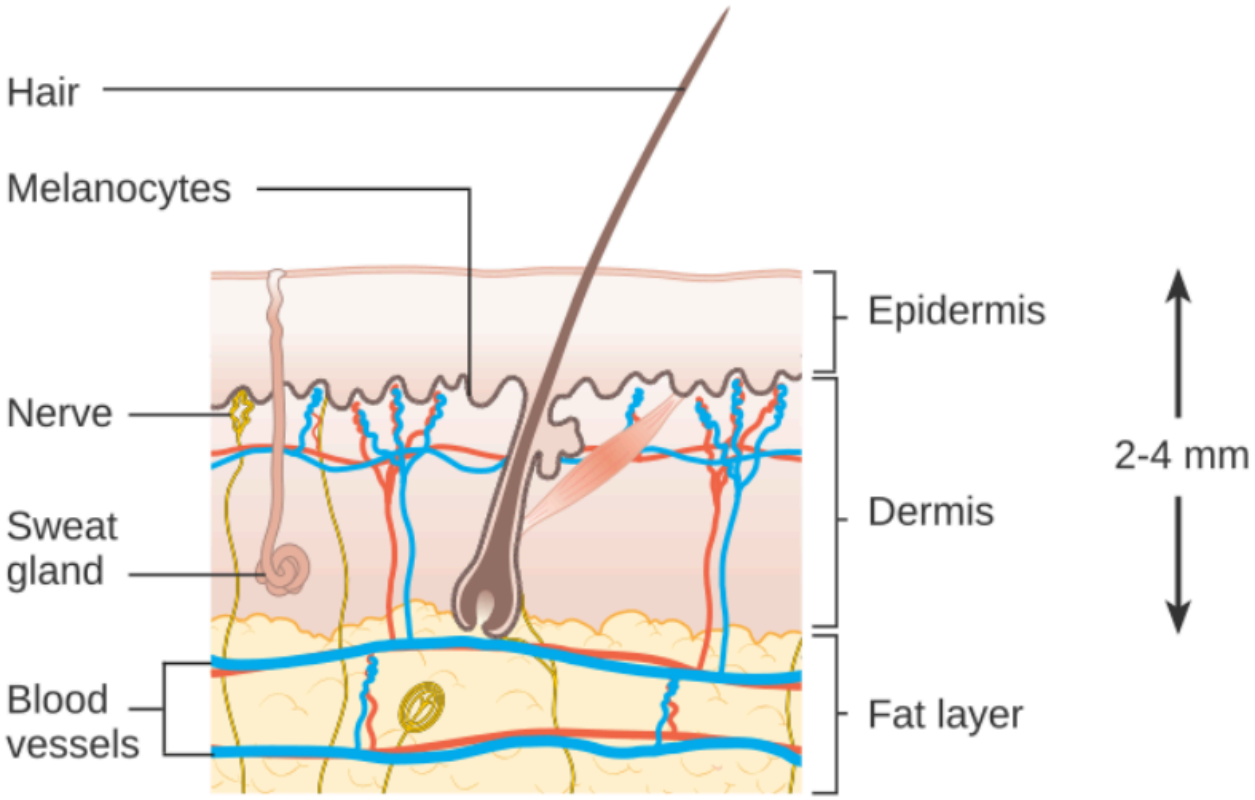
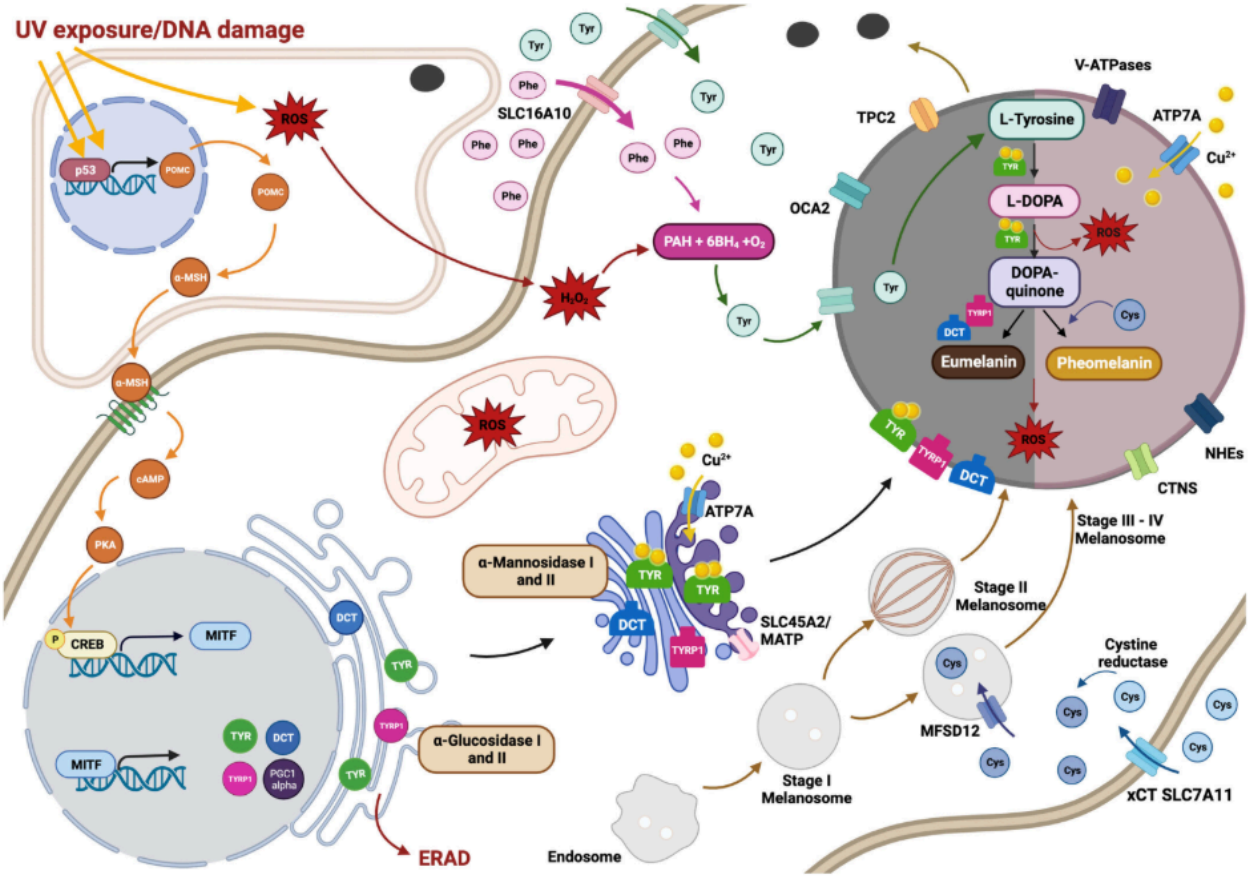


Diagram of the skin and its layers. © Cancer Research UK is licensed under a CC BY-SA (Attribution ShareAlike) license

Melanin Production and Metabolism

Keratinocytes develop at the deepest layer of the epidermis, the stratum basale, which is a single layer of stem cells which continuously divide. The stratum basale also contains melanocytes, which secrete the pigment melanin. Different subtypes of melanin protein exist, and the rate of metabolism and relative quantities of melanin ultimately dictate a person's skin color. When keratinocytes are exposed to sun, they send a chemical signal to the melanocytes which are then stimulated to produce more melanin. Through small sacs called melanosomes, maturing keratinocytes obtain and metabolize melanin into their cells. Melanin is able to act as a natural sunscreen, because its protein structure scatters and disrupts UV light, which prevents DNA damage to skin cells, which can cause skin cancer.



In depth view of melanin production pathway. © Synman et al. is licensed under a CC BY-NC-ND (Attribution NonCommercial NoDerivatives) license

Vitiligo Pathogenesis

Vitiligo pathogenesis results in the destruction of melanocytes. In the case of non-segmental vitiligo development, autoimmune attack is responsible for the destruction. A recent meta-analysis indicated that there is a genetic component, as some **human leukocyte antigen** (HLA) genes are associated with increased risk of non-segmental vitiligo, including HLA-A02, HLA-A33, and HLA-Aw31. In addition, people with vitiligo are at greater risk of autoimmune comorbidities. Although the autoimmune trigger remains unclear, it has been proposed that melanocyte proteins can act as **autoantigens** in vitiligo disease. Melanocyte-specific antibodies may induce apoptosis of melanocytes in the affected areas. Inflammation may trigger an influx of immune cells, such as Th17 cells (a subset of **helper T cells**), and **cytotoxic T cells**. Simultaneously, **regulatory T (Treg) cells** are downregulated, and as the immune response persists, melanocytes are continuously damaged. Furthermore, the activation of **inflammasomes** and intracellular protein complexes aid in the overproduction of proinflammatory **cytokines** such as IL-1β and IL-18, which elevates the destruction of melanocytes.

Diagnosis and Treatment

Vitiligo diagnosis is primarily made by visual inspection of the skin. Observations of localized hypopigmented skin patches can often be made by the naked eye, although tools such as a Woods lamp can be useful for further inspection. A Woods lamp shines long wave ultraviolet light, and in the absence of other light, it makes patches and boarders of vitiligo lesions exceptionally clear. Blood tests are also a useful tool in vitiligo diagnosis, particularly in ruling out the possibility of other skin conditions causing depigmentation. Blood examination would test for the presence of antibodies and vitamin deficiencies which could cause skin abnormalities not associated with vitiligo diagnosis. It is worth noting that vitiligo is often underdiagnosed or misdiagnosed depending on people's ethnicity or skin tone. People with darker skin may be hastily diagnosed with vitiligo despite the possibility of other skin depigmentation mechanisms. In contrast, people with lighter skin are often undiagnosed or do not seek medical attention when patches are found.

Vitiligo treatment has historically depended on the size of hypopigmented areas. If the areas are small, cosmetic coverup or topical immune suppressants may be applied. Topical immunosuppressants, such as the promising new drug Opzerula, act by altering the immune system in the skin only, opposed to the entire immune system. Such drugs can reduce or prevent the activity of T cells or cytokines, resulting in a reduction of inflammation and risk of melanocyte breakdown.

If the areas are large, systemic immune suppression, skin bleaching, or skin grafts may be used. Systemic immune suppressant drugs include corticosteroids such as Prednisone, Betamethasone, and Dexamethasone. Such drugs can reduce the activity of the entire immune system, resulting in the slowing or complete prevention of melanocyte destruction. However, if such drugs are used, close monitoring from a medical professional is necessary, as increased risk of dangerous infection and other complications become prevalent.



Michael Jackson, undoubtably the most famous person with vitiligo. Jackson used both skin grafts and cosmetic makeup to aid his condition. © Georges Biard is licensed under a CC BY-SA (Attribution ShareAlike) license

In all cases of vitiligo, it is crucial for patients to wear sunscreen, as depigmented skin lacking melanin is especially vulnerable to burns and UV radiation, which may result in skin cancer (Melanoma). Today, there is an increasing movement towards embracing the cosmetic effects of vitiligo and redefining conventional beauty standards. Because vitiligo does not inherently impose health risks, other than increased risk of UV damage, many individuals have opted out of therapeutic regimes.



Winnie Harlow is a world famous fashion model with vitiligo. She is a spokesperson in the ongoing movement of vitiligo representation and awareness. © Georges Biard is licensed under a CC BY-SA (Attribution ShareAlike) license

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Graves' Disease

Graves' Disease

DYLAN MANN AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

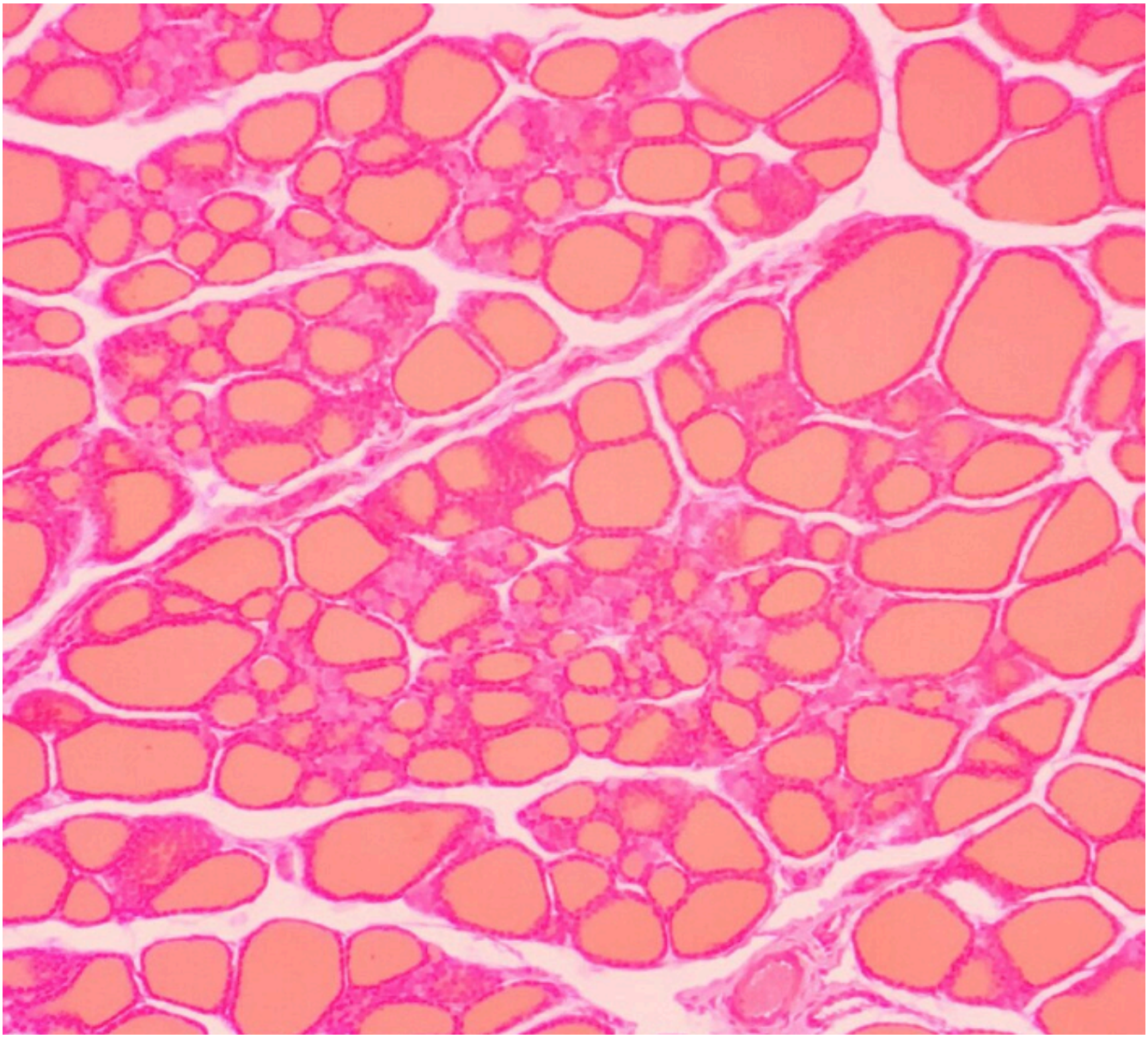
- Describe normal thyroid function and anatomy, highlighting key hormones and processes.
- Outline the autoimmune mechanism behind Graves disease incidence.
- Describe symptoms, treatment, and diagnosis of Graves disease.

Introduction

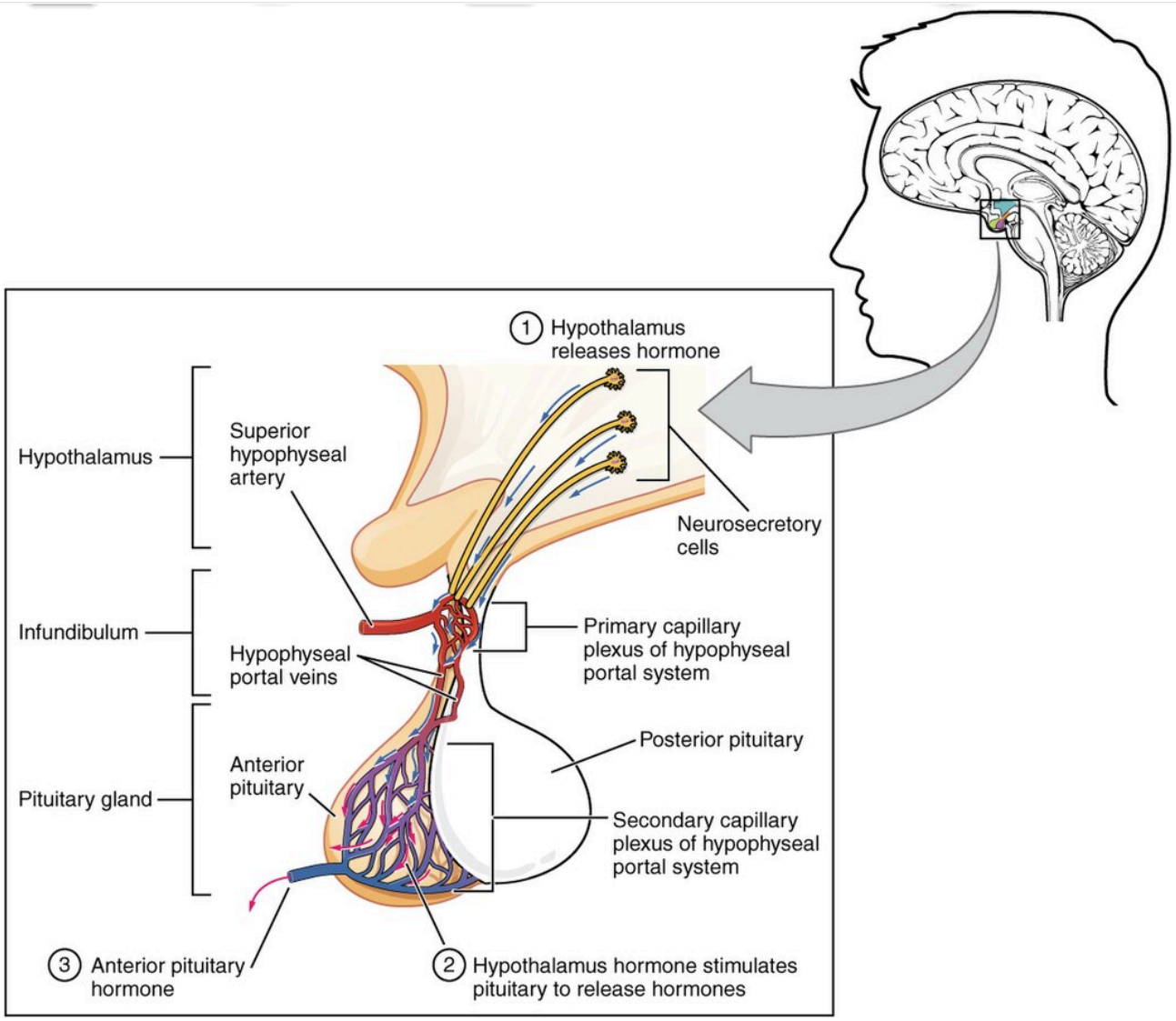
Graves' disease is an autoimmune disorder that causes hyperthyroidism, the result of excess release of thyroid hormones. It is estimated to effect approximately 1 in 100 Canadians.

Normal Thyroid Function and Anatomy

In healthy individuals, the hypothalamus detects low levels of thyroid hormones in the blood and releases **thyrotropin releasing hormone** (TRH). TRH is released from the hypothalamus into the hypophyseal portal system, a network of capillaries linking the hypothalamus to the anterior pituitary gland. When exposed to TRH, the anterior pituitary gland produces and releases **thyroid stimulating hormone** (TSH), which stimulates the thyroid gland located in the neck. The thyroid gland is made up of numerous follicles, which are small spheres lined with follicular cells. Follicular cells convert the protein thyroglobulin into two important iodine-containing hormones. These include **triiodothyronine** (T3) and **thyroxine** (T4). Once released from the thyroid gland, T3 and T4 enter the blood and bind to circulating plasma proteins, and the hormones are picked up by nearly every cell in the body. Once in the cells, most T4 is converted into T3, which is the more active hormone. T3 has many effects, including speeding up basal metabolic rate, increasing cardiac output, stimulating bone resorption, and activating the sympathetic nervous system.



Thyroid follicle section under light microscope © Panzer is licensed under a CC BY-SA (Attribution ShareAlike) license

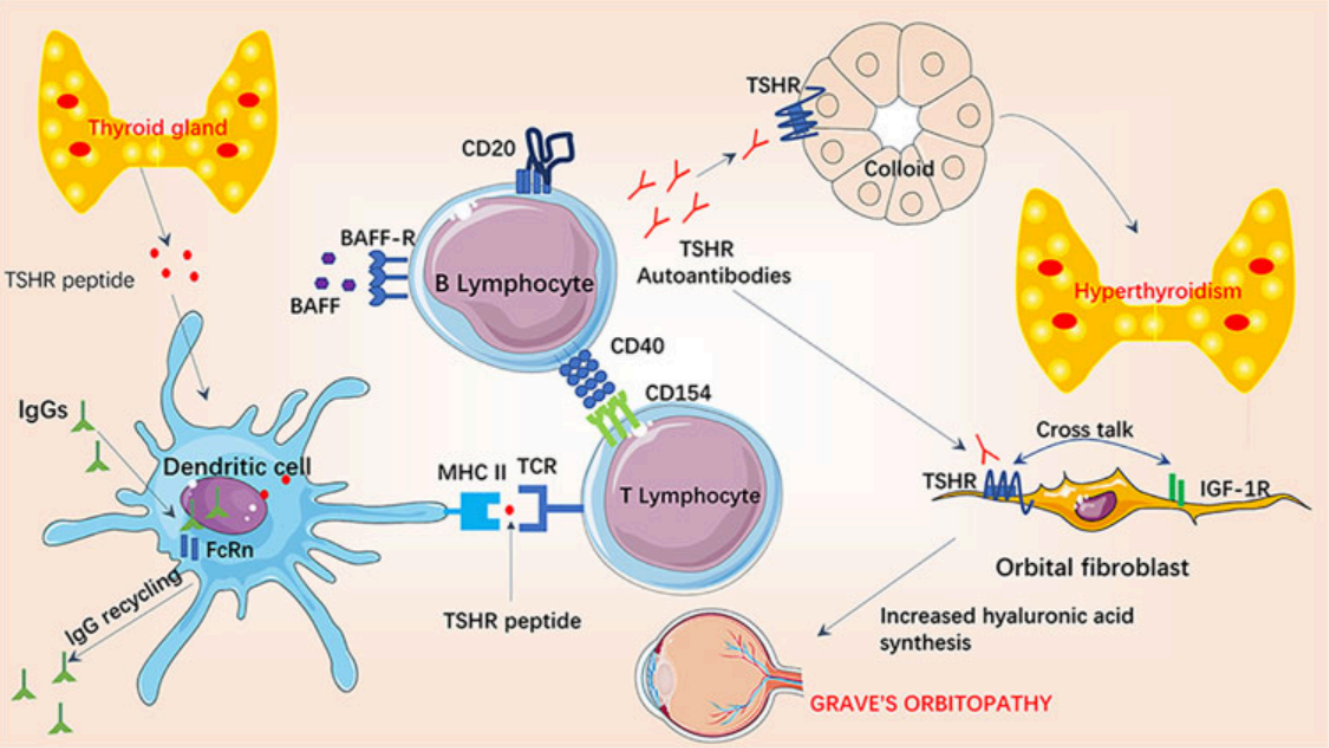


The hypophyseal portal vein connects the hypothalamus to the anterior pituitary © OpenStax College is licensed under a CC BY (Attribution) license

Autoimmune Mechanism

While the trigger of the autoimmune attack leading to Graves' disease remains unclear, pathogenesis of this disease is influenced by a combination of genetic and environmental factors. For example, middle aged women, smokers, and people who experience high levels of stress are at increased risk for developing Graves. In what is deemed as a **type II hypersensitivity reaction** , **B cells** begin to produce **antibodies** against thyroid proteins. The most common of such antibodies is thyroid stimulatory **immunoglobulin**, which binds to TSH receptors on thyroid cells and stimulates increased release of T3 and T4. Thyroid protein antibodies can also have direct effects on certain tissues. They may cause thyroid **hypertrophy**, which is characterized by growth of thyroid tissue, and hyperplasia, which results in an increased number of follicular cells. Hypertrophy and **hyperplasia** together cause thyroid enlargement, resulting in a goiter. In response to thyroid stimulatory antibodies, follicular cells begin to express molecules on their surface that attract nearby T cells that may infiltrate the thyroid gland. **Fibroblasts** in tissue surrounding the eyes and skin may also

be stimulated by thyroid stimulating antibodies. As thyroid stimulating antibodies accumulate, fibroblasts divide and make extracellular matrix proteins called glycosaminoglycans.

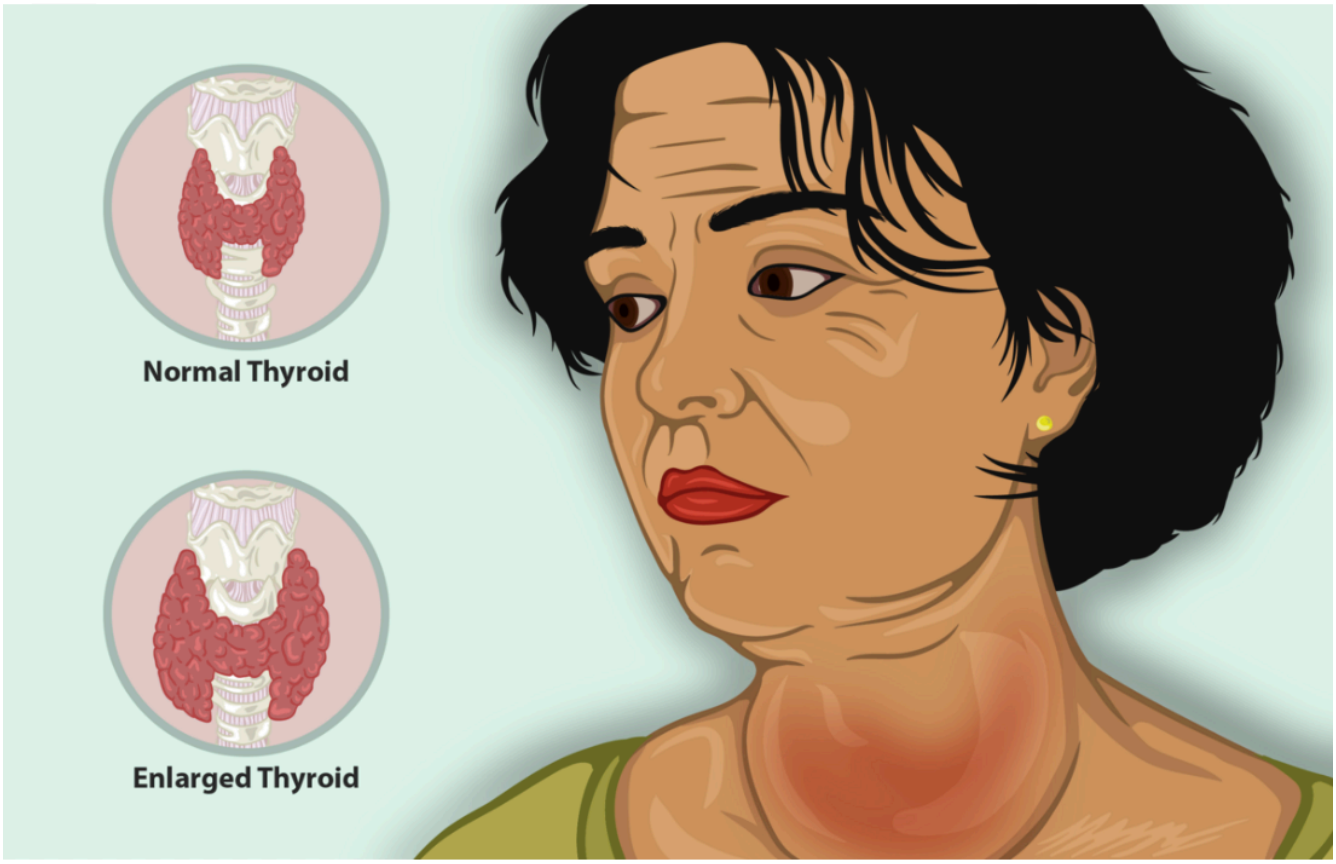


Graves disease autoimmune mechanism, including important players leading to hyperthyroidism © He et al. is licensed under a CC BY (Attribution) license

Symptoms

The main symptoms of Graves' disease include hyperthyroidism, ophthalmopathy, and dermopathy.

Untreated hyperthyroidism can lead to significant weight loss despite increased appetite due to increased basal metabolic rate, which coincides with overall heat intolerance. Hyperthyroidism also causes an increase in sympathetic nervous system activity, which may cause rapid heart rate, sweating, hyperactivity, anxiety, and insomnia. As described above, hyperthyroidism may also lead to a goiter, characterized by hyperplasia and hypertrophy of the thyroid tissue.



Thyroid enlargement, a symptom of hyperthyroidism can result in a structure called a Goiter. Licensed under a CC BY-SA *(Attribution ShareAlike) license*

In Graves ophthalmopathy, a buildup of glycosaminoglycans causes inflammation and swelling in and around the eye's follicular cells. This process can lead to exophthalmos, which is an outward bulging of the eyeball. Furthermore, this weakens the muscles that control upper eyelid movement and may damage the cornea as the individual has a difficult time blinking efficiently. Together, Graves ophthalmopathy symptoms lead to an increased risk of corneal ulcers.



Graves' disease induced ophthalmopathy © Sim Peini is licensed under a CC BY (Attribution) license

Graves dermopathy is characterized by localized thickening and swelling of the skin due to glycosaminoglycan build-up. This is a rare skin condition marked by non-pitting edema, particularly over the shins.



Graves induced dermopathy, most commonly resulting in non pitting edema on the shins © Gardner et al. is licensed under a CC BY-ND (Attribution NoDerivatives) license

People with Graves' disease can experience an acute flair in their disease called a 'thyroid storm'. A **thyroid storm** is a life-threatening increase in hyperthyroidism where the body goes into a state of sever hypermetabolism. A flare such as this can develop when a patient stops their treatment, develops infection, or has surgery. During a thyroid storm, all normal symptoms of hyperthyroidism become exaggerated. For example, heat intolerance can develop into high fever and a rapid heart rate can develop into cardiac arrythmia.

Diagnosis and Treatment

Diagnosis of hyperthyroidism is done through blood tests, where levels of TSH, T3, and T4 are measured. To confirm if hyperthyroidism is caused by Graves' disease, a blood test measuring thyroid stimulating antibodies would be performed. To further support diagnosis, radioiodine scans and measurements of iodine uptake would subsequently be tested. Radioiodine scans work by injecting small amounts of radioactive iodine, which can be traced endogenously through advanced cameras. Imaging allows medical professionals to monitor iodine absorption and function of the thyroid.

The main treatment approach for Graves' disease includes medication. Beta blockers treat the immediate symptoms of hyperthyroidism. Beta blockers do not act by directly reducing thyroid hormone production; instead, they block beta-adrenergic receptors. These receptors are the site of induction of sympathetic nervous system activity. Therefor the use of beta-blockers causes a reduction in the sympathetic nervous system hormones epinephrine and norepinephrine. Specific beta blockers may also help reduce or block the conversion of T4 into the more potent thyroid hormone T3. Anti-thyroid drugs however may directly block thyroid hormone production and release. In severe cases, the

thyroid may need to be destroyed or removed. Radio-iodine therapy partially destroys thyroid function but requires subsequent hormone replacement therapy. If the goiter becomes so large that it presses against surrounding tissue, thyroid tissue can be removed through surgery. Graves ophthalmopathy is treated separately, using steroids, radiation therapy, and surgery. Graves dermopathy is generally treated through overall stabilization of the disease, however topical immunosuppressant may be used to specifically reduce the autoimmune response in affected areas.

Review Questions



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Systemic Lupus Erythematosus

Systemic Lupus Erythematosus

DYLAN MANN AND MORGAN ALFORD

Learning Objectives

By the end of this section, you will be able to:

- Describe the autoimmune reaction behind Systemic Lupus erythematosus development.
- Explain how sex hormones lead to unequal incidence rate among biological males and females.
- Overview System Lupus erythematosus diagnosis, treatment, and symptoms.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune condition that can affect many organs and tissues, including the skin. SLE may develop in a person who carries some combination of susceptibility genes and is exposed to an environmental trigger. Susceptibility genes, much like other autoimmune conditions discussed in this chapter, are most commonly found in the human leukocyte antigens (HLA), which present antigens to T cells.

Manifestation of Autoimmune Reaction

SLE can be triggered by DNA damage. Environmental triggers include but are not limited to sunlight (UV radiation), inhaled smoke, bacteria, viruses, and medication. When DNA is damaged, the cell may repair the damage or undergo programmed cell death, in which **apoptotic bodies**containing DNA, histones, and other nuclear proteins are released from the cell. Apoptotic bodies containing nuclear antigens may stimulate an auto-immune process. Since susceptible individuals demonstrate reduced clearance of nuclear antigens, B cells may begin producing **anti-nuclear antibodies** (ANAs) to neutralize the attack.

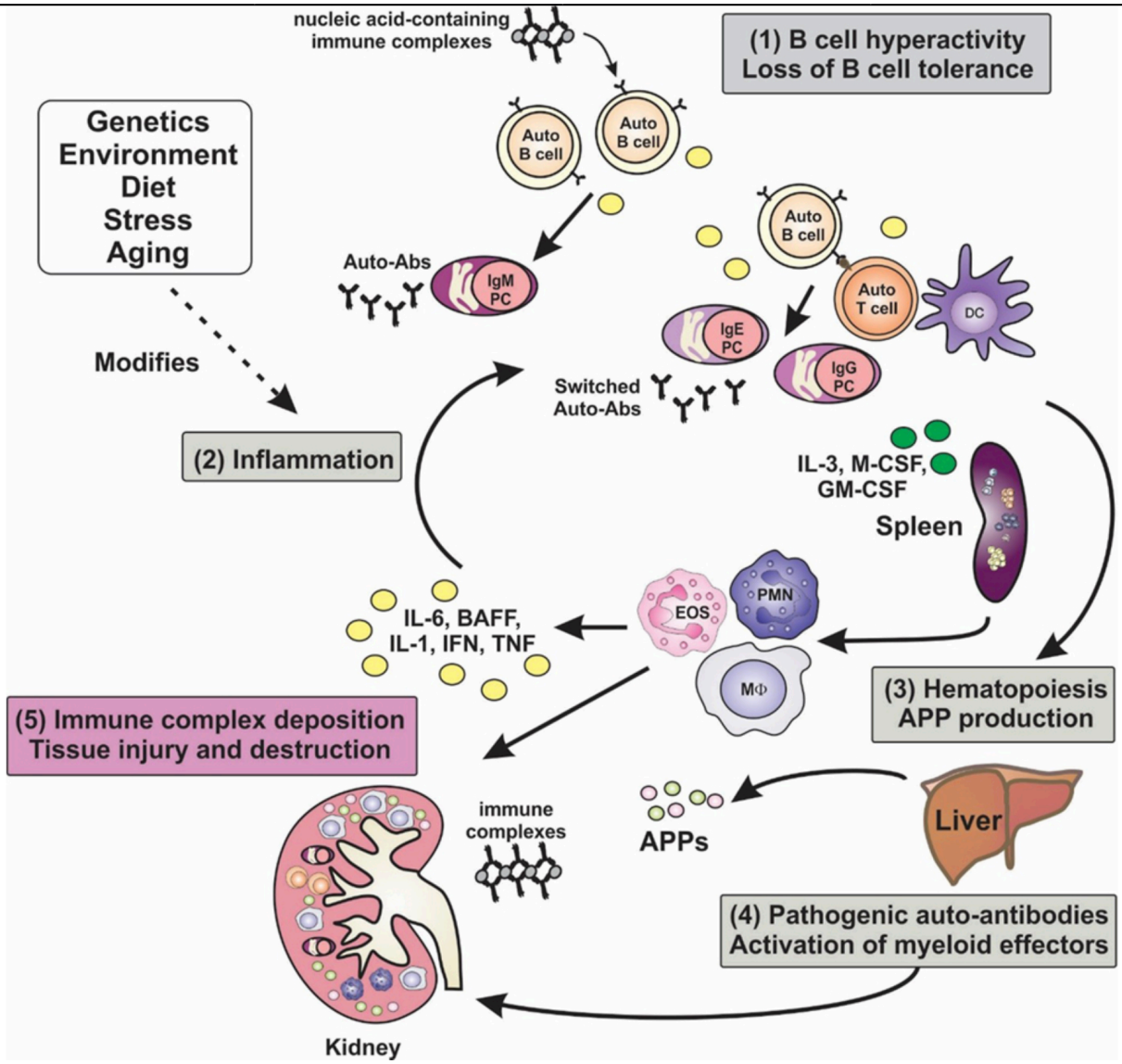


Figure highlighting key cells, tissues, and processes in autoimmune development of Systemic Lupus Erythematosus. © Gottschalk et al. is licensed under a CC BY (Attribution) license

Complement System Leads to Type III Hypersensitivity Reaction

ANAs will bind to nuclear antigens with a high degree of specificity. The resulting complexes will travel to many different tissues via the circulatory system, where they may deposit (particularly at ultrafiltration sites). The most common sites of deposition are in the skin, kidney, heart and joints. Complex deposition may initiate localized inflammation and **complement system** activation, which may lead to increased cell damage and apoptosis, promoting release of nuclear antigens further. Since the inflammatory cascade was stimulated by immune complex deposition, it is a prime example of a **type III hypersensitivity reaction**.

Sex Hormones Cause an Unequal Incidence Rate among Biological Males and Females

Estrogen plays an important role in the incidence of SLE. Estrogen levels are positively correlated to white blood cell count and robustness of immune activation. Women of child-rearing age (when peak estrogen levels are observed) are diagnosed with SLE 10x more frequently than men. However, older or younger women are diagnosed with SLE only 2x more frequently than men.

SLE Antibody and Antigen Development is not Limited to Nuclear Components

People living with SLE develop antibodies targeting both nuclear and non-nuclear antigens. For example, patients can acquire blood auto antibodies that may lead to hematologic disorders such as anemia, cytopenia, or leukopenia. Anti-smith antibodies target nuclear components such as ribonucleoproteins, and anti-dsDNA target double stranded DNA found in nuclei and are both specific to SLE. Another type of antibody includes anti-phospholipid antibodies, which usually target protein bound to phospholipids. Antibodies targeting phospholipids are particularly problematic, as phospholipids are found in cell membranes across all tissues. Such antibodies can lead to anti-phospholipid syndrome, where antibodies cause a hypercoagulable state. This causes the patient to be more prone to clots, deep vein thrombosis, hepatic vein thrombosis, and stroke.

Diagnoses and Symptoms

Given the systemic nature of SLE, symptomology is highly variable, which presents diagnostic challenges. General symptoms may include fever and weight loss, but specific symptoms depend on the affected tissues. Diagnostic criteria can be classified by the inflicted system: skin, mucosa, serosa, kidneys, joints, brain, blood, and immunity (antibodies).

Symptoms observed in the skin may include the malar (butterfly) rash, discoid rash, and photosensitivity. People with SLE infrequently report ulcers of the mucosa. Serosal inflammation may present as pleuritis, pericarditis, or endocarditis. Patients often experience joint pain and inflammation (arthritis) which can lead to permanent damage if left untreated. Additionally, individuals may exhibit proteinuria or glomerulonephritis. Severe neurological symptoms include seizure, whereas hematological symptoms include decreased counts of red and/or white blood cells. Most people living with SLE will test positive for ANAs, though the test is not specific enough to be used on its own.

Clinicians seek to identify at least four of the 11 diagnostic criteria in a patient before making a diagnosis of SLE and initiating a person on treatment to manage flare ups.

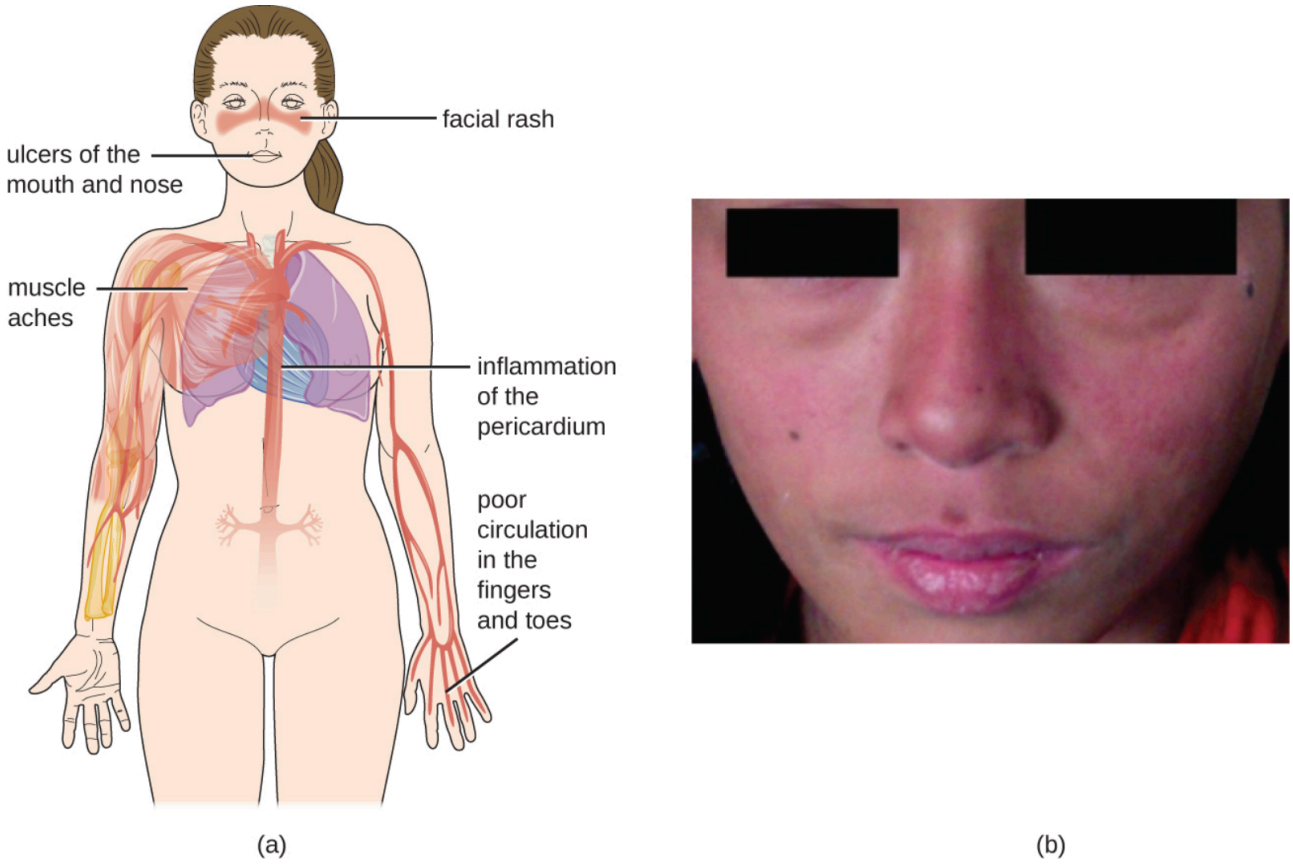
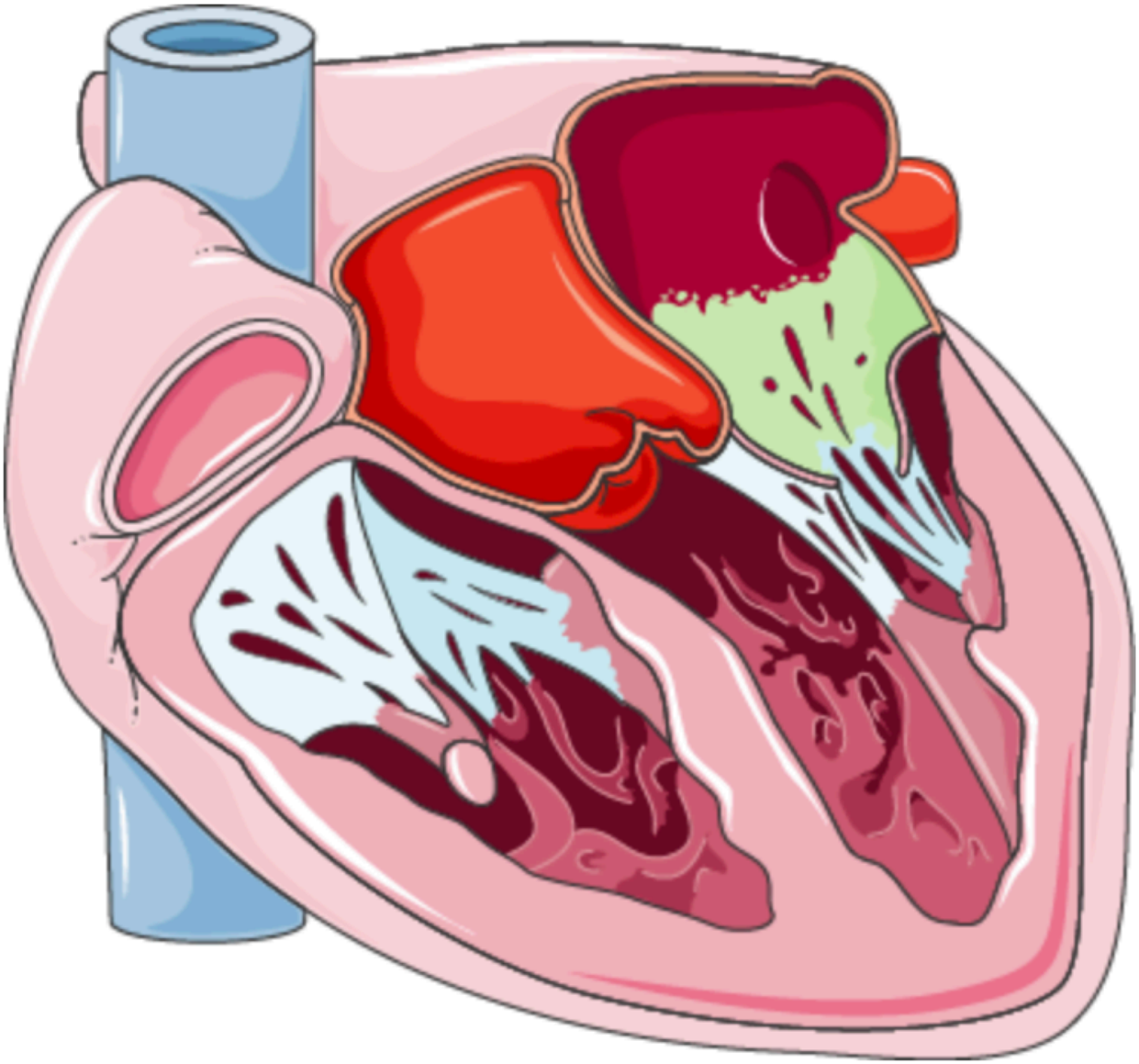


Figure highlighting common SLE symptoms, upclose image on the right shows development of a malar rash. © CNX OpenStax is licensed under a CC BY (Attribution) license



The most common cardiac manifestation of SLE includes Libman Sacks Endocarditis. This is a form of non bacterial endocarditis in which the inner layer of the heart become inflamed. © Content Partnerships Hub is licensed under a CC BY-SA (Attribution ShareAlike) license

Treatment

People with SLE alternate between states of flare and remittance. Immunosuppressant drugs, which may limit the autoimmune response topically or systematically, may be used to control flare ups. During periods of remittance, it is advised to avoid triggers including sunlight (UV) exposure and smoke in addition to practicing good hygiene.

Review Questions

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Chapter Summary and Credits

Autoimmunity Summary and Credits

DYLAN MANN AND MORGAN ALFORD

Chapter Summary

Autoimmunity occurs when the body's immune system mistakenly attacks its own cells, tissues, or organs. To understand this condition, it important to understand the components and mechanisms of a functional immune system. Autoimmune conditions may be caused by a combination of environmental and genetic factors, which may trigger an autoimmune attack. Autoimmune attacks can lead to numerous autoimmune diseases, as well as other conditions with an autoimmune component (but are not considered primarily autoimmune diseases).

Pathogens are present in our environment, entering our bodies through food, water, surfaces, and air. Mammalian immune systems have evolved to detect and combat these threats using a complex network of specialized immune cells. Features of the immune system, such as pathogen identification, specific response, amplification, retreat, and remembrance are essential for survival of infectious diseases.

The innate immune system serves as a first responder to pathogenic threats. Innate immunity includes both physical and chemical barriers as well as molecular attack. The innate immune system responds with inflammation, phagocytosis, cytokine release, destruction by NK cells, and/or the complement system. When innate mechanisms are insufficient to clear a pathogen, the adaptive immune response is mobilized.

The adaptive immune response is slower-acting, longer-lasting, and more specific than the innate response. APCs display antigens via MHC molecules to complementary naive T cells and, in response, the T cells differentiate and proliferate, becoming T_H cells or CTLs. Immunologic memory can persist after a primary exposure to a pathogen. If re-exposure occurs, the adaptive immune response can proliferate without input from the innate immune system.

Antibodies (immunoglobulins) are secreted from plasma cells and mediate the humoral immune system. There are five antibody classes which determines its mechanism of action and production site, but does not control its binding specificity. Antibodies bind antigens via variable domains and can either neutralize pathogens, mark them for phagocytosis, or activate the complement cascade.

Immune disruptions can manifest as either an insufficient immune response or a response to non-pathogenic entities. Immunodeficiency increases an individual's susceptibility to infections and even some cancers. Hypersensitivities are misdirected responses to harmless foreign particles (allergy) or host factors (autoimmunity).

Celiac disease is characterized by an autoimmune response triggered by the consumption of gluten, a protein that is found in food products containing wheat, barley, and rye. Gluten is incompletely digested into gliadin in the small intestine, and through binding to immunoglobulins, it is falsely presented to MHC II and inflammatory cytokines are produced. The current recommendation for celiac disease treatment is following a strict gluten free diet (GFD), which in most cases removes all symptoms.

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder affecting the joints. It primarily affects the synovial joints, but can also affect the skin, lungs, and other organ systems. Because synovial joints are metabolically active, the synovial membrane has many blood vessels and lymphatics running through them, which makes them more

vulnerable to autoimmune dysfunction. Rheumatoid arthritis is a progressive condition, but can be treated through anti-inflammatory or immunosuppressant drugs.

Vitiligo is a skin condition defined by localized patches of depigmentation of the skin, irises, and hair. There are two main types of the disease: non-segmental and segmental vitiligo. Non-segmental is an autoimmune condition and makes up ~85% of all vitiligo cases, while segmental vitiligo is far less common and is not autoimmune. Vitiligo treatment, although not necessary, includes cosmetic coverup, skin grafting/bleaching, and topical immune suppressants

Graves' disease is an autoimmune disorder that causes hyperthyroidism, resulting in excess release of thyroid hormones. Graves' is a type II hypersensitivity reaction, and is most common in middle aged women, smokers, and people who experience high levels of stress. The three main symptoms of Graves' disease include hyperthyroidism, ophthalmopathy, and dermopathy. Treatment includes beta blockers, anti-thyroid drugs, and in extreme cases, thyroid destruction or removal.

Systemic lupus erythematosus (SLE) is an autoimmune condition that can affect many organs and tissues, but most frequently the skin. SLE autoimmune reaction includes the activation of the complement system and is classified as a type III hypersensitivity reaction. Sex hormones play an important role in the very uneven distribution of SLE in women of child-rearing age compared to men. Treatment is aimed at avoiding environmental triggers during remittance, and immunosuppression during flares.

Key Takeaways

- Autoimmunity is a condition in which the bodies immune system mistakingly attacks its own cells, tissues, or organs
- Mammalian immune systems have evolved to detect and combat pathogens using a complex network of specialized immune cells
- The innate immune system serves as a first responder to pathogenic threats
- The adaptive immune response is slower-acting, longer-lasting, and more specific than the innate response
- Antibodies (immunoglobulins) are secreted from plasma cells and mediate the humeral immune system
- Immune disruptions can manifest as either an insufficient immune response or inappropriate immune targets
- Celiac disease is characterized by an autoimmune response triggered by the consumption of gluten
- Rheumatoid arthritis is a chronic inflammatory autoimmune disorder affecting primarily but limited to the joints
- Non-segmental vitiligo is an autoimmune condition defined by localized patches of depigmentation of the skin, irises, and hair
- Graves' disease is an autoimmune disorder that causes hyperthyroidism, resulting in excess release of thyroid hormones
- Systemic lupus erythematosus (SLE) is an autoimmune condition that can affect many organs and tissues, but most frequently the skin

Credits

Authors: Morgan Alford (UBC) and Dylan Mann (UBC)

Post-Test for Autoimmunity

Post-Test for Autoimmunity

DYLAN MANN AND MORGAN ALFORD



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NEUROMUSCULAR CONTROL OF MOTION

Neuromuscular Chapter Overview

JENNIFER KONG

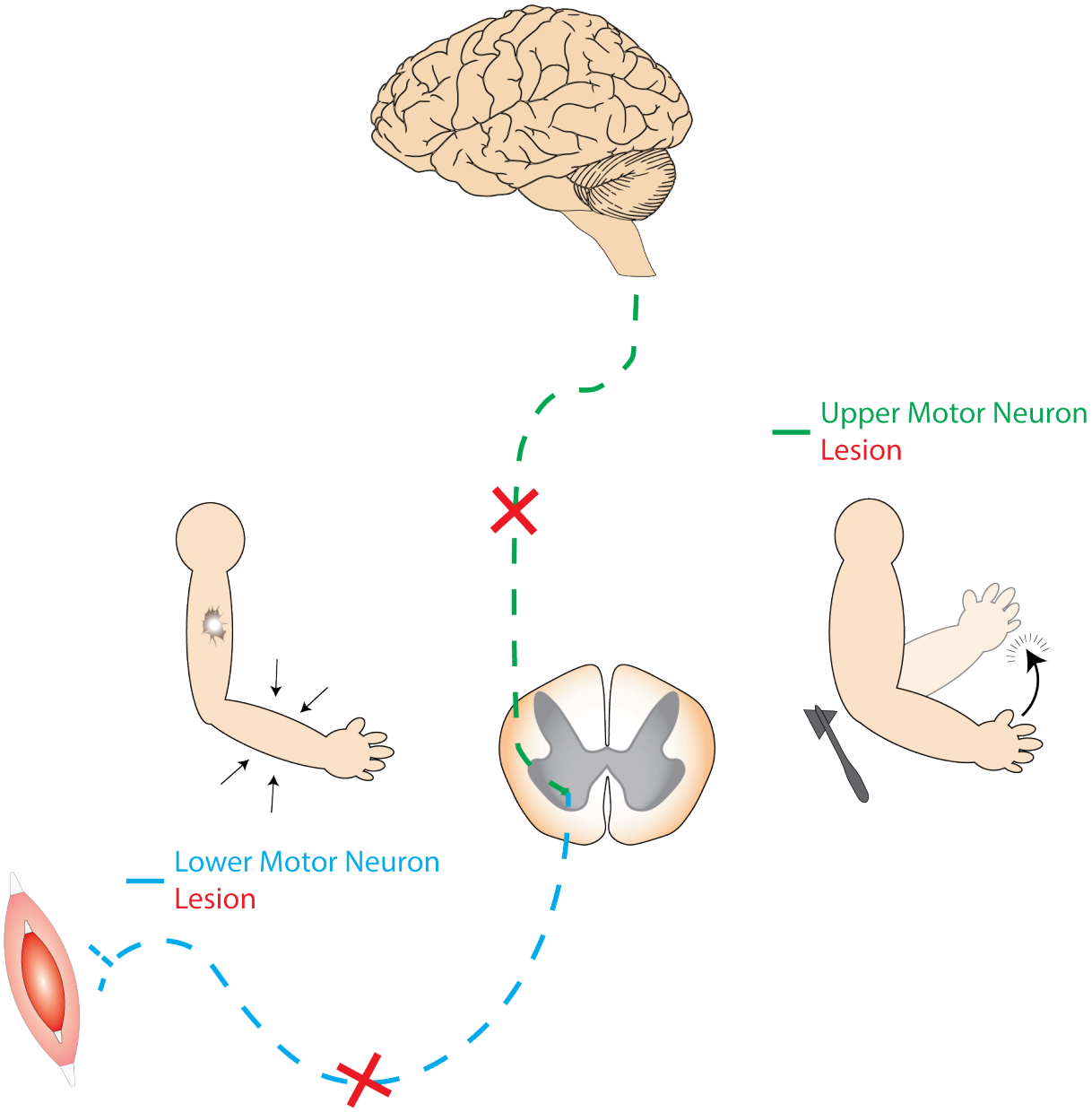
Chapter Learning Objectives

By the end of this chapter, you will be able to:

- Name the major divisions of the nervous system, both anatomical and functional.
- Describe the functional and structural differences between gray matter and white matter structures.
- List the types of glial cells and assign each to the proper division of the nervous system, along with their function(s).
- Distinguish the major functions of the nervous system: sensation, integration, and response.
- Describe the components of the membrane that establish the resting membrane potential.
- Describe the changes that occur to the membrane that result in the action potential.
- Explain the differences between types of graded potentials.
- Categorize the major neurotransmitters by chemical type and effect.

Neuromuscular control of voluntary movement is a large topic which involves the nervous system, neuromuscular control, muscle contraction, and functional joints and bones. Everything has to be functional for smooth, voluntary movement to occur. Thus, this chapter's pathologies of neuromuscular disorders are loosely categorized as issues with

- Nervous control: central vs peripheral nervous system problems
- Neuromuscular junction
- Muscular structure and/or ability to contract
- Joint and/or bone abnormalities are discussed in a future chapter



Overview of voluntary motor message – *Voluntary motor message requires both intact upper (CNS) and lower (PNS) motor neurons to result in muscle contraction. Impairments of UMN or LMN will result in impaired motion yet still have an intact spinal reflex.*

Each classification have different causes and exhibit their own set of signs, symptoms, and diagnostic findings.

This chapter is subdivided into:

- Pre-test
- Normal anatomy, physiology & histology of the nervous system and skeletal muscle tissue
- Classification & causes of neuromuscular disorders
- Pathophysiology of neuromuscular control exemplars
    - CNS: traumatic brain injury, ischemic stroke

    - CNS myelination: Multiple Sclerosis
    - PNS: diabetic neuropathy
    - Neuromuscular junction: Myasthenia Gravis
    - Muscle: Muscle strains and Muscular Dystrophy
- Clinical manifestation of problems with neuromuscular control
- Interview with health care professionals diagnosing/treating those with movement disorders
    - Prosthetics & Orthotics
    - Electroneurophysiology (EEG & EMGs)
- Post-test

Abbreviations

The following abbreviations are used throughout the chapter.

Ach	Acetylcholine
AchE	Acetylcholinesterase
AchR	Acetylcholine Receptor
ADP	Adenosine Diphosphate
ANS	Autonomic Nervous System
ATP	Adenosine Triphosphate
BBB	Blood Brain Barrier
C	Cervical
Ca^{2+}	Calcium
CN	Cranial Nerve
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DM	Diabetes Mellitus
EEG	Electroencephalogram
L	Lumbar
LMN	Lower Motor Neuron
MD	Muscular Dystrophy
MG	Myasthenia Gravis
MS	Multiple Sclerosis
NMJ	Neuromuscular Junction
PNS	Peripheral Nervous System
SNS	Sympathetic Nervous System
T	Thoracic
TBI	Traumatic Brain Injury
UMN	Upper Motor Neuron

Pre-test for Neuromuscular Control of Motion

SABA SABERI AND AVAH ZAMANI FARAHANI



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Overview of the Nervous System

J. GORDON BETTS; JAMES A. WISE; KELLY A. YOUNG; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

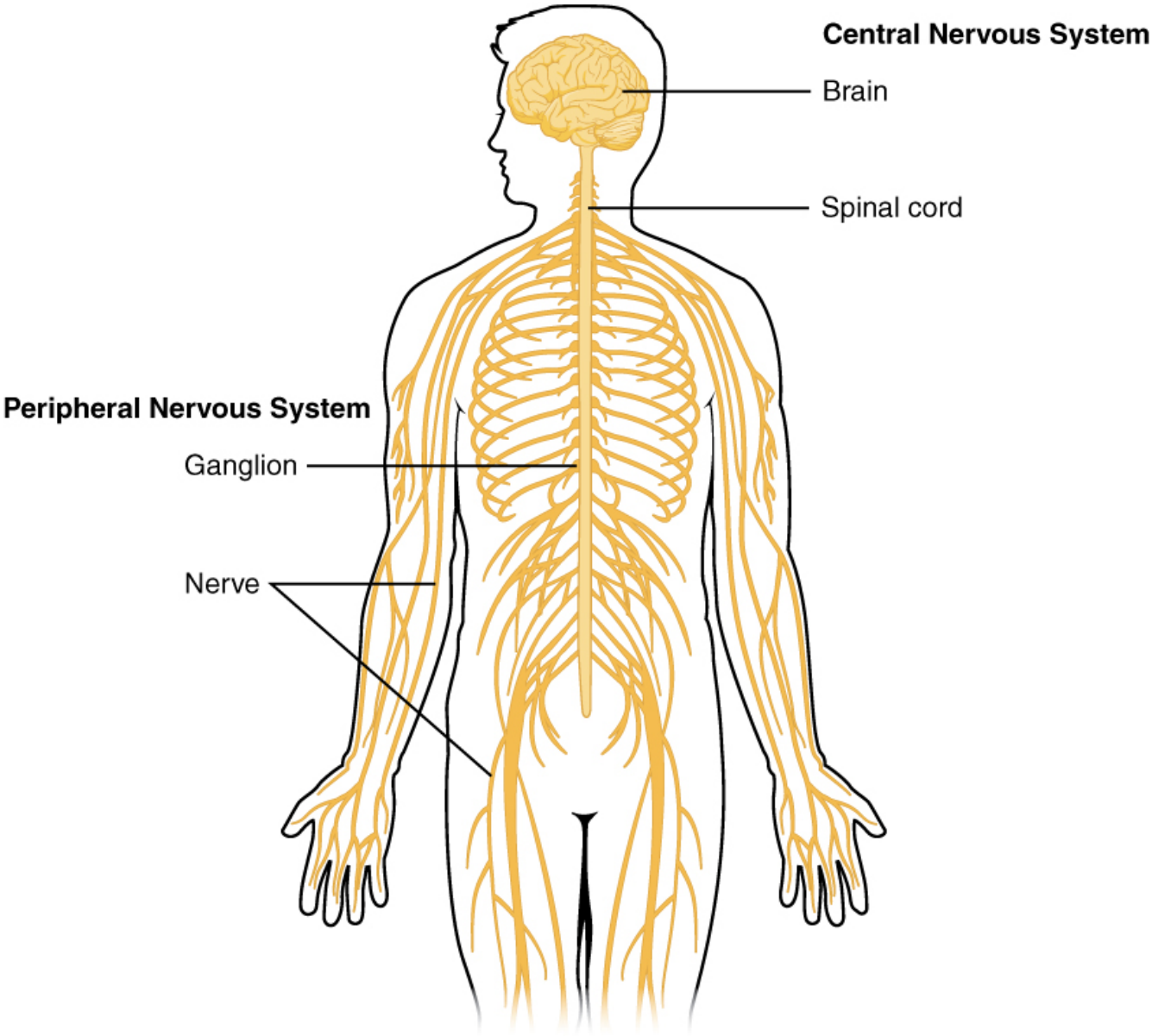
By the end of this section, you will be able to:

- Identify the anatomical and functional divisions of the nervous system.
- Relate the functional and structural differences between gray matter and white matter structures of the nervous system to the structure of neurons.
- List the basic functions of the nervous system.

The picture you have in your mind of the nervous system probably includes the brain, the nervous tissue contained within the cranium, and the spinal cord, the extension of nervous tissue within the vertebral column. That suggests it is made of two organs—and you may not even think of the spinal cord as an organ—but the nervous system is a very complex structure. Within the brain, many different and separate regions are responsible for many different and separate functions. It is as if the nervous system is composed of many organs that all look similar and can only be differentiated using tools such as the microscope or electrophysiology. In comparison, it is easy to see that the stomach is different than the esophagus or the liver, so you can imagine the digestive system as a collection of specific organs.

The Central and Peripheral Nervous Systems

The nervous system can be divided into two major regions: the central and peripheral nervous systems. The central nervous system (CNS) is the brain and spinal cord, and the peripheral nervous system (PNS) is everything else, as the figure below shows. The brain is contained within the cranial cavity of the skull, and the spinal cord is contained within the vertebral cavity of the vertebral column. It is a bit of an oversimplification to say that the CNS is what is inside these two cavities and the peripheral nervous system is outside of them, but that is one way to start to think about it. In actuality, there are some elements of the peripheral nervous system that are within the cranial or vertebral cavities. The peripheral nervous system is so named because it is on the periphery—meaning beyond the brain and spinal cord. Depending on different aspects of the nervous system, the dividing line between central and peripheral is not necessarily universal.



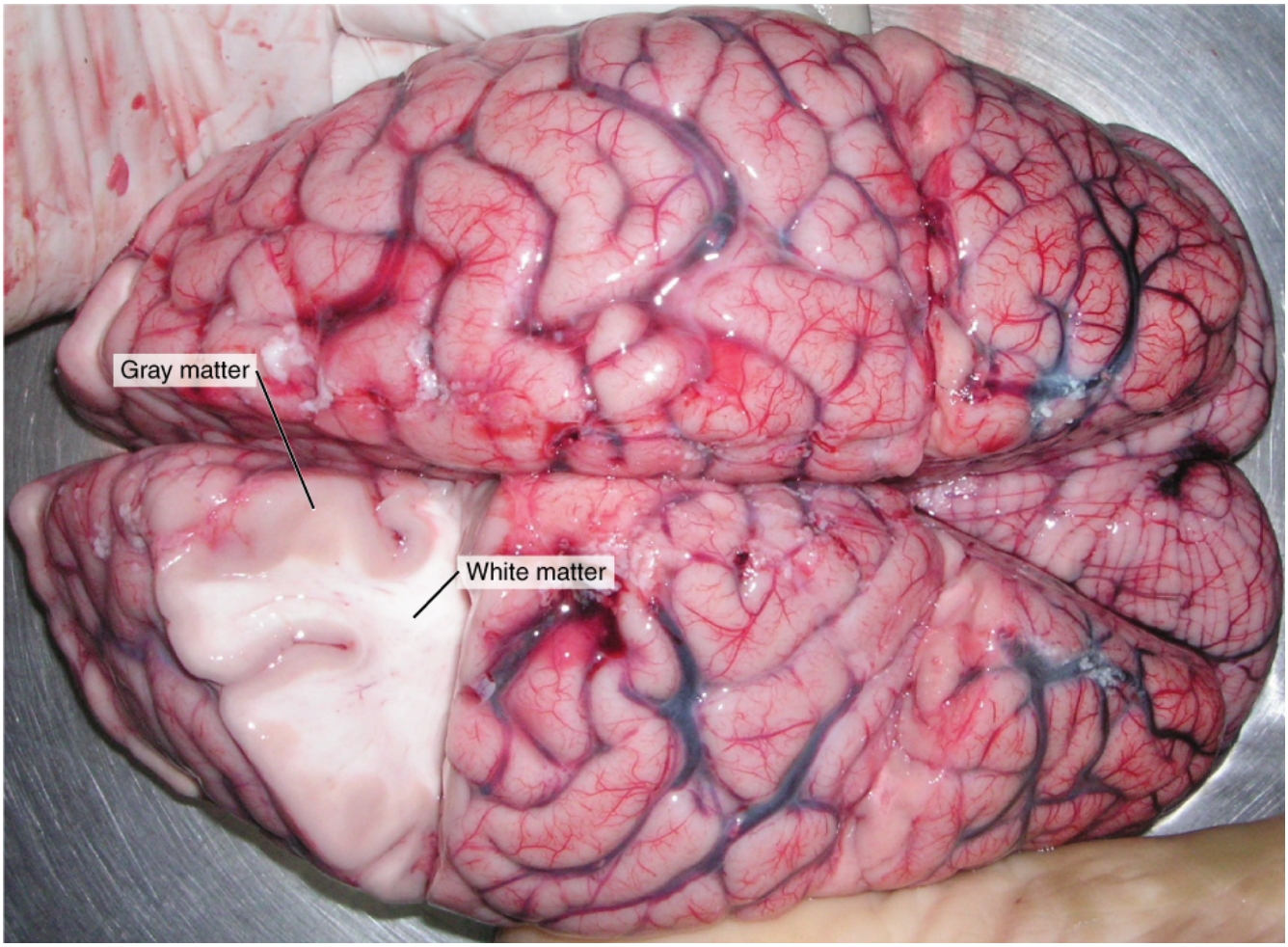
Central and Peripheral Nervous System – *The structures of the PNS are referred to as ganglia and nerves, which can be seen as distinct structures. The equivalent structures in the CNS are not obvious from this overall perspective and are best examined in prepared tissue under the microscope.*

Nervous tissue, present in both the CNS and PNS, contains two basic types of cells: neurons and glial cells. A glial cell is one of a variety of cells that provide a framework of tissue that supports the neurons and their activities. The neuron is the more functionally important of the two, in terms of the communicative function of the nervous system. To describe the functional divisions of the nervous system, it is important to understand the structure of a neuron. Neurons are cells and therefore have a soma, or cell body, but they also have extensions of the cell; each extension is generally referred to as a process. There is one important process that every neuron has called an axon, which is the fiber that connects a neuron with its target. Another type of process that branches off from the soma is the dendrite. Dendrites are responsible for receiving most of the input from other neurons.

Looking at nervous tissue, there are regions that predominantly contain cell bodies and regions that are largely composed of just axons. These two regions within nervous system structures are often referred to as gray matter (the

regions with many cell bodies and dendrites) or white matter (the regions with many axons). This image demonstrates the appearance of these regions in the brain and spinal cord. The colors ascribed to these regions are what would be seen in "fresh," or unstained, nervous tissue. Gray matter is not necessarily gray. It can be pinkish because of blood content, or even slightly tan, depending on how long the tissue has been preserved. But white matter is white because axons are insulated by a lipid-rich substance called myelin. Lipids can appear as white ("fatty") material, much like the fat on a raw piece of chicken or beef. Actually, gray matter may have that color ascribed to it because next to the white matter, it is just darker—hence, gray.

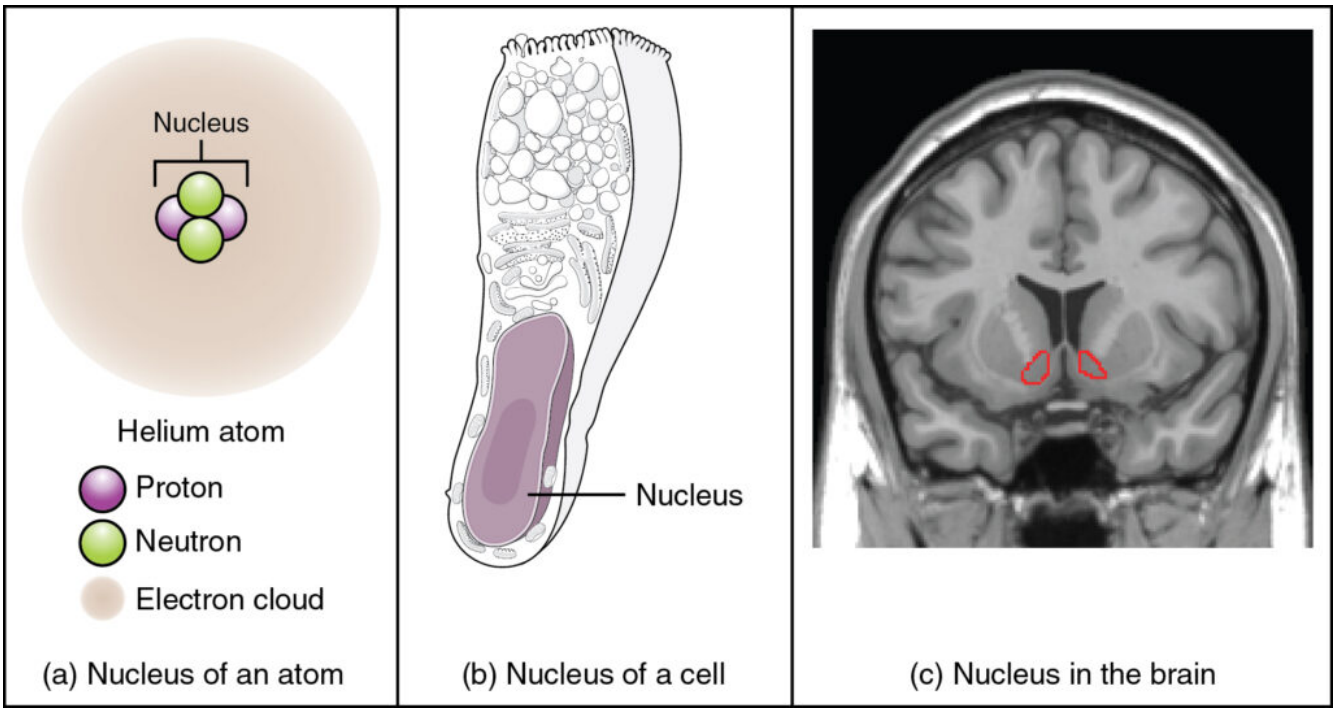
The distinction between gray matter and white matter is most often applied to central nervous tissue, which has large regions that can be seen with the unaided eye. When looking at peripheral structures, often a microscope is used and the tissue is stained with artificial colors. That is not to say that central nervous tissue cannot be stained and viewed under a microscope, but unstained tissue is most likely from the CNS—for example, a frontal section of the brain or cross section of the spinal cord.



Gray Matter and White Matter – *A brain removed during an autopsy, with a partial section removed, shows white matter surrounded by gray matter. Gray matter makes up the outer cortex of the brain. (credit: modification of work by "Suseno"/Wikimedia Commons)*

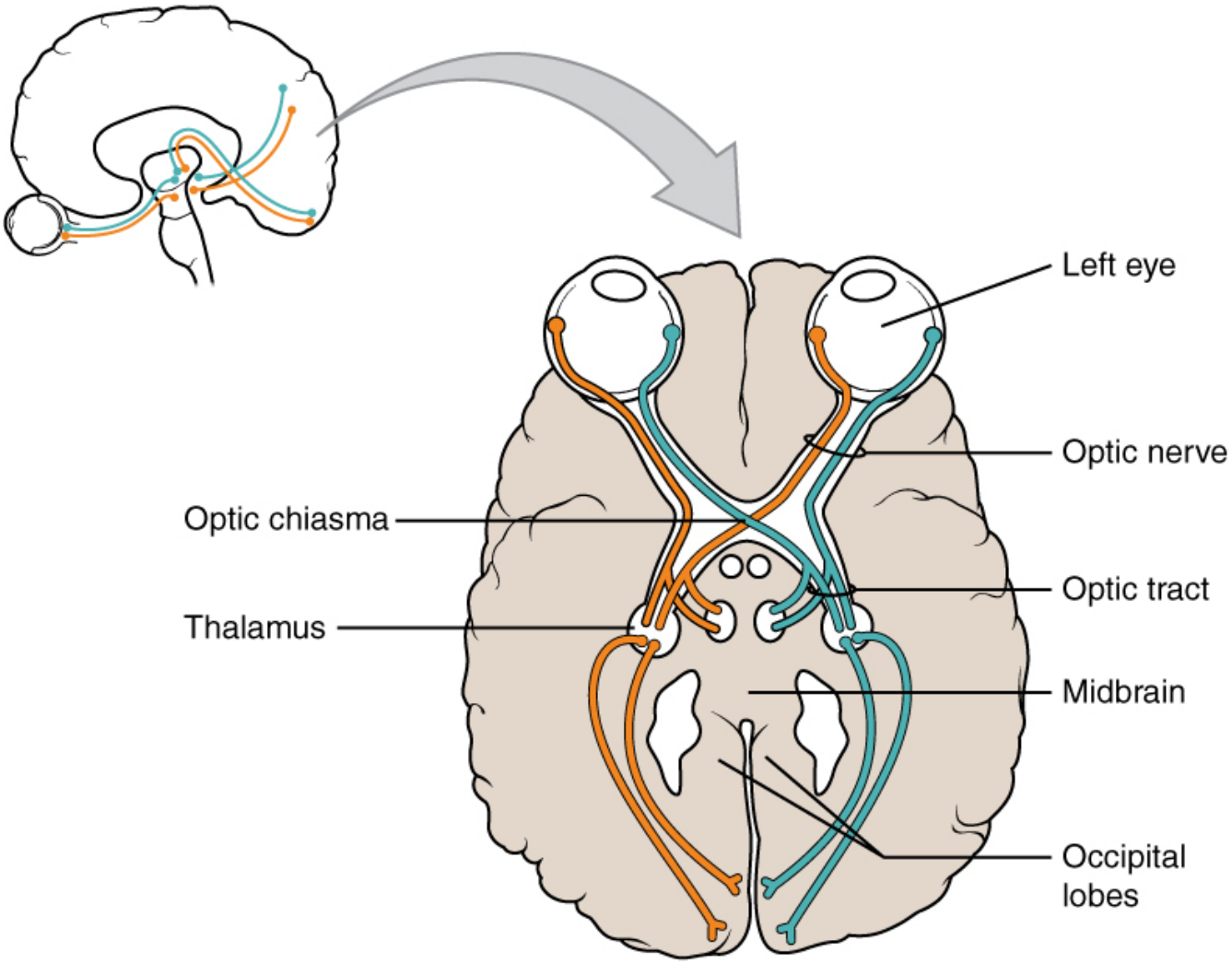
Regardless of the appearance of stained or unstained tissue, the cell bodies of neurons or axons can be located in discrete anatomical structures that need to be named. Those names are specific to whether the structure is central or peripheral. A localized collection of neuron cell bodies in the CNS is referred to as a nucleus. In the PNS, a cluster of neuron cell bodies is referred to as a ganglion. The diagram below indicates how the term nucleus has a few different

meanings within anatomy and physiology. It is the center of an atom, where protons and neutrons are found; it is the center of a cell, where the DNA is found; and it is a center of some function in the CNS. There is also a potentially confusing use of the word ganglion (plural = ganglia) that has a historical explanation. In the central nervous system, there is a group of nuclei that are connected together and were once called the basal ganglia before "ganglion" became accepted as a description for a peripheral structure. Some sources refer to this group of nuclei as the "basal nuclei" to avoid confusion.



What Is a Nucleus? – *(a) The nucleus of an atom contains its protons and neutrons. (b) The nucleus of a cell is the organelle that contains DNA. (c) A nucleus in the CNS is a localized center of function with the cell bodies of several neurons, shown here circled in red. (credit c: "Was a bee"/Wikimedia Commons)*

Terminology applied to bundles of axons also differs depending on location. A bundle of axons, or fibers, found in the CNS is called a tract whereas the same thing in the PNS would be called a nerve. There is an important point to make about these terms, which is that they can both be used to refer to the same bundle of axons. When those axons are in the PNS, the term is nerve, but if they are CNS, the term is tract. The most obvious example of this is the axons that project from the retina into the brain. Those axons are called the optic nerve as they leave the eye, but when they are inside the cranium, they are referred to as the optic tract. There is a specific place where the name changes, which is the optic chiasm, but they are still the same axons, as illustrated in the figure below. A similar situation outside of science can be described for some roads. Imagine a road called "Broad Street" in a town called "Anyville." The road leaves Anyville and goes to the next town over, called "Hometown." When the road crosses the line between the two towns and is in Hometown, its name changes to "Main Street." That is the idea behind the naming of the retinal axons. In the PNS, they are called the optic nerve, and in the CNS, they are the optic tract. This table helps to clarify which of these terms apply to the central or peripheral nervous systems.



Optic Nerve Versus Optic Tract – *This drawing of the connections of the eye to the brain shows the optic nerve extending from the eye to the chiasm, where the structure continues as the optic tract. The same axons extend from the eye to the brain through these two bundles of fibers, but the chiasm represents the border between peripheral and central.*

	CNS	**PNS**
Group of Neuron Cell Bodies (i.e. gray matter)	Nucleus	Ganglion
Bundle of Axons (i.e. white matter)	Tract	Nerve

A summary of the terminology used to describe structures in the central and peripheral nervous systems.

In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic resonance imaging (MRI). This is a tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique in the nervous system is that fat tissue and water appear as different

shades between black and white. Because white matter is fatty (from myelin) and gray matter is not, they can be easily distinguished in MRI images. Try this PhET simulation that demonstrates the use of this technology and compares it with other types of imaging technologies. Also, the results from an MRI session are compared with images obtained from X-ray or computed tomography. How do the imaging techniques shown in this game indicate the separation of white and gray matter compared with the freshly dissected tissue shown earlier?

Structures of the CNS and PNS

Functional Divisions of the Nervous System

The nervous system can also be divided on the basis of its functions, but anatomical divisions and functional divisions are different. The CNS and the PNS both contribute to the same functions, but those functions can be attributed to different regions of the brain (such as the cerebral cortex or the hypothalamus) or to different ganglia in the periphery. The problem with trying to fit functional differences into anatomical divisions is that sometimes the same structure can be part of several functions. For example, the optic nerve carries signals from the retina that are either used for the conscious perception of visual stimuli, which takes place in the cerebral cortex, or for the reflexive responses of smooth muscle tissue that are processed through the hypothalamus.

There are two ways to consider how the nervous system is divided functionally. First, the basic functions of the nervous system are sensation, integration, and response. Secondly, control of the body can be somatic or autonomic—divisions that are largely defined by the structures that are involved in the response. There is also a region of the peripheral nervous system that is called the enteric nervous system that is responsible for a specific set of the functions within the realm of autonomic control related to gastrointestinal functions.

Basic Functions

The nervous system is involved in receiving information about the environment around us (sensation) and generating responses to that information (motor responses). The nervous system can be divided into regions that are responsible for sensation (sensory functions) and for the response (motor functions). But there is a third function that needs to be included. Sensory input needs to be integrated with other sensations, as well as with memories, emotional state, or learning (cognition). Some regions of the nervous system are termed integration or association areas. The process of integration combines sensory perceptions and higher cognitive functions such as memories, learning, and emotion to produce a response.

Sensation. The first major function of the nervous system is sensation—receiving information about the environment to gain input about what is happening outside the body (or, sometimes, within the body). The sensory functions of the nervous system register the presence of a change from homeostasis or a particular event in the environment, known as a stimulus. The senses we think of most are the "big five": taste, smell, touch, sight, and hearing. The stimuli for taste and smell are both chemical substances (molecules, compounds, ions, etc.), touch is physical or mechanical stimuli that interact with the skin, sight is light stimuli, and hearing is the perception of sound, which is a physical stimulus similar to some aspects of touch. There are actually more senses than just those, but that list represents the major senses. Those five are all senses that receive stimuli from the outside world, and of which there is conscious perception. Additional

sensory stimuli might be from the internal environment (inside the body), such as the stretch of an organ wall or the concentration of certain ions in the blood.

Response. The nervous system produces a response on the basis of the stimuli perceived by sensory structures. An obvious response would be the movement of muscles, such as withdrawing a hand from a hot stove, but there are broader uses of the term. The nervous system can cause the contraction of all three types of muscle tissue. For example, skeletal muscle contracts to move the skeleton, cardiac muscle is influenced as heart rate increases during exercise, and smooth muscle contracts as the digestive system moves food along the digestive tract. Responses also include the neural control of glands in the body as well, such as the production and secretion of sweat by the eccrine and merocrine sweat glands found in the skin to lower body temperature.

Responses can be divided into those that are voluntary or conscious (contraction of skeletal muscle) and those that are involuntary (contraction of smooth muscles, regulation of cardiac muscle, activation of glands). Voluntary responses are governed by the somatic nervous system and involuntary responses are governed by the autonomic nervous system.

Integration. Stimuli that are received by sensory structures are communicated to the nervous system where that information is processed. This is called integration. Stimuli are compared with, or integrated with, other stimuli, memories of previous stimuli, or the state of a person at a particular time. This leads to the specific response that will be generated. Seeing a baseball pitched to a batter will not automatically cause the batter to swing. The trajectory of the ball and its speed will need to be considered. Maybe the count is three balls and one strike, and the batter wants to let this pitch go by in the hope of getting a walk to first base. Or maybe the batter's team is so far ahead, it would be fun to just swing away.

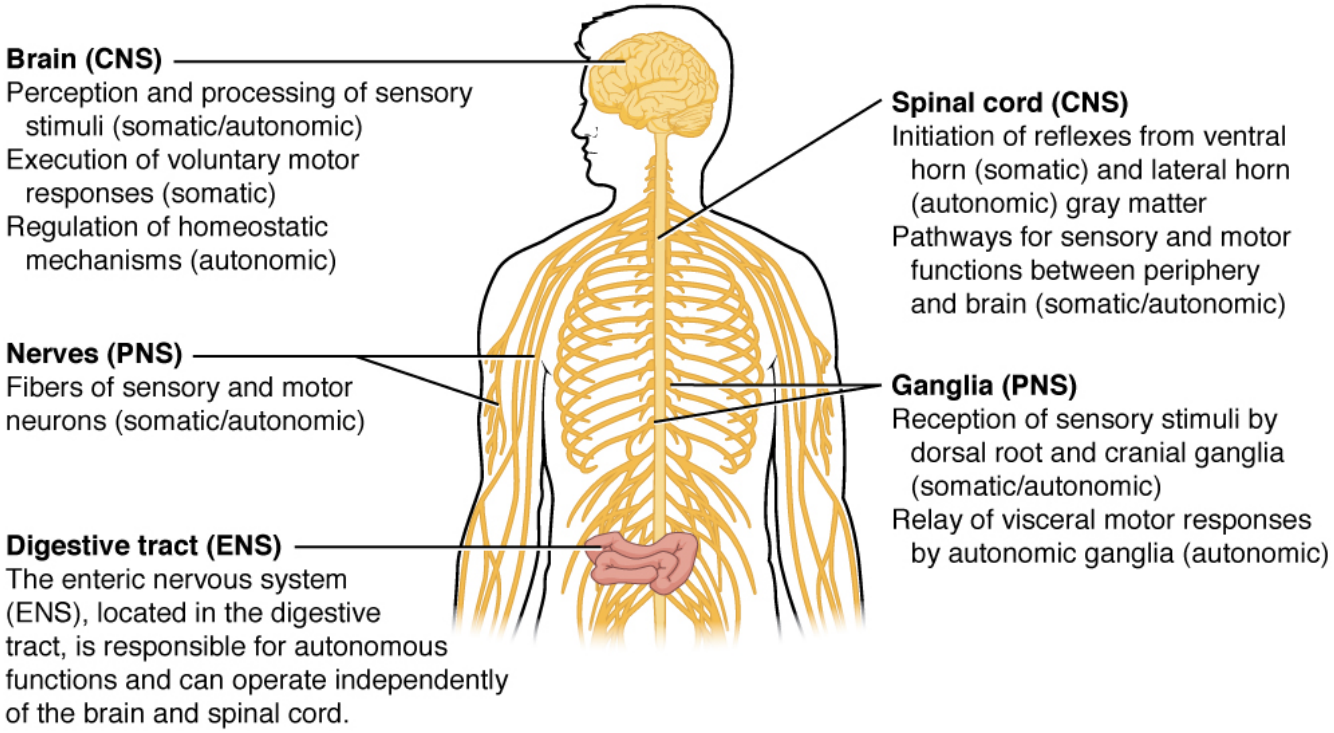
Controlling the Body

The nervous system can be divided into two parts mostly on the basis of a functional difference in responses. The somatic nervous system (SNS) is responsible for conscious perception and voluntary motor responses. Voluntary motor response means the contraction of skeletal muscle, but those contractions are not always voluntary in the sense that you have to want to perform them. Some somatic motor responses are reflexes, and often happen without a conscious decision to perform them. If your friend jumps out from behind a corner and yells "Boo!" you will be startled and you might scream or leap back. You didn't decide to do that, and you may not have wanted to give your friend a reason to laugh at your expense, but it is a reflex involving skeletal muscle contractions. Other motor responses become automatic (in other words, unconscious) as a person learns motor skills (referred to as "habit learning" or "procedural memory").

The autonomic nervous system (ANS) is responsible for involuntary control of the body, usually for the sake of homeostasis (regulation of the internal environment). Sensory input for autonomic functions can be from sensory structures tuned to external or internal environmental stimuli. The motor output extends to smooth and cardiac muscle as well as glandular tissue. The role of the autonomic system is to regulate the organ systems of the body, which usually means to control homeostasis. Sweat glands, for example, are controlled by the autonomic system. When you are hot, sweating helps cool your body down. That is a homeostatic mechanism. But when you are nervous, you might start sweating also. That is not homeostatic, it is the physiological response to an emotional state.

There is another division of the nervous system that describes functional responses. The enteric nervous system (ENS) is responsible for controlling the smooth muscle and glandular tissue in your digestive system. It is a large part of the PNS, and is not dependent on the CNS. It is sometimes valid, however, to consider the enteric system to be a part of the autonomic system because the neural structures that make up the enteric system are a component of the autonomic

output that regulates digestion. There are some differences between the two, but for our purposes here there will be a good bit of overlap. See the figure below for examples of where these divisions of the nervous system can be found.



Somatic, Autonomic, and Enteric Structures of the Nervous System – *Somatic structures include the spinal nerves, both motor and sensory fibers, as well as the sensory ganglia (posterior root ganglia and cranial nerve ganglia). Autonomic structures are found in the nerves also, but include the sympathetic and parasympathetic ganglia. The enteric nervous system includes the nervous tissue within the organs of the digestive tract.*

Visit this site to read about a woman that notices that her daughter is having trouble walking up the stairs. This leads to the discovery of a hereditary condition that affects the brain and spinal cord. The electromyography and MRI tests indicated deficiencies in the spinal cord and cerebellum, both of which are responsible for controlling coordinated movements. To what functional division of the nervous system would these structures belong?

Adaption

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Neurons: the Functional Unit of the Nervous System

J. GORDON BETTS; JAMES A. WISE; KELLY A. YOUNG; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the basic structure of a neuron.
- Describe the basic components and functions of the action potential.
- Identify the different types of neurons on the basis of polarity.
- List the glial cells of the CNS and describe their function.
- List the glial cells of the PNS and describe their function.

Nervous tissue is composed of two types of cells, neurons and glial cells. Neurons are responsible for the computation and communication that the nervous system provides. Changes in the electrical activity of neurons can create an action potential, which is the main form of cell-cell communication in the nervous system. The glial cells, or glia, are known to play a supporting role for nervous tissue. Ongoing research pursues an expanded role that glial cells might play in signaling, but neurons are still considered the basis of this function. Neurons are important, but without glial support they would not be able to perform their function.

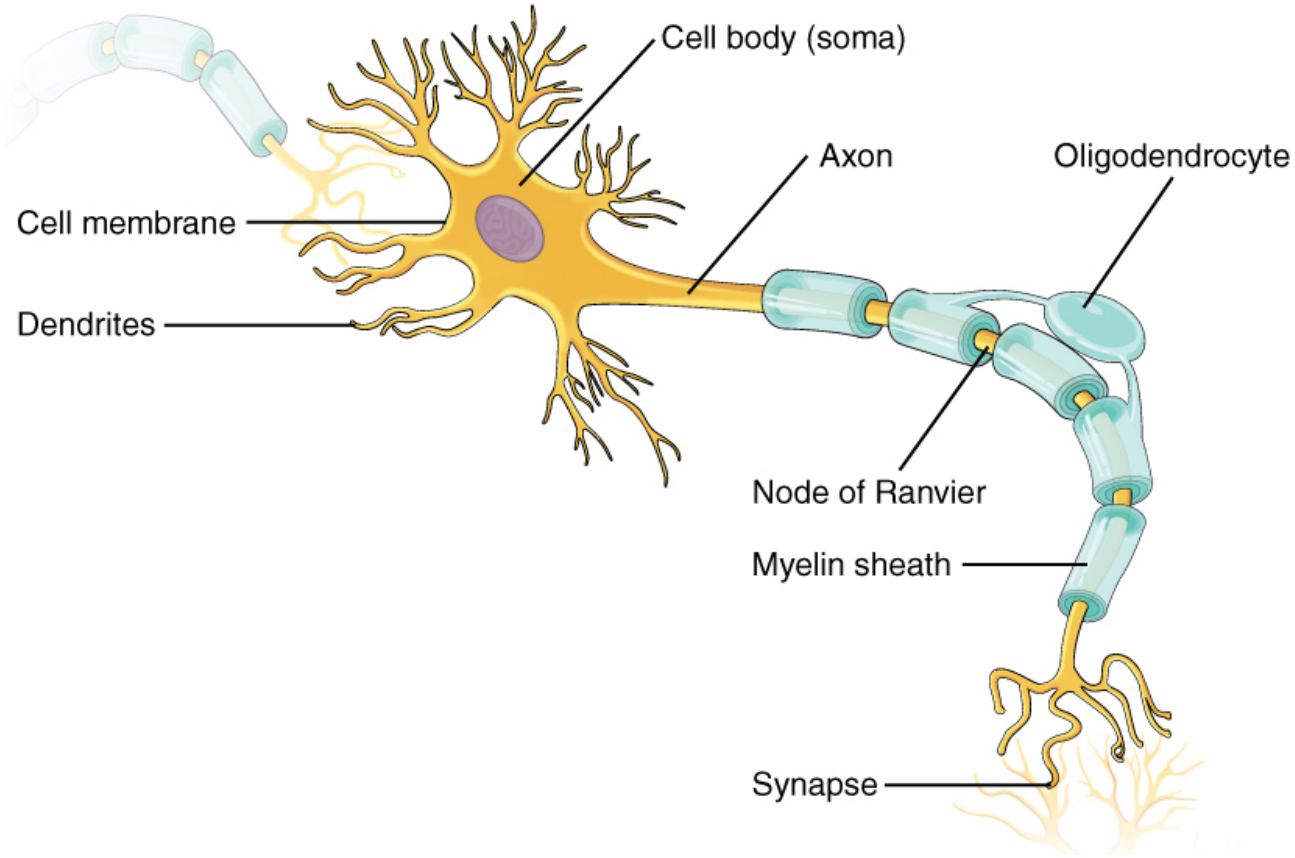
Neurons

Neurons are the cells considered to be the basis of nervous tissue. They are responsible for the electrical signals that communicate information about sensations, and that produce movements in response to those stimuli, along with inducing thought processes within the brain. An important part of the function of neurons is in their structure, or shape. The three-dimensional shape of these cells makes the immense numbers of connections within the nervous system possible.

Parts of a Neuron

The main part of a neuron is the cell body, which is also known as the soma (soma = “body”). The cell body contains the nucleus and most of the major organelles. But what makes neurons special is that they have many extensions of their cell membranes, which are referred to as processes. Neurons are usually described as having one, and only one, axon—a type of process that emerges from the cell body and projects to other neurons, known as target cells. That single axon can branch repeatedly to communicate with many target cells. It is the axon that propagates the action potential which is communicated to one or more cells. The other processes of the neuron are dendrites, which receive

information from other neurons at specialized areas of contact between two neurons called synapses. The dendrites are usually highly branched processes, providing locations for many other neurons to communicate with the cell body. Information flows through a neuron from the dendrites, across the cell body, and down the axon. This gives the neuron a polarity—meaning that information flows in this one direction. Figure 12.7 shows the relationship of these parts to one another.



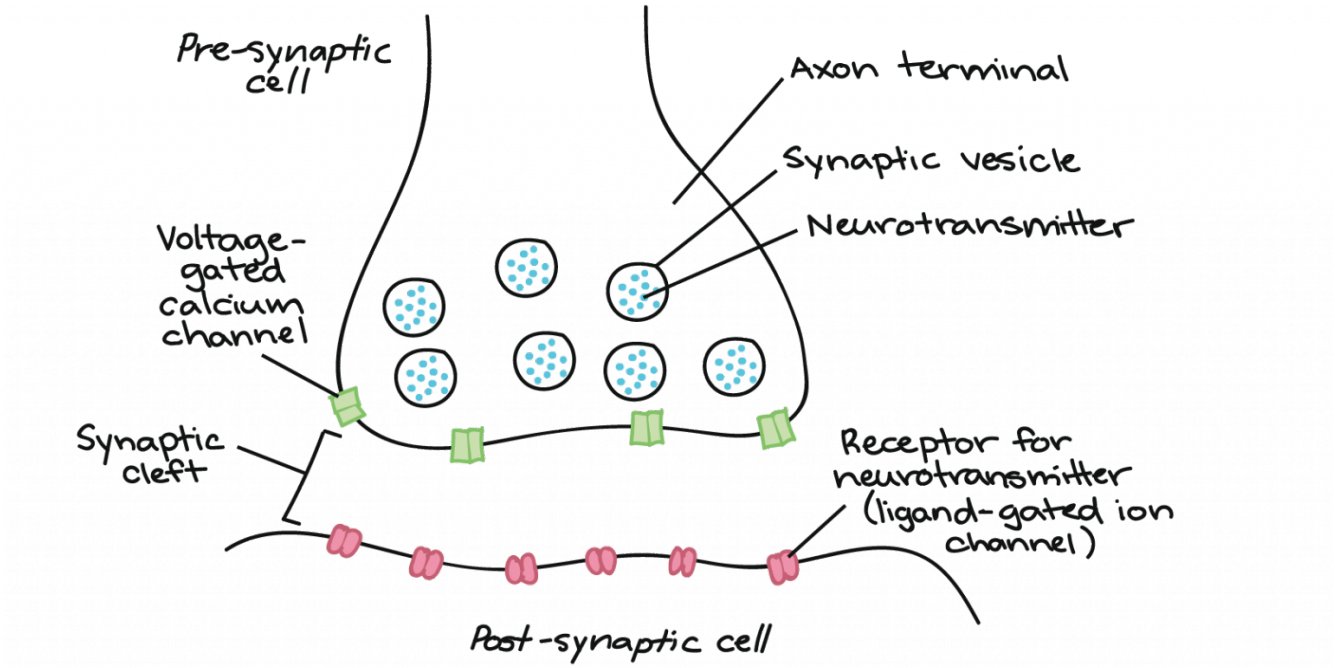
Parts of a Neuron – *The major parts of the neuron are labeled on a multipolar neuron from the CNS.*

Where the axon first emerges from the cell body, there is a special region referred to as the axon hillock. This is a tapering of the cell body toward the axon fibre. Many axons are wrapped by an insulating substance called myelin, which is actually made from glial cells. Myelin acts as insulation much like the plastic or rubber that is used to insulate electrical wires. A key difference between myelin and the insulation on a wire is that there are gaps in the myelin covering of an axon. Each gap is called a node of Ranvier and is important to the way that electrical signals travel down the axon. The length of the axon between each gap, which is wrapped in myelin, is referred to as an axon segment. At the end of the axon is the axon terminal, where there are usually several branches extending toward the target cell, each of which ends in an enlargement called a synaptic end bulb. These bulbs are what make the connection with the target cell at the synapse.

Action Potentials: The Basics

Neurons communicate with one another by propagating electrical impulses from the axon hillock down their axon segments and towards the axon terminal and synaptic end bulbs. These electrical impulses happen because positively

charged ions such as sodium (Na^+) and potassium (K^+) flow into or out of the cell very rapidly through small channels in the neuron cell membrane. Once the electrical impulse reaches the synaptic end bulbs, this serves as a trigger for the neuron to release small chemical messengers called neurotransmitters into the synapse (the space between two adjacent neurons). You may have heard of neurotransmitters like serotonin or dopamine before. These are the signals that neurons use to communicate with each other. Neurotransmitters will move through the synapse and bind to the dendrites of the next neuron and trigger a response. The type of response in the next neuron can vary, it may include promoting or preventing the firing of another action potential down it's own axon. The two neurons that are communicating with each other are sometimes called the "post-synaptic" and "pre-synaptic" cell to describe their positions relative to the synapse.



Communication between the pre-synaptic (sending) and post-synaptic (receiving) cells occur at the synapse via the release of neurotransmitters.

Glial Cells

Glial cells, or neuroglia or simply glia, are the other type of cell found in nervous tissue. They function largely in supporting neurons to carry out their functions, although new research suggests they may have more complex roles. They are considered to be supporting cells, and many functions are directed at helping neurons complete their function for communication.

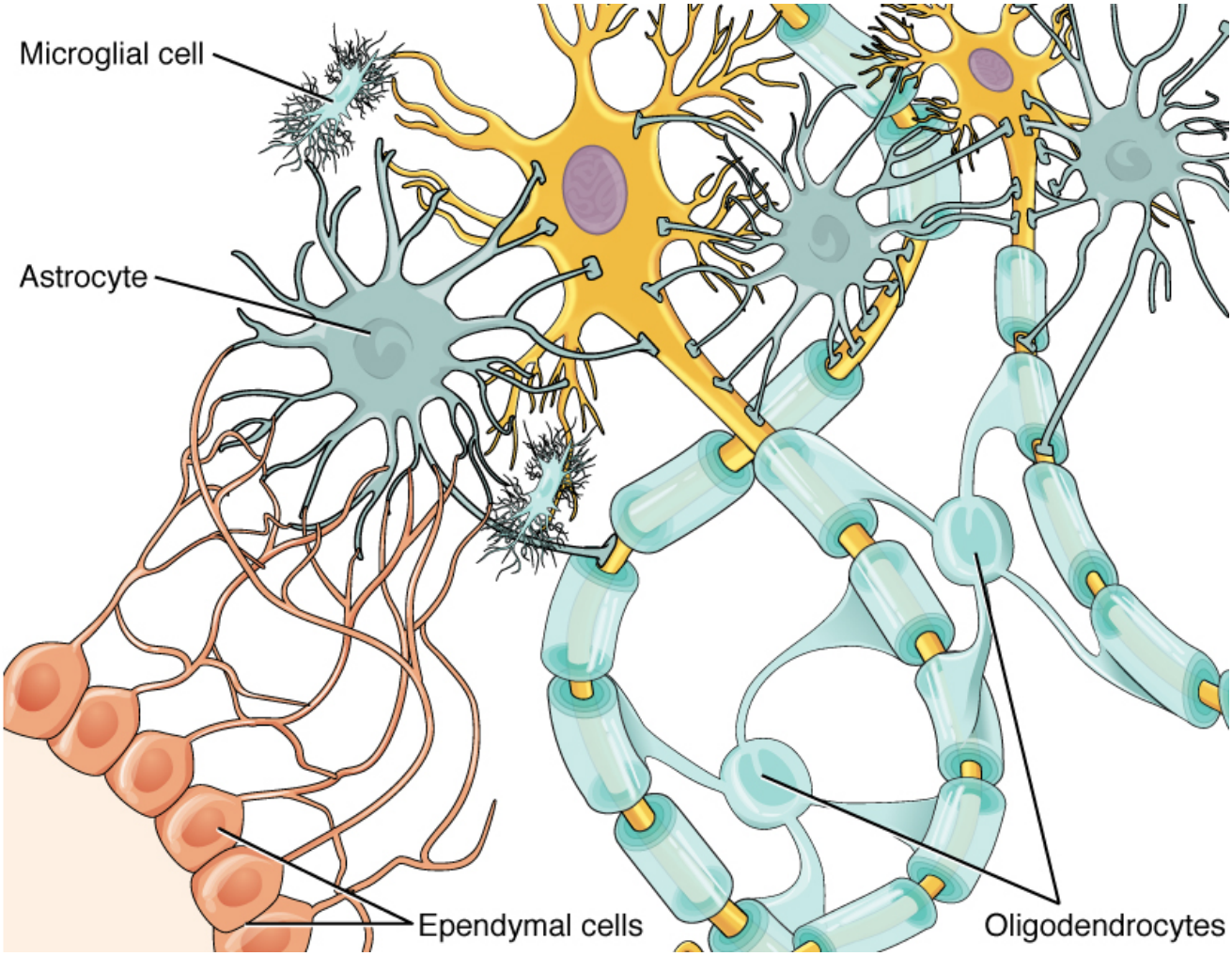
There are six types of glial cells. Four of them are found in the CNS and two are found in the PNS. The table below outlines some common characteristics and functions.

CNS glia	**PNS glia**	**Basic function**
Astrocyte	Satellite cell	Support
Oligodendrocyte	Schwann cell	Insulation, myelination
Microglia	–	Immune surveillance and phagocytosis
Ependymal cell	–	Creating CSF

Summary of the types of glial cells by location and basic function.

Glial Cells of the CNS

One cell providing support to neurons of the CNS is the astrocyte, so named because it appears to be star-shaped under the microscope (astro- = "star"). Astrocytes have many processes extending from their main cell body (not axons or dendrites like neurons, just cell extensions). Those processes extend to interact with neurons, blood vessels, or the connective tissue covering the CNS that is called the pia mater. Generally, they are supporting cells for the neurons in the central nervous system. Some ways in which they support neurons are by maintaining the concentration of chemicals in the extracellular space, removing excess signaling molecules, reacting to tissue damage, and contributing to the blood-brain barrier (BBB). The BBB is a physiological barrier that keeps many substances that circulate in the rest of the body from getting into the central nervous system, restricting what can cross from circulating blood into the CNS. Nutrient molecules, such as glucose or amino acids, can pass through the BBB, but other molecules cannot. This actually causes problems with drug delivery to the CNS. Pharmaceutical companies are challenged to design drugs that can cross the BBB and have an effect on the nervous system.



Glial Cells of the CNS – *The CNS has astrocytes, oligodendrocytes, microglia, and ependymal cells that support the neurons of the CNS in several ways.*

Another cell type found in CNS tissue is the oligodendrocyte, sometimes called just "oligo," which is the glial cell type that insulates axons in the CNS. The name means "cell of a few branches" (oligo- = "few"; dendro- = "branches"; -cyte = "cell"). There are a few processes that extend from the cell body. Each one reaches out and surrounds an axon to insulate it in myelin. The function of myelin will be discussed below.

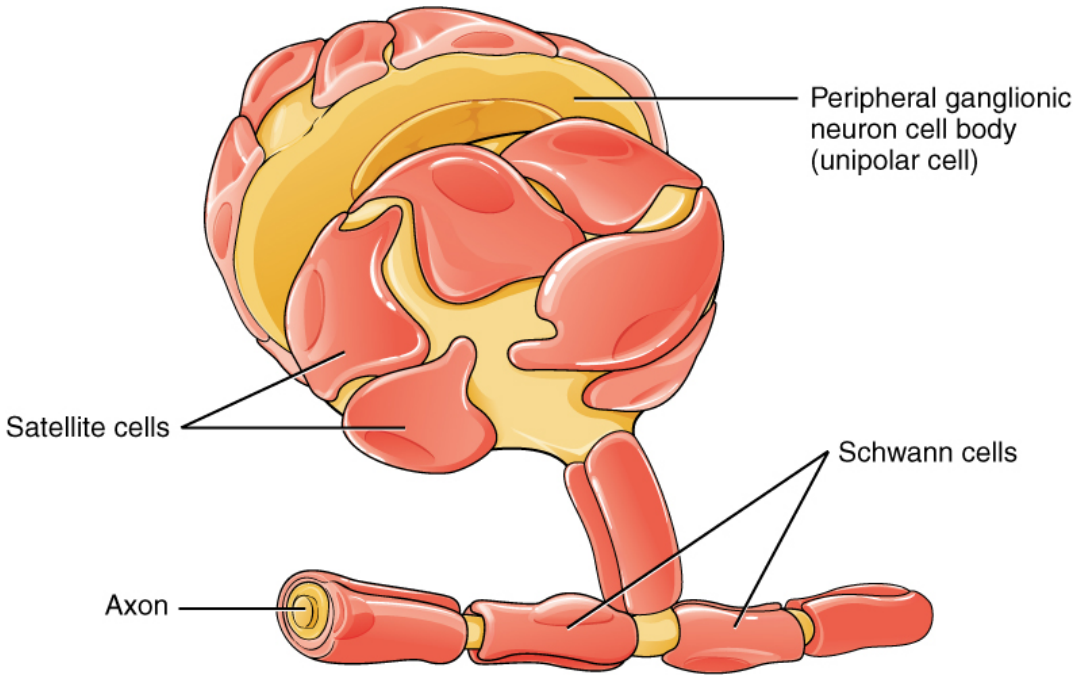
Microglia are, as the name implies, smaller than most of the other glial cells. Ongoing research into these cells, although not entirely conclusive, suggests that they may originate as white blood cells, called macrophages, that become part of the CNS during early development. While their origin is not conclusively determined, their function is related to what macrophages do in the rest of the body. When macrophages encounter diseased or damaged cells in the rest of the body, they ingest and digest those cells or the pathogens that cause disease. Microglia are the cells in the CNS that can do this in normal, healthy tissue, and they are therefore also referred to as CNS-resident macrophages.

The ependymal cell is a glial cell that filters blood to make cerebrospinal fluid (CSF), the fluid that circulates through the CNS. Because of the privileged blood supply inherent in the BBB, the extracellular space in nervous tissue does not easily exchange components with the blood. Ependymal cells line each ventricle, one of four central cavities that are remnants of the hollow center of the neural tube formed during the embryonic development of the brain. The choroid plexus is a specialized structure in the ventricles where ependymal cells come in contact with blood vessels and filter and absorb components of the blood to produce cerebrospinal fluid. Because of this, ependymal cells can be considered a component of the BBB, or a place where the BBB breaks down. These glial cells appear similar to epithelial cells, making a single layer of cells with little intracellular space and tight connections between adjacent cells. They also have cilia on their apical surface to help move the CSF through the ventricular space. The relationship of these glial cells to the structure of the CNS is seen in Figure 12.11.

Glial Cells of the PNS

One of the two types of glial cells found in the PNS is the satellite cell. Satellite cells are found in sensory and autonomic ganglia, where they surround the cell bodies of neurons. They provide support, performing similar functions in the periphery as astrocytes do in the CNS—except, of course, for establishing the BBB.

The second type of glial cell is the Schwann cell, which insulate axons with myelin in the periphery. Schwann cells are different than oligodendrocytes, in that a Schwann cell wraps around a portion of only one axon segment and no others. Oligodendrocytes have processes that reach out to multiple axon segments, whereas the entire Schwann cell surrounds just one axon segment. The nucleus and cytoplasm of the Schwann cell are on the edge of the myelin sheath. The relationship of these two types of glial cells to ganglia and nerves in the PNS is seen in the figure below.



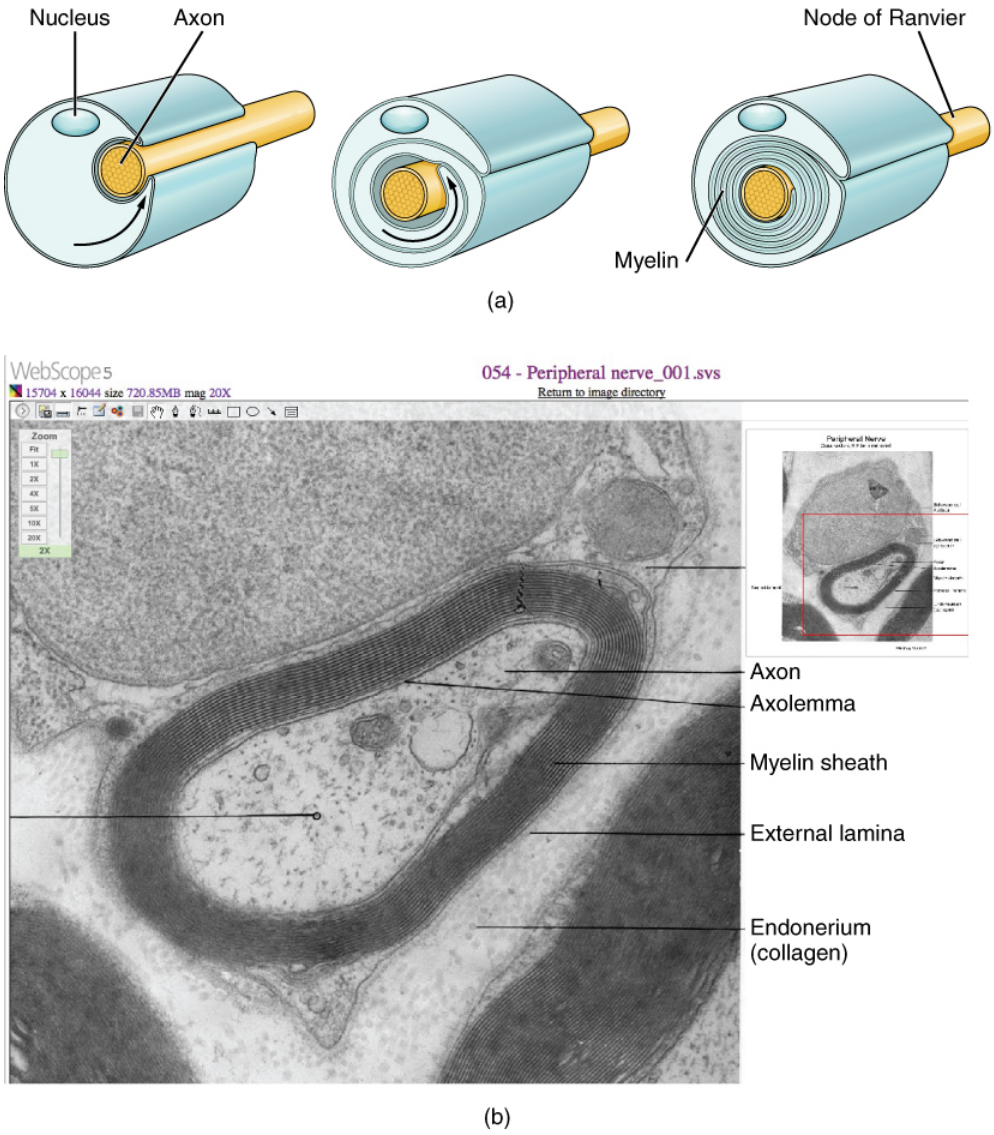
Glial Cells of the PNS – *The PNS has satellite cells and Schwann cells.*

Myelin

The insulation for axons in the nervous system is provided by oligodendrocytes in the CNS, and Schwann cells in the PNS. Myelin is a lipid-rich material that surrounds the axon and by doing so creates a sheath that facilitates the transmission of electrical signals along the axon.

The glial cell is wrapped around the axon several times with little to no cytoplasm between the glial cell layers. During development, the glial cell is loosely or incompletely wrapped around the axon. The edges of this loose enclosure extend toward each other, and one end tucks under the other. The inner edge wraps around the axon, creating several layers, and the other edge closes around the outside so that the axon is completely enclosed.

Myelin sheaths can extend for one or two millimeters, depending on the diameter of the axon. Axon diameters can be as small as 1 to 20 micrometers. Because a micrometer is 1/1000 of a millimeter, this means that the length of a myelin sheath can be 100–1000 times the diameter of the axon. The figure show the myelin sheath surrounding an axon segment, but are not to scale. If the myelin sheath were drawn to scale, the neuron would have to be immense—possibly covering an entire wall of the room in which you are sitting.



The Process of Myelination – *Myelinating glia wrap several layers of cell membrane around the cell membrane of an axon segment. A single Schwann cell insulates a segment of a peripheral nerve, whereas in the CNS, an oligodendrocyte may provide insulation for a few separate axon segments. EM × 1,460,000. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

Disorders of the Myelin Sheath

Several diseases can result from the demyelination of axons. The causes of these diseases are not the same; some have genetic causes, some are caused by pathogens, and others are the result of autoimmune disorders. Though the causes are varied, the results are largely similar. The myelin insulation of axons is compromised, making electrical signaling slower.

Multiple sclerosis (MS) is a demyelinating disease caused by our own immune systems, making it an autoimmune disorder. The antibodies produced by B lymphocytes (a type of white blood cell) mark myelin as a substance that is foreign to the body. This causes inflammation and the destruction of the myelin in the central nervous system. As the insulation around the axons is destroyed by the disease, scarring becomes obvious. This is where the name of the disease comes from; sclerosis means hardening of tissue, which is what a scar is. Multiple scars are found in the white matter of

the brain and spinal cord. The symptoms of MS include both somatic and autonomic deficits. Control of the musculature is compromised, as is control of organs such as the bladder. We will explore MS in greater detail in a later chapter.

Guillain-Barré (pronounced gee-YAN bah-RAY) syndrome is an example of a demyelinating disease of the peripheral nervous system. It is also the result of an autoimmune reaction, but the inflammation is in peripheral nerves. Sensory symptoms or motor deficits are common, and autonomic failures can lead to changes in the heart rhythm or a drop in blood pressure, especially when standing, which causes dizziness.

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The Central Nervous System

J. GORDON BETTS; KELLY A. YOUNG; JAMES A. WISE; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

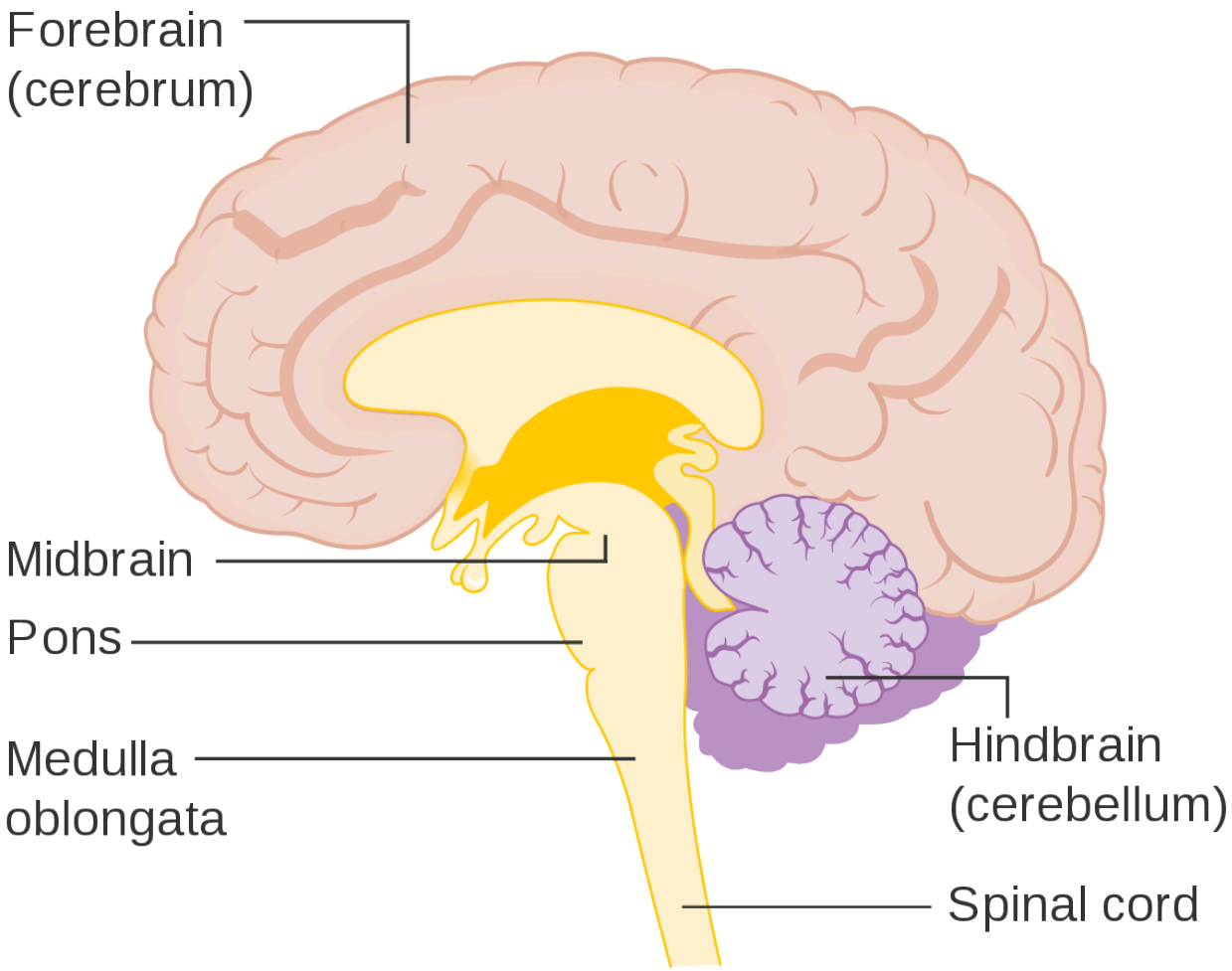
Learning Objectives

By the end of this section, you will be able to:

- Name the major regions of the adult brain.
- Describe the connections between the cerebrum and brain stem through the diencephalon, and from those regions into the spinal cord.
- Recognize the complex connections within the subcortical structures of the basal nuclei.
- Explain the arrangement of gray and white matter in the spinal cord.

The central nervous system (CNS) consists of the brain and the spinal cord, which are the main organs of the nervous system. The spinal cord is a single structure, whereas the adult brain is described in terms of four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. Neural activity in the brain and spinal cord governs many diverse and important functions in the body, for example a person's conscious experiences, the regulation of homeostasis, the coordination of reflexes, and many more.

Divisions of the CNS



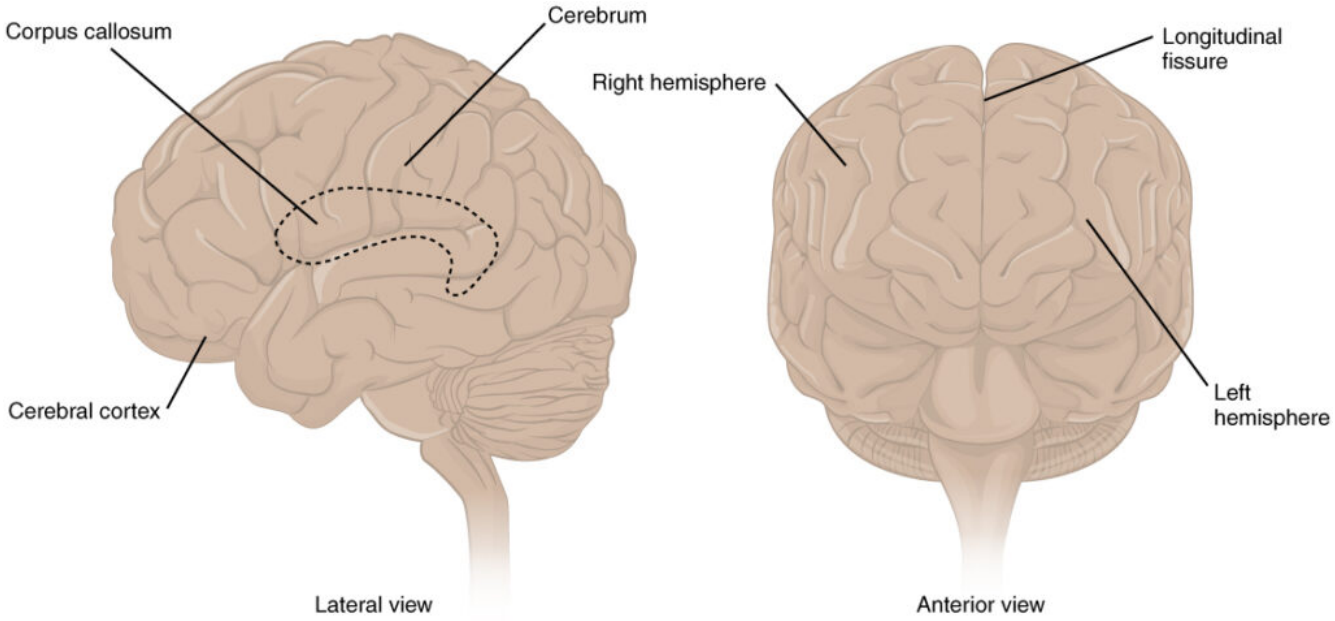
Divisions of the Central Nervous System – *Diagram showing the brain_stem which includes the medulla oblongata, the pons and the midbrain on Wikimedia Commons is used under a CC BY-SA 4.0*

The Forebrain: Cerebral Cortex and Diencephalon

The Cerebrum

The most outwardly visible gray-coloured tissue of the human brain is the cerebrum. Many of the higher neurological functions, such as memory, emotion, and consciousness, are the result of neural activity in the cerebrum. The folded portion of the tissue on the outermost surface of the cerebrum is the cerebral cortex, and the rest of the structure is beneath that outer covering. There is a distinct separation between the two sides of the cerebrum called the longitudinal fissure. It separates the cerebrum into two distinct halves, a right and left cerebral hemisphere. Deep within the

cerebrum, the white matter of the corpus callosum provides the major pathway for communication between the two hemispheres of the cerebral cortex.



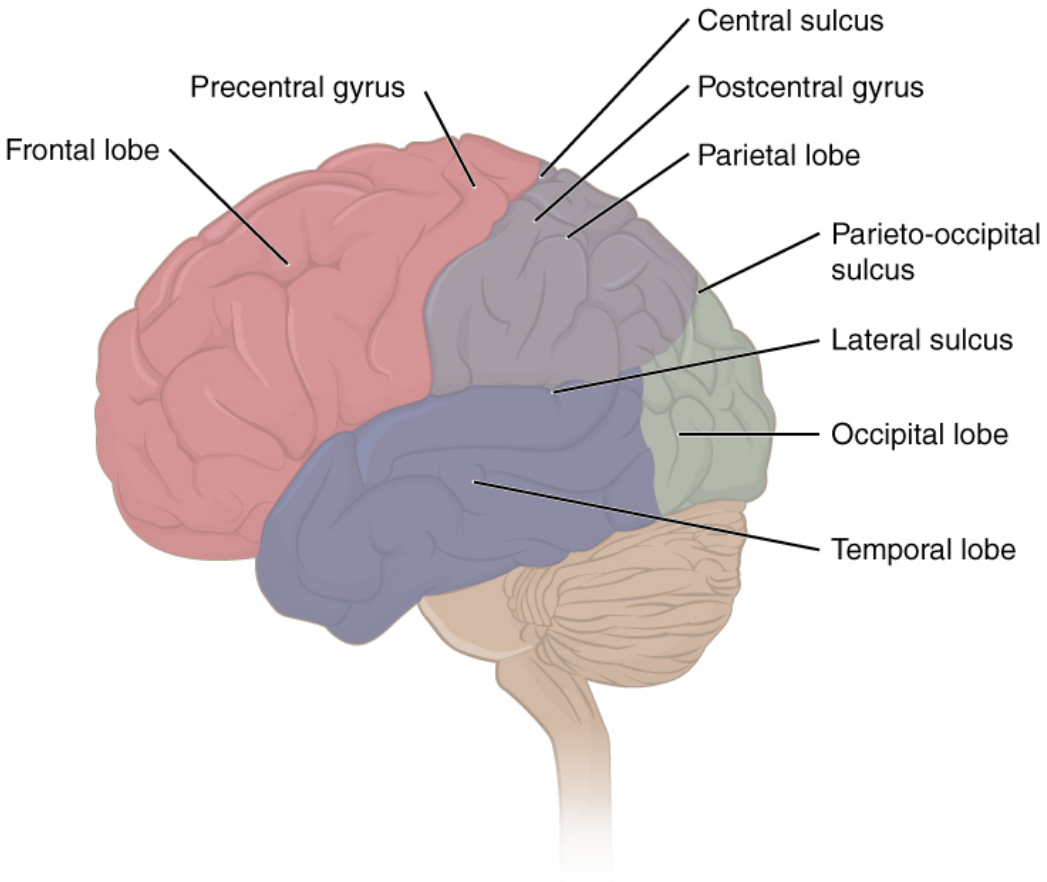
The Cerebrum – *The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.*

Cerebral Cortex

The cerebrum is covered by a continuous layer of folded gray matter that wraps around its surface—the cerebral cortex. This thin, extensive region of gray matter is responsible for the higher functions of the nervous system. A gyrus (plural = gyri) is the topmost ridge of one of those folds, and a sulcus (plural = sulci) is the furrow between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex.

The head is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cortex were peeled off of the cerebrum and laid out flat, its surface area would be roughly equal to one square meter.

During embryonic development, as the telencephalon expands within the skull, the brain goes through a regular course of growth that results in everyone's brain having a similar pattern of folds. The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes: the frontal, parietal, occipital, and temporal lobes. The lateral sulcus that separates the temporal lobe from the other regions is one such landmark. Superior to the lateral sulcus are the parietal lobe and frontal lobe, which are separated from each other by the central sulcus. The posterior region of the cortex is the occipital lobe, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, an obvious landmark separating the parietal and occipital lobes is called the parieto-occipital sulcus. The fact that there is no obvious anatomical border between these lobes is consistent with the functions of these regions being interrelated.



Lobes of the Cerebral Cortex – *The cerebral cortex is divided into four lobes. Extensive folding increases the surface area available for cerebral functions.*

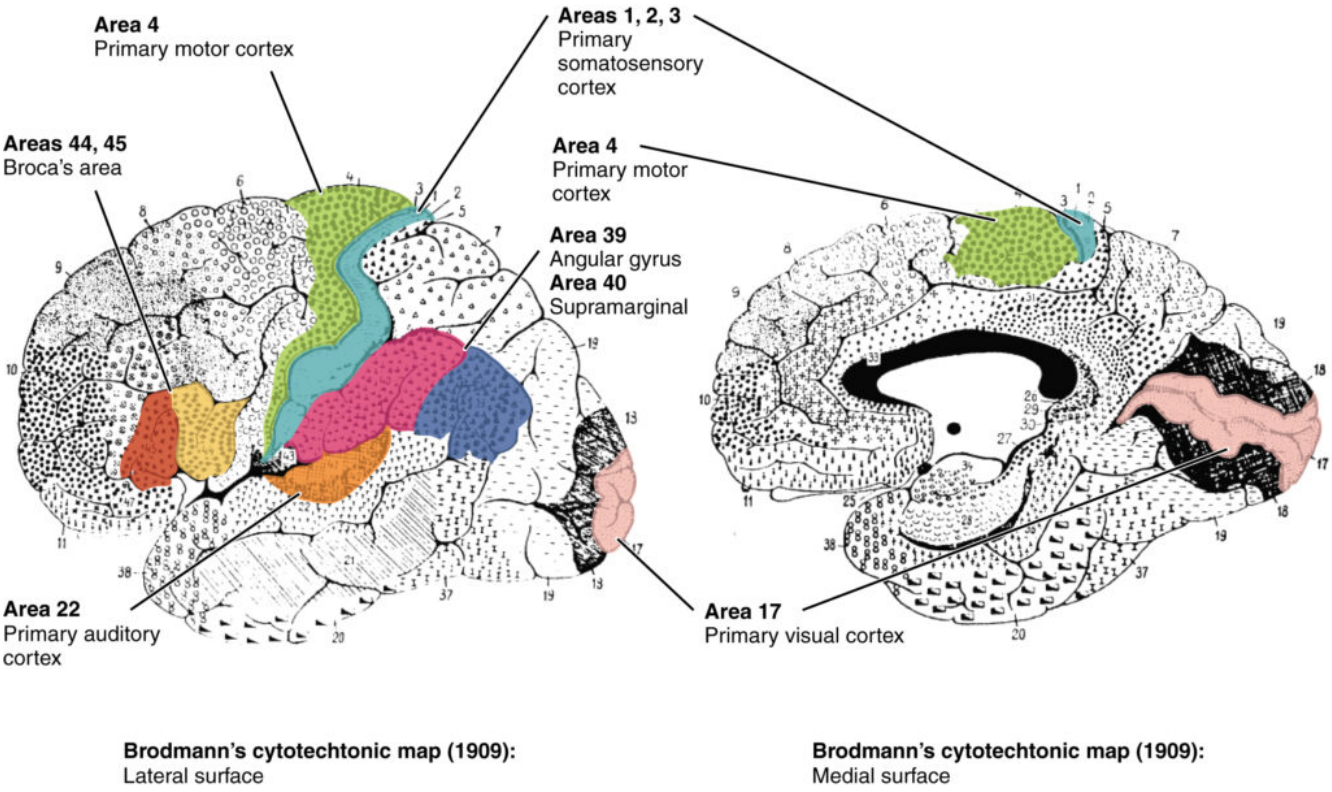
Different locations of the cerebral cortex are associated with particular functions, a concept known as localization. In the early 1900s, a German neuroscientist named Korbinian Brodmann performed an extensive study of the microscopic anatomy—the cytoarchitecture—of the cerebral cortex and divided the cortex into 52 separate regions on the basis of the histology of the cortex. His work resulted in a system of classification known as Brodmann's areas, which is still used today to describe the anatomical distinctions within the cortex. The results from Brodmann's work on the anatomy align very well with the functional differences within the cortex. Areas 17 and 18 in the occipital lobe are responsible for primary visual perception. That visual information is complex, so it is processed in the temporal and parietal lobes as well.

The temporal lobe is associated with primary auditory sensation, known as Brodmann's areas 41 and 42 in the superior temporal lobe. The main sensation associated with the parietal lobe is somatosensation, meaning the general sensations associated with the body. Posterior to the central sulcus is Brodmann's areas 1, 2, and 3, collectively called postcentral gyrus or the primary somatosensory cortex. All of the tactile senses are processed in this area, including touch, pressure, tickle, pain, itch, and vibration, as well as more general senses of the body such as proprioception and kinesthesia, which are the senses of body position and movement, respectively.

Anterior to the central sulcus is the frontal lobe, which is primarily associated with motor functions. The precentral gyrus is the primary motor cortex. Cells from this region of the cerebral cortex are the upper motor neurons that instruct lower motor neurons in the spinal cord to trigger contraction and relaxation of muscles. Anterior to this region are a few areas that are associated with planned movements. The premotor area is responsible for thinking of

a movement to be made. The frontal eye fields are important in eliciting eye movements and in attending to visual stimuli. Broca's area is responsible for the production of language, or controlling movements responsible for speech; in the vast majority of people, it is located only on the left side. Anterior to these regions is the prefrontal lobe, which serves cognitive functions that can be the basis of personality, short-term memory, and consciousness. The prefrontal lobotomy is an outdated mode of treatment for personality disorders (psychiatric conditions) that profoundly affected the personality of the patient.

The fascinating case of a man named Phineas Gage highlights the important functions of the prefrontal lobe . In the autumn of 1948, Mr. Gage was part of a work group blasting rock for the construction of a railroad south of Cavendish, Vermont. Unfortunately, a blast resulted in an iron rod piercing his cheek, passing behind his left eye, through his prefrontal lobe and exiting his skull. Amazingly, within a few months Mr. Gage regained normal motor and speech function, but his personality was drastically changed. Friends and family of Mr. Gage described him as unreliable, disrespectful, and impulsive; he was "no longer Gage" as they had once known him.



Brodmann's Areas of the Cerebral Cortex – *Brodmann mapping of functionally distinct regions of the cortex was based on its cytoarchitecture at a microscopic level.*

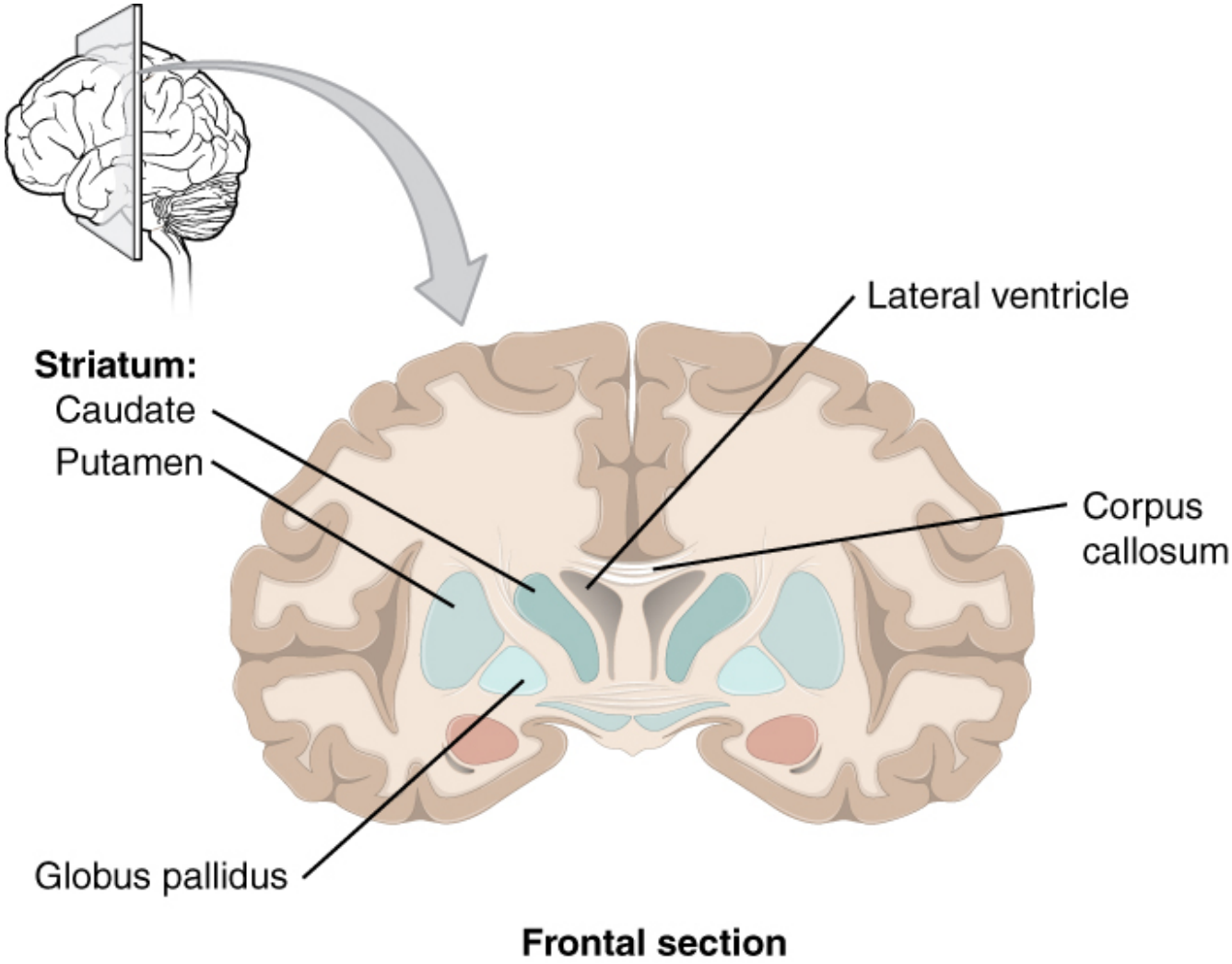
Subcortical structures

Beneath the cerebral cortex are clusters of neuron cell bodies called subcortical nuclei which are responsible for various important neural functions. These include:

- **The basal forebrain:** this group of subcortical nuclei serve as the primary location for acetylcholine production, which is a neurotransmitter that modulates the overall activity of the cortex, possibly leading to greater attention to sensory stimuli. Alzheimer's disease is associated with a loss of neurons in the basal forebrain.
- **The hippocampus and amygdala:** these are medial structures that, along with the adjacent cortex, are involved in

long-term memory formation and emotional responses.

- **The caudate, putamen, and globus pallidus:** These are a group of major nuclei in the cerebrum called the basal ganglia responsible for fine-tuning voluntary movements. The caudate is a long nucleus that follows the basic C-shape of the cerebrum from the frontal lobe, through the parietal and occipital lobes, into the temporal lobe. The putamen is mostly deep in the anterior regions of the frontal and parietal lobes. Together, the caudate and putamen are called the striatum. The globus pallidus is a layered nucleus that lies just medial to the putamen; they are called the lenticular nuclei because they look like curved pieces fitting together like lenses. The globus pallidus has two subdivisions, the external and internal segments, which are lateral and medial, respectively. These nuclei are depicted in a frontal section of the brain in the figure below.



Frontal Section of Cerebral Cortex and Basal Nuclei – *The major components of the basal nuclei, shown in a frontal section of the brain, are the caudate (just lateral to the lateral ventricle), the putamen (inferior to the caudate and separated by the large white-matter structure called the internal capsule), and the globus pallidus (medial to the putamen).*

Watch this video to learn about the basal nuclei (also known as the basal ganglia), which have two pathways

that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in "disinhibition" of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?

Watch this video to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?

The Diencephalon

The diencephalon is the one region of the adult brain that retains its name from embryologic development. The etymology of the word diencephalon translates to "through brain." It is the connection between the cerebrum and the rest of the nervous system, with one exception. The rest of the brain, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon. Output from the cerebrum passes through the diencephalon. The single exception is the system associated with olfaction, or the sense of smell, which connects directly with the cerebrum. In the earliest vertebrate species, the cerebrum was not much more than olfactory bulbs that received peripheral information about the chemical environment (to call it smell in these organisms is imprecise because they lived in the ocean).

The diencephalon is deep beneath the cerebrum and can be described as any region of the brain with "thalamus" in its name. The two major regions of the diencephalon are the thalamus itself and the hypothalamus.

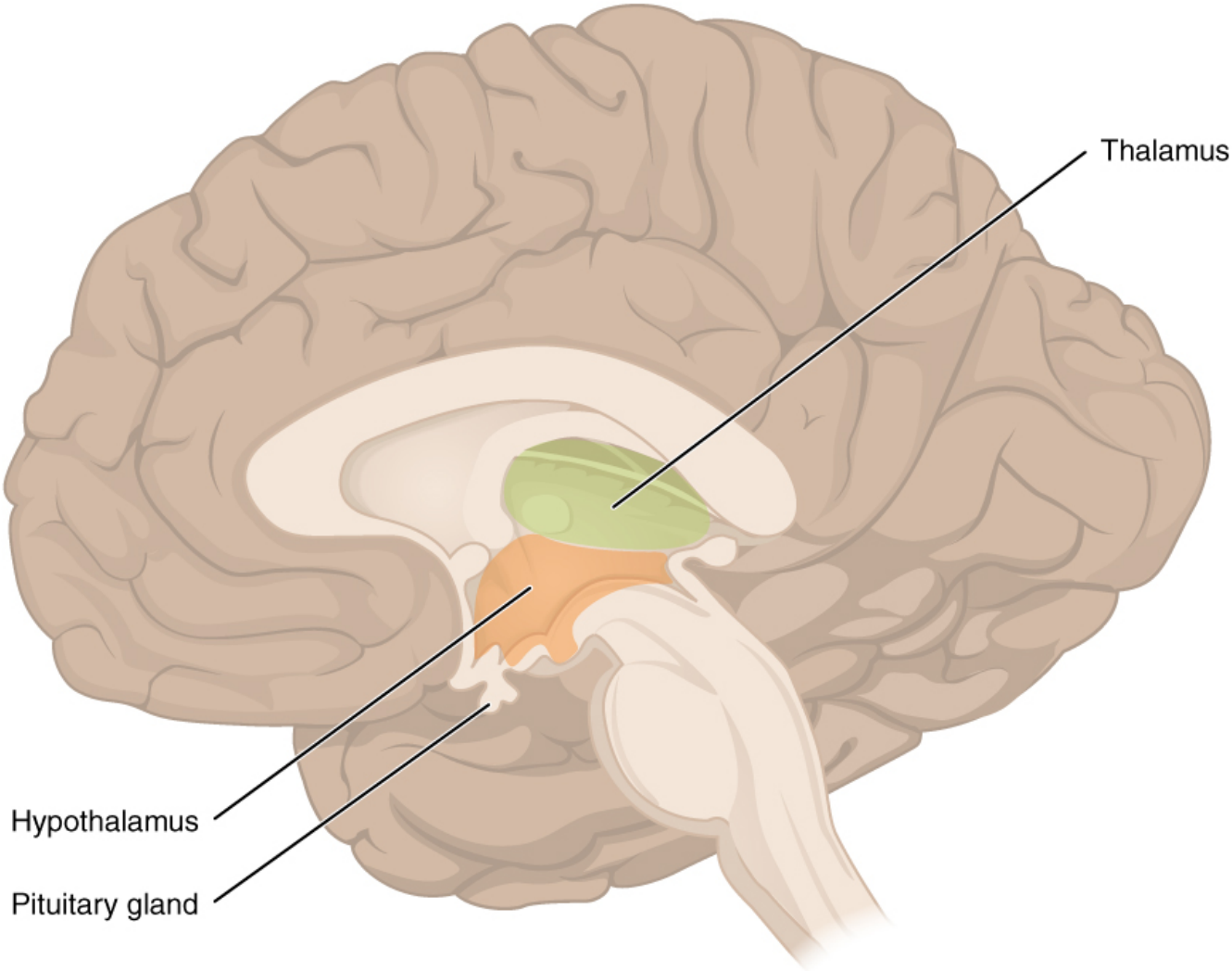
Thalamus

You can think of the thalamus as a giant postal system where information is received, processed, and sent where it needs to go. The thalamus is a collection of nuclei that relay information between the cerebral cortex and the periphery, spinal cord, or brain stem. All sensory information, except for the sense of smell, passes through the thalamus before processing by the cortex. Axons from the peripheral sensory organs synapse in the thalamus and thalamic neurons project directly to the cerebrum. It is a requisite synapse in any sensory pathway, except for olfaction. The thalamus does not just pass the information on, it also processes that information. For example, the portion of the thalamus that receives visual information will influence what visual stimuli are important, or what receives attention.

The cerebrum also sends information down to the thalamus, which usually communicates motor commands. This involves interactions with the cerebellum and other nuclei in the brain stem. The cerebrum interacts with the basal ganglia, which involves connections with the thalamus. The primary output of the basal ganglia is to the thalamus, which relays that output to the cerebral cortex. The cortex also sends information to the thalamus that will then influence the effects of the basal nuclei.

Hypothalamus

Inferior and slightly anterior to the thalamus is the hypothalamus, the other major region of the diencephalon. The hypothalamus is a collection of nuclei that are largely involved in regulating homeostasis. The hypothalamus is the executive region in charge of the autonomic nervous system and the endocrine system through its regulation of the anterior pituitary gland. Other parts of the hypothalamus are involved in memory and emotion as part of the limbic system.



The Diencephalon *-The diencephalon is composed primarily of the thalamus and hypothalamus. The thalami are two elongated, ovoid structures on either side of the midline that make contact in the middle. The hypothalamus is inferior and anterior to the thalamus, culminating in a sharp angle to which the pituitary gland is attached.*

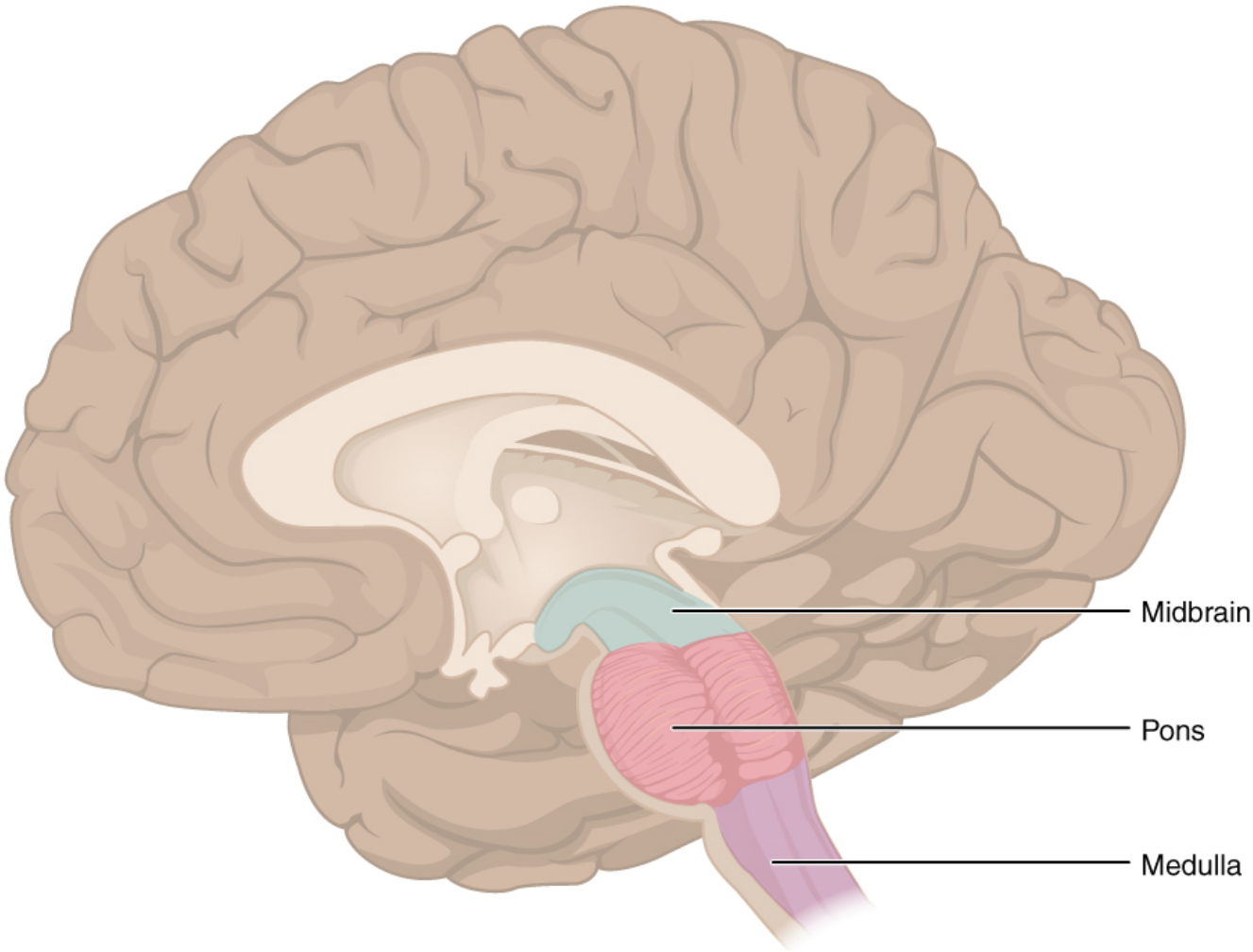
Midbrain and Hindbrain

Brain Stem

Parts of the midbrain and hindbrain (composed of the pons and the medulla) are collectively referred to as the brain

stem. The structure emerges from the ventral surface of the forebrain as a tapering cone that connects the brain to the spinal cord. Attached to the brain stem, but considered a separate region of the hindbrain, is the cerebellum. The midbrain coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces. The pons is the main connection with the cerebellum. The pons and the medulla regulate several crucial functions, including the cardiovascular and respiratory systems and rates.

The cranial nerves connect through the brain stem and provide the brain with the sensory input and motor output associated with the head and neck, including most of the special senses. The major ascending and descending pathways between the spinal cord and brain, specifically the cerebrum, pass through the brain stem.



The Brain Stem – *The brain stem comprises three regions: the midbrain, the pons, and the medulla.*

Midbrain

One of the original regions of the embryonic brain, the midbrain is a small region between the thalamus and pons. It is separated into the tectum and tegmentum, from the Latin words for roof and floor, respectively. The cerebral aqueduct passes through the center of the midbrain, such that these regions are the roof and floor of that canal.

The tectum is composed of four bumps known as the colliculi (singular = colliculus), which means "little hill" in Latin. The inferior colliculus is the inferior pair of these enlargements and is part of the auditory brain stem pathway. Neurons of the inferior colliculus project to the thalamus, which then sends auditory information to the cerebrum for the

conscious perception of sound. The superior colliculus is the superior pair and combines sensory information about visual space, auditory space, and somatosensory space. Activity in the superior colliculus is related to orienting the eyes to a sound or touch stimulus. If you are walking along the sidewalk on campus and you hear chirping, the superior colliculus coordinates that information with your awareness of the visual location of the tree right above you. That is the correlation of auditory and visual maps. If you suddenly feel something wet fall on your head, your superior colliculus integrates that with the auditory and visual maps and you know that the chirping bird just relieved itself on you. You want to look up to see the culprit, but do not.

The tegmentum is continuous with the gray matter of the rest of the brain stem. Throughout the midbrain, pons, and medulla, the tegmentum contains the nuclei that receive and send information through the cranial nerves, as well as regions that regulate important functions such as those of the cardiovascular and respiratory systems.

Pons

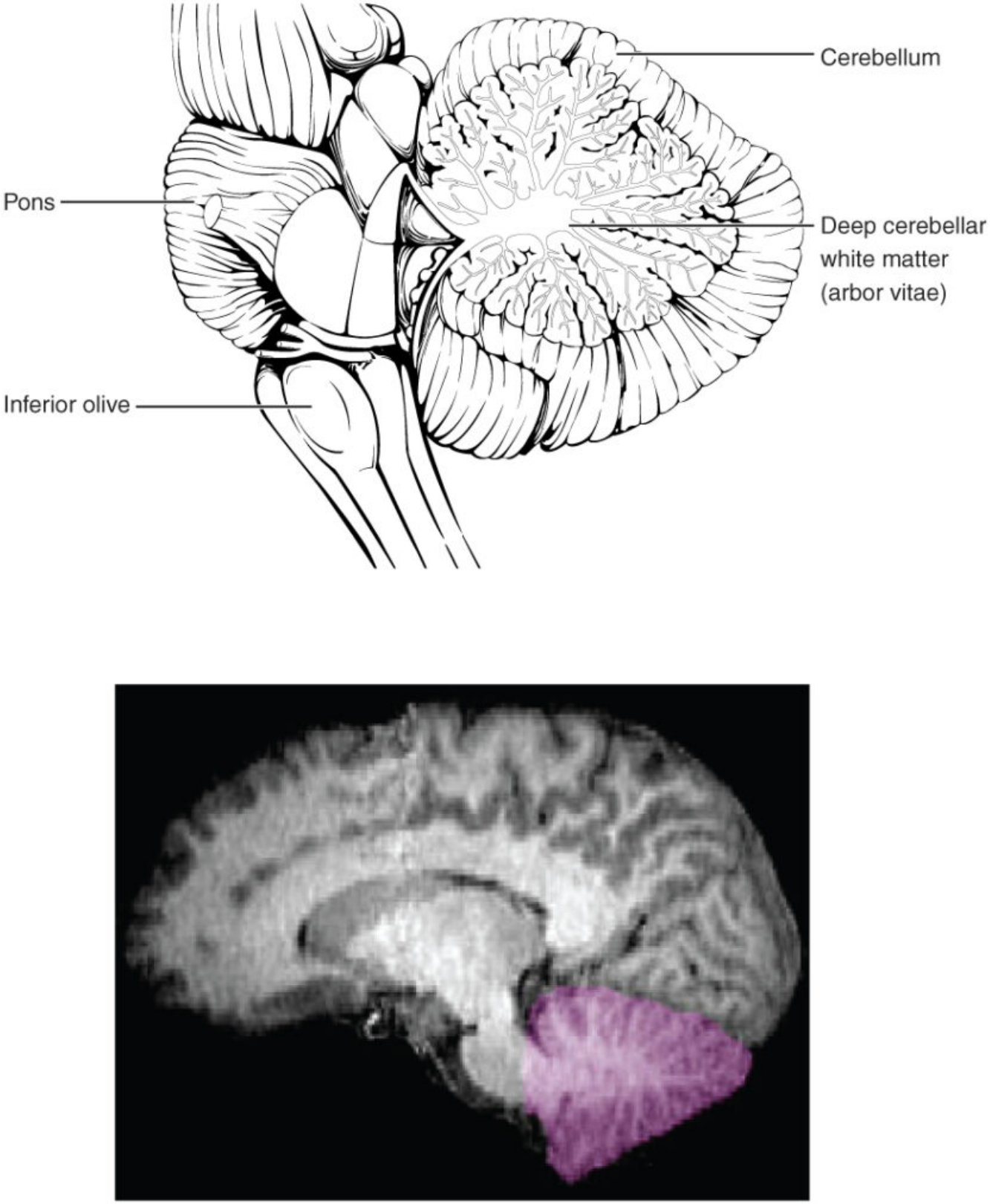
The word pons comes from the Latin word for bridge. It is visible on the anterior surface of the brain stem as the thick bundle of white matter attached to the cerebellum. The pons is the main connection between the cerebellum and the brain stem. The bridge-like white matter is only the anterior surface of the pons; the gray matter beneath that is a continuation of the tegmentum from the midbrain. Gray matter in the tegmentum region of the pons contains neurons receiving descending input from the forebrain that is sent to the cerebellum.

Medulla

The medulla is the region known as the myelencephalon in the embryonic brain. The initial portion of the name, "myel," refers to the significant white matter found in this region—especially on its exterior, which is continuous with the white matter of the spinal cord. The tegmentum of the midbrain and pons continues into the medulla because this gray matter is responsible for processing cranial nerve information. A diffuse region of gray matter throughout the brain stem, known as the reticular formation, is related to sleep and wakefulness, such as general brain activity and attention.

The Cerebellum

The cerebellum, as the name suggests, is the "little brain." It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain. The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain.



The Cerebellum – *The cerebellum is situated on the posterior surface of the brain stem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.*

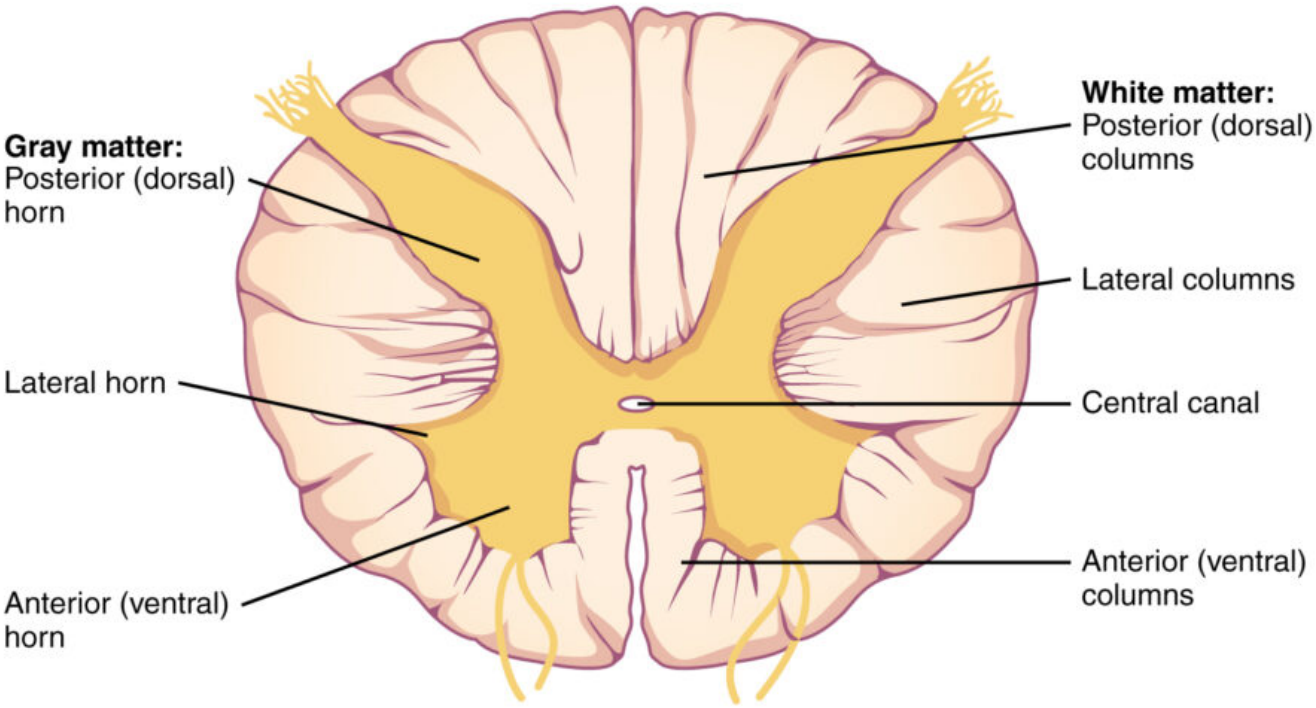
Descending fibers from the cerebrum have branches that connect to neurons in the pons. Those neurons project into the cerebellum, providing a copy of motor commands sent to the spinal cord. Sensory information from the periphery, which enters through spinal or cranial nerves, is copied to a nucleus in the medulla known as the inferior olive. Fibers from this nucleus enter the cerebellum and are compared with the descending commands from the cerebrum. If the primary motor cortex of the frontal lobe sends a command down to the spinal cord to initiate walking, a copy of that instruction is sent to the cerebellum. Sensory feedback from the muscles and joints, proprioceptive information about the movements of walking, and sensations of balance are sent to the cerebellum through the inferior olive and the cerebellum compares them. If walking is not coordinated, perhaps because the ground is uneven or a strong wind is blowing, then the cerebellum sends out a corrective command to compensate for the difference between the original cortical command and the sensory feedback. The output of the cerebellum is into the midbrain, which then sends a descending input to the spinal cord to correct the messages going to skeletal muscles.

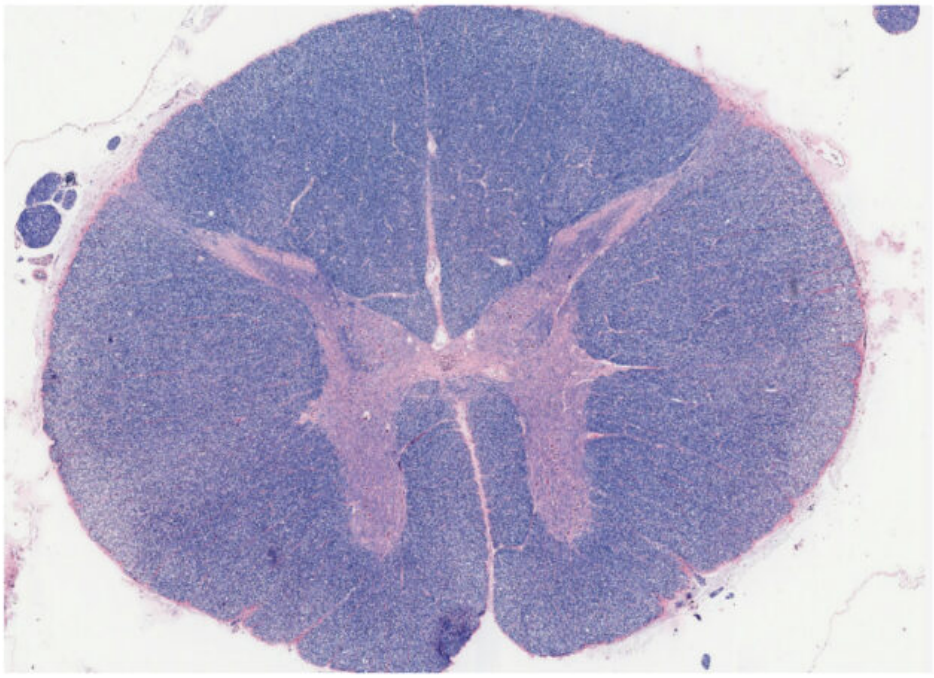
The Spinal Cord

The description of the CNS is concentrated on the structures of the brain, but the spinal cord is another major organ of the system. The spinal cord is a long tube-like structure which begins at the medulla oblongata in the brainstem and extends down the spine. It serves to connect the CNS with the peripheral nervous system (PNS).

The Spinal Cord in Cross-Section: Gray and White Matter

A striking feature of the spinal cord when viewed in cross section is it's organization of gray and white matter. As we learned before, gray matter refers to the cell bodies of neurons while white matter signifies the myelinated axon processes of nerves. You can remember this by thinking of the lipid-rich contents of myelin, which appear white. The gray matter of the spinal cord is organized into horns, while the white matter is organized into columns. In cross-section, the gray matter of the spinal cord has the appearance of an ink-blot test, with the spread of the gray matter on one side replicated on the other—a shape reminiscent of a bulbous capital "H."





Cross-section of Spinal Cord – *The cross-section of a thoracic spinal cord segment shows the posterior, anterior, and lateral horns of gray matter, as well as the posterior, anterior, and lateral columns of white matter. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

Gray Horns

As shown in the figure above, the gray matter is subdivided into regions that are referred to as horns. The posterior horn is responsible for sensory processing, while the anterior horn sends out motor signals to the skeletal muscles. Note that it is common to see the terms dorsal (dorsal = "back") and ventral (ventral = "belly") used interchangeably with posterior and anterior, particularly in reference to nerves and the structures of the spinal cord. You should learn to be comfortable with both. The lateral horn, which is only found in the thoracic, upper lumbar, and sacral regions, contains cell bodies of motor neurons of the autonomic nervous system.

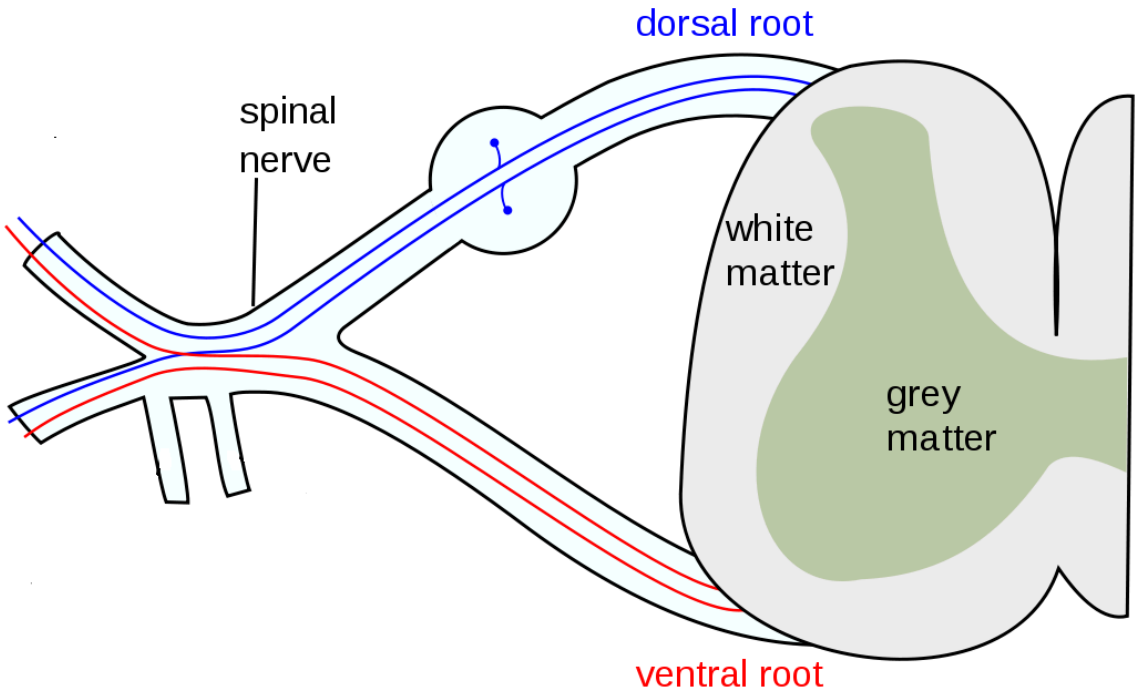
Some of the largest neurons of the spinal cord are the multipolar motor neurons in the anterior horn. The fibers that cause contraction of skeletal muscles are the axons of these neurons. The motor neuron that causes contraction of the big toe, for example, is located in the sacral spinal cord. The axon that has to reach all the way to the belly of that muscle may be a meter in length. The neuronal cell body that maintains that long fiber must be quite large, possibly several hundred micrometers in diameter, making it one of the largest cells in the body.

White Columns

Just as the gray matter is separated into horns, the white matter of the spinal cord is separated into columns. Ascending tracts of nervous system fibers in these columns carry sensory information up to the brain, whereas descending tracts carry motor commands from the brain to the muscles. Looking at the spinal cord longitudinally, the columns extend along its length as continuous bands of white matter. Between the two posterior horns of gray matter are the posterior columns. Between the two anterior horns, and bounded by the axons of motor neurons emerging from that gray matter area, are the anterior columns. The white matter on either side of the spinal cord, between the posterior horn and the axons of the anterior horn neurons, are the lateral columns. The posterior columns are composed of axons of ascending tracts. The anterior and lateral columns are composed of many different groups of axons of both ascending and descending tracts—the latter carrying motor commands down from the brain to the spinal cord to control output to the periphery.

Spinal Cord Segments

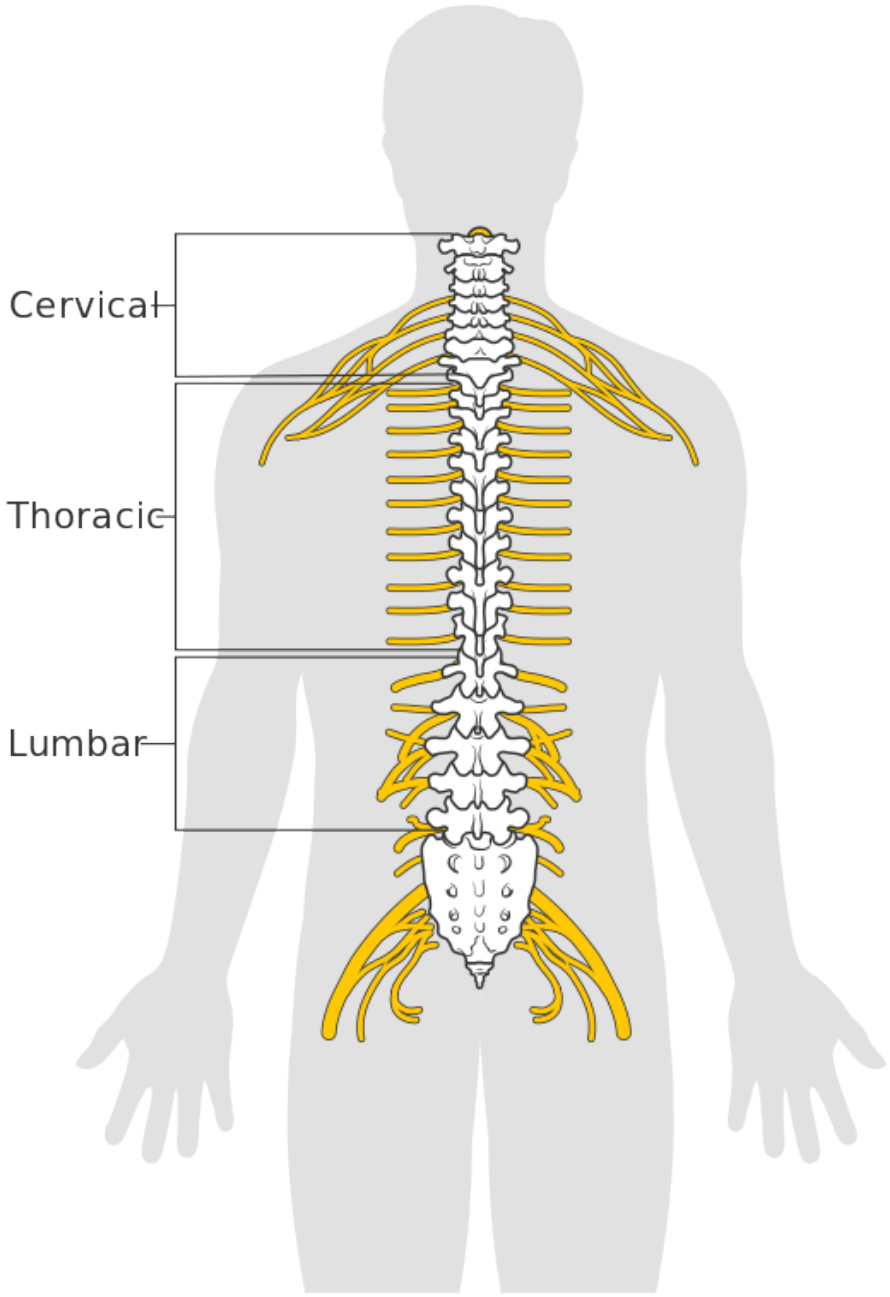
The spinal cord itself is composed of a number of segments, each of which has bundles of axons exiting and entering the cord in structures called roots. Axons enter the posterior side through the dorsal (posterior) nerve root. The axons emerging from the anterior side do so through the ventral (anterior) nerve root. On the whole, the posterior regions are responsible for sensory functions and the anterior regions are associated with motor functions, just like the corresponding anterior and posterior horns of gray matter. The roots then combine to form a pair of spinal nerves, one for each component of the spine.



Spinal Nerve – *A spinal nerve is formed from the merging of the dorsal and ventral roots. Each spinal nerve emerges from the spinal column in between vertebrae. Modified image originally by Tristanb.*

The spinal cord is surrounded and protected by the bones in our back, which are called vertebrae. These are the protruding boney structures that you can feel in your neck and back. Each of these segments of spinal cord is named according to the level at which it's spinal nerves pass through the intervertebral foramina, which is the space between two vertebrae. For example, the first pair of spinal nerves are the first cervical nerves (C1), which exits the spinal cord above the first cervical vertebrae (CI). You should take note of this nomenclature- spinal nerves are numbered with arabic numerals (1, 2, 3, 4, etc.) while vertebrae are numbered with roman numerals (I, II, III, IV, etc.)

The spinal cord is also split lengthwise into five major regions. Immediately adjacent to the brain stem is the cervical region, followed by the thoracic, then the lumbar, the sacral, and finally the coccygeal region. The spinal cord is not the full length of the vertebral column because the spinal cord does not grow significantly longer after the first or second year, but the skeleton continues to grow. The nerves that emerge from the spinal cord pass through the intervertebral foramina at the respective levels. As the vertebral column grows, these nerves grow with it and result in a long bundle of nerves that resembles a horse's tail and is named the cauda equina. The sacral spinal cord is at the level of the upper lumbar vertebral bones. The spinal nerves extend from their various levels to the proper level of the vertebral column.



The different regions of the vertebrae and spinal cord. By Cancer Research UK and used under CC license.

Watch this video to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures

for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

DISORDERS OF THE Basal Nuclei

Parkinson's disease is a disorder of the basal nuclei, specifically of the substantia nigra, that demonstrates the effects of the direct and indirect pathways. Parkinson's disease is the result of neurons in the substantia nigra pars compacta dying. These neurons release dopamine into the striatum. Without that modulatory influence, the basal nuclei are stuck in the indirect pathway, without the direct pathway being activated. The direct pathway is responsible for increasing cortical movement commands. The increased activity of the indirect pathway results in the hypokinetic disorder of Parkinson's disease.

Parkinson's disease is neurodegenerative, meaning that neurons die that cannot be replaced, so there is no cure for the disorder. Treatments for Parkinson's disease are aimed at increasing dopamine levels in the striatum. Currently, the most common way of doing that is by providing the amino acid L-DOPA, which is a precursor to the neurotransmitter dopamine and can cross the blood-brain barrier. With levels of the precursor elevated, the remaining cells of the substantia nigra pars compacta can make more neurotransmitter and have a greater effect. Unfortunately, the patient will become less responsive to L-DOPA treatment as time progresses, and it can cause increased dopamine levels elsewhere in the brain, which are associated with psychosis or schizophrenia.

Visit this site for a thorough explanation of Parkinson's disease.

Adaption

This chapter was adapted by Valerie Swanston from the following text:

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Circulation and the CNS

J. GORDON BETTS; JAMES A. WISE; KELLY A. YOUNG; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- Describe the vessels that supply the CNS with blood.
- Name the components of the ventricular system and the regions of the brain in which each is located.
- Explain the production of cerebrospinal fluid and its flow through the ventricles.
- Explain how a disruption in circulation would result in a stroke.

The CNS is crucial to the operation of the body, and any compromise to the blood flow to the brain and spinal cord can lead to severe difficulties. The CNS has a privileged blood supply, meaning that the entry and exit of substances in the brain is tightly regulated. This is accomplished by a structure known as the blood-brain barrier (BBB). Very little can pass through by diffusion. Most substances that cross the wall of a blood vessel into the CNS must do so through an active transport process. Because of this, only specific types of molecules can enter the CNS. Glucose—the primary energy source—is allowed, as are amino acids. Water and some other small particles, like gases and ions, can enter. But most everything else cannot, including white blood cells, which are one of the body's main lines of defense. While the BBB protects the CNS from exposure to toxic or pathogenic substances, it also keeps out the cells that could protect the brain and spinal cord from disease and damage.

Because of this privileged blood flow, the CNS needs specialized structures to maintain and regulate it's circulation. This begins with a unique arrangement of blood vessels carrying fresh blood into the CNS. Beyond the supply of blood, the CNS filters that blood into cerebrospinal fluid (CSF), which is then circulated through the cavities of the brain and spinal cord called ventricles. All fluids (venous blood and CSF) return to the general circulation via the great veins of the brain.

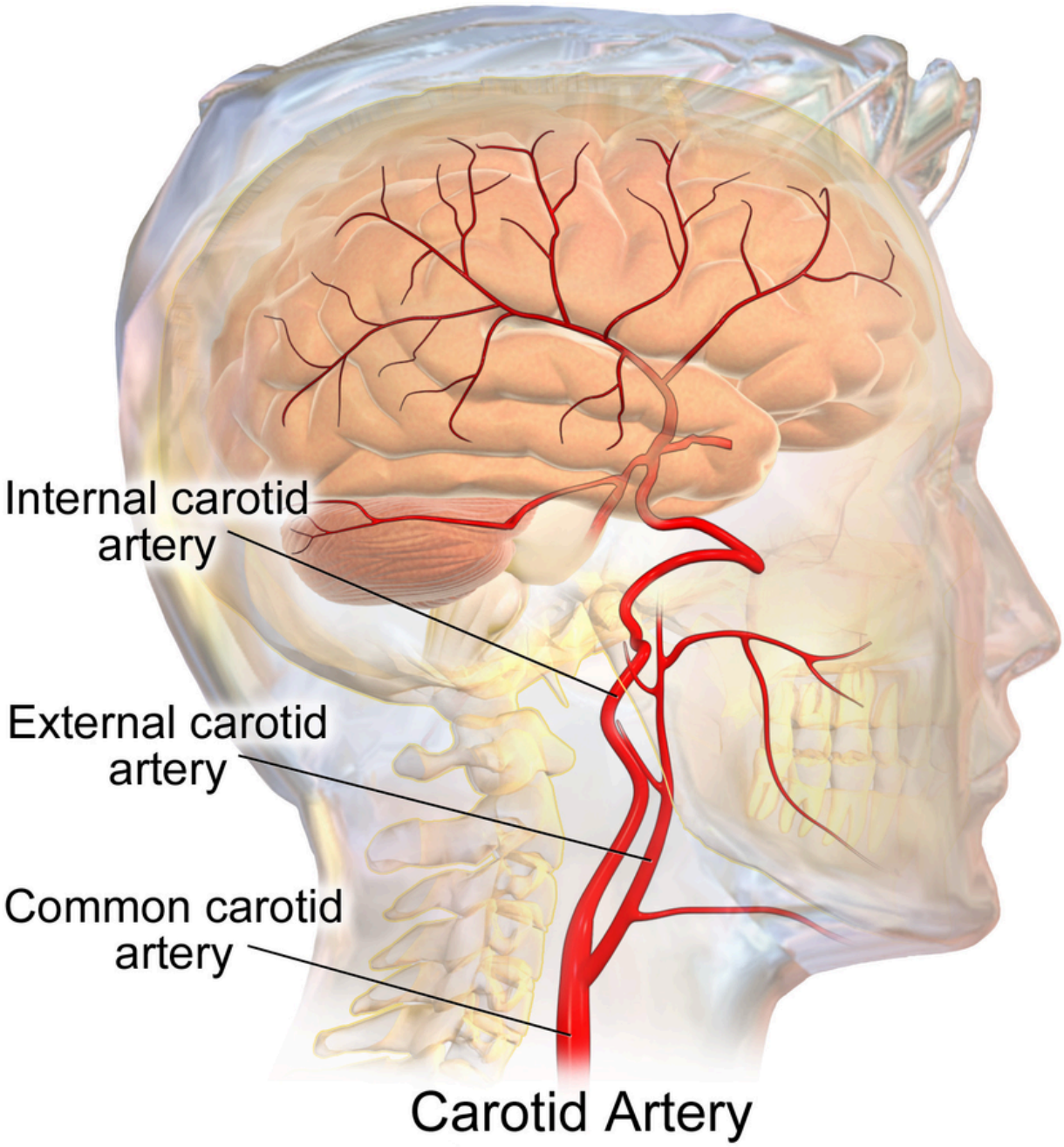
Blood Supply to the Brain

A lack of oxygen to the CNS can be devastating, and the cardiovascular system has specific regulatory reflexes to ensure that the blood supply is not interrupted. There are multiple routes for blood to get into the CNS, with specializations to protect that blood supply and to maximize the ability of the brain to get an uninterrupted perfusion.

Arterial Supply

The major artery carrying recently oxygenated blood away from the heart is the aorta. The very first branches off the

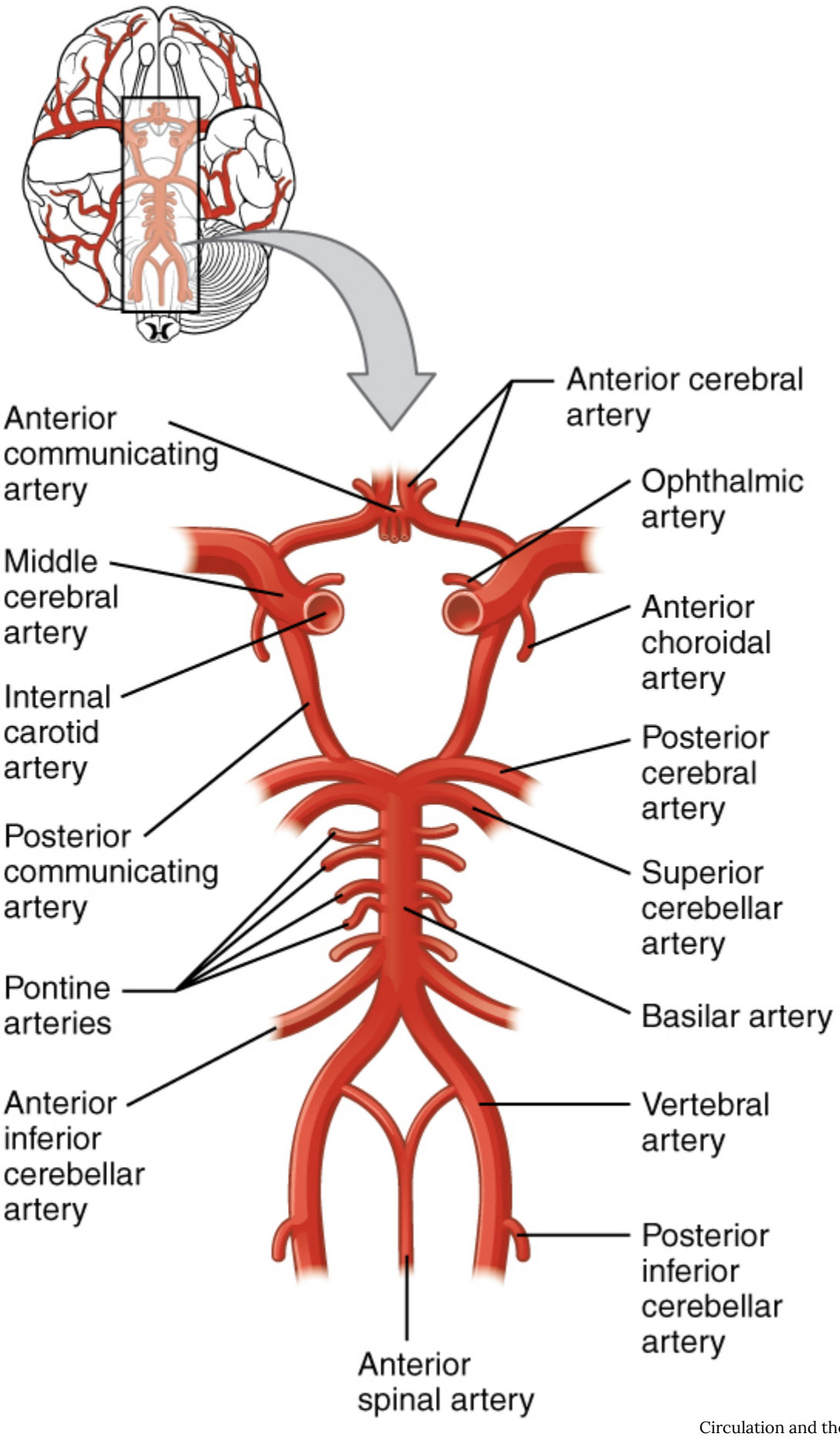
aorta supply the heart with nutrients and oxygen. The next branches give rise to the common carotid arteries, which further branch into the internal carotid arteries. The external carotid arteries supply blood to the tissues on the surface of the cranium. The bases of the common carotids contain stretch receptors that immediately respond to the drop in blood pressure upon standing. The orthostatic reflex is a reaction to this change in body position, so that blood pressure is maintained against the increasing effect of gravity (orthostatic means "standing up"). Heart rate increases—a reflex of the sympathetic division of the autonomic nervous system—and this raises blood pressure.



The Carotid Artery – *The carotid artery carries oxygenated blood to the brain. By BruceBlaus used under Creative Commons license.*

The internal carotid artery enters the cranium by passing through a canal in the skull bone. A second set of vessels that supply the CNS are the vertebral arteries, which merge into the basilar artery, the vessel that supplies blood to the

brain stem and cerebellum. The left and right internal carotid arteries and branches of the basilar artery all join together in a structure known as the circle of Willis, a confluence of arteries that can maintain perfusion of the brain even if narrowing or a blockage limits flow through one part.

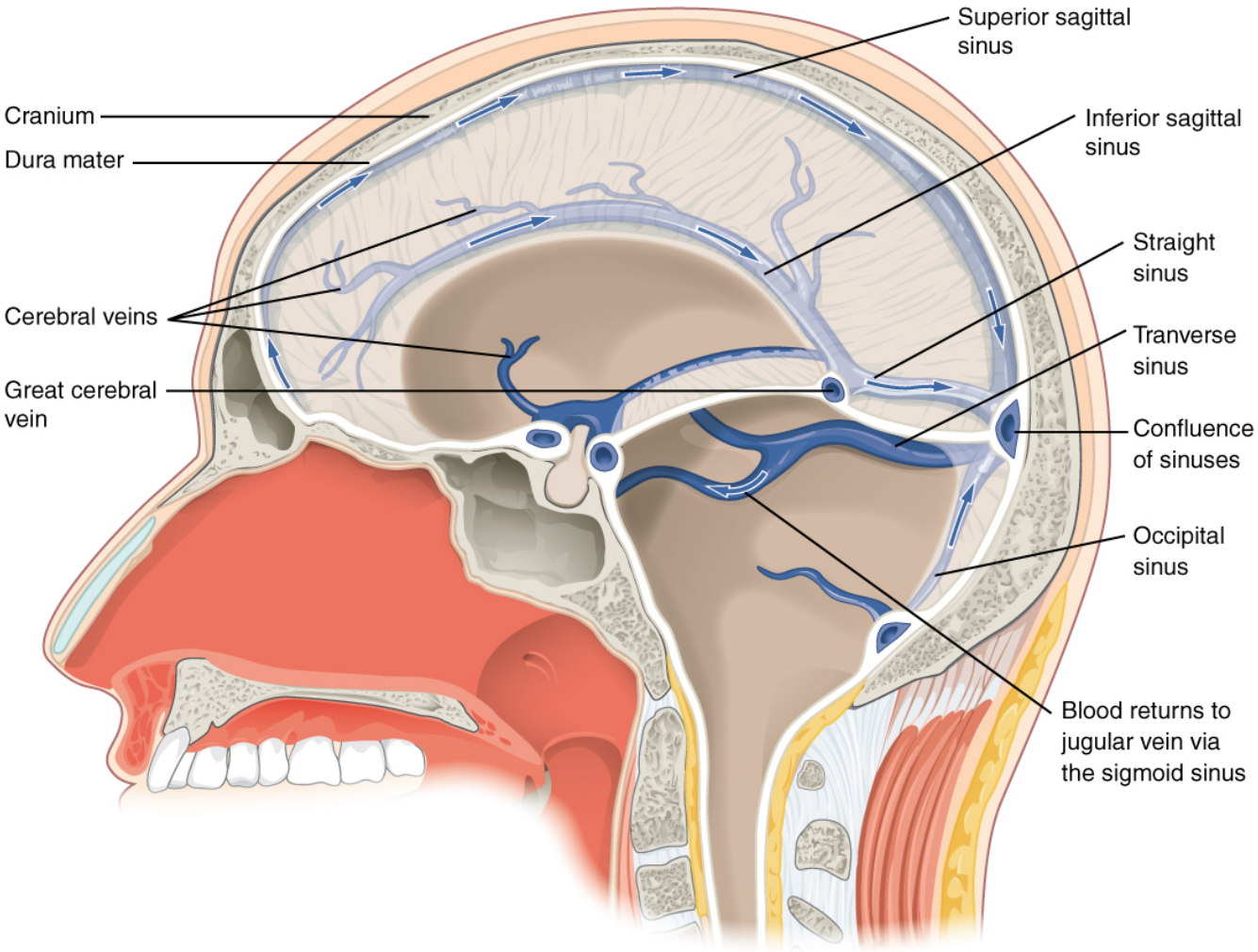

Anterior cerebral artery
Anterior communicating artery
Ophthalmic artery
Middle cerebral artery
Anterior choroidal artery
Internal carotid artery
Posterior cerebral artery
Posterior communicating artery
Superior cerebellar artery
Pontine arteries
Basilar artery
Anterior inferior cerebellar artery
Vertebral artery
Posterior inferior cerebellar artery
Anterior spinal artery

Circle of Willis *– The blood supply to the brain enters through the internal carotid arteries and the vertebral arteries, eventually giving rise to the circle of Willis.*

Watch this animation to see how blood flows to the brain and passes through the circle of Willis before being distributed through the cerebrum. The circle of Willis is a specialized arrangement of arteries that ensure constant perfusion of the cerebrum even in the event of a blockage of one of the arteries in the circle. The animation shows the normal direction of flow through the circle of Willis to the middle cerebral artery. Where would the blood come from if there were a blockage just posterior to the middle cerebral artery on the left?

Venous Return

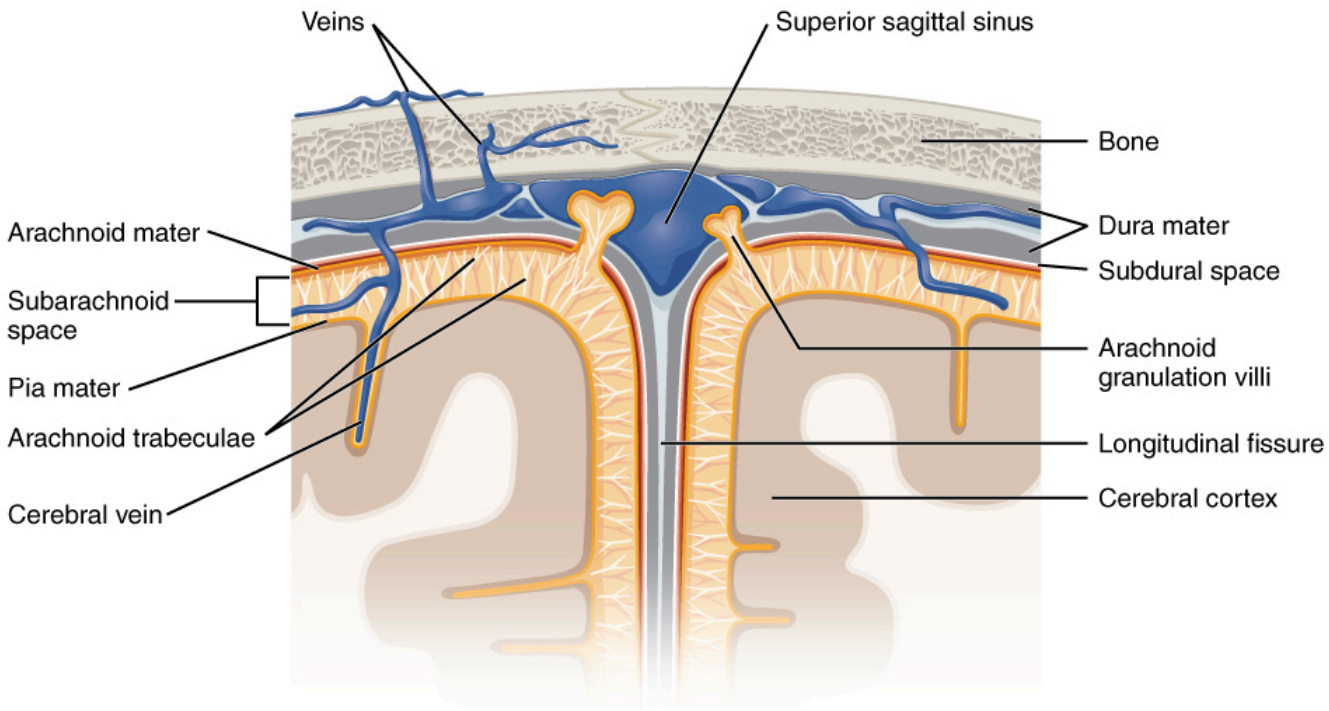
After passing through the CNS, blood returns to the circulation through a series of dural sinuses and veins, as shown in the diagram below. The superior sagittal sinus runs in the groove of the longitudinal fissure, where it absorbs CSF from the meninges (the protective membranes which cover the brain). The superior sagittal sinus drains to the confluence of sinuses, along with the occipital sinuses and straight sinus, to then drain into the transverse sinuses. The transverse sinuses connect to the sigmoid sinuses, which then connect to the jugular veins. From there, the blood continues toward the heart to be pumped to the lungs for reoxygenation.



Dural Sinuses and Veins – *Blood drains from the brain through a series of sinuses that connect to the jugular veins.*

Protective Coverings of the Brain and Spinal Cord

The outer surface of the CNS is covered by a series of membranes composed of connective tissue called the meninges, which protect the brain. Starting from outside in, the dura mater is a thick fibrous layer and a strong protective sheath over the entire brain and spinal cord. It is anchored to the inner surface of the cranium and vertebral cavity. Next, the arachnoid mater is a membrane of thin fibrous tissue that forms a loose sac around the CNS. Beneath the arachnoid is a thin, filamentous mesh called the arachnoid trabeculae, which looks like a spider web, giving this layer its name. Lastly, directly adjacent to the surface of the CNS is the pia mater, a thin fibrous membrane that follows the convolutions of gyri and sulci in the cerebral cortex and fits into other grooves and indentations.



Meningeal Layers of Superior Sagittal Sinus – *The layers of the meninges in the longitudinal fissure of the superior sagittal sinus are shown, with the dura mater adjacent to the inner surface of the cranium, the pia mater adjacent to the surface of the brain, and the arachnoid and subarachnoid space between them. An arachnoid villus is shown emerging into the dural sinus to allow CSF to filter back into the blood for drainage.*

Dura Mater

Like a thick cap covering the brain, the dura mater is a tough outer covering. The name comes from the Latin for "tough mother" to represent its physically protective role. It encloses the entire CNS and the major blood vessels that enter the cranium and vertebral cavity. It is directly attached to the inner surface of the bones of the cranium and to the very end of the vertebral cavity.

Arachnoid Mater

The middle layer of the meninges is the arachnoid, named for the spider-web–like trabeculae between it and the pia mater. The arachnoid defines a sac-like enclosure around the CNS. The trabeculae are found in the subarachnoid space, which is filled with circulating CSF. The arachnoid emerges into the dural sinuses as the arachnoid granulations, where the CSF is filtered back into the blood for drainage from the nervous system.

The subarachnoid space is filled with circulating CSF, which also provides a liquid cushion to the brain and spinal cord. Similar to clinical blood work, a sample of CSF can be withdrawn to find chemical evidence of neuropathology or metabolic traces of the biochemical functions of nervous tissue.

Pia Mater

The outer surface of the CNS is covered in the thin fibrous membrane of the pia mater. It is thought to have a continuous layer of cells providing a fluid-impermeable membrane. The name pia mater comes from the Latin for "tender mother," suggesting the thin membrane is a gentle covering for the brain. The pia extends into every convolution of the CNS, lining the inside of the sulci in the cerebral and cerebellar cortices. At the end of the spinal cord, a thin filament extends from the inferior end of CNS at the upper lumbar region of the vertebral column to the sacral end of the vertebral column. Because the spinal cord does not extend through the lower lumbar region of the vertebral column, a needle can be inserted through the dura and arachnoid layers to withdraw CSF. This procedure is called a lumbar puncture and avoids the risk of damaging the central tissue of the spinal cord. Blood vessels that are nourishing the central nervous tissue are between the pia mater and the nervous tissue.

DISORDERS OF THE MENINGES

Meningitis is an inflammation of the meninges, the three layers of fibrous membrane that surround the CNS. Meningitis can be caused by infection by bacteria or viruses. The particular pathogens are not special to meningitis; it is just an inflammation of that specific set of tissues from what might be a broader infection. Bacterial meningitis can be caused by *Streptococcus*, *Staphylococcus*, or the tuberculosis pathogen, among many others. Viral meningitis is usually the result of common enteroviruses (such as those that cause intestinal disorders), but may be the result of the herpes virus or West Nile virus. Bacterial meningitis tends to be more severe.

The symptoms associated with meningitis can be fever, chills, nausea, vomiting, light sensitivity, soreness of the neck, or severe headache. More important are the neurological symptoms, such as changes in mental state (confusion, memory deficits, and other dementia-type symptoms). A serious risk of meningitis can be damage to peripheral structures because of the nerves that pass through the meninges. Hearing loss is a common result of meningitis.

The primary test for meningitis is a lumbar puncture. A needle inserted into the lumbar region of the spinal column through the dura mater and arachnoid membrane into the subarachnoid space can be used to withdraw the fluid for chemical testing. Fatality occurs in 5 to 40 percent of children and 20 to 50 percent of adults with bacterial meningitis. Treatment of bacterial meningitis is through antibiotics, but viral meningitis cannot be treated with antibiotics because viruses do not respond to that type of drug. Fortunately, the viral forms are milder.

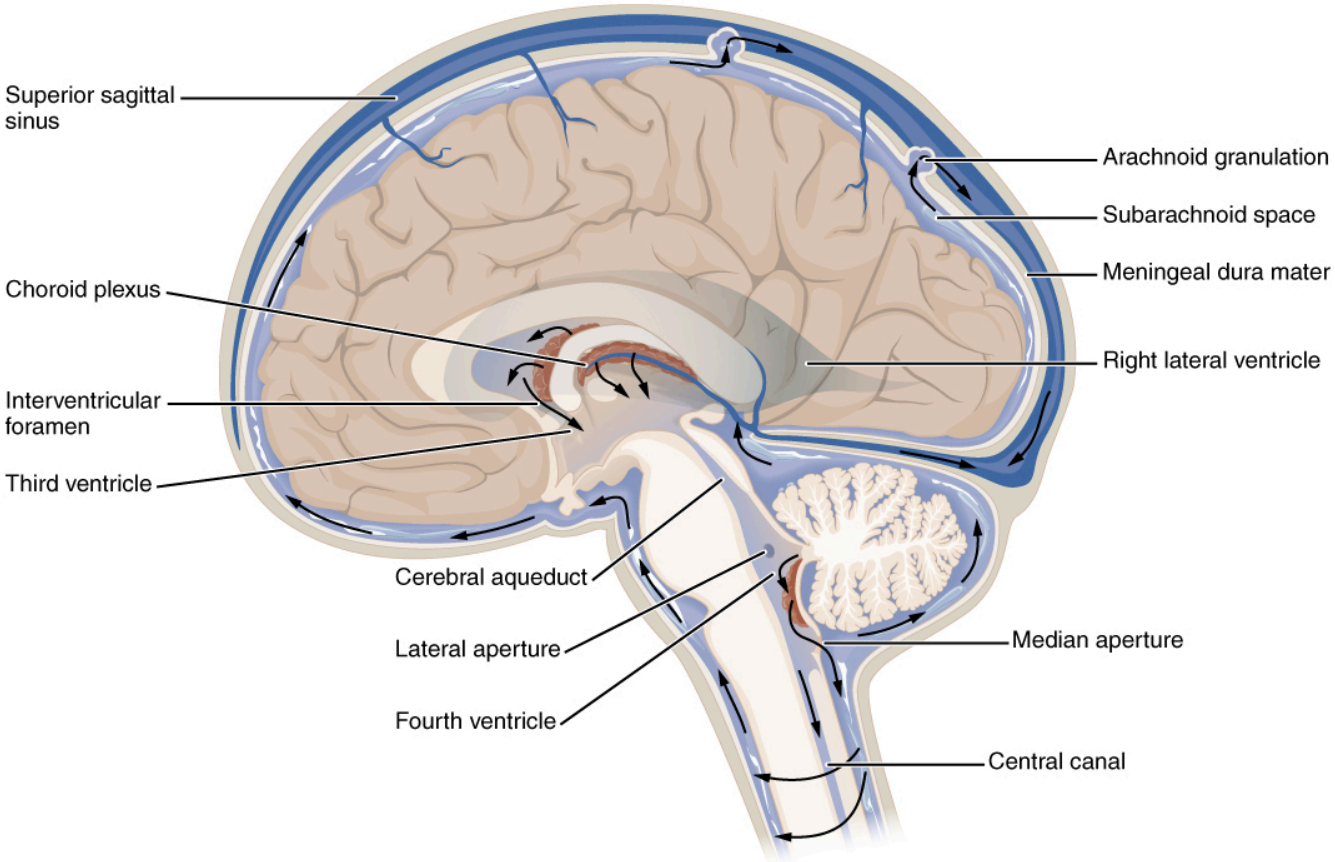
Watch this video that describes the procedure known as the lumbar puncture, a medical procedure used to sample the CSF. Because of the anatomy of the CNS, it is a relative safe location to insert a needle. Why is the lumbar puncture performed in the lower lumbar area of the vertebral column?

The Ventricular System

Cerebrospinal fluid (CSF) circulates throughout and around the CNS. In other tissues, water and small molecules are filtered through capillaries as the major contributor to the interstitial fluid. In the brain, CSF is produced in special structures to perfuse through the nervous tissue of the CNS and is continuous with the interstitial fluid. Specifically, CSF circulates to remove metabolic wastes from the interstitial fluids of nervous tissues and return them to the blood stream. The ventricles are the open spaces within the brain where CSF circulates. In some of these spaces, CSF is produced by filtering of the blood that is performed by a specialized membrane known as a choroid plexus. The CSF circulates through all of the ventricles to eventually emerge into the subarachnoid space where it will be reabsorbed into the blood.

The Ventricles

There are four ventricles within the brain, all of which developed from the original hollow space within the neural tube, the central canal. The first two are named the lateral ventricles and are deep within the cerebrum. These ventricles are connected to the third ventricle by two openings called the interventricular foramina. The third ventricle is the space between the left and right sides of the diencephalon, which opens into the cerebral aqueduct that passes through the midbrain. The aqueduct opens into the fourth ventricle, which is the space between the cerebellum and the pons and upper medulla, shown below.



Cerebrospinal Fluid Circulation – *The choroid plexus in the four ventricles produce CSF, which is circulated through the ventricular system and then enters the subarachnoid space through the median and lateral apertures. The CSF is then reabsorbed into the blood at the arachnoid granulations, where the arachnoid membrane emerges into the dural sinuses.*

Cerebrospinal Fluid Circulation

Cerebrospinal fluid is produced within the ventricles by a type of specialized membrane called a choroid plexus. Ependymal cells (one of the types of glial cells described in the introduction to the nervous system) surround blood capillaries and filter the blood to make CSF. The fluid is a clear solution with a limited amount of the constituents of blood. It is essentially water, small molecules, and electrolytes. Oxygen and carbon dioxide are dissolved into the CSF, as they are in blood, and can diffuse between the fluid and the nervous tissue.

The choroid plexuses are found in all four ventricles. Observed in dissection, they appear as soft, fuzzy structures that may still be pink, depending on how well the circulatory system is cleared in preparation of the tissue. The CSF is produced from components extracted from the blood, so its flow out of the ventricles is tied to the pulse of cardiovascular circulation.

From the lateral ventricles, the CSF flows into the third ventricle, where more CSF is produced, and then through the cerebral aqueduct into the fourth ventricle where even more CSF is produced. A very small amount of CSF is filtered at any one of the plexuses, for a total of about 500 milliliters daily, but it is continuously made and pulses through the ventricular system, keeping the fluid moving. From the fourth ventricle, CSF can continue down the central canal of the spinal cord, but this is essentially a cul-de-sac, so more of the fluid leaves the ventricular system and moves into the subarachnoid space through the median and lateral apertures.

Within the subarachnoid space, the CSF flows around all of the CNS, providing two important functions. As with elsewhere in its circulation, the CSF picks up metabolic wastes from the nervous tissue and moves it out of the CNS. It also acts as a liquid cushion for the brain and spinal cord. By surrounding the entire system in the subarachnoid space, it provides a thin buffer around the organs within the strong, protective dura mater. The arachnoid granulations are outpocketings of the arachnoid membrane into the dural sinuses so that CSF can be reabsorbed into the blood, along with the metabolic wastes. From the dural sinuses, blood drains out of the head and neck through the jugular veins, along with the rest of the circulation for blood, to be reoxygenated by the lungs and wastes to be filtered out by the kidneys.

Watch this animation that shows the flow of CSF through the brain and spinal cord, and how it originates from the ventricles and then spreads into the space within the meninges, where the fluids then move into the venous sinuses to return to the cardiovascular circulation. What are the structures that produce CSF and where are they found? How are the structures indicated in this animation?

DISORDERS OF THE CENTRAL NERVOUS SYSTEM

The supply of blood to the brain is crucial to its ability to perform many functions. Without a steady supply of oxygen, and to a lesser extent glucose, the nervous tissue in the brain cannot keep up its extensive electrical activity. These nutrients get into the brain through the blood, and if blood flow is interrupted, neurological function is compromised.

The common name for a disruption of blood supply to the brain is a stroke. It is caused by a blockage to an artery in the brain. The blockage is from some type of embolus: a blood clot, a fat embolus, or an air bubble. When the blood cannot travel through the artery, the surrounding tissue that is deprived starves and dies. Strokes will often result in the loss of very specific functions. A stroke in the lateral medulla, for example, can cause a loss in the ability to swallow. Sometimes, seemingly unrelated functions will be lost because they are dependent on structures in the same region. Along with the swallowing in the previous example, a stroke in that region could affect sensory functions from the face or extremities because important white matter pathways also pass through the lateral medulla. Loss of blood flow to specific regions of the cortex can lead to the loss of specific higher functions, from the ability to recognize faces to the ability to move a particular region of the body. Severe or limited memory loss can be the result of a temporal lobe stroke.

Related to strokes are transient ischemic attacks (TIAs), which can also be called "mini-strokes." These are events in which a physical blockage may be temporary, cutting off the blood supply and oxygen to a region, but not to the extent that it causes cell death in that region. While the neurons in that area are recovering from the event, neurological function may be lost. Function can return if the area is able to recover from the event.

Adaptation

This chapter was adapted by Valerie Swanston from the following texts:

Circulation and the Central Nervous System **in** Anatomy and Physiology by OSCRiceUniversity is licensed under a Creative Commons Attribution 4.0 International License

Chapter 3 – The blood–brain barrier in Handbook of Clinical Neurology by Obermeier B, Verma A, and Ransohoff RM. https://doi.org/10.1016/B978-0-444-63432-0.00003-7

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The Peripheral Nervous System

J. GORDON BETTS; JAMES A. WISE; KELLY A. YOUNG; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

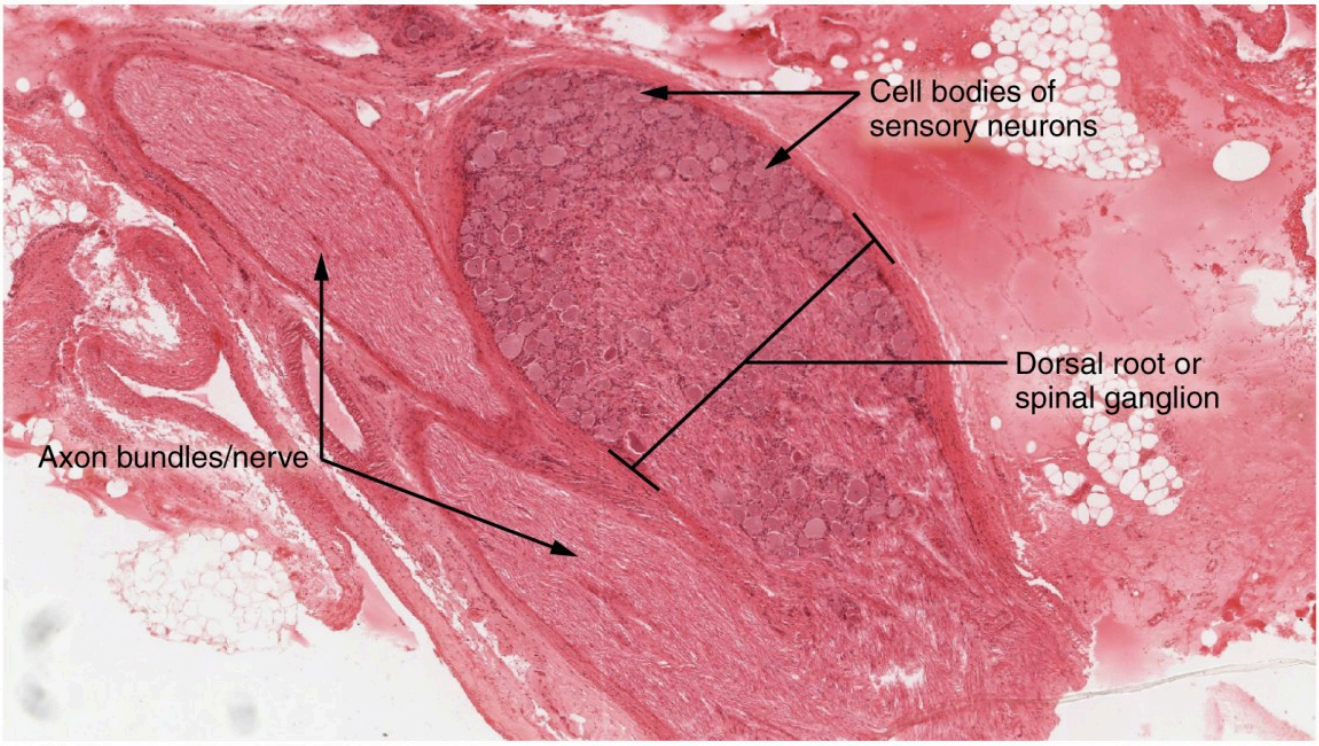
By the end of this section, you will be able to:

- Describe the structures found in the PNS.
- Distinguish between somatic and autonomic structures, including the special peripheral structures of the enteric nervous system.
- Name the twelve cranial nerves and explain the functions associated with each.
- Describe the sensory and motor components of spinal nerves and the plexuses that they pass through.

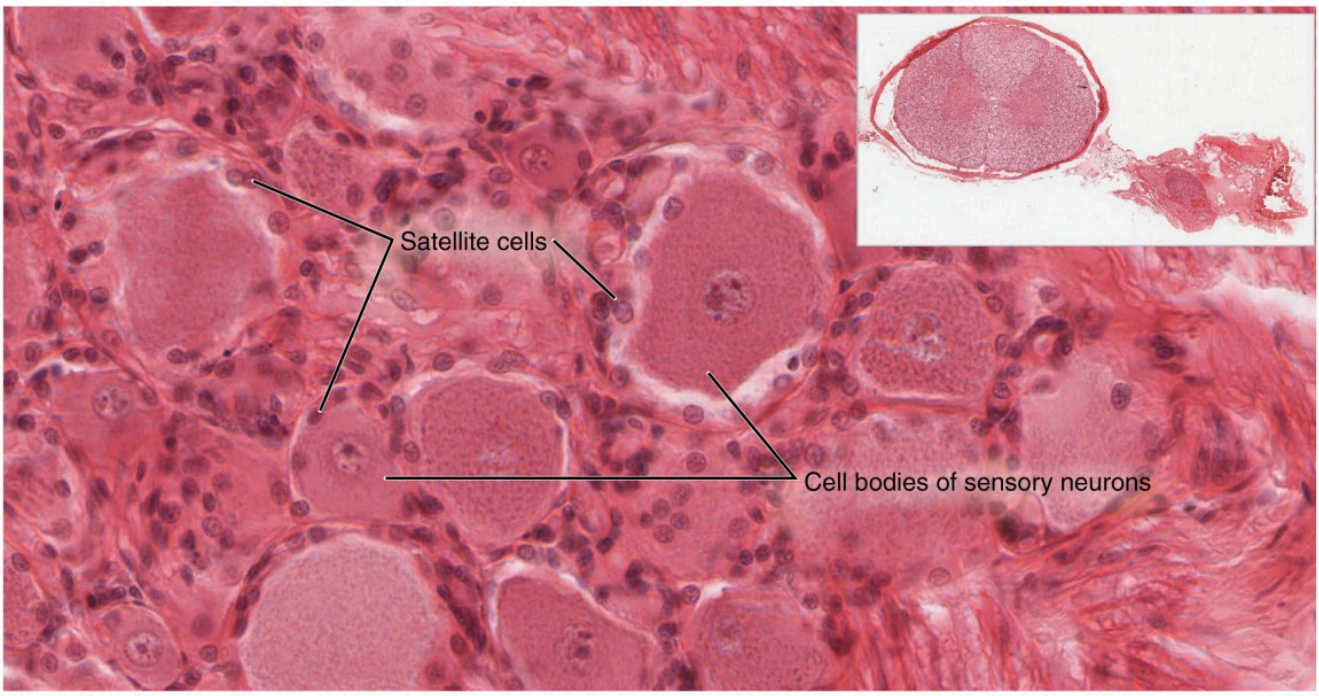
The peripheral nervous system (PNS) is defined as nervous tissue that is outside the CNS. In describing the anatomy of the PNS, it is necessary to describe the common structures, the nerves and the ganglia, as they are found in various parts of the body. Many of the neural structures in the periphery are features of the digestive system; these structures are known as the enteric nervous system and are a special subset of the PNS.

Ganglia

A ganglion is a group of neuron cell bodies in the periphery. Remember the clusters of neuron cell bodies in the CNS called nuclei that we learned about previously? These are similar, but when they are found outside the CNS they are referred to as ganglia. Ganglia can be categorized, for the most part, as either sensory ganglia or autonomic ganglia, referring to their primary functions. The most common type of sensory ganglion is a dorsal (posterior) root ganglion. These ganglia are the cell bodies of neurons within the dorsal root of a spinal nerve. They function as specialized sensors in the periphery, such as in the skin, and that extend into the CNS through the dorsal nerve root. Under microscopic inspection, it can be seen to include the cell bodies of the neurons, as well as bundles of fibers that are the posterior nerve root (Dorsal Root Ganglion). Also, the small round nuclei of satellite cells can be seen surrounding—as if they were orbiting—the neuron cell bodies.



Dorsal Root Ganglion – *The cell bodies of sensory neurons, which are unipolar neurons by shape, are seen in this photomicrograph. Also, the fibrous region is composed of the axons of these neurons that are passing through the ganglion to be part of the dorsal nerve root (tissue source: canine). LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*



Spinal Cord and Root Ganglion – The slide includes both a cross-section of the lumbar spinal cord and a section of the dorsal root ganglion (see also Dorsal Root Ganglion) (tissue source: canine). LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

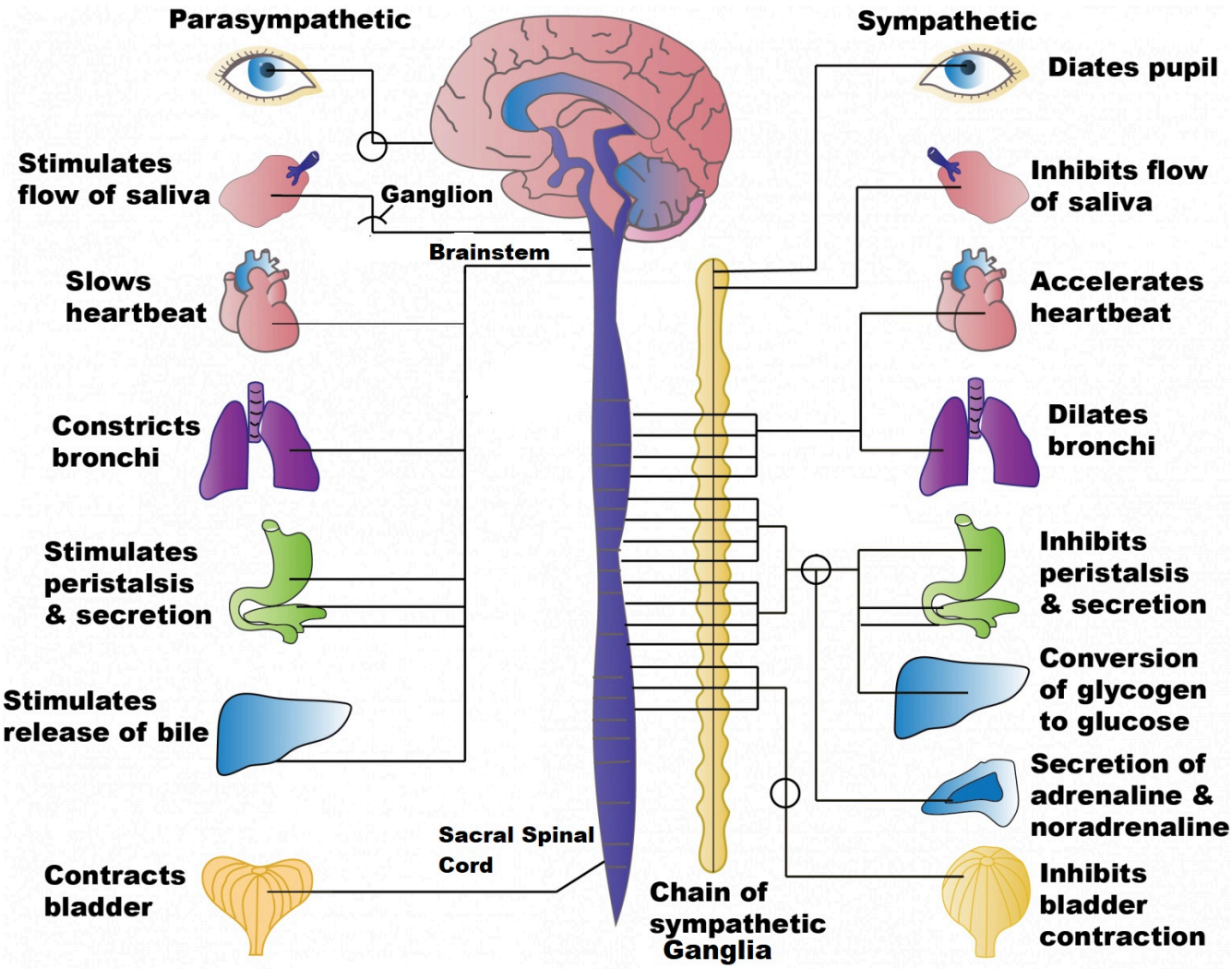
View the University of Michigan WebScope to explore the tissue sample in greater detail. If you zoom in on the dorsal root ganglion, you can see smaller satellite glial cells surrounding the large cell bodies of the sensory neurons. From what structure do satellite cells derive during embryologic development?

Another type of sensory ganglion is a cranial nerve ganglion. This is analogous to the dorsal root ganglion, except that it is associated with a cranial nerve instead of a spinal nerve. The roots of cranial nerves are within the cranium, whereas the ganglia are outside the skull. For example, the trigeminal ganglion contains the cell bodies of neurons attached to the mid-pons region of the brain stem. We'll learn more about cranial nerves later on in this chapter.

The other major category of ganglia are those of the autonomic nervous system, which is divided into the sympathetic and parasympathetic nervous systems. The autonomic nervous system controls many different bodily processes and aims to maintain homeostasis, which is a state of relative internal stability despite changing environments. For example, the autonomic nervous system controls and regulates blood pressure, heart rate, pupil size, and bladder function. It does this involuntarily, meaning that we have very little to no awareness or control over these functions*. The two divisions of the autonomic nervous system, the sympathetic and parasympathetic systems, generally have opposing functions. The sympathetic system is known as our "fight or flight" response and controls the body's response to stressful situations. For example, if you are giving a speech in front of a crowd, your sympathetic nervous system may cause your blood pressure and heart rate to rise. On the other hand, the parasympathetic nervous system controls our "rest and digest" functions, for example aiding in digestion while we are resting.

The conduction system of the ANS consists of two neurons which synapse at a ganglion. The preganglionic neuron begins at the lateral horn of the gray matter within the spinal cord or in various nuclei within brainstem. It projects to a ganglion where it synapses with the postganglionic neuron, which then innervates the target tissue. The sympathetic ganglia form a chain that is located on either side of the vertebral column in the the thoracic and upper lumbar spinal cord regions.

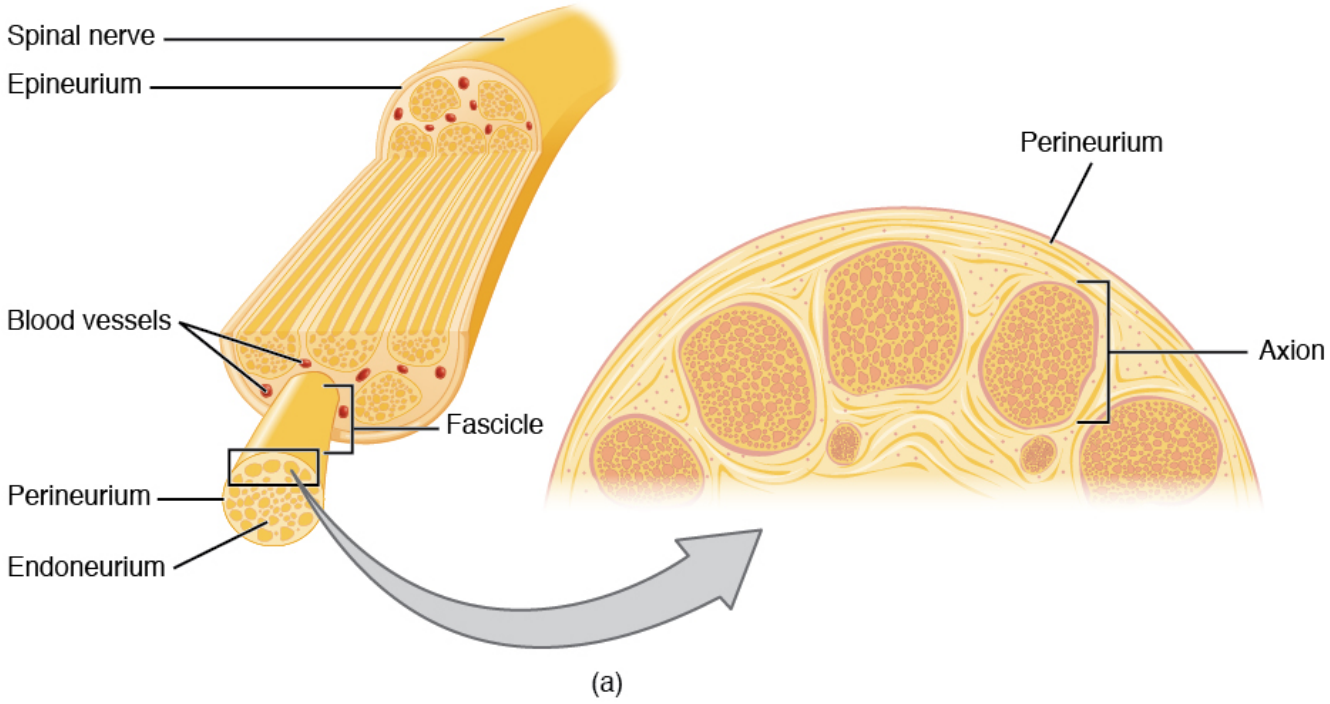
The parasympathetic ganglia receive input from cranial nerves in the brainstem or sacral spinal nerves. Unlike sympathetic ganglia, which are located near the spinal cord, parasympathetic ganglia are usually located within or in very close proximity to the tissues they innervate. This means that their preganglionic neurons are generally much longer than those in the sympathetic nervous system. These two sets of ganglia, sympathetic and parasympathetic, often project to the same organs to regulate the overall function in an opposing fashion. For example, the heart receives two inputs such as these; one increases heart rate (sympathetic nervous system), and the other decreases it (parasympathetic nervous system). See the figure below for an overview of the structure and function of the autonomic nervous system.

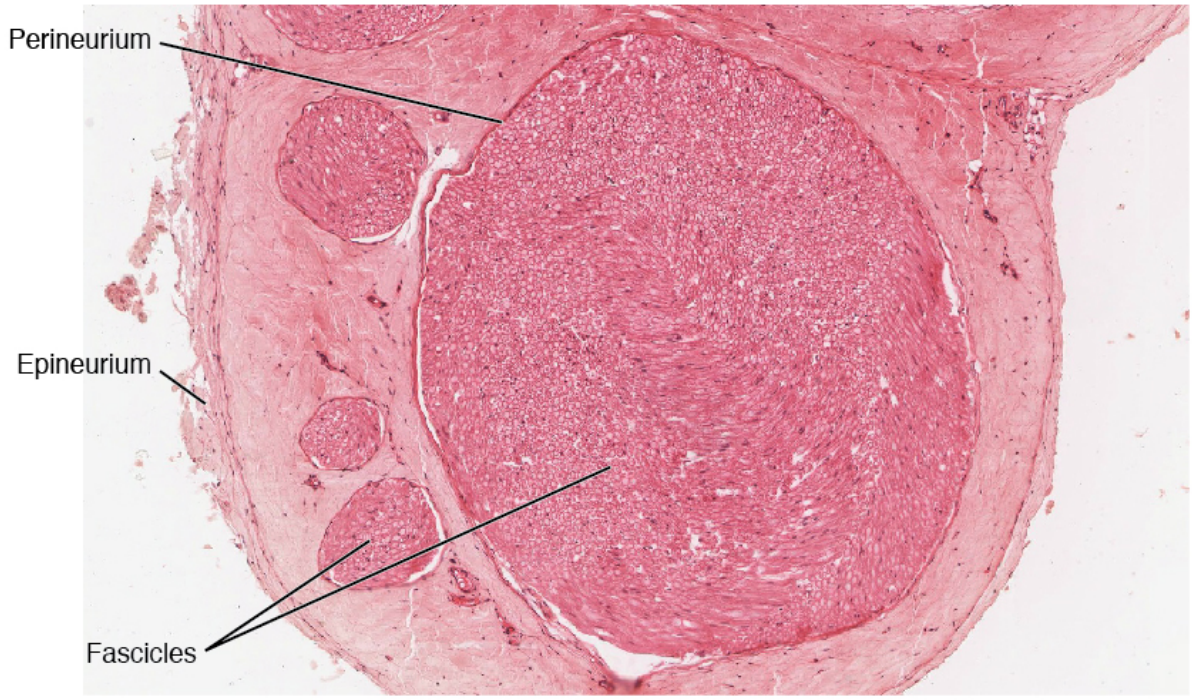


Autonomic Ganglia – *Used under creative commons license. Original author Nursing Pharmacology by Open Resources for Nursing (Open RN)*

Nerves

Bundles of axons in the PNS are referred to as nerves. These structures in the periphery are different than the central counterpart, called a tract. Nerves are composed of more than just nervous tissue. They have connective tissues invested in their structure, as well as blood vessels supplying the tissues with nourishment. The outer surface of a nerve is a surrounding layer of fibrous connective tissue called the epineurium. Within the nerve, axons are further bundled into fascicles, which are each surrounded by their own layer of fibrous connective tissue called perineurium. Finally, individual axons are surrounded by loose connective tissue called the endoneurium. These three layers are similar to the connective tissue sheaths for muscles. Nerves are associated with the region of the CNS to which they are connected, either as cranial nerves connected to the brain or spinal nerves connected to the spinal cord. The figure below shows the organization and layers of a nerve.





Nerve Structure – *The structure of a nerve is organized by the layers of connective tissue on the outside, around each fascicle, and surrounding the individual nerve fibers (tissue source: simian). LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*



Close-Up of Nerve Trunk – *Nerve trunk containing the endoneurium, perineurium, and epineurium in greater detail (tissue source: simian). LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

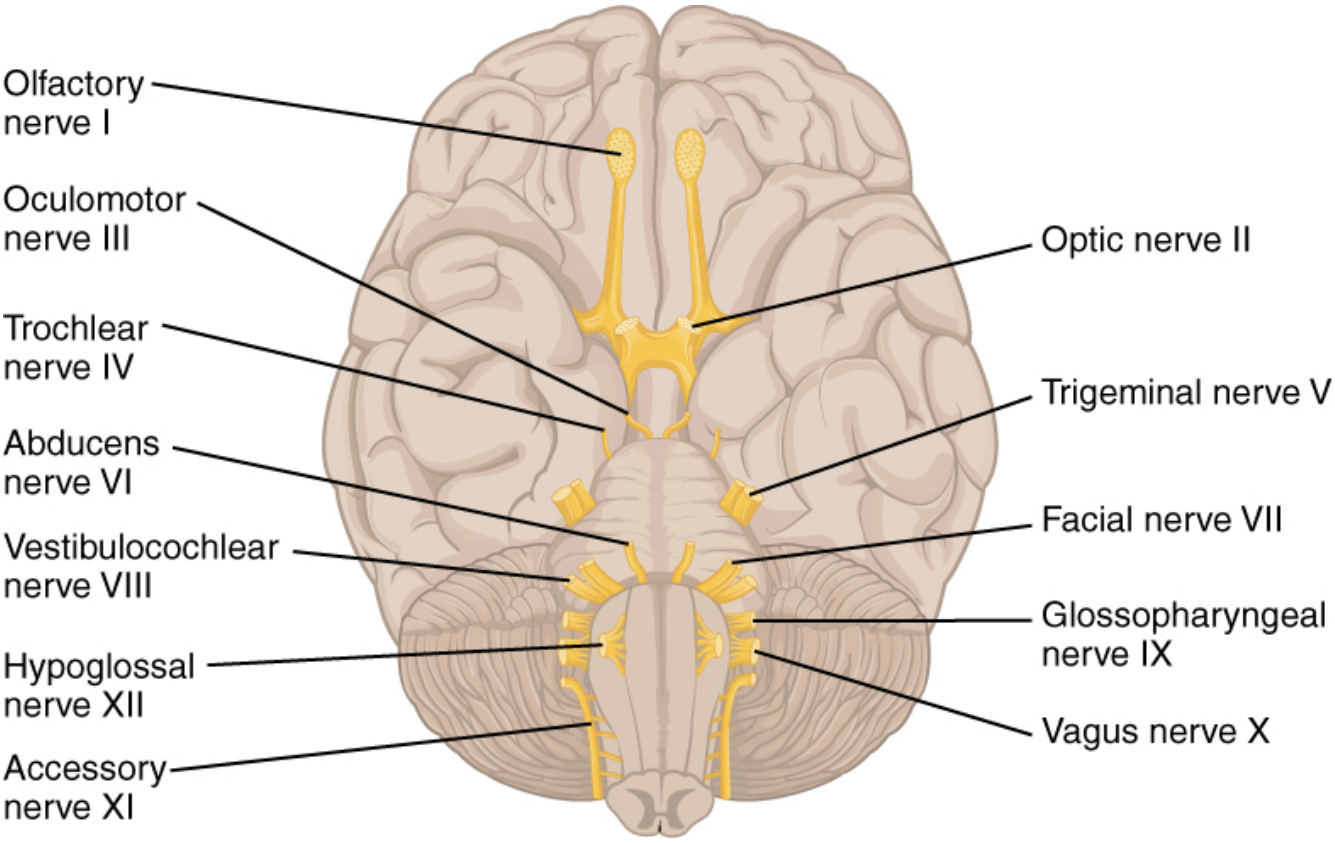
View the University of Michigan WebScope to explore the tissue sample in greater detail. With what structures in a skeletal muscle are the endoneurium, perineurium, and epineurium comparable?

Cranial Nerves

The nerves attached to the brain are the cranial nerves, which are primarily responsible for the sensory and motor functions of the head and neck (one of these nerves targets organs in the thoracic and abdominal cavities as part of the parasympathetic nervous system). There are twelve cranial nerves, which are designated CNI through CNXII for "Cranial Nerve," using Roman numerals for 1 through 12. They can be classified as sensory nerves, motor nerves, or a combination of both, meaning that the axons in these nerves originate out of sensory ganglia external to the cranium or motor nuclei within the brain stem. Sensory axons enter the brain to synapse in a nucleus. Motor axons connect to skeletal muscles of the head or neck. Three of the nerves are solely composed of sensory fibers; five are strictly motor; and the remaining four are mixed nerves.

Learning the cranial nerves is a tradition in anatomy courses, and students have always used mnemonic devices to remember the nerve names. A traditional mnemonic is the rhyming couplet, "On Old Olympus' Towering Tops/A Finn And German Viewed Some Hops," in which the initial letter of each word corresponds to the initial letter in the name of each nerve. The names of the nerves have changed over the years to reflect current usage and more accurate naming. An exercise to help learn this sort of information is to generate a mnemonic using words that have personal significance. The names of the cranial nerves are listed in this table along with a brief description of their function, their source (sensory ganglion or motor nucleus), and their target (sensory nucleus or skeletal muscle).

The olfactory nerve and optic nerve are responsible for the sense of smell and vision, respectively. The oculomotor nerve is responsible for eye movements by controlling four of the extraocular muscles. It is also responsible for lifting the upper eyelid when the eyes point up, and for pupillary constriction. The trochlear nerve and the abducens nerve are both responsible for eye movement, but do so by controlling different extraocular muscles. The trigeminal nerve is responsible for cutaneous sensations of the face and controlling the muscles of mastication. The facial nerve is responsible for the muscles involved in facial expressions, as well as part of the sense of taste and the production of saliva. The vestibulocochlear nerve is responsible for the senses of hearing and balance. The glossopharyngeal nerve is responsible for controlling muscles in the oral cavity and upper throat, as well as part of the sense of taste and the production of saliva. The vagus nerve is responsible for contributing to homeostatic control of the organs of the thoracic and upper abdominal cavities. The spinal accessory nerve is responsible for controlling the muscles of the neck, along with cervical spinal nerves. The hypoglossal nerve is responsible for controlling the muscles of the lower throat and tongue.



The Cranial Nerves – *The anatomical arrangement of the roots of the cranial nerves observed from an inferior view of the brain.*

Three of the cranial nerves also contain autonomic fibers, and a fourth is almost purely a component of the autonomic system. The oculomotor, facial, and glossopharyngeal nerves contain fibers that contact autonomic ganglia. The oculomotor fibers initiate pupillary constriction, whereas the facial and glossopharyngeal fibers both initiate salivation. The vagus nerve primarily targets autonomic ganglia in the thoracic and upper abdominal cavities.

Visit this site to read about a man who wakes with a headache and a loss of vision. His regular doctor sent

him to an ophthalmologist to address the vision loss. The ophthalmologist recognizes a greater problem and immediately sends him to the emergency room. Once there, the patient undergoes a large battery of tests, but a definite cause cannot be found. A specialist recognizes the problem as meningitis, but the question is what caused it originally. How can that be cured? The loss of vision comes from swelling around the optic nerve, which probably presented as a bulge on the inside of the eye. Why is swelling related to meningitis going to push on the optic nerve?

Another important aspect of the cranial nerves that lends itself to a mnemonic is the functional role each nerve plays. The nerves fall into one of three basic groups. They are sensory, motor, or both (see this table). The sentence, "Some Say Marry Money But My Brother Says Brains Beauty Matter More," corresponds to the basic function of each nerve. The first, second, and eighth nerves are purely sensory: the olfactory (CNI), optic (CNII), and vestibulocochlear (CNVIII) nerves. The three eye-movement nerves are all motor: the oculomotor (CNIII), trochlear (CNIV), and abducens (CNVI). The spinal accessory (CNXI) and hypoglossal (CNXII) nerves are also strictly motor. The remainder of the nerves contain both sensory and motor fibers. They are the trigeminal (CNV), facial (CNVII), glossopharyngeal (CNIX), and vagus (CNX) nerves. The nerves that convey both are often related to each other. The trigeminal and facial nerves both concern the face; one concerns the sensations and the other concerns the muscle movements. The facial and glossopharyngeal nerves are both responsible for conveying gustatory, or taste, sensations as well as controlling salivary glands. The vagus nerve is involved in visceral responses to taste, namely the gag reflex. This is not an exhaustive list of what these combination nerves do, but there is a thread of relation between them.

Mnemonic	#	Name	Function (S/M/B)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
On	I	Olfactory	Smell (S)	Olfactory bulb	Olfactory epithelium
Old	II	Optic	Vision (S)	Hypothalamus/thalamus/midbrain	Retina (retinal ganglion cells)
Olympus'	III	Oculomotor	Eye movements (M)	Oculomotor nucleus	Extraocular muscles (other 4), levator palpebrae superioris, ciliary ganglion (autonomic)
Towering	IV	Trochlear	Eye movements (M)	Trochlear nucleus	Superior oblique muscle
Tops	V	Trigeminal	Sensory/motor – face (B)	Trigeminal nuclei in the midbrain, pons, and medulla	Trigeminal
A	VI	Abducens	Eye movements (M)	Abducens nucleus	Lateral rectus muscle
Finn	VII	Facial	Motor – face, Taste (B)	Facial nucleus, solitary nucleus, superior salivatory nucleus	Facial muscles, Geniculate ganglion, Pterygopalatine ganglion (autonomic)
And	VIII	Auditory (Vestibulocochlear)	Hearing/balance (S)	Cochlear nucleus, Vestibular nucleus/cerebellum	Spiral ganglion (hearing), Vestibular ganglion (balance)
German	IX	Glossopharyngeal	Motor – throat Taste (B)	Solitary nucleus, inferior salivatory nucleus, nucleus ambiguus	Pharyngeal muscles, Geniculate ganglion, Otic ganglion (autonomic)
Viewed	X	Vagus	Motor/sensory – viscera (autonomic) (B)	Medulla	Terminal ganglia serving thoracic and upper abdominal organs (heart and small intestines)
Some	XI	Spinal Accessory	Motor – head and neck (M)	Spinal accessory nucleus	Neck muscles
Hops	XII	Hypoglossal	Motor – lower throat (M)	Hypoglossal nucleus	Muscles of the larynx and lower pharynx

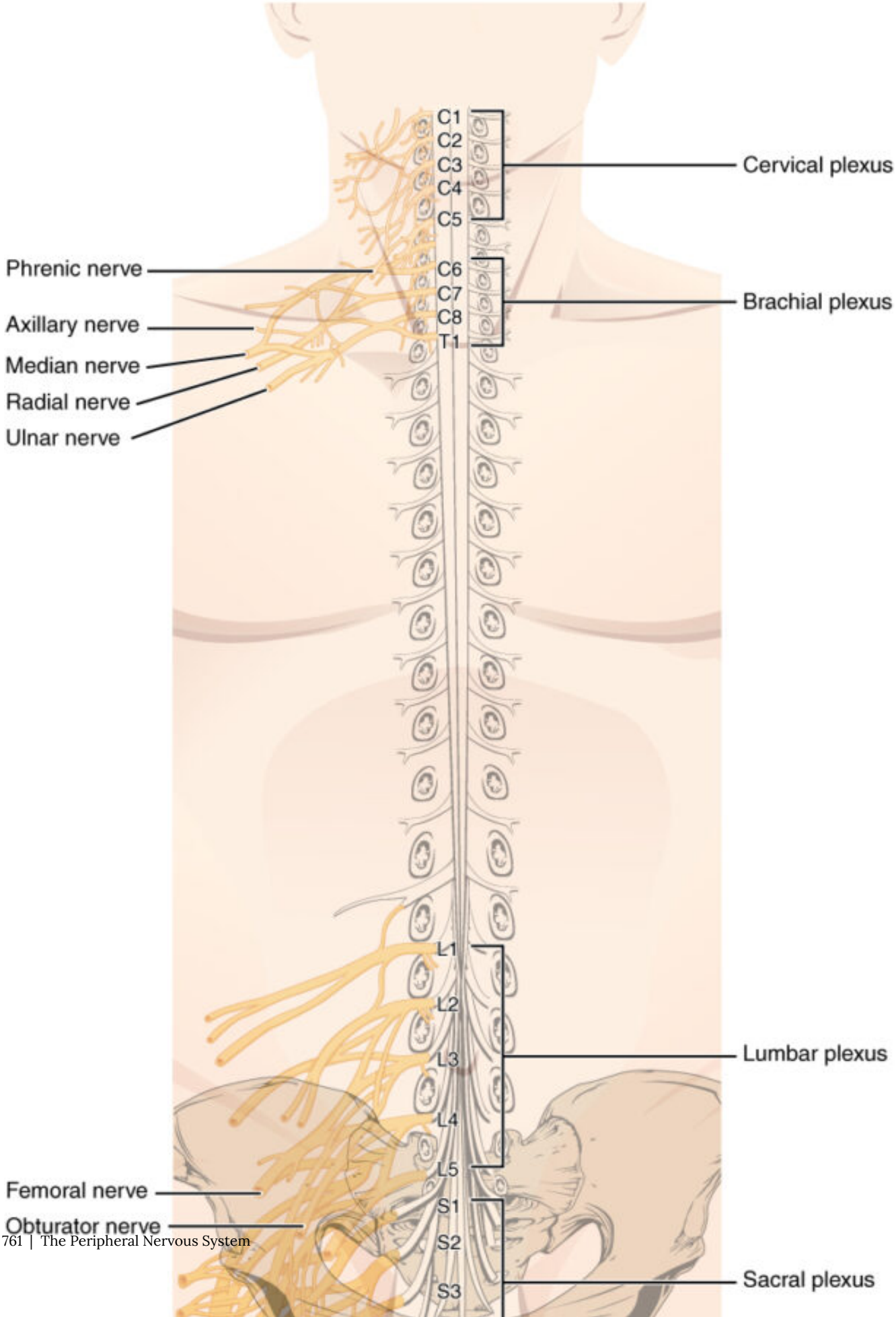
Summary of the twelve cranial nerves.

Spinal Nerves

The nerves connected to the spinal cord are the spinal nerves. The arrangement of these nerves is much more regular than that of the cranial nerves. All of the spinal nerves are combined sensory and motor axons that separate into two nerve roots. The sensory axons enter the spinal cord as the dorsal nerve root. The motor fibers, both somatic and autonomic, emerge as the ventral nerve root. The dorsal root ganglion for each nerve is an enlargement of the spinal nerve.

There are 31 spinal nerves, named for the level of the spinal cord at which each one emerges. There are eight pairs of cervical nerves designated C1 to C8, twelve thoracic nerves designated T1 to T12, five pairs of lumbar nerves designated L1 to L5, five pairs of sacral nerves designated S1 to S5, and one pair of coccygeal nerves. The nerves are numbered from the superior to inferior positions, and each emerges from the vertebral column through the intervertebral foramen, the space between two adjacent vertebrae, at its level. The first nerve, C1, emerges between the first cervical vertebra and the occipital bone at the base of the skull. The second nerve, C2, emerges between the first and second cervical vertebrae. The same occurs for C3 to C7, but C8 emerges between the seventh cervical vertebra and the first thoracic vertebra. For the thoracic and lumbar nerves, each one emerges below the vertebra that has the same designation. The sacral nerves emerge from foramina along the length of the sacrum, which are five sacral vertebrae fused into a single bone. Below the sacrum is the coccyx, a bone formed from the fusion of a variable number of coccygeal vertebrae, usually four.

Spinal nerves extend outward from the vertebral column to innervate the periphery. The nerves in the periphery are not straight continuations of the spinal nerves, but rather the reorganization of the axons in those nerves to follow different courses. Axons from different spinal nerves will come together into a systemic nerve. This occurs at four places along the length of the vertebral column, nerve fibers form branching networks called a nerve plexus. Of the four nerve plexuses, two are found at the cervical level, one at the lumbar level, and one at the sacral level (see figure below).


C1
C2
C3
C4
C5
Cervical plexus
Phrenic nerve
C6
C7
C8
T1
Brachial plexus
Axillary nerve
Median nerve
Radial nerve
Ulnar nerve
L1
L2
L3
Lumbar plexus
L4
L5
Femoral nerve
S1
Obturator nerve
S2
S3
Sacral plexus

Nerve Plexuses of the Body *– The four main nerve plexuses in the human body. The cervical plexus supplies nerves to the posterior head and neck, as well as to the diaphragm. The brachial plexus supplies nerves to the arm. The lumbar plexus supplies nerves to the anterior leg. The sacral plexus supplies nerves to the posterior leg.*

The cervical plexus is composed of axons from spinal nerves C1 through C5 and branches into nerves in the posterior neck and head, as well as the phrenic nerve, which connects to the diaphragm at the base of the thoracic cavity. The other plexus from the cervical level is the brachial plexus. Spinal nerves C4 through T1 reorganize through this plexus to give rise to the nerves of the arms, as the name brachial suggests. The lumbar plexus arises from all the lumbar spinal nerves and gives rise to nerves enervating the pelvic region and the anterior leg. The sacral plexus comes from the lower lumbar nerves L4 and L5 and the sacral nerves S1 to S4. The most significant systemic nerve to come from this plexus is the sciatic nerve, which is a combination of the tibial nerve and the fibular nerve. The sciatic nerve extends across the hip joint and is most commonly associated with the condition sciatica, which is the result of compression or irritation of the nerve or any of the spinal nerves giving rise to it.

These plexuses are described as arising from spinal nerves and giving rise to certain systemic nerves, but they contain fibers that serve sensory functions or fibers that serve motor functions. This means that some fibers extend from cutaneous or other peripheral sensory surfaces and send action potentials into the CNS. Those are axons of sensory neurons in the dorsal root ganglia that enter the spinal cord through the dorsal nerve root. Other fibers are the axons of motor neurons of the anterior horn of the spinal cord, which emerge in the ventral nerve root and send action potentials to cause skeletal muscles to contract in their target regions. For example, the radial nerve within the brachial plexus contains fibers of cutaneous sensation in the arm, as well as motor fibers that move muscles in the arm.

Spinal nerves of the thoracic region, T2 through T11, are not part of the plexuses but rather emerge and give rise to the intercostal nerves found between the ribs, which articulate with the vertebrae surrounding the spinal nerve.

Aging and the Nervous System

Anosmia is the loss of the sense of smell. It is often the result of the olfactory nerve being severed, usually because of blunt force trauma to the head. The sensory neurons of the olfactory epithelium have a limited lifespan of approximately one to four months, and new ones are made on a regular basis. The new neurons extend their axons into the CNS by growing along the existing fibers of the olfactory nerve. The ability of these neurons to be replaced is lost with age. Age-related anosmia is not the result of impact trauma to the head, but rather a slow loss of the sensory neurons with no new neurons born to replace them.

Smell is an important sense, especially for the enjoyment of food. There are only five tastes sensed by the tongue, and two of them are generally thought of as unpleasant tastes (sour and bitter). The rich sensory experience of food is the result of odor molecules associated with the food, both as food is moved into the mouth, and therefore passes under the nose, and when it is chewed and molecules are released to move up the pharynx into the posterior nasal cavity. Anosmia results in a loss of the enjoyment of food.

As the replacement of olfactory neurons declines with age, anosmia can set in. Without the sense of smell, many sufferers complain of food tasting bland. Often, the only way to enjoy food is to add seasoning that can be sensed on the tongue, which usually means adding table salt. The problem with this solution, however, is that

this increases sodium intake, which can lead to cardiovascular problems through water retention and the associated increase in blood pressure.

Adaptation

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McCorry LK. Physiology of the autonomic nervous system. Am J Pharm Educ. 2007 Aug 15;71(4):78. doi: 10.5688/aj710478.

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Somatic Nervous System

J. GORDON BETTS; JAMES A. WISE; KELLY A. YOUNG; EDDIE JOHNSON; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; PETER DESAIX; AND BRANDON POE

Learning Objectives

By the end of this section, you will be able to:

- Describe the components of the somatic nervous system.
- Describe the different types and classifications of sensory receptors.
- Name the modalities and submodalities of the sensory systems.
- Distinguish between general and special senses.
- Describe regions of the central nervous system that contribute to somatic functions.
- Explain the stimulus-response motor pathway.

The somatic nervous system is traditionally considered a division within the peripheral nervous system. However, this misses an important point: somatic refers to a functional division, whereas peripheral refers to an anatomic division. The somatic nervous system is responsible for our conscious sensation and perception of the environment and for our responses to that perception by means of voluntary movement of skeletal muscles. Additionally, the somatic nervous system also controls some involuntary muscle movements known as reflexes.

In this chapter, we will focus on the sensory aspects of the somatic nervous system, specifically the somatosensory system. For now, just keep in mind that the somatic nervous system includes *both* sensation and motor responses.

Sensation

The sensory systems throughout our body share a single purpose: to help us detect important stimuli in our external environment. Stimuli from varying sources, and of different types, are detected and converted into the electrochemical signals of the nervous system. This occurs when a stimulus changes the cell membrane potential of a sensory neuron. The stimulus causes the sensory cell to produce an action potential that is relayed into the central nervous system (CNS), where it is integrated with other sensory information—or sometimes higher cognitive functions—to become a conscious perception of that stimulus. The central integration may then lead to a motor response.

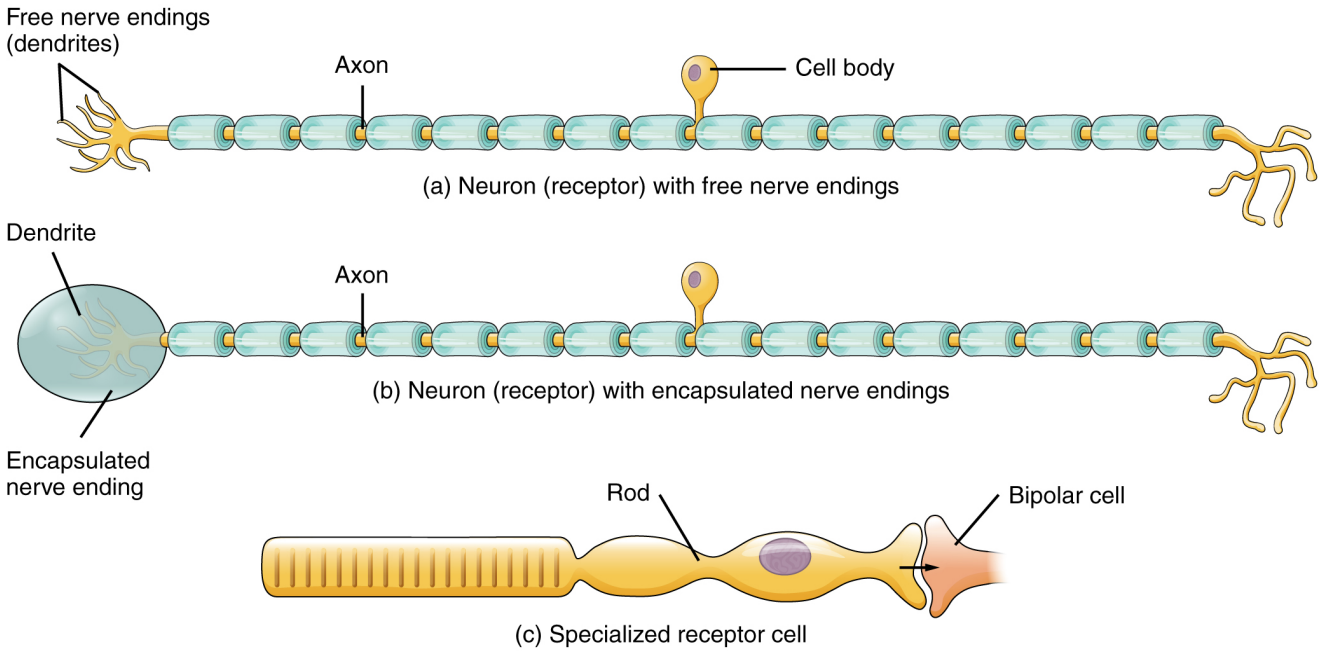
An important distinction to make here is between sensation and perception, which are often mistakenly used interchangeably in everyday language. Sensation is the activation of sensory receptor cells at the level of the stimulus, for example thermoreceptors in the skin detecting heat from your hand touching a hot stove. Perception is the central processing of sensory stimuli into a meaningful pattern, for example perceiving that contact with the stove as being hot and painful. Perception is dependent on sensation, but not all sensations are perceived.

Sensory Receptors

Stimuli in the environment activate specialized receptor cells in the peripheral nervous system, for example heat activating thermoreceptors in the skin as explained above. Different types of stimuli are sensed by different types of receptor cells. Receptor cells can be classified into types on the basis of three different criteria: cell type, position, and function. Receptors can be classified structurally on the basis of cell type and their position in relation to stimuli they sense. They can also be classified functionally on the basis of the transduction of stimuli, or how the mechanical stimulus, light, or chemical changes the cell membrane potential.

Structural Receptor Classifications

The cells that interpret information about the environment can be either (1) a neuron that has a free nerve ending, with dendrites embedded in tissue that would receive a sensation; (2) a neuron that has an encapsulated ending in which the sensory nerve endings are encapsulated in connective tissue that enhances their sensitivity; or (3) a specialized receptor cell, which has distinct structural components that interpret a specific type of stimulus (Receptor Classification by Cell Type). The pain and temperature receptors in the dermis of the skin are examples of neurons that have free nerve endings. Also located in the dermis of the skin are lamellated corpuscles, neurons with encapsulated nerve endings that respond to pressure and touch. The cells in the retina that respond to light stimuli are an example of a specialized receptor, a photoreceptor.



Receptor Classification by Cell Type – *Receptor cell types can be classified on the basis of their structure. Sensory neurons can have either (a) free nerve endings or (b) encapsulated endings. Photoreceptors in the eyes, such as rod cells, are examples of (c) specialized receptor cells. These cells release neurotransmitters onto a bipolar cell, which then synapses with the optic nerve neurons.*

Another way that receptors can be classified is based on their location relative to the stimuli. An exteroceptor is a receptor that is located near a stimulus in the external environment, such as the somatosensory receptors that are located in the skin. An interoceptor is one that interprets stimuli from internal organs and tissues, such as the receptors

that sense the increase in blood pressure in the aorta or carotid sinus. Finally, a proprioceptor is a receptor located near a moving part of the body, such as a muscle, that interprets the positions of the tissues as they move.

Functional Receptor Classifications

The third classification of receptors is by how the receptor transduces stimuli into membrane potential changes. Stimuli are of three general types. Some stimuli are ions and macromolecules that affect transmembrane receptor proteins when these chemicals diffuse across the cell membrane. Some stimuli are physical variations in the environment that affect receptor cell membrane potentials. Other stimuli include electromagnetic radiation from visible light. For humans, the only electromagnetic energy that is perceived by our eyes is visible light. Some other organisms have receptors that humans lack, such as the heat sensors of snakes, the ultraviolet light sensors of bees, or magnetic receptors in migratory birds.

Receptor cells can be further categorized on the basis of the type of stimuli they transduce. Chemical stimuli can be interpreted by a chemoreceptor that interprets chemical stimuli, such as an object's taste or smell. Osmoreceptors respond to solute concentrations of body fluids. Additionally, pain is primarily a chemical sense that interprets the presence of chemicals from tissue damage, or similar intense stimuli, through a nociceptor. Physical stimuli, such as pressure and vibration, as well as the sensation of sound and body position (balance), are interpreted through a mechanoreceptor. Another physical stimulus that has its own type of receptor is temperature, which is sensed through a thermoreceptor that is either sensitive to temperatures above (heat) or below (cold) normal body temperature.

Sensory Modalities

Ask anyone what the senses are, and they are likely to list the five major senses—taste, smell, touch, hearing, and sight. However, these are not all of the senses. The most obvious omission from this list is balance. Also, what is referred to simply as touch can be further subdivided into pressure, vibration, stretch, and hair-follicle position, on the basis of the type of mechanoreceptors that perceive these touch sensations. Other overlooked senses include temperature perception by thermoreceptors and pain perception by nociceptors.

Within the realm of physiology, senses can be classified as either general or specific. A general sense is one that is distributed throughout the body and has receptor cells within the structures of other organs. Mechanoreceptors in the skin, muscles, or the walls of blood vessels are examples of this type. General senses often contribute to the sense of touch, as described above, or to proprioception (body movement) and kinesthesia (body movement), or to a visceral sense, which is most important to autonomic functions. A special sense is one that has a specific organ devoted to it, namely the eye, inner ear, tongue, or nose.

Each of the senses is referred to as a sensory modality. Modality refers to the way that information is encoded, which is similar to the idea of transduction. The main sensory modalities can be described on the basis of how each is transduced. The chemical senses are taste and smell. The general sense that is usually referred to as touch includes chemical sensation in the form of nociception, or pain. Pressure, vibration, muscle stretch, and the movement of hair by an external stimulus, are all sensed by mechanoreceptors. Hearing and balance are also sensed by mechanoreceptors. Finally, vision involves the activation of photoreceptors.

Listing all the different sensory modalities, which can number as many as 17, involves separating the five major senses into more specific categories, or submodalities, of the larger sense. An individual sensory modality represents the

sensation of a specific type of stimulus. For example, the general sense of touch, which is known as somatosensation, can be separated into light pressure, deep pressure, vibration, itch, pain, temperature, or hair movement.

Somatic Nervous System and the CNS

Specific regions of the CNS coordinate different somatic processes using sensory inputs and motor outputs of peripheral nerves. A simple case is the withdrawal reflex caused by a synapse between a dorsal sensory neuron axon and a motor neuron in the ventral horn like we discussed before. More complex arrangements are possible to integrate peripheral sensory information with higher processes. The important regions of the CNS that play a role in somatic processes can be separated into the spinal cord brain stem, diencephalon, cerebral cortex, and subcortical structures.

Spinal Cord and Brain Stem

A sensory pathway that carries peripheral sensations to the brain is referred to as an ascending pathway, or ascending tract. The various sensory modalities each follow specific pathways through the CNS. Tactile and other somatosensory stimuli activate receptors in the skin, muscles, tendons, and joints throughout the entire body. However, the somatosensory pathways are divided into two separate systems on the basis of the location of the receptor neurons. Somatosensory stimuli from below the neck pass along the sensory pathways of the spinal cord, whereas somatosensory stimuli from the head and neck travel through the cranial nerves—specifically, the trigeminal system.

The dorsal column system (sometimes referred to as the dorsal column–medial lemniscus) and the spinothalamic tract are two major pathways that bring sensory information to the brain. The sensory pathways in each of these systems are composed of three successive neurons.

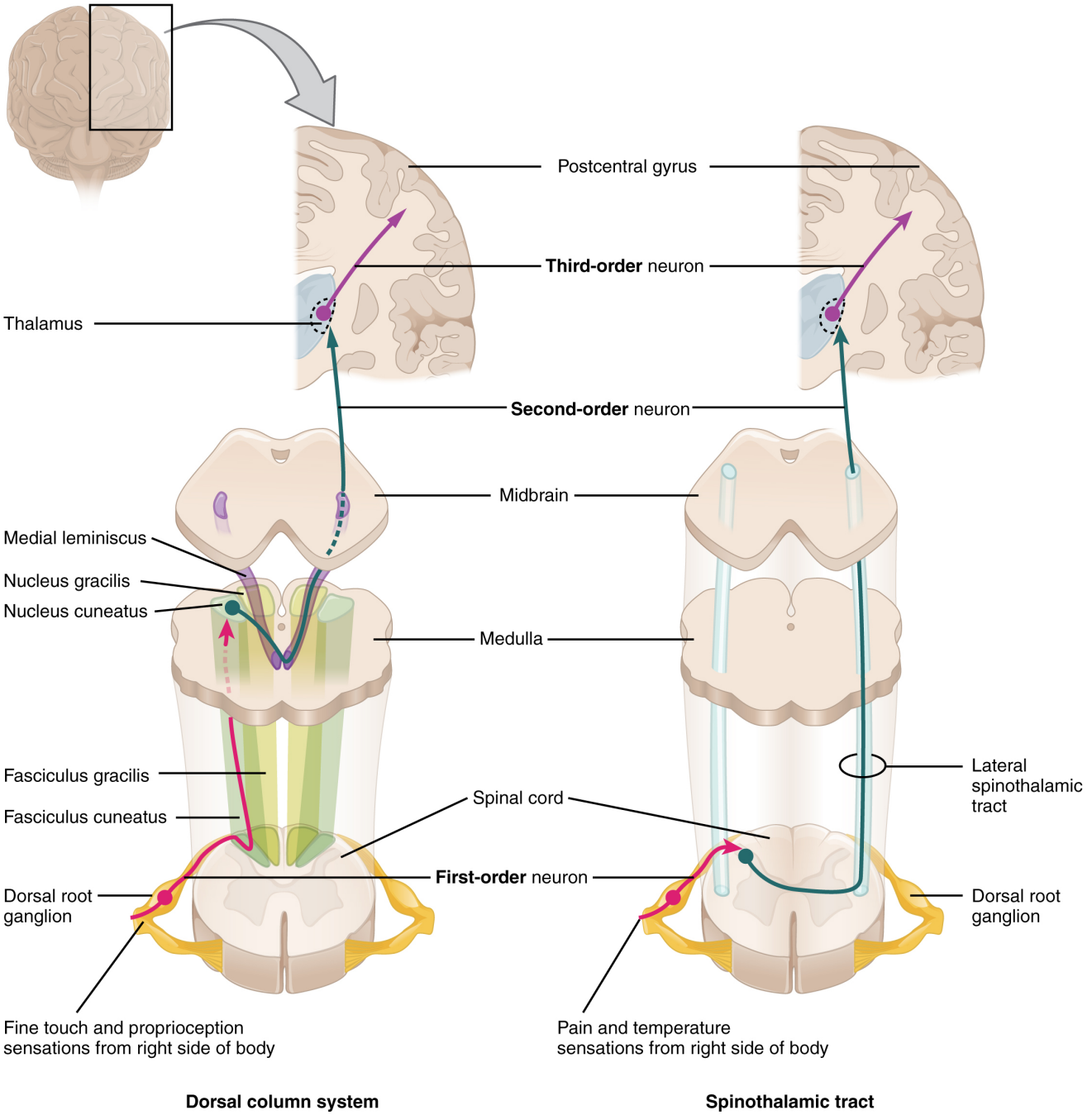
The dorsal column system begins with the axon of a dorsal root ganglion neuron entering the dorsal root and joining the dorsal column white matter in the spinal cord. As axons of this pathway enter the dorsal column, they take on a positional arrangement so that axons from lower levels of the body position themselves medially, whereas axons from upper levels of the body position themselves laterally. The dorsal column is separated into two component tracts, the fasciculus gracilis that contains axons from the legs and lower body, and the fasciculus cuneatus that contains axons from the upper body and arms.

The axons in the dorsal column terminate in the nuclei of the medulla, where each synapses with the second neuron in their respective pathway. The nucleus gracilis is the target of fibers in the fasciculus gracilis, whereas the nucleus cuneatus is the target of fibers in the fasciculus cuneatus. The second neuron in the system projects from one of the two nuclei and then decussates, or crosses the midline of the medulla. These axons then continue to ascend the brain stem on the contralateral (opposite) side as a bundle called the medial lemniscus. These axons terminate in the thalamus, where each synapses with the third neuron in their respective pathway. The third neuron in the system projects its axons to the postcentral gyrus of the cerebral cortex, where somatosensory stimuli are initially processed and the conscious perception of the stimulus occurs.

The other major pathway, the spinothalamic tract, also begins with neurons in a dorsal root ganglion. These neurons extend their axons to the dorsal horn, where they synapse with the second neuron in their respective pathway. The name “spinothalamic” comes from this second neuron, which has its cell body in the spinal cord gray matter and connects to the thalamus. Axons from these second neurons then decussate within the spinal cord and ascend to the brain and enter the thalamus, where each synapses with the third neuron in its respective pathway. The neurons in the thalamus then project their axons to the spinothalamic tract, which synapses in the postcentral gyrus of the cerebral cortex.

These two systems are similar in that they both begin with dorsal root ganglion cells, as with most general sensory

information. The dorsal column system is primarily responsible for touch sensations and proprioception, whereas the spinothalamic tract pathway is primarily responsible for pain and temperature sensations. Another similarity is that the second neurons in both of these pathways are contralateral because they project across the midline to the other side of the brain or spinal cord. In the dorsal column system, this decussation takes place in the brain stem; in the spinothalamic pathway, it takes place in the spinal cord at the same spinal cord level at which the information entered. The third neurons in the two pathways are essentially the same. In both, the second neuron synapses in the thalamus, and the thalamic neuron projects to the somatosensory cortex.



Ascending Sensory Pathways of the Spinal Cord – *The dorsal column system and spinothalamic tract are the major ascending pathways that connect the periphery with the brain.*

The trigeminal pathway carries somatosensory information from the face, head, mouth, and nasal cavity. As with the previously discussed nerve tracts, the sensory pathways of the trigeminal pathway each involve three successive neurons. First, axons from the trigeminal ganglion enter the brain stem at the level of the pons. These axons project to one of three locations. The spinal trigeminal nucleus of the medulla receives information similar to that carried by spinothalamic tract, such as pain and temperature sensations. Other axons go to either the chief sensory nucleus in the pons or the mesencephalic nuclei in the midbrain. These nuclei receive information like that carried by the dorsal column system, such as touch, pressure, vibration, and proprioception. Axons from the second neuron decussate and ascend to the thalamus along the trigeminothalamic tract. In the thalamus, each axon synapses with the third neuron in its respective pathway. Axons from the third neuron then project from the thalamus to the primary somatosensory cortex of the cerebrum.

Diencephalon

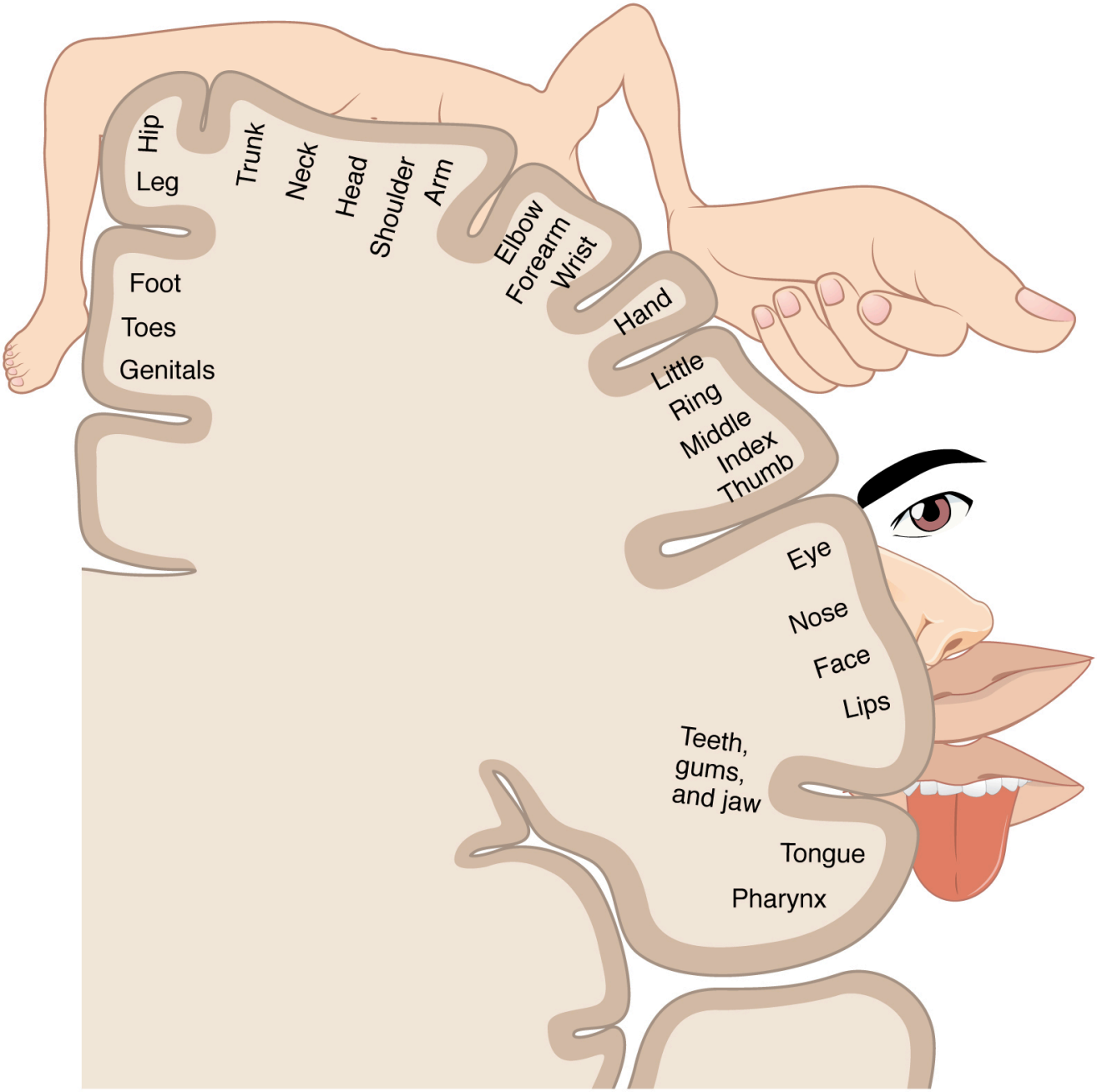
The diencephalon is beneath the cerebrum and includes the thalamus and hypothalamus. In the somatic nervous system, the thalamus is an important relay for communication between the cerebrum and the rest of the nervous system. The hypothalamus has both somatic and autonomic functions. In addition, the hypothalamus communicates with the limbic system, which controls emotions and memory functions.

Sensory input to the thalamus comes from most of the special senses and ascending somatosensory tracts. Each sensory system is relayed through a particular nucleus in the thalamus. The thalamus is a required transfer point for most sensory tracts that reach the cerebral cortex, where conscious sensory perception begins. The one exception to this rule is the olfactory system. The olfactory tract axons from the olfactory bulb project directly to the cerebral cortex, along with the limbic system and hypothalamus.

Cortical Processing

As described earlier, many of the sensory axons are positioned in the same way as their corresponding receptor cells in the body. This allows identification of the position of a stimulus on the basis of which receptor cells are sending information. The cerebral cortex also maintains this sensory topography in the particular areas of the cortex that correspond to the position of the receptor cells. The somatosensory cortex provides an example in which, in essence, the locations of the somatosensory receptors in the body are mapped onto the somatosensory cortex. This mapping is often depicted using a sensory homunculus (The Sensory Homunculus).

The term homunculus comes from the Latin word for “little man” and refers to a map of the human body that is laid across a portion of the cerebral cortex. In the somatosensory cortex, the external genitals, feet, and lower legs are represented on the medial face of the gyrus within the longitudinal fissure. As the gyrus curves out of the fissure and along the surface of the parietal lobe, the body map continues through the thighs, hips, trunk, shoulders, arms, and hands. The head and face are just lateral to the fingers as the gyrus approaches the lateral sulcus. The representation of the body in this topographical map is medial to lateral from the lower to the upper body. Note that this correspondence does not result in a perfectly miniature scale version of the body, but rather exaggerates the more sensitive areas of the body, such as the fingers and lower face. Less sensitive areas of the body, such as the shoulders and back, are mapped to smaller areas on the cortex.



The Sensory Homunculus – *A cartoon representation of the sensory homunculus arranged adjacent to the cortical region in which the processing takes place.*

Adaption

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Motor Responses

J. GORDON BETTS; JAMES A. WISE; KELLY A. YOUNG; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

- List the components of the basic processing stream for the motor system.
- Describe the pathway of descending motor commands from the cortex to the skeletal muscles.
- Compare different descending pathways, both by structure and function.
- Explain the initiation of movement from the neurological connections.
- Describe several reflex arcs and their functional roles.

The defining characteristic of the somatic nervous system is that it controls skeletal muscles. Somatic senses inform the nervous system about the external environment, but the response to that is through voluntary muscle movement. The term "voluntary" suggests that there is a conscious decision to make a movement. However, some aspects of the somatic system use voluntary muscles without conscious control. One example is the ability of our breathing to switch to unconscious control while we are focused on another task. However, the muscles that are responsible for the basic process of breathing are also utilized for speech, which is entirely voluntary.

Cortical Responses

You can think of the pathway of motor responses as being opposite to that of sensation. As we learned, the sensory pathway starts with a receptor that detects a stimuli in our environment and sends an action potential to the spinal cord, which is then communicated to the CNS by ascending pathways in the brainstem and spinal cord. Conversely, the motor pathway starts in the CNS with specialized cortical areas that initiate movement. Then, descending pathways communicate this information down the spinal cord to motor neurons, which control voluntary movements of our skeletal muscles.

Let's start with sensory stimuli that have been registered through receptor cells and the information relayed to the CNS along ascending pathways. In the cerebral cortex, the initial processing of sensory perception progresses to associative processing and then integration in multimodal areas of cortex. These levels of processing can lead to the incorporation of sensory perceptions into memory, but more importantly, they lead to a response. The completion of cortical processing through the primary, associative, and integrative sensory areas initiates a similar progression of motor processing, usually in different cortical areas.

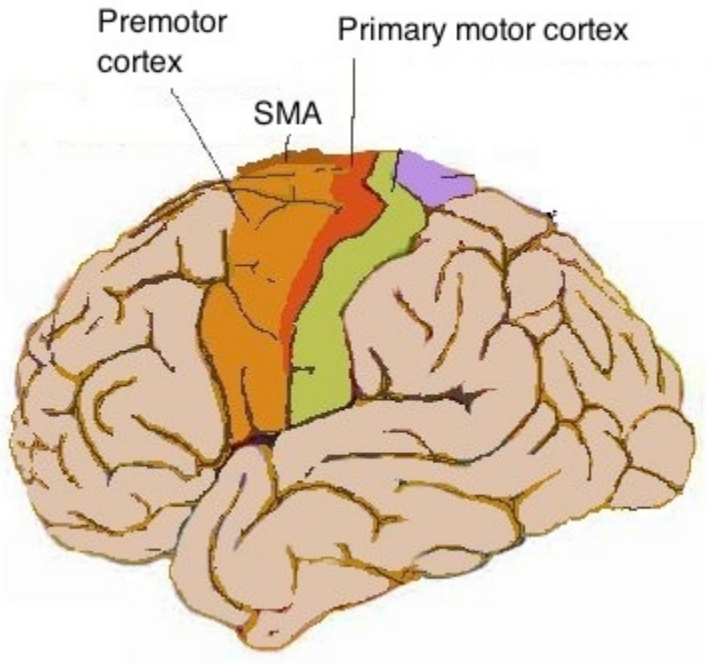
Whereas the sensory cortical areas are located in the occipital, temporal, and parietal lobes, motor functions are largely controlled by the frontal lobe (See Lobes of the Cerebral Cortex). The most anterior regions of the frontal lobe—the

prefrontal areas—are important for executive functions, which are those cognitive functions that lead to goal-directed behaviors.

Secondary Motor Cortices

In generating motor responses, the executive functions of the prefrontal cortex will need to initiate actual movements. One way to define the prefrontal area is any region of the frontal lobe that does not elicit movement when electrically stimulated. These are primarily in the anterior part of the frontal lobe. The regions of the frontal lobe that remain are the regions of the cortex that produce movement. The prefrontal areas project into the secondary motor cortices, which include the premotor cortex and the supplemental motor area.

These regions assist in planning and coordinating movements and are located adjacent to the primary motor cortex. The premotor cortex is more lateral, whereas the supplemental motor area is more medial and superior (The Motor Cortex). The premotor area aids in controlling movements of the core muscles to maintain posture during movement, whereas the supplemental motor area is hypothesized to be responsible for planning and coordinating movement. The supplemental motor area also manages sequential movements that are based on prior experience (that is, learned movements). Neurons in these areas are most active leading up to the initiation of movement. For example, these areas might prepare the body for the movements necessary to drive a car in anticipation of a traffic light changing.



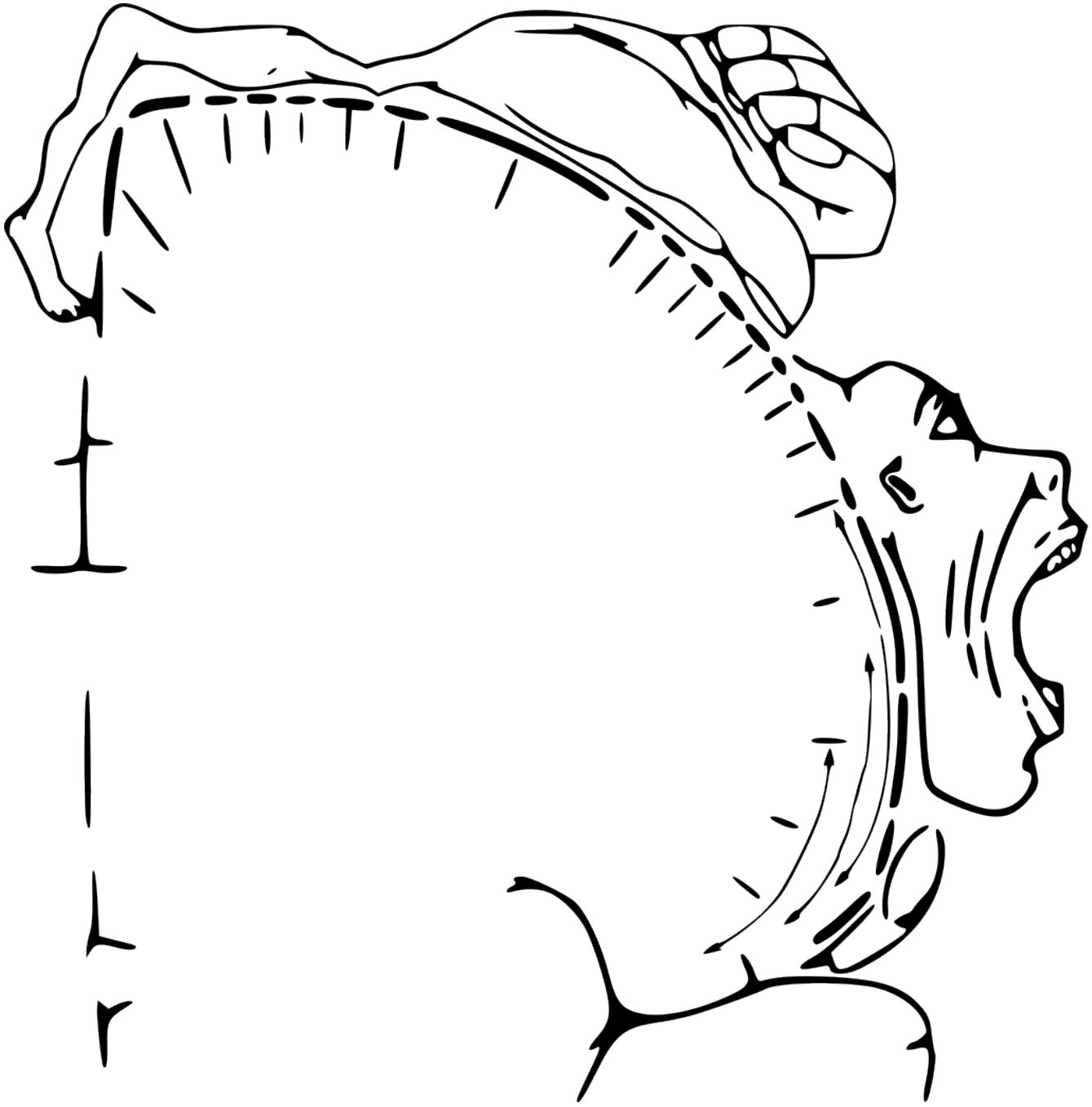
The Motor Cortex – *Components of the motor cortex, including the premotor cortex, supplementary motor area (SMA), and primary motor cortex. Sensory areas are also shown in green and purple.*

Adjacent to these two regions are two specialized motor planning centers. The frontal eye fields are responsible for moving the eyes in response to visual stimuli. Also, anterior to the premotor cortex and primary motor cortex is Broca's area. This area is responsible for controlling movements of the structures of speech production. The area is named after a French surgeon and anatomist who studied patients who could not produce speech. They did not have impairments to understanding speech, only to producing speech sounds, suggesting a damaged or underdeveloped Broca's area.

Primary Motor Cortex

The primary motor cortex is located in the precentral gyrus of the frontal lobe. A neurosurgeon, Walter Penfield, described much of the basic understanding of the primary motor cortex by electrically stimulating the surface of the cerebrum. Penfield would probe the surface of the cortex while the patient was only under local anesthesia so that he could observe responses to the stimulation. This led to the belief that the precentral gyrus directly stimulated muscle movement. We now know that the primary motor cortex receives input from several areas that aid in planning movement, and its principle output stimulates spinal cord neurons to stimulate skeletal muscle contraction.

The primary motor cortex is arranged in a similar fashion to the primary somatosensory cortex, in that it has a topographical map of the body, creating a motor homunculus. The neurons responsible for musculature in the feet and lower legs are in the medial wall of the precentral gyrus, with the thighs, trunk, and shoulder at the crest of the longitudinal fissure. The hand and face are in the lateral face of the gyrus. Also, the relative space allotted for the different regions is exaggerated in muscles that have greater innervation. The greatest amount of cortical space is given to muscles that perform fine, agile movements, such as the muscles of the fingers and the lower face. The "power muscles" that perform coarser movements, such as the buttock and back muscles, occupy much less space on the motor cortex.



The Motor Homonculus *– Just like the sensory homonculus, there is a topographical "map" on the motor cortex where certain cortical areas are responsible for initiating muscle movement in a certain region of the body. Muscles responsible for finely detailed movements, such as the fingers and face, are overrepresented compared to their muscle size. Image by Was a bee, used under creative commons license.*

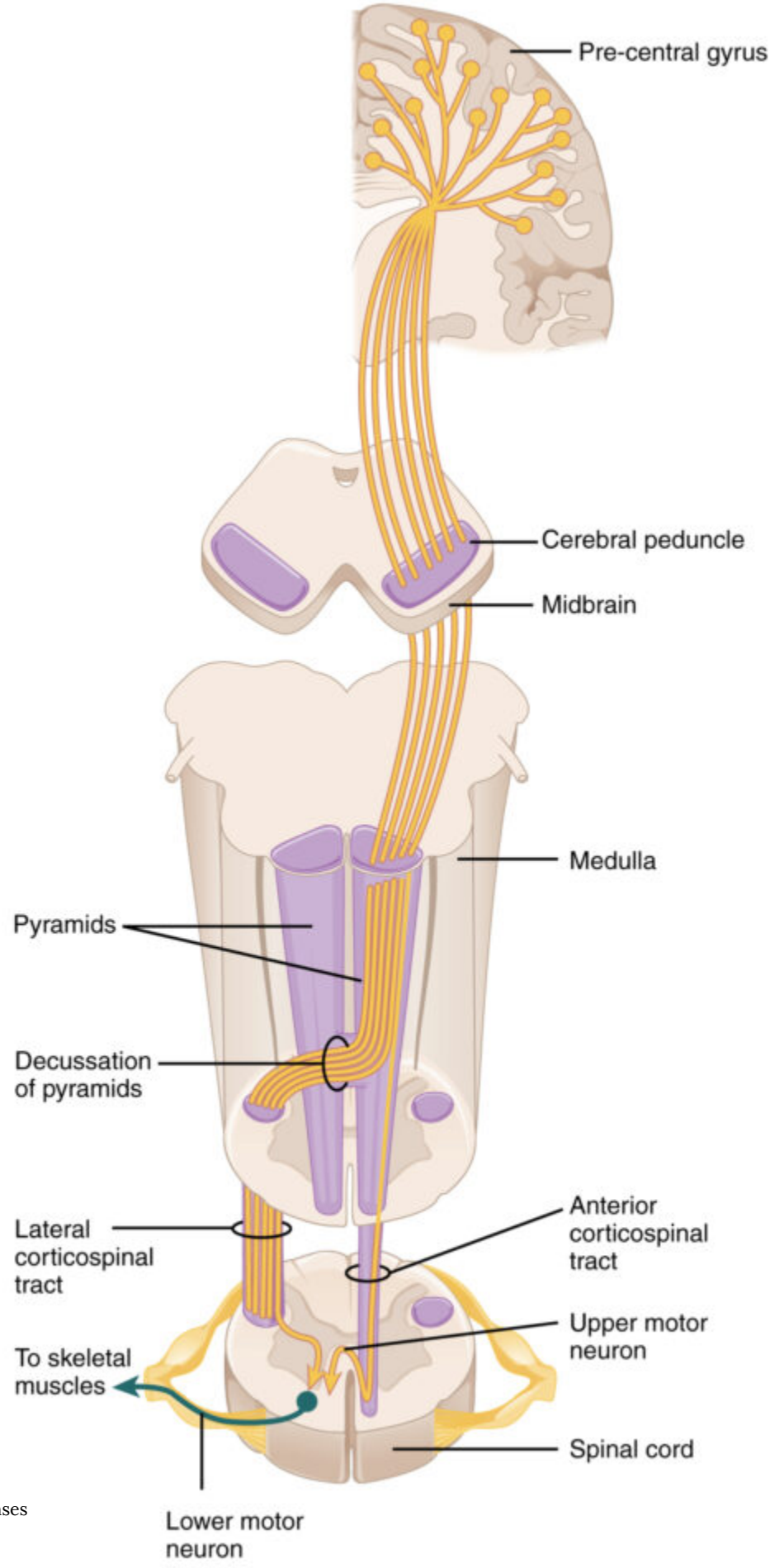
Descending Pathways

The motor output from the cortex descends into the brain stem and to the spinal cord to control the musculature through motor neurons. Neurons located in the primary motor cortex, named Betz cells, are large cortical neurons that synapse with lower motor neurons in the brain stem or in the spinal cord. The two descending pathways travelled by the

axons of Betz cells are the corticobulbar tract and the corticospinal tract, respectively. Both tracts are named for their origin in the cortex and their targets—either the brain stem (the term "bulbar" refers to the brain stem as the bulb, or enlargement, at the top of the spinal cord) or the spinal cord.

These two descending pathways are responsible for the conscious or voluntary movements of skeletal muscles. Any motor command from the primary motor cortex is sent down the axons of the Betz cells to activate lower motor neurons in either the cranial motor nuclei or in the ventral horn of the spinal cord. The axons of the corticobulbar tract are ipsilateral, meaning they project from the cortex to the motor nucleus on the same side of the nervous system. Conversely, the axons of the corticospinal tract are largely contralateral, meaning that they cross the midline of the brain stem or spinal cord and synapse on the opposite side of the body. Therefore, the right motor cortex of the cerebrum controls muscles on the left side of the body, and vice versa.

The corticospinal tract descends from the cortex through the deep white matter of the cerebrum. It then passes between the caudate nucleus and putamen of the basal nuclei as a bundle called the internal capsule. The tract then passes through the midbrain as the cerebral peduncles, after which it burrows through the pons. Upon entering the medulla, the tracts make up the large white matter tract referred to as the pyramids. The defining landmark of the medullary-spinal border is the pyramidal decussation, which is where most of the fibers in the corticospinal tract cross over to the opposite side of the brain. At this point, the tract separates into two parts, which have control over different domains of the musculature.


Pre-central gyrus
Cerebral peduncle
Midbrain
Medulla
Pyramids
Decussation of pyramids
Lateral corticospinal tract
Anterior corticospinal tract
Upper motor neuron
To skeletal muscles
Spinal cord
Lower motor neuron
Key

Corticospinal Tract *– The major descending tract that controls skeletal muscle movements is the corticospinal tract. It is composed of two neurons, the upper motor neuron and the lower motor neuron. The upper motor neuron has its cell body in the primary motor cortex of the frontal lobe and synapses on the lower motor neuron, which is in the ventral horn of the spinal cord and projects to the skeletal muscle in the periphery.*

Appendicular Control

The lateral corticospinal tract is composed of the fibers that cross the midline at the pyramidal decussation (see the figure above). The axons cross over from the anterior position of the pyramids in the medulla to the lateral column of the spinal cord. These axons are responsible for controlling appendicular muscles.

This influence over the appendicular muscles means that the lateral corticospinal tract is responsible for moving the muscles of the arms and legs. The ventral horn in both the lower cervical spinal cord and the lumbar spinal cord both have wider ventral horns, representing the greater number of muscles controlled by these motor neurons. The cervical enlargement is particularly large because there is greater control over the fine musculature of the upper limbs, particularly of the fingers. The lumbar enlargement is not as significant in appearance because there is less fine motor control of the lower limbs.

Axial Control

The anterior corticospinal tract is responsible for controlling the muscles of the body trunk (see the figure above). These axons do not decussate in the medulla. Instead, they remain in an anterior position as they descend the brain stem and enter the spinal cord. These axons then travel to the spinal cord level at which they synapse with a lower motor neuron. Upon reaching the appropriate level, the axons decussate, entering the ventral horn on the opposite side of the spinal cord from which they entered. In the ventral horn, these axons synapse with their corresponding lower motor neurons. The lower motor neurons are located in the medial regions of the ventral horn, because they control the axial muscles of the trunk.

Because movements of the body trunk involve both sides of the body, the anterior corticospinal tract is not entirely contralateral. Some collateral branches of the tract will project into the ipsilateral ventral horn to control synergistic muscles on that side of the body, or to inhibit antagonistic muscles through interneurons within the ventral horn. Through the influence of both sides of the body, the anterior corticospinal tract can coordinate postural muscles in broad movements of the body. These coordinating axons in the anterior corticospinal tract are often considered bilateral, as they are both ipsilateral and contralateral.

Watch this video to learn more about the descending motor pathway for the somatic nervous system. The autonomic connections are mentioned, which are covered in another chapter. From this brief video, only some of the descending motor pathway of the somatic nervous system is described. Which division of the pathway is described and which division is left out?

Extrapyramidal Controls

Other descending connections between the brain and the spinal cord are called the extrapyramidal system. The name comes from the fact that this system is outside the corticospinal pathway, which includes the pyramids in the medulla. A few pathways originating from the brain stem contribute to this system.

The tectospinal tract projects from the midbrain to the spinal cord and is important for postural movements that are driven by the superior colliculus. The name of the tract comes from an alternate name for the superior colliculus, which is the tectum. The reticulospinal tract connects the reticular system, a diffuse region of gray matter in the brain stem, with the spinal cord. This tract influences trunk and proximal limb muscles related to posture and locomotion. The reticulospinal tract also contributes to muscle tone and influences autonomic functions. The vestibulospinal tract connects the brain stem nuclei of the vestibular system with the spinal cord. This allows posture, movement, and balance to be modulated on the basis of equilibrium information provided by the vestibular system.

The pathways of the extrapyramidal system are influenced by subcortical structures. For example, connections between the secondary motor cortices and the extrapyramidal system modulate spine and cranium movements. The basal nuclei, which are important for regulating movement initiated by the CNS, influence the extrapyramidal system as well as its thalamic feedback to the motor cortex.

The conscious movement of our muscles is more complicated than simply sending a single command from the precentral gyrus down to the proper motor neurons. During the movement of any body part, our muscles relay information back to the brain, and the brain is constantly sending "revised" instructions back to the muscles. The cerebellum is important in contributing to the motor system because it compares cerebral motor commands with proprioceptive feedback. The corticospinal fibers that project to the ventral horn of the spinal cord have branches that also synapse in the pons, which project to the cerebellum. Also, the proprioceptive sensations of the dorsal column system have a collateral projection to the medulla that projects to the cerebellum. These two streams of information are compared in the cerebellar cortex. Conflicts between the motor commands sent by the cerebrum and body position information provided by the proprioceptors cause the cerebellum to stimulate the red nucleus of the midbrain. The red nucleus then sends corrective commands to the spinal cord along the rubrospinal tract. The name of this tract comes from the word for red that is seen in the English word "ruby."

A good example of how the cerebellum corrects cerebral motor commands can be illustrated by walking in water. An original motor command from the cerebrum to walk will result in a highly coordinated set of learned movements. However, in water, the body cannot actually perform a typical walking movement as instructed. The cerebellum can alter the motor command, stimulating the leg muscles to take larger steps to overcome the water resistance. The cerebellum can make the necessary changes through the rubrospinal tract. Modulating the basic command to walk also relies on spinal reflexes, but the cerebellum is responsible for calculating the appropriate response. When the cerebellum does not work properly, coordination and balance are severely affected. The most dramatic example of this is during the overconsumption of alcohol. Alcohol inhibits the ability of the cerebellum to interpret proprioceptive feedback, making it more difficult to coordinate body movements, such as walking a straight line, or guide the movement of the hand to touch the tip of the nose.

Visit this site to read about an elderly woman who starts to lose the ability to control fine movements, such as speech and the movement of limbs. Many of the usual causes were ruled out. It was not a stroke, Parkinson's disease, diabetes, or thyroid dysfunction. The next most obvious cause was medication, so her pharmacist had to be consulted. The side effect of a drug meant to help her sleep had resulted in changes in

motor control. What regions of the nervous system are likely to be the focus of haloperidol side effects?

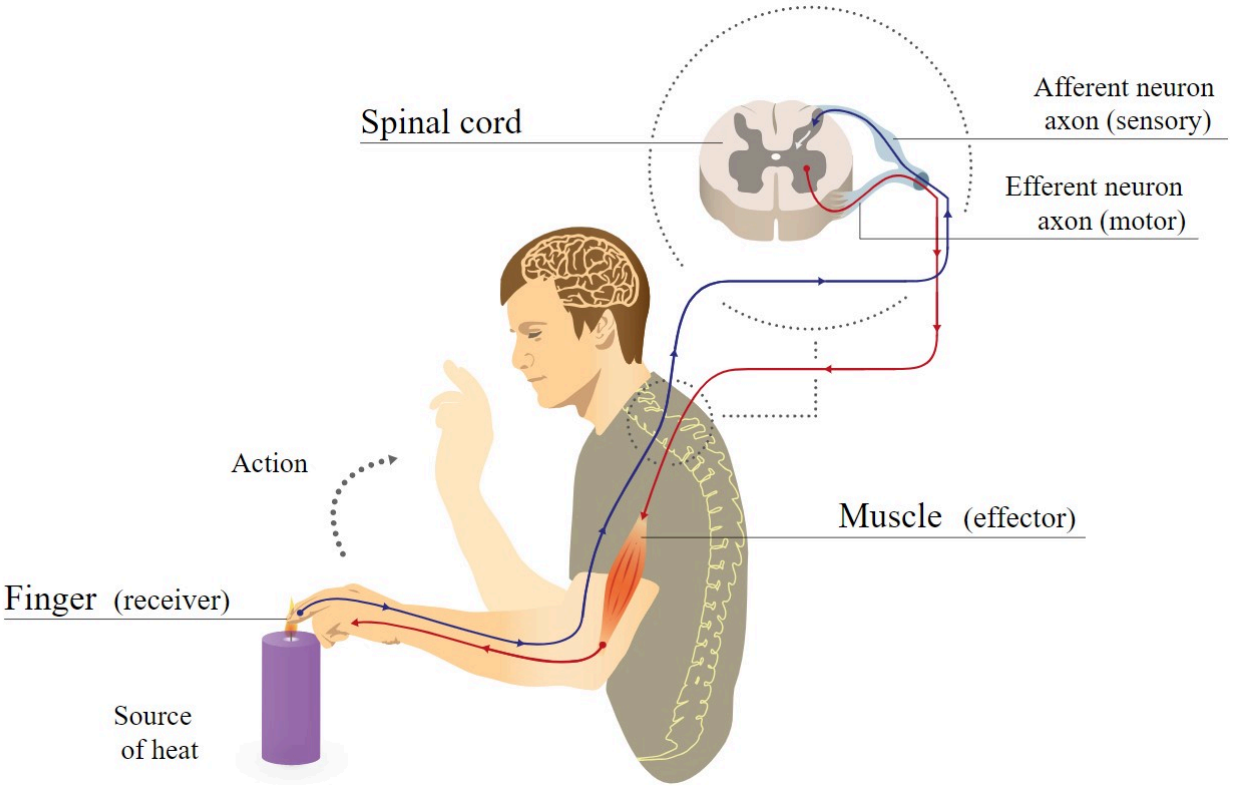
Ventral Horn Output

The somatic nervous system provides output strictly to skeletal muscles. The lower motor neurons, which are responsible for the contraction of these muscles, are found in the ventral horn of the spinal cord. These large, multipolar neurons have a corona of dendrites surrounding the cell body and an axon that extends out of the ventral horn. This axon travels through the ventral nerve root to join the emerging spinal nerve. The axon is relatively long because it needs to reach muscles in the periphery of the body. The diameters of cell bodies may be on the order of hundreds of micrometers to support the long axon; some axons are a meter in length, such as the lumbar motor neurons that innervate muscles in the first digits of the feet.

The axons will also branch to innervate multiple muscle fibers. Together, the motor neuron and all the muscle fibers that it controls make up a motor unit. Motor units vary in size. Some may contain up to 1000 muscle fibers, such as in the quadriceps, or they may only have 10 fibers, such as in an extraocular muscle. The number of muscle fibers that are part of a motor unit corresponds to the precision of control of that muscle. Also, muscles that have finer motor control have more motor units connecting to them, and this requires a larger topographical field in the primary motor cortex. The motor neuron axons connect to muscle fibers at the neuromuscular junction, which we learn about shortly.

Reflexes

The components of the somatic nervous system can most easily be demonstrated through a simple reflex action, outlined in this figure below. When you touch a hot stove, you pull your hand away. Sensory receptors in the skin sense extreme temperature and the early signs of tissue damage. This triggers an action potential, which travels along the afferent sensory fiber from the skin, through the dorsal spinal root to the spinal cord, and directly activates a ventral horn motor neuron. That neuron sends a signal along its axon to excite the biceps brachii, causing contraction of the muscle and flexion of the forearm at the elbow to withdraw the hand from the hot stove. The withdrawal reflex has more components, such as inhibiting the opposing muscle and balancing posture while the arm is forcefully withdrawn, which will be further explored at the end of this chapter. This basic withdrawal reflex includes sensory input (the painful stimulus), central processing (the synapse in the spinal cord), and motor output (activation of a ventral motor neuron that causes contraction of the biceps brachii).



Withdrawal Reflex – *Outline of the basic withdrawal reflex initiated by someone touching a hot object. Used under creative commons license, original author Nefronus.*

As you withdraw your hand from the stove, you do not want to slow that reflex down. As the biceps brachii contracts, the antagonistic triceps brachii needs to relax. Because the neuromuscular junction is strictly excitatory, the biceps will contract when the motor nerve is active. Skeletal muscles do not actively relax. Instead the motor neuron needs to "quiet down," or be inhibited. In the hot-stove withdrawal reflex, this occurs through an interneuron in the spinal cord. The interneuron's cell body is located in the dorsal horn of the spinal cord. The interneuron receives a synapse from the axon of the sensory neuron that detects that the hand is being burned. In response to this stimulation from the sensory neuron, the interneuron then inhibits the motor neuron that controls the triceps brachii. This is done by releasing a neurotransmitter or other signal that hyperpolarizes the motor neuron connected to the triceps brachii, making it less likely to initiate an action potential. With this motor neuron being inhibited, the triceps brachii relaxes. Without the antagonistic contraction, withdrawal from the hot stove is faster and keeps further tissue damage from occurring.

Simple somatic reflexes such as the withdrawal reflex do not include the higher centers discussed for conscious or voluntary aspects of movement. Reflexes can be spinal or cranial, depending on the nerves and central components that are involved.

A specialized reflex to protect the surface of the eye is the corneal reflex, or the eye blink reflex. When the cornea is stimulated by a tactile stimulus, or even by bright light in a related reflex, blinking is initiated. The sensory component travels through the trigeminal nerve, which carries somatosensory information from the face, or through the optic nerve, if the stimulus is bright light. The motor response travels through the facial nerve and innervates the orbicularis oculi on the same side. This reflex is commonly tested during a physical exam using an air puff or a gentle touch of a cotton-tipped applicator.

Watch this video to learn more about the reflex arc of the corneal reflex. When the right cornea senses a tactile stimulus, what happens to the left eye? Explain your answer.

Watch this video to learn more about newborn reflexes. Newborns have a set of reflexes that are expected to have been crucial to survival before the modern age. These reflexes disappear as the baby grows, as some of them may be unnecessary as they age. The video demonstrates a reflex called the Babinski reflex, in which the foot flexes dorsally and the toes splay out when the sole of the foot is lightly scratched. This is normal for newborns, but it is a sign of reduced myelination of the spinal tract in adults. Why would this reflex be a problem for an adult?

Adaption

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The Neuromuscular Junction and Nervous Control of Skeletal Muscle

J. GORDON BETTS; JAMES A. WISE; KELLY A. YOUNG; EDDIE JOHNSON; BRANDON POE; DEAN H. KRUSE; OKSANA KOROL; JODY E. JOHNSON; MARK WOMBLE; AND PETER DESAIX

Learning Objectives

By the end of this section, you will be able to:

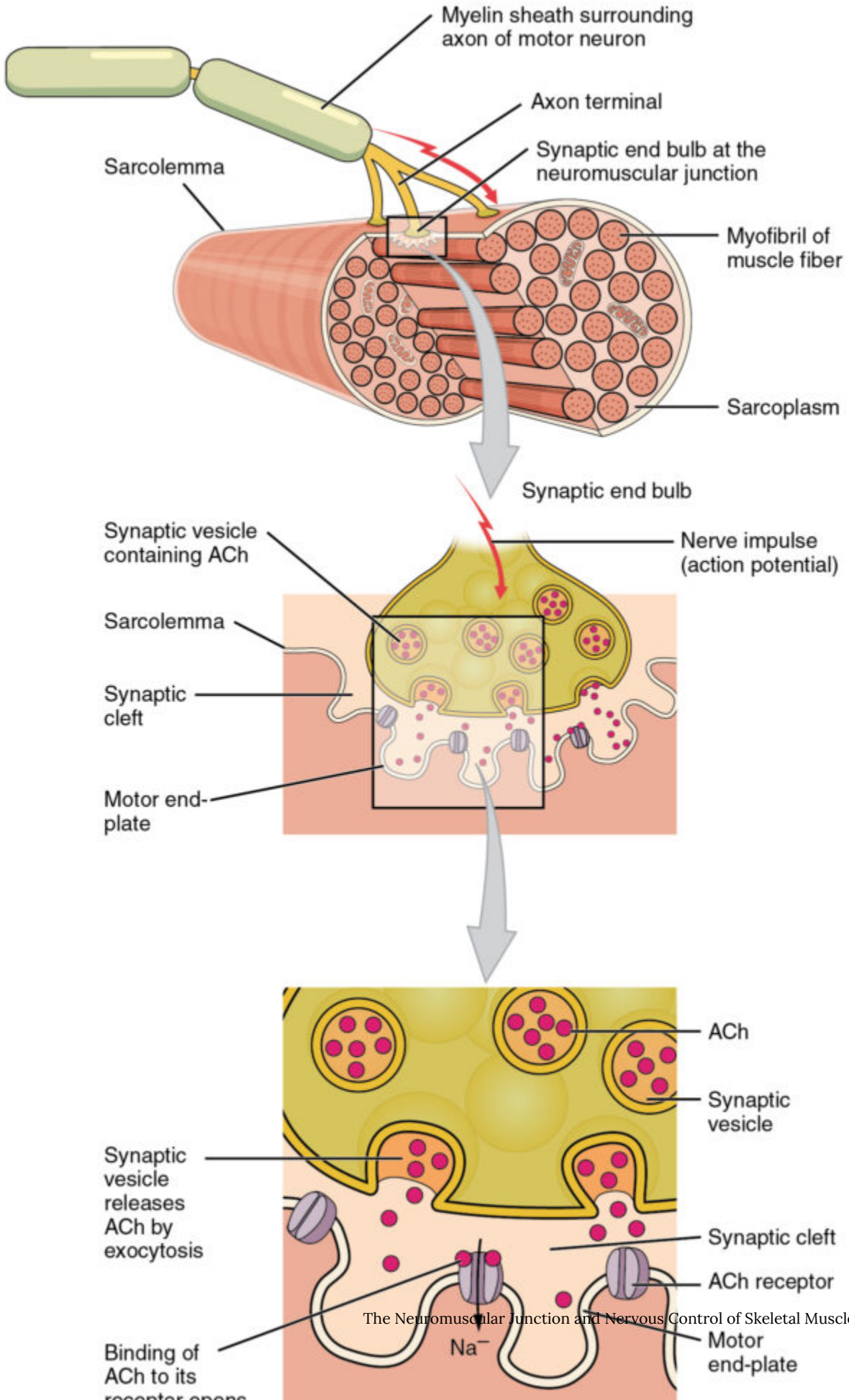
- Identify the components of the neuromuscular junction.
- Describe excitation-contraction coupling and formation of a power stroke.
- Explain how muscles contract and relax.
- Describe the mechanisms of ATP regeneration for use in muscle contraction.

The Neuromuscular Junction

A specialization of the skeletal muscle is the site where a motor neuron's terminal meets the muscle fiber—called the neuromuscular junction (NMJ). This is where the muscle fiber first responds to electrical signaling by the motor neuron. Every skeletal muscle fiber in every skeletal muscle is innervated by a motor neuron at the NMJ. Excitation signals from the neuron are the only way to functionally activate the fiber to contract.

The sequence of events that result in the contraction of an individual muscle fiber begins with a signal—the neurotransmitter, acetylcholine (ACh)—from the motor neuron innervating that muscle fiber. The sarcolemma, the membrane surrounding the fibers, will depolarize as positively charged sodium ions (Na^+) enter. This is where the Excitation-Contraction Coupling begins.

Every skeletal muscle fiber is supplied by a motor neuron at the NMJ. Watch this video to learn more about what happens at the NMJ. (a) What is the definition of a motor unit? (b) What is the structural and functional difference between a large motor unit and a small motor unit? (c) Can you give an example of each? (d) Why is the neurotransmitter acetylcholine degraded after binding to its receptor?


Myelin sheath surrounding axon of motor neuron
Axon terminal
Synaptic end bulb at the neuromuscular junction
Sarcolemma
Myofibril of muscle fiber
Sarcoplasm
Synaptic end bulb
Synaptic vesicle containing ACh
Nerve impulse (action potential)
Sarcolemma
Synaptic cleft
Motor end-plate
ACh
Synaptic vesicle
Synaptic vesicle releases ACh by exocytosis
Synaptic cleft
ACh receptor
Na⁻
Motor end-plate
Binding of ACh to its

Motor End-Plate and Innervation *– At the NMJ, the axon terminal releases acetylcholine (ACh). The motor end-plate is the location of the ACh-receptors in the muscle fiber sarcolemma. When ACh molecules are released, they diffuse across a minute space called the synaptic cleft and bind to the receptors.*

Excitation-Contraction Coupling

All living cells have membrane potentials, or electrical gradients across their membranes. The inside of the membrane is usually around -60 to -90 mV, relative to the outside. This is referred to as a cell's membrane potential. Neurons and muscle cells can use their membrane potentials to generate electrical signals. They do this by controlling the movement of charged particles, called ions, across their membranes to create electrical currents. This is achieved by opening and closing specialized proteins in the membrane called ion channels. Although the currents generated by ions moving through these channel proteins are very small, they form the basis of both neural signaling and muscle contraction.

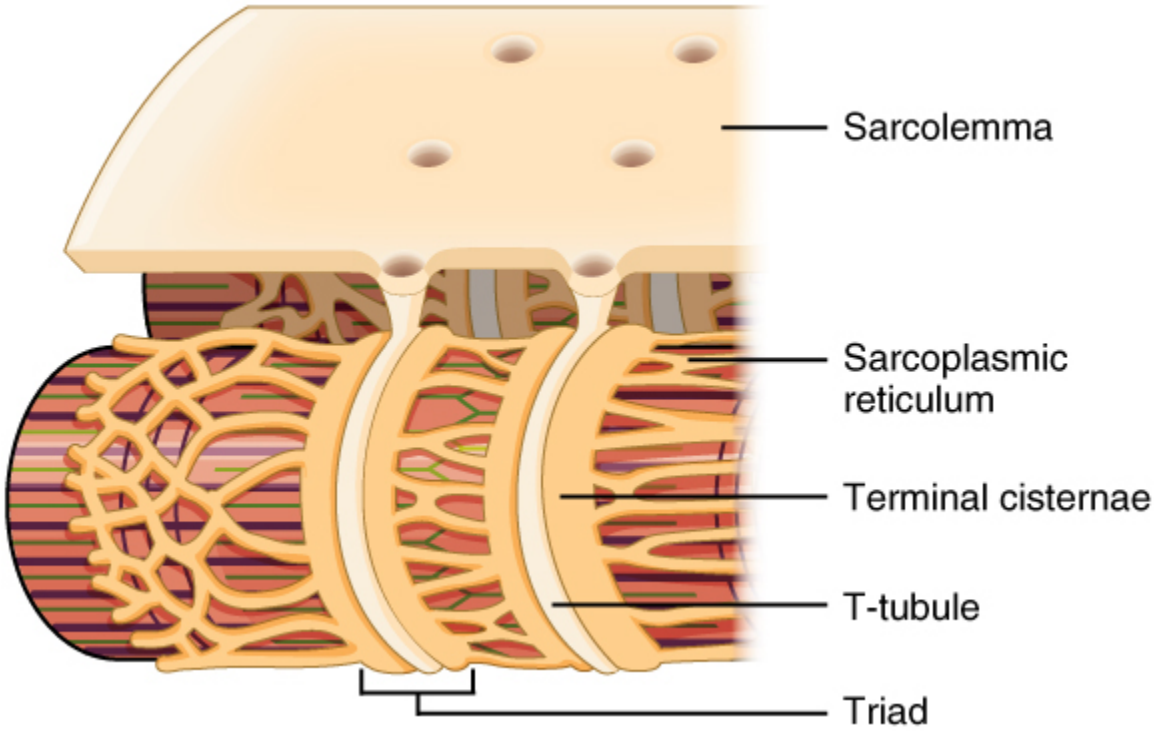
Both neurons and skeletal muscle cells are electrically excitable, meaning that they are able to generate action potentials. An action potential is a special type of electrical signal that can travel along a cell membrane as a wave. This allows a signal to be transmitted quickly and faithfully over long distances.

For a skeletal muscle fiber to contract, its membrane must first be "excited"—in other words, it must be stimulated to fire an action potential. The muscle fiber action potential, which sweeps along the sarcolemma as a wave, is "coupled" to the actual contraction through the release of calcium ions (Ca^{++}) from the SR. Once released, the Ca^{++} interacts with the shielding proteins, forcing them to move aside so that the actin-binding sites are available for attachment by myosin heads. The myosin then pulls the actin filaments toward the center, shortening the muscle fiber.

Signaling begins when a neuronal action potential travels along the axon of a motor neuron, and then along the individual branches to terminate at the NMJ. At the NMJ, the axon terminal releases a chemical messenger, or neurotransmitter, called acetylcholine (ACh). The ACh molecules diffuse across a minute space called the synaptic cleft and bind to ACh receptors located within the motor end-plate of the sarcolemma on the other side of the synapse. Once ACh binds, a channel in the ACh receptor opens and positively charged ions can pass through into the muscle fiber, causing it to depolarize, meaning that the membrane potential of the muscle fiber becomes less negative (closer to zero.)

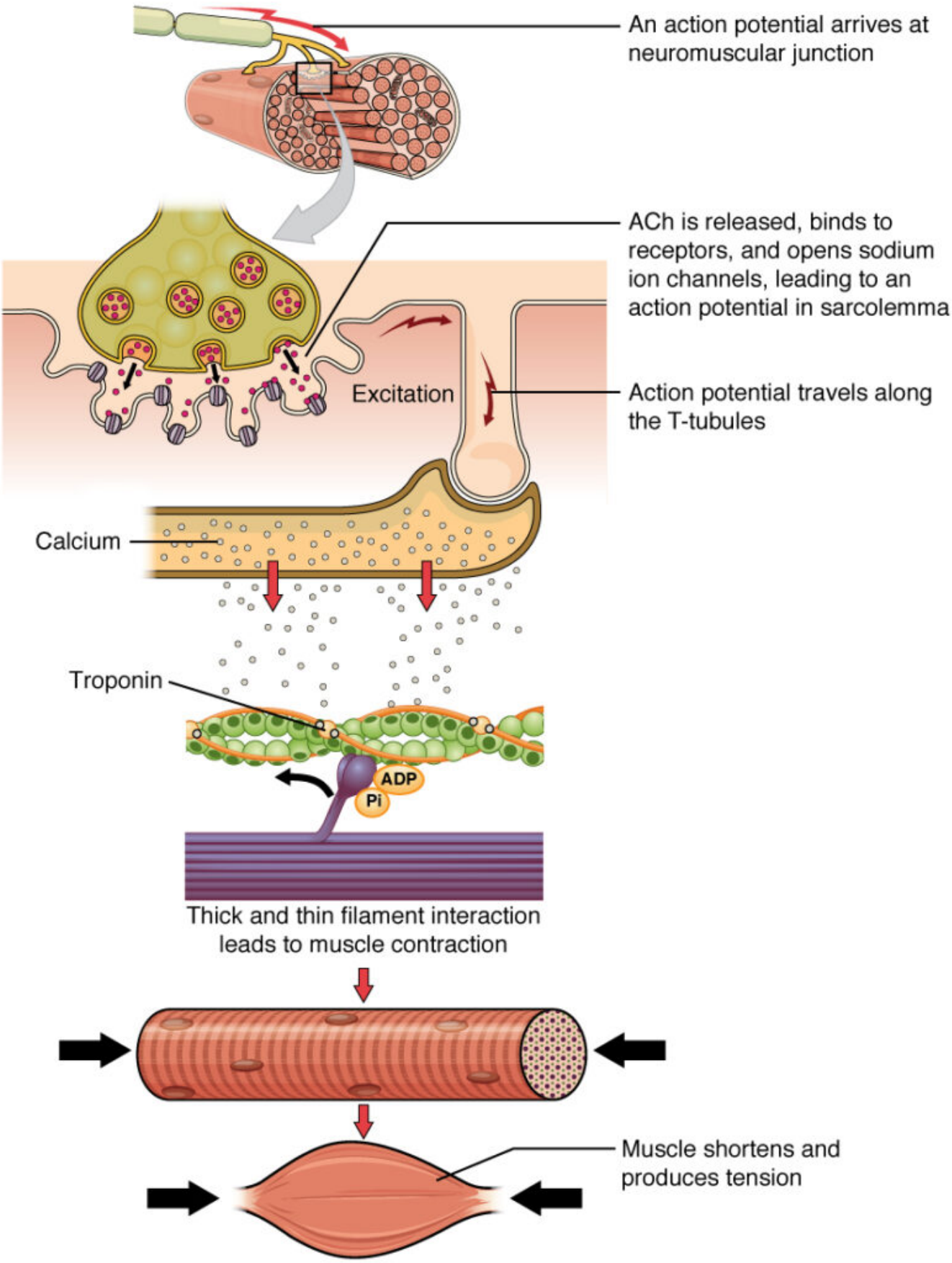
As the membrane depolarizes, another set of ion channels called voltage-gated sodium channels are triggered to open. Sodium ions enter the muscle fiber, and an action potential rapidly spreads (or "fires") along the entire membrane to initiate excitation-contraction coupling.

Propagation of an action potential along the sarcolemma is the excitation portion of excitation-contraction coupling. Recall that this excitation actually triggers the release of calcium ions (Ca^{++}) from its storage in the cell's sarcoplasmic reticulum (SR). For the action potential to reach the membrane of the SR, there are periodic invaginations in the sarcolemma, called T-tubules ("T" stands for "transverse"). You will recall that the diameter of a muscle fiber can be up to 100 μm, so these T-tubules ensure that the membrane can get close to the SR in the sarcoplasm. The arrangement of a T-tubule with the membranes of SR on either side is called a triad (The T-tubule). The triad surrounds the cylindrical structure called a myofibril, which contains actin and myosin.



The T-tubule – *Narrow T-tubules permit the conduction of electrical impulses. The SR functions to regulate intracellular levels of calcium. Two terminal cisternae (where enlarged SR connects to the T-tubule) and one T-tubule comprise a triad—a "threesome" of membranes, with those of SR on two sides and the T-tubule sandwiched between them.*

The T-tubules carry the action potential into the interior of the cell, which triggers the opening of calcium channels in the membrane of the adjacent SR, causing Ca^{++} to diffuse out of the SR and into the sarcoplasm. It is the arrival of Ca^{++} in the sarcoplasm that initiates contraction of the muscle fiber by its contractile units, or sarcomeres. This sets the stage for the power stroke of the sliding filament theory.



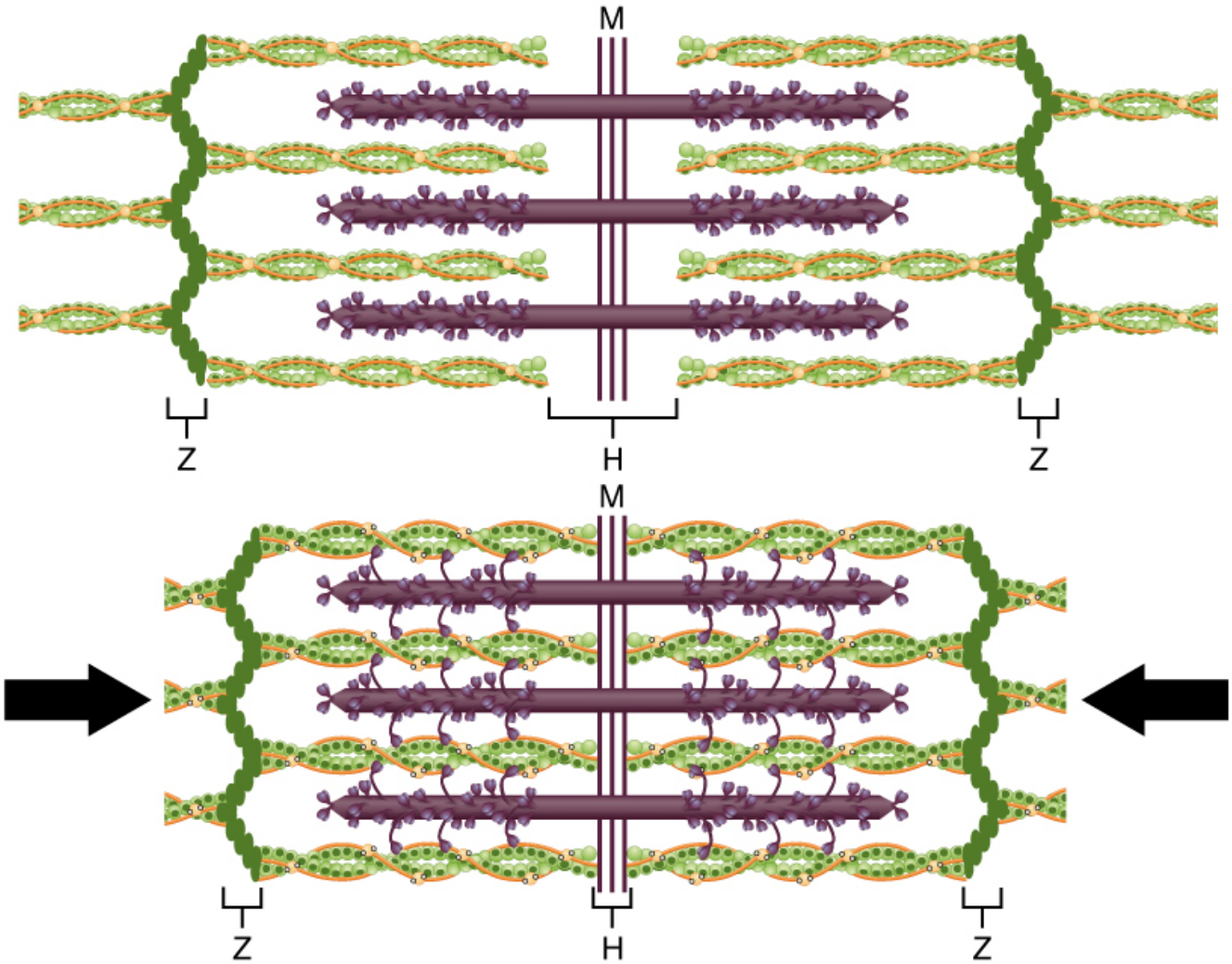
Contraction of a Muscle Fiber – *A cross-bridge forms between actin (thin filament) and the myosin (thick filament) heads triggering*

contraction.

The Sliding Filament Model of Contraction

The sliding filament model of contraction can be used to demonstrate the process of muscle contraction. When signaled by a motor neuron, a skeletal muscle fiber contracts as actin is pulled and then slides past the myosin within the fiber's sarcomeres. The sliding can only occur when myosin-binding sites on the actin filaments are exposed by a series of steps as explained above.

When a sarcomere contracts, the Z lines, or the junction of actin filaments marking the boundaries of each sarcomere, move closer together. The I bands, or areas of myosin only, becomes smaller. The A band, or areas of both actin and myosin, stays the same width. At full contraction, the actin and myosin filaments overlap completely.



The Sliding Filament Model of Muscle Contraction – *The upper panel demonstrates a relaxed muscle whereas the lower panel demonstrates a muscle in contraction. Z lines anchor the ends of actin filaments marking the boundaries of each sarcomere. The M line is the attachment site for thick filaments and is in the center of the A band. The H band is a region which contains only myosin while I bands contain only actin. The A band is the site where filament movement starts and contains both actin and myosin and has a dense appearance. A myofibril is composed of many sarcomeres running along its length; thus, myofibrils and muscle cells contract as the sarcomeres contract.*

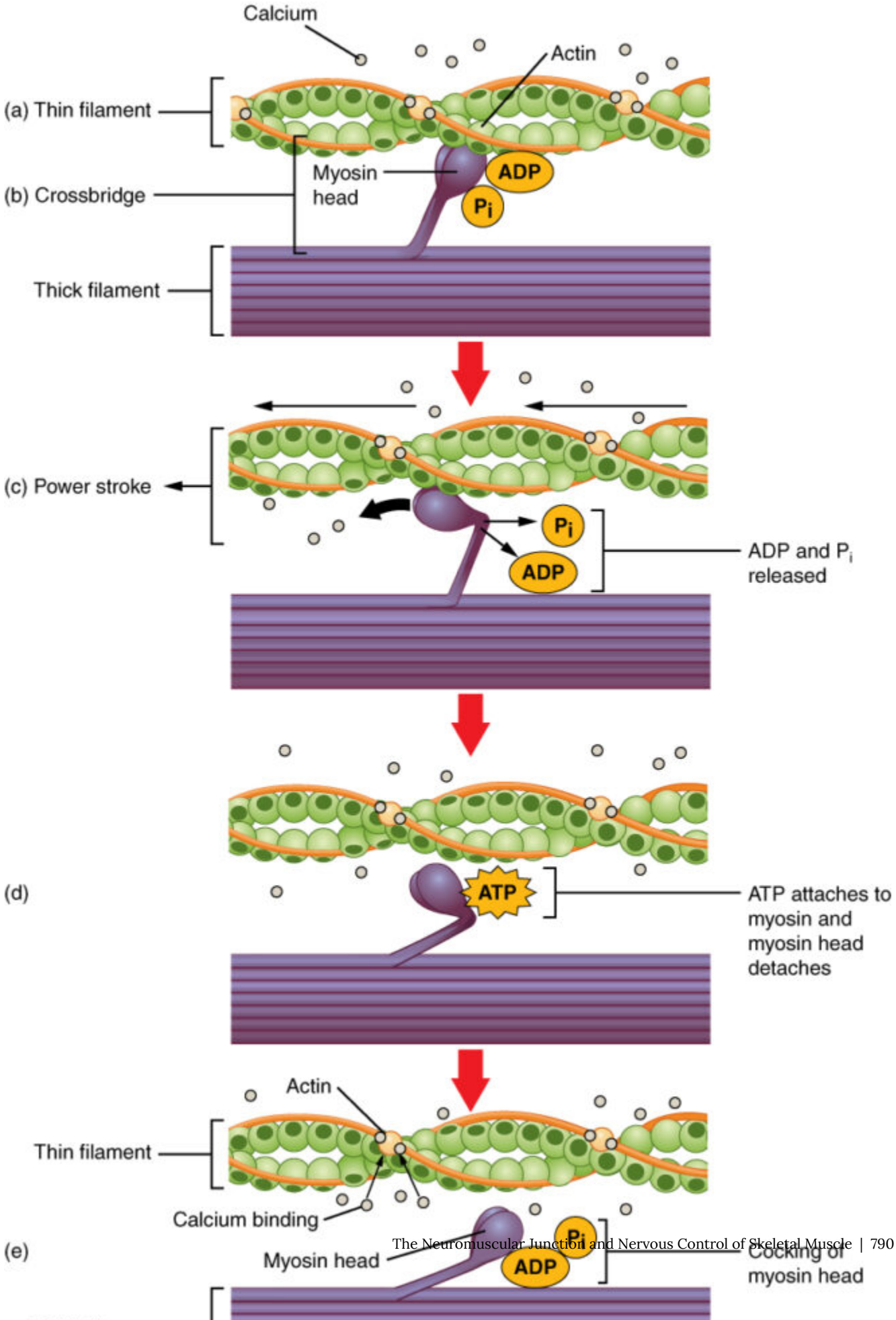
The Power Stroke, ATP and Muscle Contraction

Tropomyosin (a protein that winds around actin and covers actin's myosin-binding sites) binds to troponin to form a complex. This troponin-tropomyosin complex prevents the myosin "heads" from binding to the active sites on the actin microfilaments. To initiate muscle contraction, tropomyosin has to expose the myosin-binding site on an actin filament. The first step in the process of contraction is for Ca^{2+} to bind to Ca^{2+} binding sites on troponin so that tropomyosin can slide away from the binding sites on the actin strands. This allows the myosin heads to bind to these exposed binding sites and form cross-bridges. The actin filaments are then pulled by the myosin heads to slide past the myosin filaments toward the center of the sarcomere. But each head can only pull a very short distance before it has reached its limit and must be "re-cocked" (or reset) before it can pull again, a step that requires energy provided by ATP.

For actin filaments to continue to slide past myosin filaments during muscle contraction, myosin heads must:

1. Pull the actin at the binding sites
2. Detach
3. Re-cock (reset)
4. Repeat (attach to more binding sites)

This repeated movement is known as the cross-bridge cycle. This motion of the myosin heads is similar to the oars when an individual rows a boat: The paddle of the oars (the myosin heads) pull, are lifted from the water (detach), repositioned (re-cocked) and then immersed again to pull, as shown in the figure below.


Calcium
Actin
(a) Thin filament
Myosin head
(b) Crossbridge
ADP
Pi
Thick filament
(c) Power stroke
Pi
ADP
ADP and Pi released
(d)
ATP
ATP attaches to myosin and myosin head detaches
Actin
Thin filament
Calcium binding
(e)
Myosin head
Pi
ADP
Cocking of myosin head

Skeletal Muscle Contraction *– (a) The active site on actin is exposed as Ca2+ binds to troponin. (b) The myosin (thick filament) head is attracted to actin (thin filament), and myosin binds actin at its actin-binding site, forming the cross-bridge. (c) During the power stroke, the phosphate generated in the previous contraction cycle is released. This results in the myosin head pivoting toward the center of the sarcomere, after which the attached ADP and phosphate group are released. (d) A new molecule of ATP attaches to the myosin head, causing the cross-bridge to detach. (e) The myosin head hydrolyzes ATP to ADP and phosphate, which returns the myosin to the cocked position.*

Cross-bridge formation occurs when the myosin head attaches to the actin while adenosine diphosphate (ADP) and inorganic phosphate (P_i) are still bound to myosin (Skeletal Muscle Contraction – a, b). P_i is then released, causing myosin to form a stronger attachment to the actin, after which the myosin head moves toward the M-line, pulling the actin along with it. The filaments move approximately 10 nm toward the M-line. This movement is called the power stroke (Skeletal Muscle Contraction – c). In the absence of ATP, the myosin head will not detach from actin.

One part of the myosin head attaches to the binding site on the actin, but has another binding site for ATP that allows the myosin head to detach from the actin (Skeletal Muscle Contraction – d). After this occurs, ATP is converted to ADP and P_i by the intrinsic ATPase activity of myosin. The energy released during ATP hydrolysis changes the angle of the myosin head into a cocked position (Skeletal Muscle Contraction – e). The myosin head is now in position for further movement.

When the myosin head is cocked, myosin is in a high-energy configuration. This energy is expended as the myosin head moves through the power stroke. At the end of the power stroke, the myosin head is in a low-energy position. After the power stroke, ADP is released; however, the formed cross-bridge is still in place, and actin and myosin are bound together. As long as ATP is available, it readily attaches to myosin, the cross-bridge cycle can recur, and muscle contraction can continue.

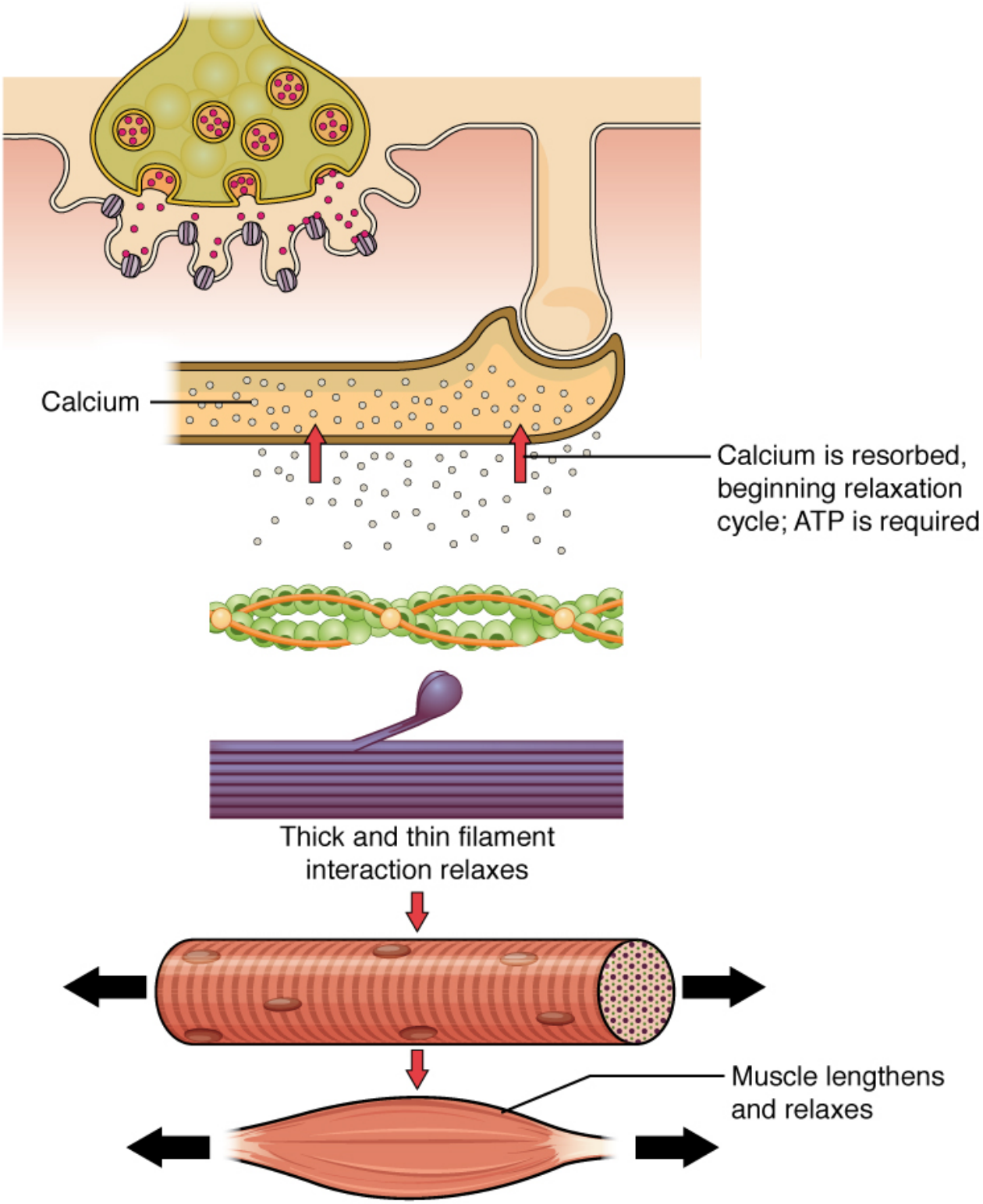
Note that each thick filament of roughly 300 myosin molecules has multiple myosin heads, and many cross-bridges form and break continuously during muscle contraction. Multiply this by all of the sarcomeres in one myofibril, all the myofibrils in one muscle fiber, and all of the muscle fibers in one skeletal muscle, and you can understand why so much ATP is needed to keep skeletal muscles working. In fact, it is the loss of ATP that results in the rigor mortis observed soon after someone dies. With no further ATP production possible, there is no ATP available for myosin heads to detach from the myosin-binding sites on actin, so the cross-bridges stay in place, causing the rigidity in the skeletal muscles.

Relaxation of a Skeletal Muscle

Things happen very quickly in the world of excitable membranes (just think about how quickly you can snap your fingers as soon as you decide to do it). Immediately following depolarization of the membrane, it repolarizes, re-establishing the negative membrane potential. Meanwhile, the ACh in the synaptic cleft is degraded by the enzyme acetylcholinesterase (AChE) so that the ACh cannot rebind to a receptor and reopen its channel, which would cause unwanted extended muscle excitation and contraction.

Muscle contraction usually stops when signaling from the motor neuron ends. This repolarizes the sarcolemma and T-tubules, and closes the voltage-gated Ca^{2+} channels in the SR. Ca^{2+} ions are then pumped back into the SR, which causes the tropomyosin to reshield the binding sites on the actin strands. A muscle also can stop contracting when it runs out of ATP and becomes fatigued (Muscle Relaxation).

Thus, this combination of repolarized membranes (in both the motor neuron and sarcolemma) and the lack of Ca+2 available for troponin causes the skeletal muscle to relax and prepare for the next contraction.



Muscle Relaxation – *Muscle relaxes as Ca2+ ions are pumped back into the SR.*

Muscle Strength

The number of skeletal muscle fibers in a given muscle is genetically determined and does not change. Muscle strength is directly related to the amount of myofibrils and sarcomeres within each fiber. Factors, such as hormones and stress (and artificial anabolic steroids), acting on the muscle can increase the production of sarcomeres and myofibrils within the muscle fibers. This change is called hypertrophy, which results in the increased mass and bulk in a skeletal muscle. Likewise, decreased use of a skeletal muscle – whether due to inactivity or lack of nervous stimulation – results in atrophy, where the number of sarcomeres and myofibrils disappear (but not the number of muscle fibers).

Disorders of the Muscular System

Duchenne muscular dystrophy (DMD), one of several diseases collectively referred to as "muscular dystrophy," is a progressive weakening of the skeletal muscles. DMD is caused by a lack of the protein dystrophin, which helps actin bind to the sarcolemma. Without sufficient dystrophin, muscle contractions cause the sarcolemma to tear, causing an influx of Ca^{2+}, leading to cellular damage and muscle fiber degradation. Over time, muscle mass is lost, and greater functional impairments develop.

DMD is an inherited disorder caused by a mutation in the gene that codes for dystrophin in an abnormal X chromosome. It primarily affects males, and it is usually diagnosed in early childhood. DMD usually first appears as difficulty with balance and motion, and then progresses to an inability to walk. It continues progressing upward in the body from the lower extremities to the upper body, where it affects the muscles responsible for breathing and circulation. It ultimately causes death due to respiratory failure, and those afflicted do not usually live past their 20s.

Section Review

Muscle contraction starts with ACh release which prompts the sarcolemma to depolarize (Na^+ enters), creating an action potential. Ca^{2+} is then released from the SR which binds to troponin so that tropomyosin slides away to keep myosin-binding sites exposed. This allows myosin heads to bind to actin for contraction. In the sliding filament model of muscle contraction, actin is pulled and slides past myosin. In a power stroke, phosphate and ADP (hydrolyzed from the ATP used to release the myosin head from the previous contraction cycle) is released, causing the myosin head to have a stronger attachment to actin. The myosin head then moves actin towards the M line (sarcomere center). Myosin detaches from actin when ATP attaches to the myosin head and resets the head for more contraction cycles. Repolarization occurs when ACh has stopped being released and Ca^{2+} returns to the SR. In the absence of Ca^{2+}, tropomyosin reshields the myosin-binding sites on actin which prevents myosin heads from binding.

Interactive Link Questions

The release of Ca^{2+} initiates muscle contractions. Watch this video to learn more about the role of Ca^{2+}.

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Review Questions

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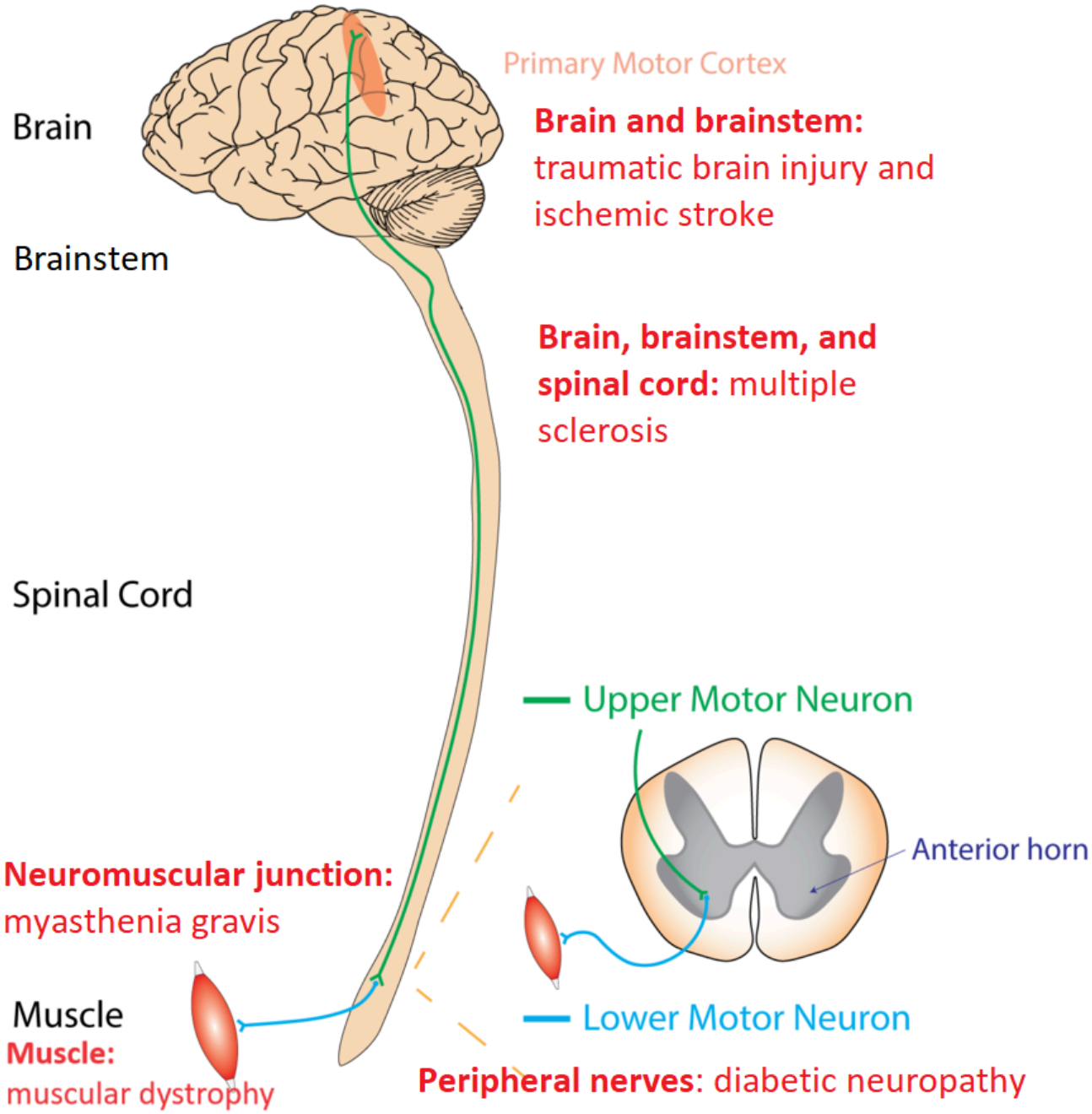
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Overview of Exemplars of Pathologies in Neuromuscular Control

JENNIFER KONG AND VALERIE SWANSTON

In our previous chapters, we explored several components of the neuromuscular system including the brain, brainstem, spinal cord, peripheral nerves, neuromuscular junction, and muscle. In this chapter we will build on this knowledge by discussing the pathophysiology of different diseases that involve the neuromuscular system. There are a huge number of diseases that can impact the neuromuscular system. In the following sections, we have chosen to highlight six different diseases that act on different components of the neuromuscular system. It's important to understand that neuromuscular disorders can result from deficits *anywhere* along the pathway from the cerebral cortex to the skeletal muscle.



A summary of the neuromuscular system. The diseases that we covered in this chapter are indicated in red, along with their principal site of action along the pathway of neuromuscular transmission. Used and adapted under creative commons license, original author Rcchang16 (File:UMN vs LMN.png – Wikimedia Commons).

As we go through these diseases, think back to our previous chapters where we learned about the *normal* physiology and anatomy of each component. It's important to understand what happens in normal conditions so we can begin to learn about the consequences to the body during disease or injury. You may feel overwhelmed while reading this chapter – the neuromuscular system is complex! Make sure you review our previous chapters when you need to refresh your knowledge of these challenging topics.

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Pathophysiology of Neuromuscular Control: CNS Issues in the Motor Cortex (Traumatic Brain Injury & Ischemic Stroke)

VALERIE SWANSTON

Learning Objectives

- Describe some of the proposed pathophysiologic changes that contribute to TBI and ischemic stroke.
- Describe the classification of TBI into primary and secondary injury.
- Identify two common etiologies of ischemic stroke.

Exemplar of Damage to Brain (Motor Cortex) or Brain Stem: Traumatic Brain Injury (TBI)

Traumatic brain injury (TBI) is a leading cause of disability and death worldwide, and has a lasting impact on patients and those who care for them. TBIs occur on a spectrum, and their severity can range anywhere from a mild concussion to a severe TBI with lifelong consequences to a person's function. In Canada, there are approximately 20 000 hospitalizations for TBI every year. TBI commonly arises from motor vehicle accidents, sports, and falls, but can occur anytime there is risk of trauma to the head. Immediate symptoms of a TBI may include nausea, dizziness, memory loss (also called amnesia), and headache. In more severe TBIs, long term symptoms may include altered cognitive and behavioral deficit. Some evidence suggests that severe TBIs may even contribute to the development of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

Primary and Secondary Injury in TBI

The progression of a TBI is often divided into two stages: the immediate primary injury and the delayed secondary injury. The primary injury refers to the immediate damage caused to the brain by the traumatic event. In a "closed head" injury, the skull remains intact and injury occurs due to linear or rotational acceleration of the brain colliding with the inner surface of the skull. An example of this would be a head strike from an accident or fall. In a "penetrating" injury an object is embedded into the skull, meninges, or brain tissue. A bullet embedded in the skull as a result of a gunshot wound is an example of a penetrating injury. Damage from a penetrating injury can come as a result of the delicate brain tissue becoming exposed to the external environment.

The secondary injury includes the long-term and slowly progressing changes that occur in the brain as results of the

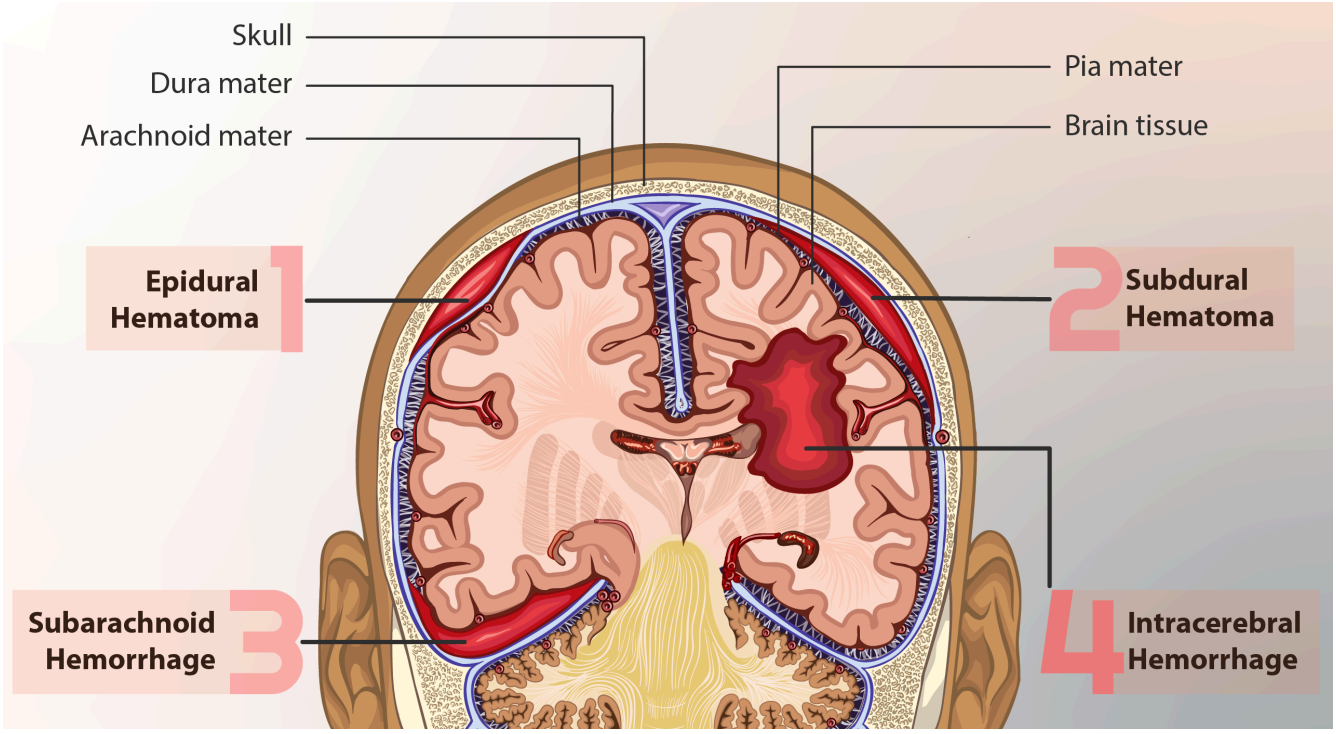
trauma. It is thought that the progression of the secondary injury is the most critical contributing factor to the patient's recovery.

Pathophysiology of TBI

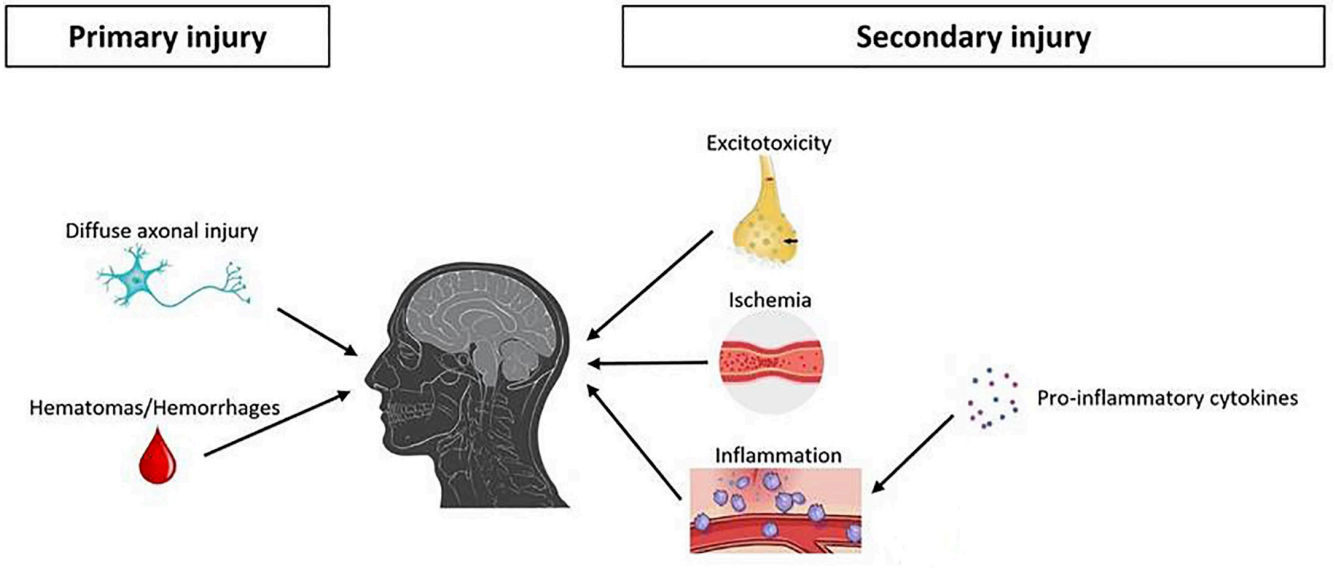
We certainly don't know all of the pathophysiologic changes that occur during TBI, and those we have studied are not yet fully understood. The following table outlines some of the possible changes that occur in the brain and it's surrounding structures, but understand that this list is incomplete and more research is required on this topic.

Pathophysiological Change	Mechanism
Diffuse axonal injury	Direct damage to the neuronal axons within the brain due to destruction of the cytoskeletal network
Hemorrhage	Damage to the blood vessels within the CNS causing bleeding within the brain, which in turn damages tissue and reduces cerebral blood flow to other brain tissue (Figure 12.50)
Hematoma	Accumulation of blood in between layers of the meninges causing compression of the underlying brain tissue (Figure 12.50)
Brain ischemia	Damage to the vascular endothelial cells in the circulatory system within the CNS results in loss of the brain's ability to regulate its blood flow. This may cause decreased blood flow to the brain, resulting in a shortage of oxygen in brain tissue, which is clinically called ischemia.
Release of excitatory chemical messengers	Damage to the re-uptake transporters for excitatory neurotransmitters such as glutamate causes cellular excitotoxicity, leading to mitochondrial damage and accumulation of damaging reactive oxygen species (ROS)
Inflammation	Prolonged release of inflammatory cytokines by the immune system causes disruption to the blood brain barrier, leading to accumulation of excess fluids, which is known as brain edema. If untreated, the excess fluids can cause increased intra-cerebral pressure (ICP), which causes further damage to the brain.

Pathophysiological mechanisms of brain tissue is injured



Depiction of the meningeal layers and various types of hemorrhages and hematomas. Notice that the hematomas are named based off of their location within the meninges; a subdural hematoma is located below the dura mater, for example.



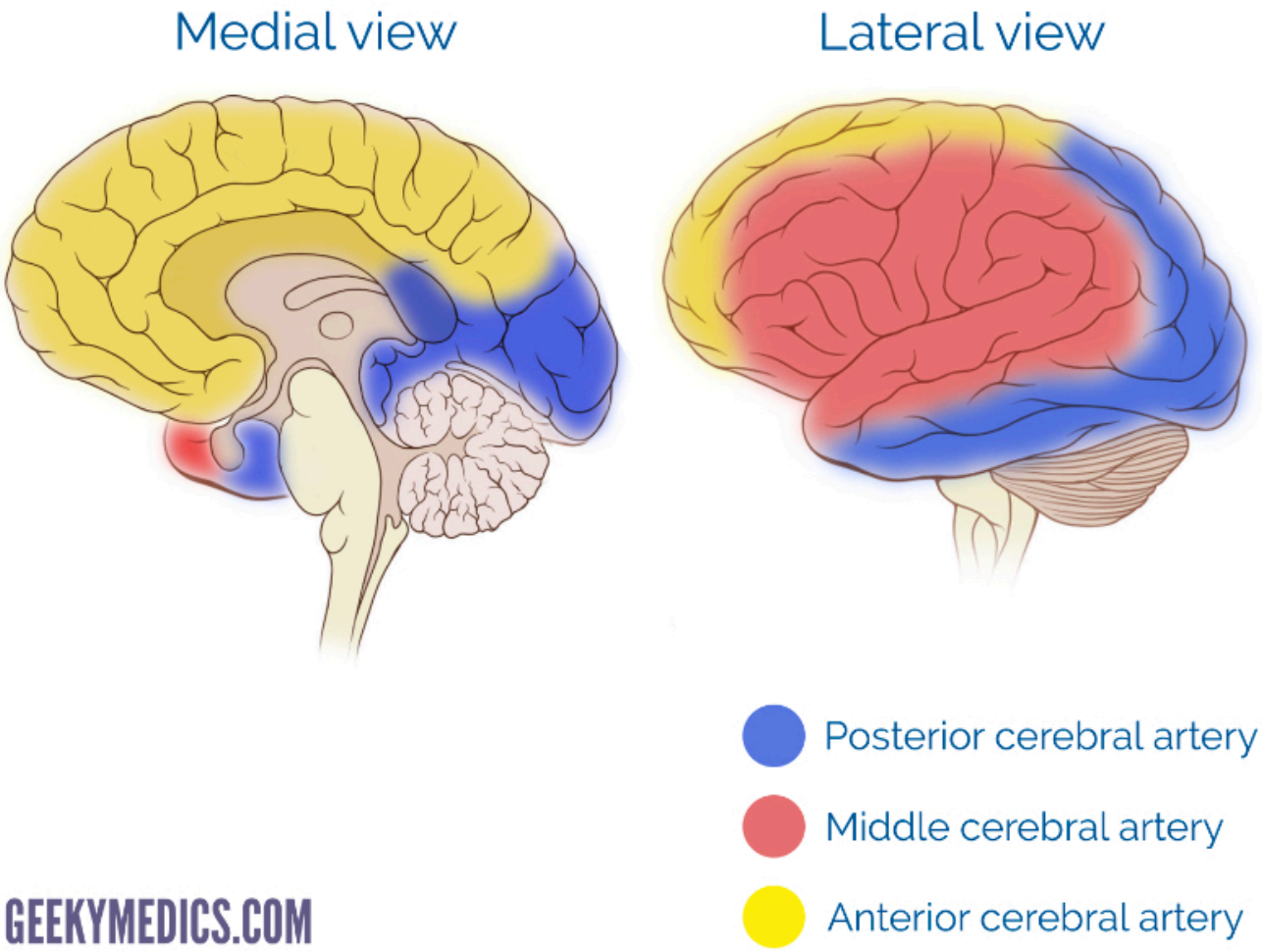
Proposed pathophysiologic mechanisms of primary and secondary traumatic brain injury

Exemplar of Damage to Brain (Motor Cortex) or Brain Stem: Ischemic Stroke

A stroke is a life threatening health emergency that occurs when blood flow to a region of the brain stops, resulting in neuron cell damage and death. Strokes are one of the leading causes of death in Canada; in the year 2019 the incidence of stroke was estimated to be 280 per 100 000 adults aged 20 years and older. There are two broad types of strokes: ischemic stroke and hemorrhagic stroke. Ischemic stroke, which is the focus of this chapter, occurs when a blood vessel within the brain is suddenly blocked, interrupting blood flow. Hemorrhagic stroke, which is comparatively rarer and occurs in approximately 20% of acute strokes, is caused by damage to blood vessels within the brain that leads to significant bleeding into the brain tissue.

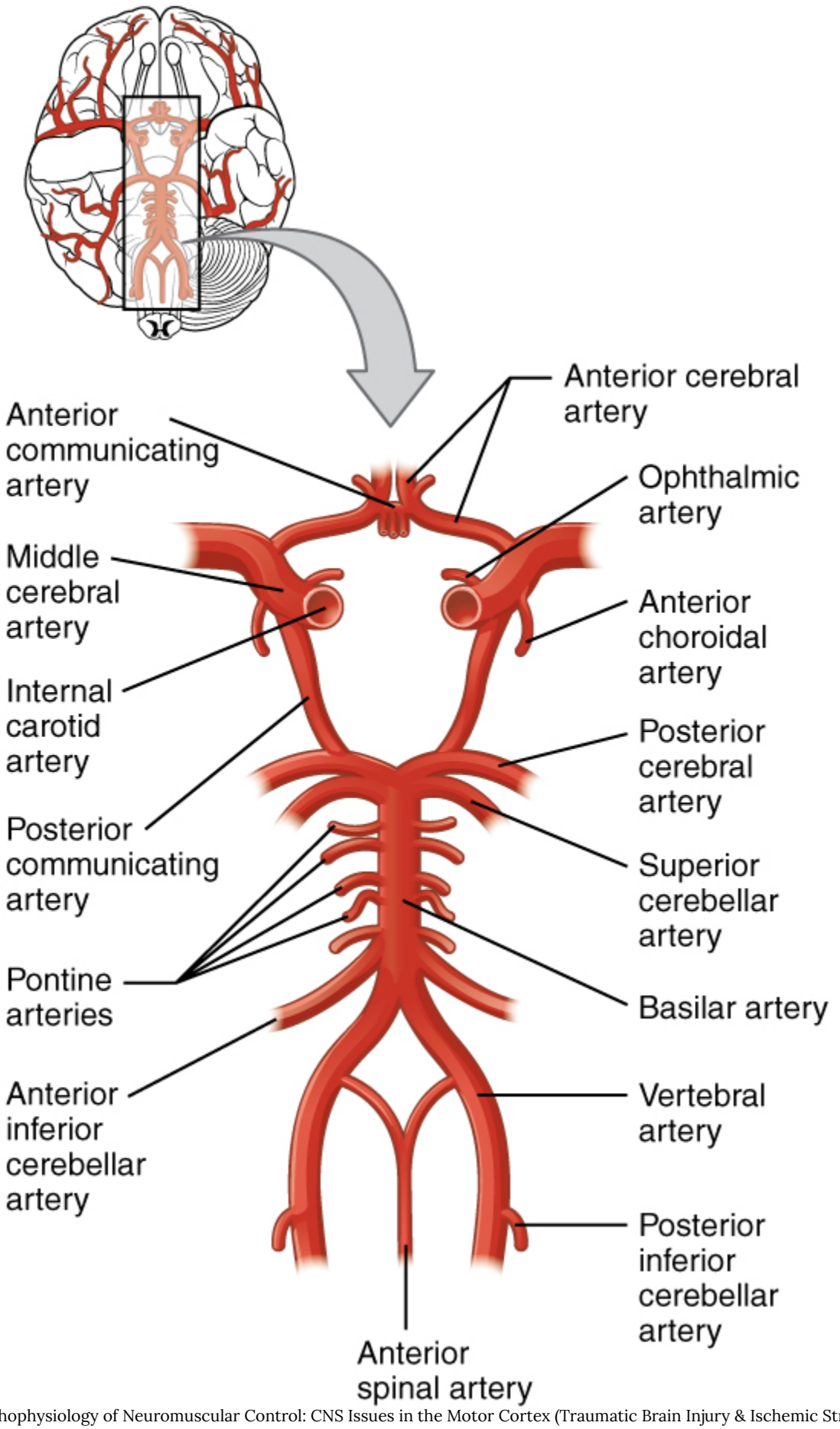
Blood Circulation in the CNS

To understand the consequences of a stroke, it's important to understand the anatomy of the circulatory system within the CNS. Make sure you review the information in Circulation in the CNS. There are three main arteries that supply the cerebral cortex with blood: the anterior, middle, and posterior cerebral arteries. We can use our knowledge of the function of different brain areas in combination with the perfusion area (the area of brain that is supplied with blood) of an artery to work through what the symptoms of an ischemic stroke may be. For example, as the figure below shows, the pre-central gyrus (which contains the motor cortex) is supplied with blood by the anterior and middle cerebral arteries. An ischemic stroke affecting the *right* middle or anterior cerebral artery will result in motor deficits to the *left* side of the body (recall what we learned in The Peripheral Nervous System: the motor neurons cross over the innervate muscles on the other side of the body).



Depiction of the perfusion areas of the three arteries that supply the cerebral cortex with blood; the posterior, middle, and anterior cerebral arteries.

An important anatomical feature of the circulatory system with respect to strokes is a structure called the Circle of Willis. This structure is an anastomosis (connection) of arteries within the CNS that functions to create redundancy within the circulatory system. Essentially, if one artery within the circle becomes blocked, blood flow from other vessels within the circle can accommodate to maintain blood flow and prevent significant ischemia from occurring. This important anatomical feature can prevent significant brain tissue damage in the case of an ischemic stroke.


Anterior cerebral artery
Anterior communicating artery
Ophthalmic artery
Middle cerebral artery
Anterior choroidal artery
Internal carotid artery
Posterior cerebral artery
Posterior communicating artery
Superior cerebellar artery
Pontine arteries
Basilar artery
Anterior inferior cerebellar artery
Vertebral artery
Posterior inferior cerebellar artery
Anterior spinal artery

Circle of Willis *– The blood supply to the brain enters through the internal carotid arteries and the vertebral arteries, eventually giving rise to the circle of Willis.*

Watch this helpful video for further review of the brain anatomy, CNS circulation, and the types of strokes.

Causes of Ischemic Stroke

Now that we've learned about what an ischemic stroke is, you might be wondering what are the causes of stroke – that is, what actually blocks the blood vessel? We'll briefly discuss two common mechanisms that can cause an ischemic stroke – cardioembolism and large vessel disease.

Cardioembolism

An embolus is any material that may become lodged and cause a blockage within a blood vessel, called an embolism. Embolisms can be caused by many materials, including fat and air bubbles. When an embolism is caused by a blood clot, is it called a thrombus. In the case of a cardioembolism, the embolus originates in the heart, as suggested by its name. The embolus may travel into the circulation within the CNS, where it can become lodged in a vessel and interrupt blood flow, causing an ischemic stroke. Cardioembolism accounts for approximately 20% of ischemic strokes.

Large Vessel Disease

In large vessel disease, the blockage originates in large vessels such as the internal carotid arteries, aorta, vertebral, or basilar arteries. The most common cause is atherosclerosis, where fatty plaques of cholesterol and other lipids cause narrowing of the vessel. Over time, plaques may rupture and travel to the CNS circulation, causing a stroke. Atherosclerotic plaques are generally caused by diseases of abnormal lipid levels, such as dyslipidemia (high or abnormal levels of blood lipids) or hypercholesterolemia (high blood cholesterol).

Refer to our previous chapter on atherosclerosis to learn about how these fatty plaques originate in the heart, rupture, and then travel to the brain (Atherosclerosis and Angina).

Do you know the signs of a stroke? It could save a life

If you suspect someone is having a stoke, looking for signs with the FAST acronym

- **Face:** is it drooping
- **Arms**: can they raise both?
- **Speech**: is it slurred?
- **Time**: time to call 9-1-1

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Pathophysiology of Neuromuscular Control: CNS Issues in White Matter (Multiple Sclerosis)

MENA BURR AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Explain the pathophysiology and histopathology of MS.
- Correlate the signs and symptoms of MS with your understanding of the pathophysiology of MS.
- Describe the diagnosis of MS.
- Describe the treatment of MS.

Multiple Sclerosis (MS) is the most common non-trauma cause of nervous system related disability in young adults, with the typical age of diagnosis being between 20-40 years old. It is a disease of the central nervous system (CNS) in which the ability of neurons to transmit neural signals breaks down. As a result, the body cannot interpret and respond to environmental stimuli as effectively. Since MS can affect various parts of the CNS, it can have a wide variety of symptoms, ranging from motor, sensory, or cognitive deficits. Usually, patients initially experience unpredictable episodes of symptoms before progressing to more persistent and permanent states of disability.

Pathophysiology of MS

The pathophysiological hallmark of MS is the formation of demyelinating lesions in the central nervous system (an area with loss of myelin and relative preservation of axons). Since the role of myelin is to increase the speed of neuronal action potentials, the breakdown of myelin in MS results in slower or potentially absent signals. Some of the most commonly affected sites are the optic nerves (esp optic chiasm and tract), white matter serving the cortex (subcortical), areas around the ventricles of the brain (periventricular), and grey matter below the cortex (deep grey nuclei).

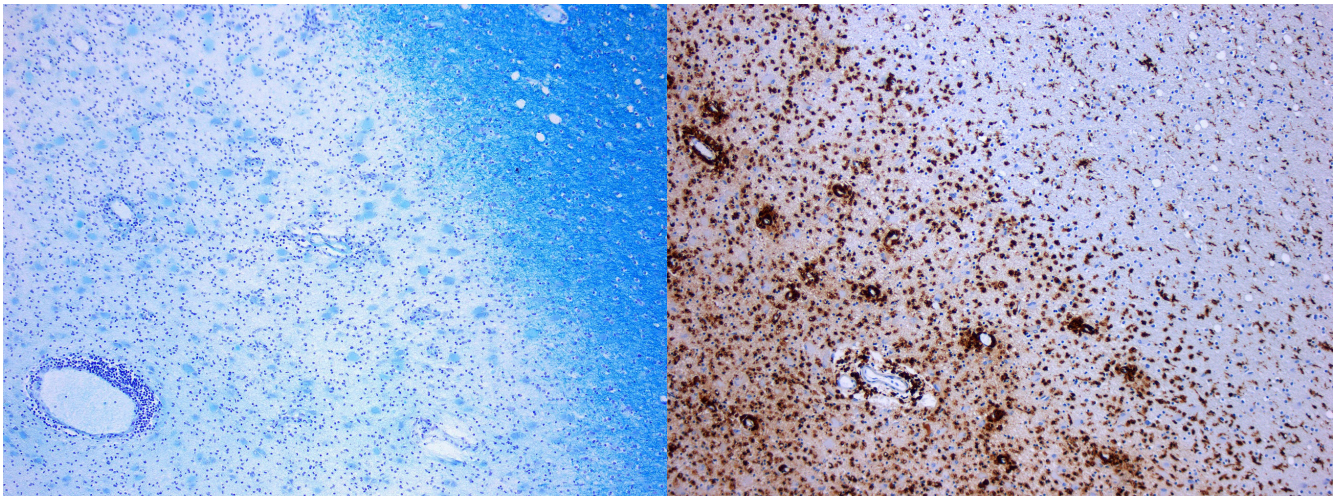
While the exact cause of MS is not completely understood, it is considered an immune mediated disease influenced by both genetic and environmental factors. It is thought that a breakdown of the blood brain barrier (BBB) occurs, which promotes the infiltration of reactive immune cells such as T cells, B cells, and myeloid cells into the CNS tissue. These immune cells produce antibodies that mark myelin as foreign, causing inflammation and the destruction of the myelin. This inflammatory component of MS likely may explain the on and off nature of symptoms that most patients initially experience (this type of MS is called relapsing-remitting MS).

Through the demyelination around axons, scarring and fibrosis also occurs. This is where the name of the disease comes from; sclerosis means hardening or scarring of tissue. Multiple scars are found in the white matter of the brain and spinal cord. Although new myelin may be formed in these lesions, this remyelination is often limited and variable between patients.

In addition to neuronal conduction, myelin also functions to protect and nourish axons. Thus, prolonged areas of demyelination can eventually lead axonal loss as well, causing irreversible clinical and cognitive deficits (this type of MS is called progressive MS). However, for unknown reasons, a small subset of patients experience a progressive style MS right from disease onset.

Histopathology of MS

MS lesions can be designated as active, inactive, or mixed active/inactive. This differentiation is based on the distribution of inflammatory cells around the plaque and the existence of demyelination. Histological and immunohistological stains can be used for identifying these lesions. For example, myelin can be seen with special stains (e.g. Luxol fast blue, Klüver-Barerra-Stains) while cell morphology can be seen with hematoxylin and eosin stains. Moreover, inflammatory cells such as macrophages can be seen with immunohistochemical markers (e.g. CD68). Thus, a combination of the pre-mentioned stains can help illuminate the loss of myelin in neurons caused by macrophages.



Histologic staining of MS lesion Histologic staining of MS lesion showing loss of myelin staining (left) and increase in macrophage staining (right). The picture on the left shows brain tissue stained with Klüver-Barerra, which colours myelinated tissue a bright navy blue. The area of discolouration indicates demyelinated MS plaque tissue. The picture on the right shows immunohistochemical staining for CD68, in which the brown dots indicate the presence of macrophages. This image shows that there are many more macrophages within the lesion compared to the normal tissue.

It should be noted that the presence of inflammatory cells within the plaques varies depending on the lesion's stage. While active lesions tend to contain many macrophages, inactive/chronic lesions often contain few or none. Thus, stains such as CD68 may help determine lesion stage.

MS Pathology with Common Signs and Symptoms

Patients often have many complaints of problems with sensory and/or motor control long before an official diagnosis. Because demyelination can occur in any white matter in the CNS (i.e. brain and spinal cord), signs and symptoms can be separated from each geographically and temporally. For example, a patient may have issues with vision of right eye

(sensory) and then problems with controlling the left foot (motor) two months later. Below is a table of some common signs and symptoms reported in MS. Please note that this is not an exhaustive list.

Area of demyelination	Sign or Symptom
the optic nerve (cranial nerve II)	blurry vision or partial or complete loss of vision in one eye
white matter serving the cerebral cortex	depression, mood disturbances, fatigue, and cognitive deficits such as slowed thinking
spinal cord	Sensory: unusual sensations like tingling or numbness, often on one side of the body Motor: numbness, movement issues like loss of balance and/or coordination. Autonomic functions: bladder or bowel impairments and sexual dysfunction
brainstem, cerebellum, and cranial nerves	Sensory: unusual sensation affecting the face, vertigo Motor: weakness of facial muscles, difficulty swallowing, slurred speech
oculomotor nerve (cranial nerve III)	sensory: prolonged double vision motor: non-consensual eye movements,

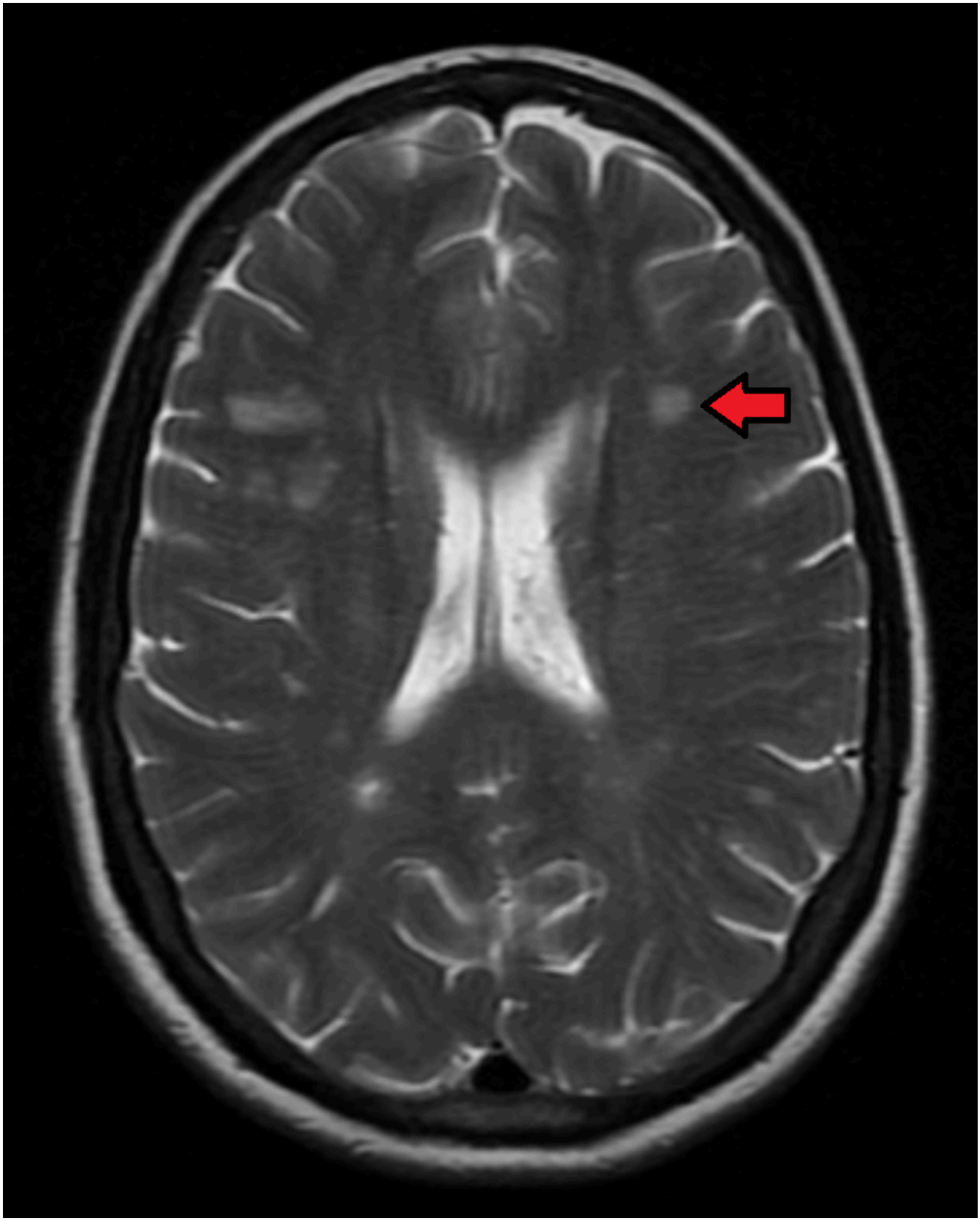
Signs and symptoms of MS and location of demyelination

Diagnosis of MS

The diagnosis of MS is largely based on the signs and symptoms. Moreover, it is also required that there be multiple lesions that vary in time and space, and to exclude other conditions with similar symptoms. In other words, the lesions must be in various stages and various locations within the CNS. This can be determined using tests such as magnetic resonance imaging (MRI) of the brain and spinal cord, cerebral spinal fluid (CSF) analysis, or measuring electricity flowing in nerves (evoked potentials).

MRI of CNS

Through MRI, a contrast agent called gadolinium is used to highlight lesions with active demyelination. The McDonald criteria is the most commonly used criteria to diagnose MS, combining both clinical assessment of symptoms and the additional tests mentioned. In order to diagnose MS using this criteria, a patient must have a least one symptomatic episode, as well as an MRI scan showing lesions at various stages and locations in the CNS.



MRI showing MS lesion (red arrow) using gadolinium contrast

CSF Analysis

Cerebral spinal fluid is collected by an invasive procedure known as lumbar puncture. Because CSF circulates around both the brain and spinal cord, this CSF sample can show the presence of antibodies, which are abnormally present during MS.

Evoked Potential Tests

Evoked potential tests measure the electricity of the nervous system upon a stimulus (visual or electrical). While being stimulated (e.g. watching a visual pattern or by electrical stimulation via electrodes), electrical impulses are applied to the affected limbs and electrodes measure the speed the electricity travels down the nerves.

Treatment of MS

There is no cure for multiple sclerosis. Some people have mild symptoms where no treatment is necessary and others have flare ups with periods of remission. However, when MS affects health and activities of daily living, treatment focuses on reducing the inflammatory and circulating antibodies associated with MS.

Corticosteroids are prescribed to reduce inflammation, particularly the inflammatory process which is attacking the myelin.

Plasma exchange (plasmapheresis) occurs when MS has a bout of new, severe symptoms which don't respond to corticosteroids. Plasmapheresis involves separating whole blood into blood cells (e.g. red and white blood cells) and the watery plasma where antibodies are found. After antibody removal, the plasma is mixed back with the blood cells and put back into circulation.

Monoclonal antibodies are synthetic antibodies made to directly interfere with the B cells to prevent their formation of the offending antibodies that cause demyelination.

Review Questions

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=7668#h5p-409

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Pathophysiology of Neuromuscular Control: PNS Issues (Diabetic Neuropathy)

VALERIE SWANSTON AND CARTER ALLEN

Learning Objectives

By the end of this section, you will be able to:

- Define peripheral neuropathy.
- Identify the causes of neuropathy.
- Explain the pathophysiology of diabetic neuropathy.

Neuropathy is defined as a disease of the nervous system, especially as it pertains to damage to the nerves. There are several types of neuropathy, to simplify we will think in three distinct classes, the location of the neuropathy, the type of damage being done to a nerve, and the type of nerve affected.

Classification by damage	**Classification by location**	**Classification by affected nerve**
Axonal: Neuropathy that is caused by damage of the axon	Polyneuropathy: Neuropathy in multiple sites simultaneously	Motor
Demyelinated: Neuropathy that is caused by damage to the myelin sheath	Mononeuropathy: Neuropathy in one site. typically the result of trauma or entrapment	Sensory
Mixed: Neuropathy that relates both to the axon and to the myelin sheath	Distal Symmetric Polyneuropathy: neuropathy on both sides on limbs distant from the torso	Autonomic
	Proximal polyneuropathy: neuropathy on limbs close to the torso	

Classification of neuropathy based on location, type of damage, and affected nerve

Etiology Of Neuropathies

Neuropathies can occur both in the CNS and PNS. However, most of the etiologies listed here pertain to PNS, referred to as peripheral neuropathies.

Peripheral neuropathies are a group of diseases with many possible etiologies but one common result: damage to peripheral nerves. Peripheral neuropathies may be caused problems with nerves being made (i.e. congenital), maintaining nerve function (i.e. impaired perfusion, nutritional deficiencies), and direct damage by toxins (ie ethanol) or antibodies (i.e. autoimmune), and mechanical compression (i.e. entrapment).

Entrapment

The nerve is mechanically compressed by some anatomical feature which can be caused by swelling (like swelling of tendons in the wrist causing carpal tunnel syndrome) or development of a growth or cyst. Additionally it can be caused by trauma that causes internal features to put pressure on a nerve, such as a fracture or compartment syndrome, or by a penetrating injury where a foreign object is putting pressure on or severing a nerve. [1]

Accumulation of Substances

Ethanol and certain drugs like chemotherapy drugs will cause toxicity and damage to nerves in high doses over time. Depending on the substance the pathology differs.[1]

Autoimmunity

Autoantibodies can be mistakenly generated to recognize some component of the nerve as foreign and proceed to attack the nerve. For example, Guillain Barre is an autoimmune peripheral neuropathy which is thought to happen as a result of identification of nerve gangliosides as foreign. Antibodies are produced which target nerve gangliosides which lead to degradation of these structures, which in turn affects nerve function. There are many types of Guillain Barre, which can manifest as either axonal or demyelinating neuropathy. [1]

Impaired perfusion

Poor blood flow to nerves will cause both decreased delivery of oxygen, water, and nutrients and accumulation of wastes to the affected nerve. There are many causes of reduced blood flow, such as atherosclerotic plaques, which affect all nerves downstream of the obstruction. The reduced oxygen delivery will force the nerve tissue to anaerobic metabolism causing toxic byproducts which will further damage the nerve.

Nutritional Deficiencies

Deficiency of vitamin B1, B6, B12 can lead to peripheral neuropathy as these vitamins are important in nerve metabolism and cellular reproduction.

Vitamin B1 is an essential factor of glucose metabolism and energy production, being an electron transporter in the citric acid cycle. Due to the fact that nerve cells consume so much energy, a lack of B1 can lead to additional oxidative damage to nerve cells specifically. B1 deficiency is also very common in diabetics and alcoholics, which may be one of the factor in diabetic neuropathy and neuropathy related to alcohol substance use disorder.

Vitamin B6 is a coenzyme involved in the production of neurotransmitters and GABA. GABA is an inhibitory chemical in the nervous system, so low GABA levels will lead to hyperactive nerve activity which can lead to nerve toxicity.

Vitamin B12 is involved in the synthesis of chemicals necessary for nerve health and for the synthesis of myelin.

Therefore a Vitamin B12 deficiency can lead to decreased upkeep of nerve cell health and lack of remyelination of nerves. [8]

Exemplar to Damage to the PNS: Diabetic Neuropathy

Diabetes mellitus (DM) is one of the most common chronic health complications worldwide, and has been steadily increasing in prevalence in recent years. DM is commonly classified into two major categories: type one DM is due to autoimmune causes and commonly begins in childhood whereas type two DM occurs later in life and is a multifactorial disease caused by a combination of a person's genetics, lifestyle, and environment. You can review the detailed pathophysiology of DM in Diabetes Mellitus. In summary, both type one and type two DM are due to a deficit or lack of function or production of insulin, which is a hormone that normally reduced blood sugar. The result is chronically raised blood sugars, known as hyperglycemia.

Pathophysiology of Diabetic Peripheral Neuropathy

Though the exact process is unknown, there are two leading hypothesis for the manifestation of diabetic neuropathy. The first is the metabolic theory: over time, hyperglycemia leads to a buildup of certain substances in the bloodstream and tissues which damage nerves, such as reactive oxygen species (ROS) and sugar alcohols. Additionally, factors in the blood such as insulin-like growth factor which promote neuronal growth are downregulated in patients with DM. The second hypothesis is concerned with impeded perfusion to nerves as a result of atherosclerosis caused by hyperglycemia. Nerves are damaged by the buildup of toxic byproducts of anoxic energy production in the nerves.[7]

Hyperglycemia and Peripheral Nerves

The most widespread type of peripheral neuropathy is that caused by exposure of nerves to a state of chronic hyperglycemia in insufficiently treated DM. The exact pathophysiology of diabetic peripheral neuropathy is unknown, and there are thought to many possible contributing factors. Over time, hyperglycemia leads to increased substances in the bloodstream and tissues which damages nerves, such as reactive oxygen species (ROS) and sugar alcohols. In addition, factors in the blood such as insulin-like growth factor which promote neuronal growth are downregulated. Damage may also occur due to dysfunction of endothelial cells within blood vessels, leading to decreased blood flow to nerves and hypoxia.

Over time, damage to peripheral nerves results in deficits to sensation, motor function, proprioception, and most commonly, pain. Neuropathic pain from diabetic peripheral neuropathy has negative consequences for a patient's quality of life, and there are few effective therapies. It is estimated that as many as 30% of patients with DM experience neuropathic pain. Sensory deficits are a result of damage to the somatosensory nerves that detect pressure on the body's surface and transmit action potentials to higher brain regions to create the perception of touch. A patient with damage to their somatosensory nerves may complain of numbness in their hands and feet. As the damage progresses motor nerves may become involved, causing muscle weakness and, in advanced cases, muscle atrophy.

Clinical Presentation of Diabetic Peripheral Neuropathy

Sensory: Tingling sensation, neuropathic pain, slower healing, and complete loss of sensation. Complete loss of sensation in patients can lead to lack of attention to injury, which can lead to the formation of ulcers and infection.

Motor: Movement becomes more difficult, get tired quicker, loss of motor function which can lead to atrophy of muscles

Autonomic: Delayed changes in heart rate during movement. slowed digestion or paralysis of the digestive tract which can have a host of repercussions. Hypoglycemia unawareness can lead people to not properly manage their blood sugar and enter hypoglycemic states.[6]

Critical Thinking Exercise

Consider the following etiologies of neuropathy, and what you might think appropriate treatments may be.

- Diabetes Mellitus:

  Diabetes management, better blood glucose monitoring, proper insulin administration, proper diet. Type 2 diabetics may benefit from a variety of medications to help manage their glucose levels and reduce their insulin resistance.
- Entrapment:

  Surgical intervention to clear the entrapment, if entrapment is caused by swelling then antihistamines, or arthritis medications can be used.
- AutoImmunity:

  Immune suppressing medications such as corticosteroids, low dose chemotherapy drugs.
- Nutritional deficiencies:

  Rectifying the nutritional deficiency, which in this case would mean the supplementing of a b vitamin into the diet.

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8. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin

Pathophysiology of Neuromuscular Control: Issues with Neuromuscular Junction (Myasthenia Gravis)

VALERIE SWANSTON AND CARTER ALLEN

Learning Objectives

By the end of this section, you will be able to:

- Define Myasthenia Gravis.
- Explain the pathophysiology of Myasthenia Gravis.
- Identify the common signs and symptoms seen in Myasthenia Gravis.
- List treatments for Myasthenia Gravis.

Recall what we learned about the NMJ. An action potential is conducted down a motor neuron and travels to the axon terminal, triggering the opening of Ca^{2+} channels. Influx of Ca^{2+} ions into the neuron causes V-snare proteins on the vesicles to bind with T-snares on the synaptic bulb membrane leading to release of the neurotransmitter acetylcholine (ACh). In the synaptic cleft, ACh binds to ACh receptors (AChR) on the muscle fibre end plate, triggering a new action potential in the sarcolemma of the muscle fibre (end plate potential). The action potential leads to a conformational change in certain receptors (also along the sarcolemma) which opens flow of Ca^{2+} out of the sarcoplasmic reticulum (which is where calcium is stored in muscles). Ca^{2+} binds to troponin which causes a conformational change, exposing the actin to myosin heads, which leads to cross bridging, which causes contraction of the muscle.

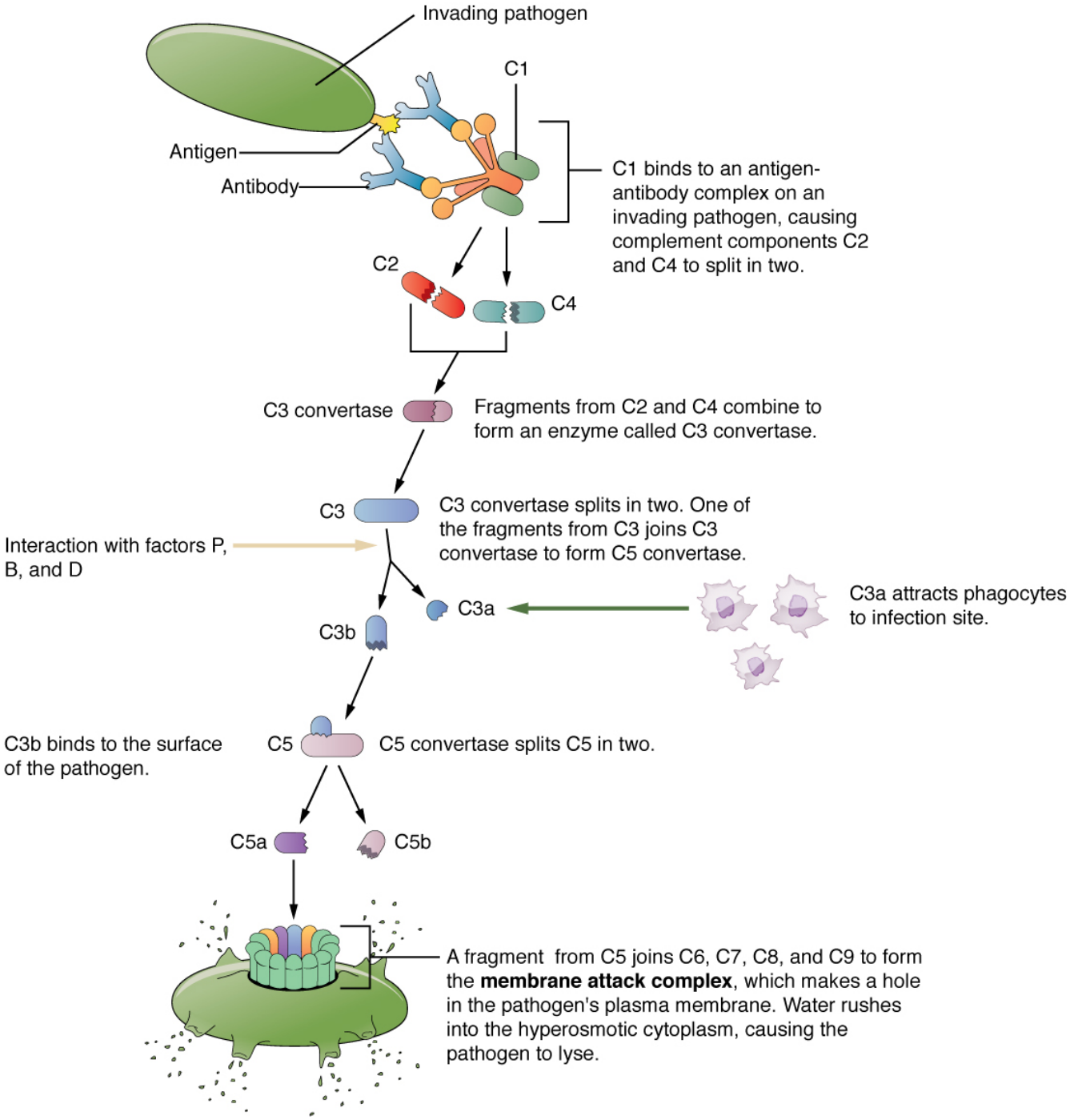
Pathophysiology of Myasthenia Gravis

Myasthenia Gravis (MG) is an autoimmune disorder, meaning it is caused by the body's immune system mistakenly identifying normal parts of the body as foreign and mounting an immune response against them. The identification of self peptides as foreign by helper T-cells leads to B-cells production of autoantibodies (antibodies against self) to a variety of proteins involving ACh transmission at the neuromuscular junction (NMJ). This interrupts acetylcholine action at the NMJ, preventing the neural control of voluntary motor movement. The following are the kinds of autoantibodies associated with Myasthenia Gravis.

1: Anti AChR Autoantibodies

This is the most common presentation of MG and most MG patients with autoantibodies against other proteins will also test positive for AChR autoantibodies. The AChR autoantibodies are thought to block transmission through the NMJ by three mechanisms:

1. Autoantibodies competitively antagonize AChR therefore inhibiting ACh binding.
2. Promoting endocytosis (internalization) of AChR into the muscle fibre so it is no longer at the cell surface.
3. Activate complement. The complement cascade outlined below will inevitably lead to the creation of the membrane attack complex, which will bring about the lysis of the postsynaptic membrane.



Complement Cascade and Function – *The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.*

2: MuSK Autoantibodies

MuSK is a protein expressed only in our skeletal muscle, it is thought to play a key role in presentation of high density of AChR at the NMJ. Thus antibodies against MuSK will result in less receptors on the muscle to start initiation of contraction.

3: LRP-4 Autoantibodies

LRP-4 acts upstream in regulation of AChR clustering much like MuSK, and regulation of presynaptic membrane organization. [1]

4: Agrin Autoantibodies

Agrin is a protein responsible for the activation of MuSK.

5: Cortactin Autoantibodies

Cortactin is involved in regulation of both synaptic and post synaptic membranes at the NMJ. [2]

As a result of inhibition destruction of any of these structures by autoantibodies, communication between the muscle and motor neuron is blocked or impaired, leading to fluctuating muscle weakness.

Clinical Presentation

MG appears more frequently either before the age of 30 or at 50 yrs and older. MG has a higher frequency in females less than 30 years of age, which is typical of autoimmune disorders. Patients with MG most commonly present with symptoms involving the fatiguing of ocular muscles. This often presents as ptosis, a characteristic “drooping” of the eyelid.

There are two kinds of MG: ocular (localized in eye muscles) and generalized. As mentioned, patients most often present with only eye symptoms. Ocular MG presents with signs and symptoms isolated only to the eye(s) and vision. Ocular MG presents with ptosis, decreased movement of the eyeball, and weakness of the eyelids. Ocular MG can progress to generalized MG. Patients with generalized MG may also have ocular symptoms.

Patients with MG often have muscle weakness that gets worse throughout the day. When disease spreads to different muscle groups it can cause a host of different problems including trouble regulating swallowing (dysphagia), trouble speaking (dysarthria), and reduced facial expression. Patients’ dysphagia might cause them to need to be put on special diets. Patients may reduce their oral intake because of fatigue of chewing and swallowing muscles. In the appendages patients will have muscle weakness. This generally affects proximal muscles (closer to the torso) more than distal ones. In extreme cases, severe weakness of respiratory muscles can cause respiratory failure requiring mechanical ventilation.

Did you know: botulinum toxin

You may have heard of people getting "Botox" treatments for cosmetic reasons, such as reducing the appearance of facial wrinkles. The substance responsible for this effect is botulinum, a neurotoxin produced from the bacteria *Clostridium botulinum.* Similarly to the AChR autoantibodies in MG, botulinum acts at the NMJ to prevent transmission of action potentials from the motor neuron to the muscle fibre. However, its exact mechanism is different; it acts at the axon terminal at the motor neuron by preventing ACh release. Botulinum is injected into the facial muscles to force them to relax, which has a smoothing effect on the overlying skin. Botulinum is also used for medical reasons such as treating muscle spasticity.

Diagnostic Tests

To determine whether ocular symptoms are caused by MG vs other neuromuscular pathologies, a series of clinical exams for fatigue of eye muscles during gaze and unsynchronized eyelid movements.

In addition to clinical presentation, diagnosis can be made by investigating the presence of autoantibodies to AchR. A serum sample is taken and tested for Myasthenia Gravis antibodies.[3]

Treatment of MG

Acetylcholinesterase breaks acetylcholine down into acetate and choline in the synaptic cleft of an NMJ. Therefore inhibition of acetylcholinesterase will lead to an increase of acetylcholine available in the NMJ, which will compensate for a reduction in the number of active receptors

Immunosuppressants inhibit the production and release of interleukin II which reduces proliferation and activity of T-cells and B-cells (which produce antibodies)

Corticosteroids suppress the immune and inflammatory response. Immunosuppressant medications that reduce the expression and activity of immune cells in the body.

4

Complement Interruption

Drugs that act as antibodies which can block or even signal for the destruction of complement proteins. Blocking the correct complement proteins, such as C5, can effectively stop the complement cascade.[5]

Thymectomy

Removal of the thymus gland can reduce autoimmunity, as the thymus is where T-cells mature.

Plasmapheresis

Machine filtration of autoantibodies out of blood. This however does not prevent the production of new autoantibodies, and is therefore only a temporary treatment

Intravenous Immunoglobulin

Influx of detectable antibodies in the body reduces the production of autoantibodies.[6]

Review Questions



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- 2212_Complement_Cascade_and_Function © OpenStax College is licensed under a CC BY (Attribution) license

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Pathophysiology of Neuromuscular Control: Muscle Structure and Function (Muscle Strains and Muscular Dystrophy)

MEIHUA E. SU AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Describe how muscle fatigue manifests in movement disorders.
- Explain the role of dystrophin and how it relates to muscular dystrophy.
- List some common manifestations of muscular dystrophy.

As already mentioned, movement disorders can occur when there is a dysfunction in nerves, neuromuscular junction, or muscle function. This chapter will focus on muscular disorders that are more benign (e.g. muscle fatigue and strains/sprains) and insidious (e.g. muscular dystrophy).

Muscle Fatigue and Strains

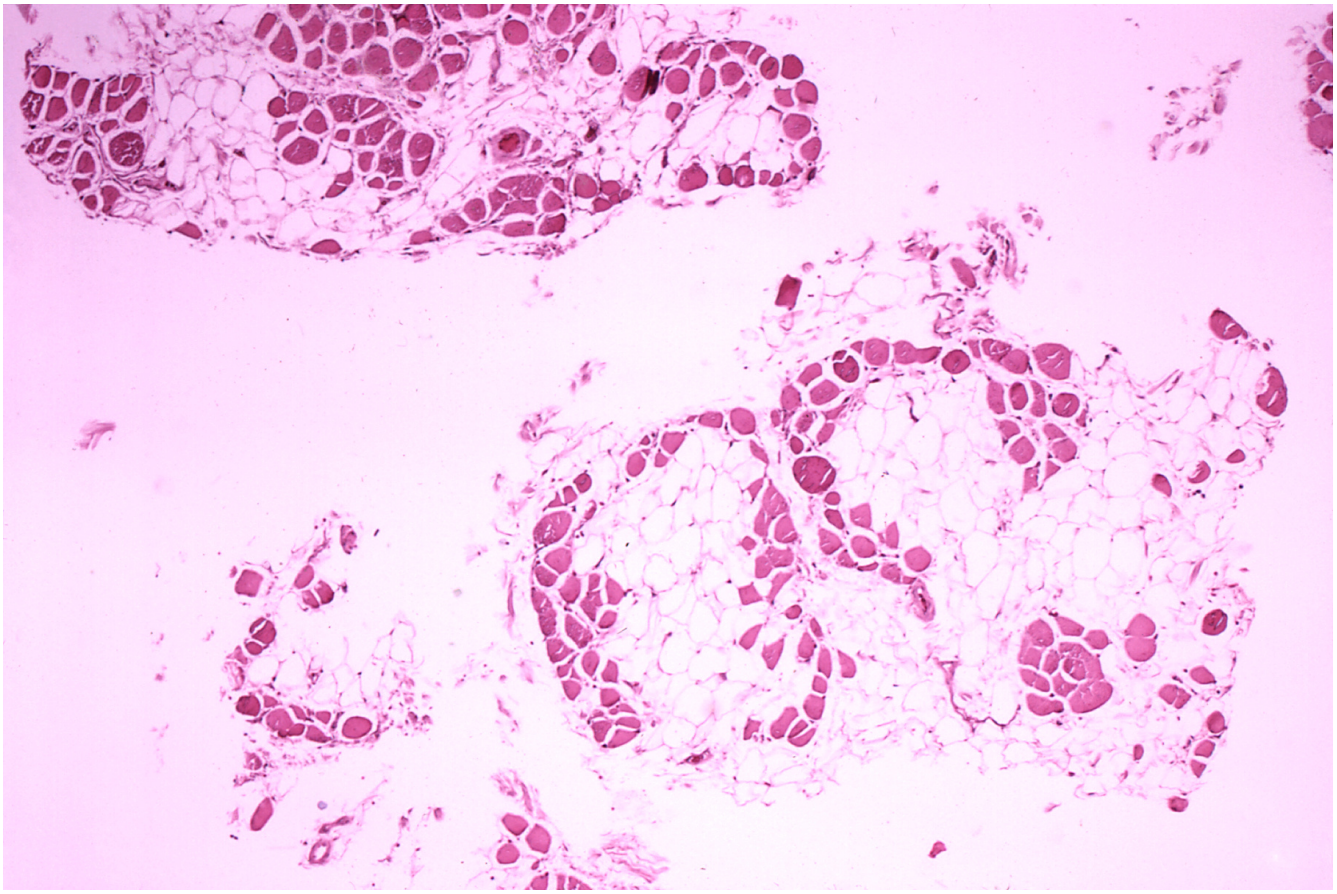
At some point in our active lifestyles, we may have had a muscle problem – whether it be muscle fatigue after a particularly strenuous activity and/or a strain (i.e. tear in the tendon or the muscle itself). In both situations, the anatomy of the muscle itself is normal, but there is an issue with its function. In the case of muscle fatigue, there was a point in time where the muscle did not have sufficient oxygen for efficient aerobic metabolism. As a result, the muscle shifted to anaerobic metabolism which creates lactic acid as a byproduct (assuming oxygen debt was not repaid). As a result, there is physical damage to the muscle tissue from the acidic environment. Similarly, muscle tears also involve physical damage to a localized area. In both situations, the inflammatory response follows, leading to the characteristic features of possible swelling, heat, redness, and pain. While the muscle tissue undergoes inflammation and healing, the function of the muscle is impaired, often manifesting as lack of strength, decreased flexibility, and pain upon use. This would appear as a movement disorder due to the impaired strength and flexibility of the injured muscles. Sometimes, a mobility aid (e.g. crutch) is required to offload weight which lends support to the weaker muscles. However, once the muscle heals, muscular function returns and there is no longer any movement disorder.

Muscular Dystrophy

As mentioned previously, muscle cells have the protein dystrophin to protect myocytes from overstretching and tearing.

Dystrophin is a rod-shaped protein that acts like a coil or "shock absorber" at the cellular level. It expands in response to the forces of contraction and stretching to prevent tearing. Muscle strains are the result of physical exertion exceeding the protective capabilities of dystrophin.

In the genetic condition of muscular dystrophy (MD), the gene for dystrophin contains errors resulting in non-functional dystrophin. Without functional dystrophin, the myocytes lose both their abilities to recoil and to maintain stability and strength during contraction. This results in myocytes being constantly damaged after every use: akin to muscle strains with every use. Inflammation occurs and new myocytes grow to replace the damaged ones. However, the new myocytes also contain dysfunctional dystrophin. Over time, the muscle tissue is replaced with scar tissue and fat due to chronic muscle damage, resulting in loss of muscle strength and function.



Histopathologic changes found in a skeletal muscle with Duchenne Muscular Dystrophy – *This photomicrograph revealed histopathologic changes found in a skeletal muscle tissue harvested from the gastrocnemius muscle of a patient with a fatal case of Duchenne muscular dystrophy (DMD), also known as pseudohypertrophic muscular dystrophy. This cross section of the muscle, shows extensive replacement of muscle fibers (dark red), by adipocytes, or fat cells (clear/white).*

There are many kinds of MD, differing in severity, age of presentation, heritability, and affected muscles. However, they share the common feature of defective dystrophin production.

Duchenne and Becker muscular dystrophy (DMD & BMD), are types of "muscular dystrophy," that leads to a progressive weakening of the skeletal muscles of the upper legs and upper arms due to the lack of dystrophin. In DMD & BMD, muscle contractions cause the cell membrane (sarcolemma) to rupture, causing an uncontrolled influx of ions, especially Ca^{2+}, through the breach. This influx leads to further to cellular damage and a disruption of the environment needed for mitochondrial function and electrical excitability.

DMD/BMD is a sex-linked inherited disorder (abnormal X chromosome) of the dystrophin gene. Because it is X-linked, it presents primarily in males as males rely on that X-chromosome for dystrophin expression. DMD can also manifest in females, but its presentation might take longer to be evident as it is dependent on whether one or both X chromosomes express the defective dystrophin gene. In males, DMD is usually diagnosed in early childhood. For reasons not yet known, BMD presents later in life (adulthood) yet it involves the same gene as DMD. There are many other types of MD which are not sex-linked, meaning that it affects both males and females equally.

MD usually first appears as difficulty with balance and/or motor strength & endurance. If presenting during infancy and childhood, this may manifest in developmental delays in rolling over, sitting up, standing and walking. As muscle tissue is lost, MD presents as easy tiring upon walking, waddling, and wide-based gait (waddling or hip swinging) with arms swings to help maintain balance. MD can progress to an inability to walk if hip and leg muscles are further affected. MD can also affect muscles responsible for breathing, swallowing, and circulation (the heart) which can ultimately cause death due to respiratory failure.

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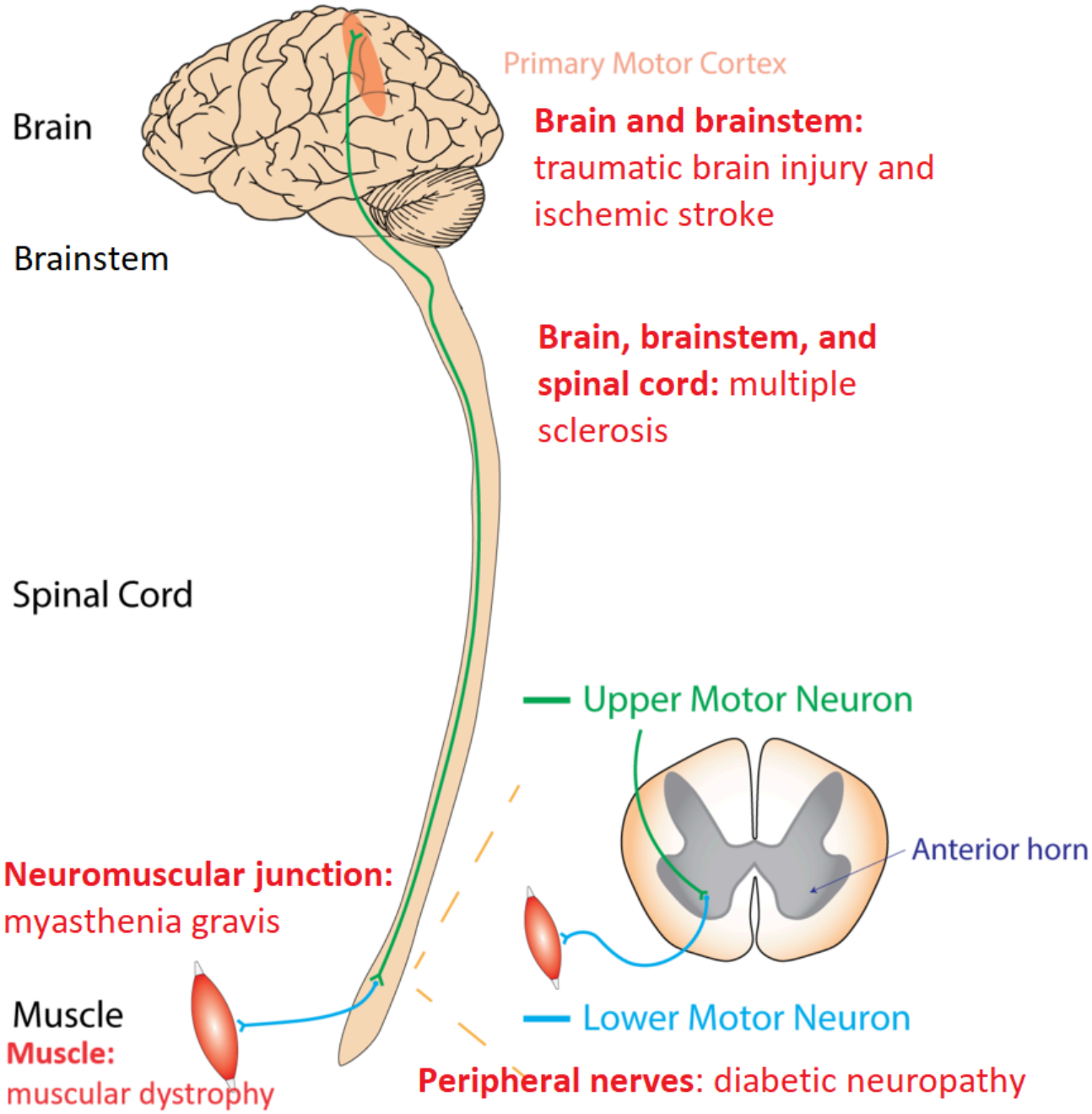
Clinical Manifestations of Neuromuscular Disorders

VALERIE SWANSTON

Learning Objectives

- Describe the clinical manifestations of traumatic brain injury, ischemic stroke, multiple sclerosis, and peripheral neuropathies

Now that we have learned about multiple different conditions affecting the neuromuscular system, let's put this information together to understand how there can be many possible etiologies (causes) of a patient experiencing a neuromuscular symptom or deficit. Starting from top to bottom, muscle contraction is initiated in the motor association areas and primary motor cortex in the frontal lobe of the cerebral cortex. An action potential is transmitted down the upper motor neuron through the brainstem and spinal cord, which synapses with a lower motor neuron in the anterior horn of the spinal cord. The lower motor neuron exits the spinal cord in the anterior root and travels to the muscle. Action potential transmission at the synapse between the lower motor neuron and the muscle fibre (also known as the NMJ) results in contraction of the muscle and production of voluntary movement. Weakness or paralysis of a muscle may be due to interruption *at any point* along this pathway. Think about the pathophysiology of the neuromuscular conditions we just learned about and how they may interrupt this pathway and result in motor symptoms, as demonstrated the figure below.



A *summary of the neuromuscular system* – *The diseases that we covered in this chapter are indicated in red, along with their principal site of action along the pathway of neuromuscular transmission. Used and adapted under creative commons license, original author Rcchang16 (File:UMN vs LMN.png – Wikimedia Commons).*

In this chapter, we will discuss some of the typical neuromuscular deficits observed in each condition we learned about previously. Think back to the pathophysiology of each condition and see if you can rationalize the symptoms we're learning about.

Direct Observations of Neuromuscular Disorders

Patients realize they have a neuromuscular disorder before any test is taken: mostly because it is affecting their activities of daily living. However, problems with voluntary movement is a manifestation of impairments of the incoming sensory message, outgoing motor message, the neuromuscular junction, or muscle contraction. By observing the following changes, one can hone in on the site of pathology.

While the clinical examination of neuromuscular disorders is out of the scope of this book, there is another Open Education resource which demonstrates these clinical examinations. Clinical neurological exams. A skilled health care practitioner will be able to determine normal vs. impaired neuromuscular functions and whether these impairments are on the sensory, motor, or both sets of nerves. These test results are loosely summarized as below.

Clinical Manifestation	Impairment of sensory, motor, or both
Changes in sensation in a localized area	Ascending sensory nerve, spinal cord (sensory), brain
Changes in sensation in different geographic locations	Ascending sensory nerve, spinal cord (sensory), brain
Decrease in sensation AND motor in the same localized area	Peripheral nervous system (esp where sensory and motor nerves are bundled together)
Changes in speed or strength of motor movement	Descending motor nerve (upper/lower motor neuron), neuromuscular junction
Changes in muscle bulk	Loss of muscle tissue or loss of muscle tone due to decr nervous control
Changes in reflex	Spinal cord at the level of the reflex, lower motor neuron,
Loss of sensation and motor	Brain
Changes in motor in different geographic locations	Upper/lower motor neuron; peripheral nervous system?

Clinical manifestations and where the area of impairment lies

Traumatic Brain Injury

A traumatic brain injury (TBI) can have a severe impact on the health and function of the brain, brainstem, and/or spinal cord. Many TBI patients experience significant neuromotor dysfunction and disability, at times for the rest of their lives. Here we'll discuss some of the typical neuromuscular symptoms a patient with a TBI may experience.

The Three Stages of Recovery

Patients with TBI typically go through three stages of recovery following their accident. The first involves a period of unconsciousness or coma, and can last anywhere from seconds to several weeks or months. Following this there is a second stage of behavioral and memory challenges, such as agitation, disorientation, and amnesia. Lastly, the third stage involves a lengthy period of diverse challenges including behavioral, cognitive, and sensorimotor changes.

Possible Neuromuscular Symptoms

The exact neuromuscular deficit a patient with a TBI will experience depends entirely on the location of the damage within the brain, brainstem, or spinal cord. A patient with diffuse axonal injury affecting many different areas of the brain may have multiple unpredictable motor impairments. On the other hand, a patient with a focal injury involving a specific component of the corticospinal tract may have symptoms that follow an expected pattern depending on exactly which component is damaged. For example, damage to the topmost aspect of the primary motor cortex in the left hemisphere may result in weakness to the right upper limbs (recall what we learned about the motor homonculus!) Overall, long term motor weakness following TBI is relatively rare. However, balance issues are more frequently reported, which can impact patients' gait and mobility.

Disorder	**Description**	**Example**
Dysarthria	Difficulty producing speech due to deficits in the motor system that creates the movements for talking.	Damage to cranial nerve five, the trigeminal nerve, which controls the jaw muscles.
Spasticity	Rigidity and increased tone of skeletal muscles	Spasticity may be caused by damage to upper motor neurons in the brain or spinal cord, which causes an imbalance in excitatory and inhibitory signals sent to the lower motor neuron and the muscle.
Gait disorders	Abnormalities in limb movements, posture, and/or muscle tone leads causes abnormal walking	Damage to the cerebellum resulting in uncoordinated motor responses can negatively impact gait

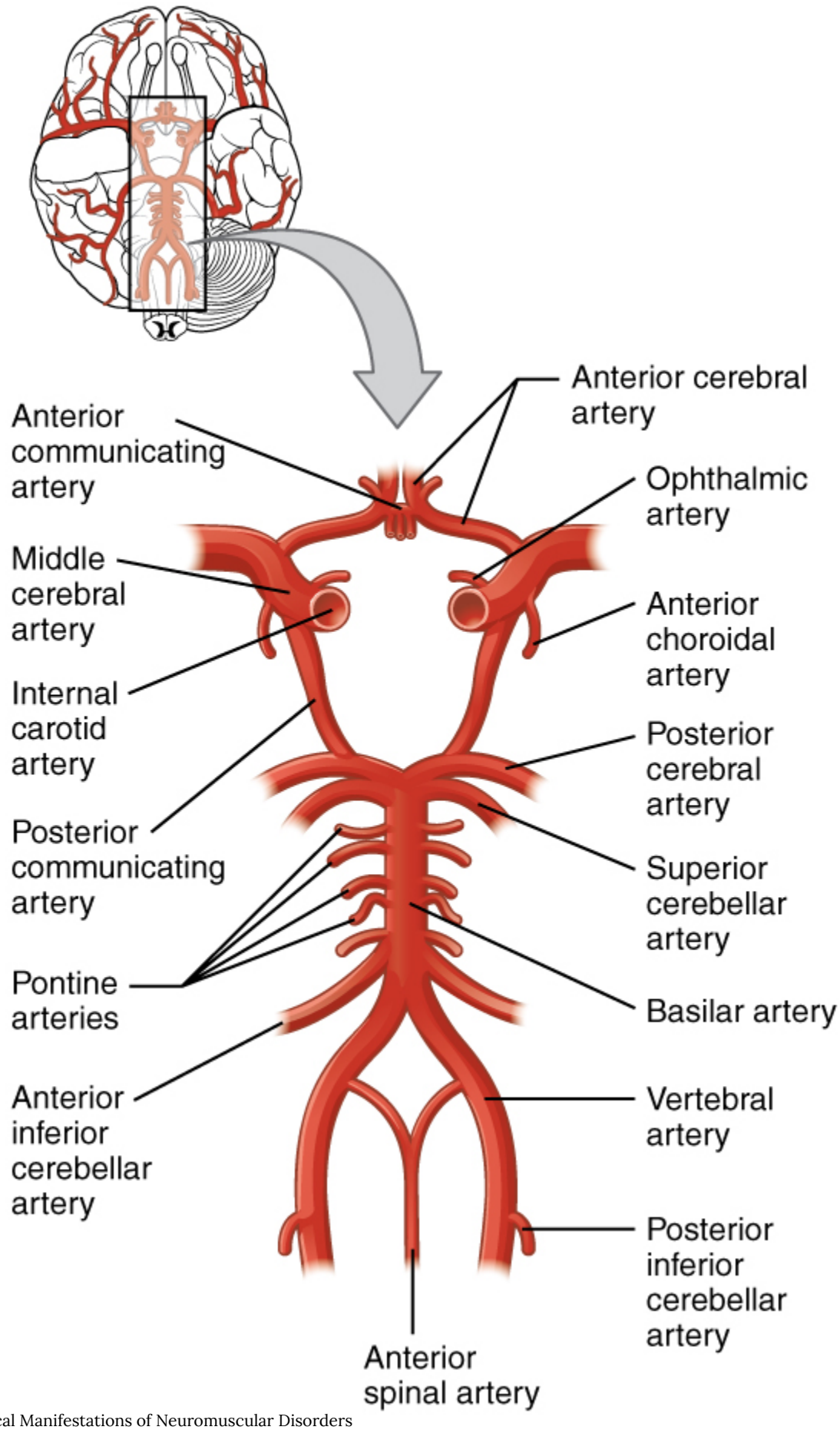
Neuromotor disorders a patient with a TBI may experience.

Ischemic Stroke

Ischemic stroke is large contributor to neuromuscular disability worldwide, and has a profound impact on patients and their families. Ischemic stroke is caused by a blockage in the vasculature within the brain, causing tissue infarction and death. If motor areas of the central nervous system are impacted, there may be permanent disability.

Possible Neuromuscular Symptoms

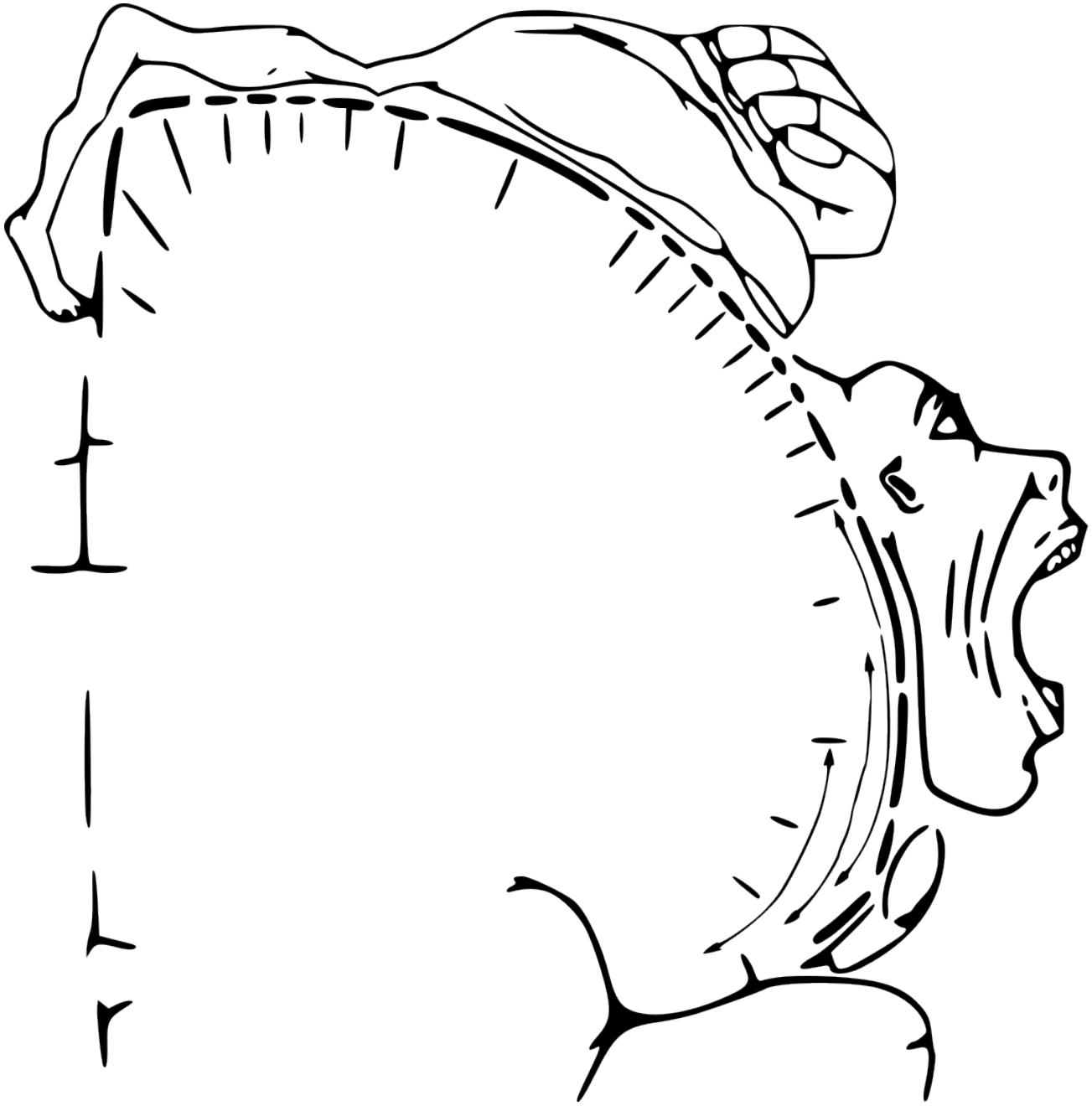
The exact symptoms of a stroke depend on which artery is occluded, causing various "syndromes" with characteristic symptoms. For example, middle cerebral artery syndrome occurs when the middle cerebral artery (MCA) is occluded, and the typical presenting symptoms include hemiplegia and hemianesthesia. Refer back to previous chapters to refresh your knowledge on the vasculature in the central nervous system.


Anterior cerebral artery
Anterior communicating artery
Ophthalmic artery
Middle cerebral artery
Anterior choroidal artery
Internal carotid artery
Posterior cerebral artery
Posterior communicating artery
Superior cerebellar artery
Pontine arteries
Basilar artery
Anterior inferior cerebellar artery
Vertebral artery
Posterior inferior cerebellar artery
Anterior spinal artery

Circle of Willis – *The blood supply to the brain enters through the internal carotid arteries and the vertebral arteries, eventually giving rise to the circle of Willis.*

Clinical manifestation	Description	Location of Occlusion (stroke syndrome)	Anatomical Explanation
Aphasia	Disordered speech production and/or comprehension	Left middle cerebral artery occlusion	The middle cerebral artery supplies blood to Broca's and Wernicke's areas, which are responsible for speech production and comprehension, respectively. Because the language areas of the brain are located in the dominant hemisphere, aphasia is usually caused by an ischemic event on the left side.
Ataxia and gait disorders	Abnormalities in limb movements, posture, and/or muscle tone leads causes abnormal walking	Vertebral-basilar occlusion	Branches of the vertebral arteries supply the cerebellum with blood. When there are occluded, infarction in the cerebellum can alter coordination of movements and alter walking and balance.
Left lower extremity paresis	Weakness or paralysis of the left leg	Right anterior cerebral artery occlusion	The anterior cerebral artery supplies blood to the midline portion of the frontal lobe, which includes the motor cortex. Recall the motor homonculus, where the cortical areas that provide function to the upper extremities are in close proximity to the midline.

Possible symptoms of an ischemic stroke and the location of blockage



The Motor Homonculus *– Just like the sensory homonculus, there is a topographical "map" on the motor cortex where certain cortical areas are responsible for initiating muscle movement in a certain region of the body. Muscles responsible for finely detailed movements, such as the fingers and face, are overrepresented compared to their muscle size. Image by Was a bee, used under creative commons license.*

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is a complex disease that causes significant neuromuscular disability. Up to 50% of diabetics can expect to develop neuropathy in their lifetime, therefore this condition impacts a large amount of the population.

Distal Symmetrical Polyneuropathy

The most common clinical presentation of diabetic neuropathy is distal symmetrical polyneuropathy. Let's try to understand this condition by understanding the meaning of each word.

- **Distal**: away from the center of the body, and is opposite to proximal
- **Symmetrical**: same on both sides of the body
- **Polyneuropathy**: damage to many neurons

Therefore, distal symmetrical polyneuropathy begins distally in the feet, involves both sides, and is caused by damage to many peripheral nerves. The condition begins with sensory disturbances in the toes, such as numbness and paresthesia (tingling), which gradually spreads upwards. As the condition progresses, autonomic nerves become involved as well. In severe cases, motor nerves innervating muscles in the most distal part of the lower limbs may be involved, which can lead to muscle weakness and wasting.

Diabetic Foot

Foot complications are common among people with diabetic peripheral neuropathy. Sensory loss in the feet may cause injuries to go unnoticed, which can lead to ulcerations, musculoskeletal (MSK) complications, and, in extreme cases, may require amputation. Foot complications may be prevented by daily foot care and inspections, and by close monitoring by a foot specialist.

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Neuropathy – Diabetes Canada

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Interprofessional Collaboration During Diagnosis and Management of Neuromuscular Disorders

JENNIFER KONG

Control of voluntary movement is complex as there are so many parts to neuromuscular control, with pathologies arising when there is a deficit in any part. Thus, diagnosis and management of neuromuscular pathologies requires a team of health care providers.

Throughout this chapter, we have mentioned blood tests and medical imaging – both professions we have covered in chapters. As neuromuscular control involves electrical messages flowing through nerves and muscles, electroneurophysiology is an important field to help determine where the pathology lies.

Electroneurophysiology

Electroneurophysiology technologists measure the electrical activity of the the CNS: using an electroencephalography (EEG) for the brain and electromyography for the peripheral nerves. Electroneurophysiology technologists work with the health care team when there is a suspicion of abnormal alterations in brain electrical activity (e.g. seizures, epilepsy, strokes), spinal cord injuries, or interruptions in conduction of the PNS caused by inflammation, mechanical compression, etc. The data gathered will help locate the geographic area of the abnormal electrical conduction, and hence, function.

Electroencephalography



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Electromyography



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Management of Neuromuscular Control Pathologies

As previously mentioned, many neuromuscular pathologies have no cure. Thus these conditions can be managed to allow for as much mobility and stability as possible. Prosthetics and Orthotics is a field which helps with mobility and stability, regardless of the cause of their neuromuscular pathology.

An orthotist is a healthcare provider who makes and fits devices (orthoses) for people who need added support for mobility and stability due to injury or disorders in neuromuscular control. These orthotic devices (e.g. braces, splints) can help distribute the person's weight and/or prevent undesirable dropping of limbs due to to a loss of neuromuscular control (e.g. foot drop). Orthoses allow for movement and stability.

A prosthetist is a healthcare provider who makes and fits prostheses (artificial limbs) for those people who have lost a limb due to injury or disease process. Although none of the pathologies discussed in this chapter involves limb loss, some pathologies – esp diabetic neuropathy – can lead to amputation if the disease is poorly managed.

Prosthetics & Orthotics



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Neuromuscular Summary & Credits

JENNIFER KONG

Chapter Summary

Smooth, voluntary movement is a result of a complex set of pathways working correctly and in synchronicity. A voluntary message/action potential starts in the primary motor cortex in the brain (grey matter in the precentral gyri of the cerebral cortex of the brain) and travels along the white matter tracts down – through the subcortical fibers, brainstem, and into the spinal cord. At the level of the desired muscle, the motor message/action potential leaves the CNS (spinal cord) and relays its message to the corresponding peripheral nerve of the PNS. The peripheral nerve then synapses with its desired muscle target, at the neuromuscular junction (NMJ), using the neurotransmitter acetylcholine. Upon Ach binding to its receptor on the skeletal muscle, electrical excitation occurs allowing for muscle contraction to happen. Any interruption in any of these aforementioned steps will lead to problems with neuromuscular control.

Issues with the generation of motor message/action potential generation can be caused by direct damage to the cerebral cortex, whether by physical trauma (traumatic brain injury) or lack of blood flow (stroke).

Issues with conduction of the motor message along a nerve can be caused by loss of myelin in the white matter and/or death of the axon. This causes a 'short circuiting' of action potential such that the message never reaches the PNS and muscles. Demyelination of CNS is a hallmark of multiple sclerosis whereas widespread neuronal damage of the PNS is commonly seen with diabetic neuropathy.

Problems at the pivotal neuromuscular junction can be caused by autoimmune condition which attacks the acetylcholine receptors on muscle, resulting in lack of muscle stimulation. Myasthenia Gravis, although rare, presents as difficulties in mobility even with functional nerves and muscles since the NMJ is impaired.

Muscle damage is common with movement and is considered as muscle strain (esp with tendons) or sprain (as with ligaments that join the bones over a joint). Muscles and tendons have an incredible ability to heal, such that impaired mobility is relatively shortlived. However, the genetic condition muscular dystrophy has a faulty dystrophin protein in its muscles, resulting in all muscles being damaged with each use causing scarring and progressive loss of mobility.

Clinical presentation of neuromuscular disorders is wide and varied, dependent on the location and nature of the pathology along the CNS, PNS, NMJ, and/or muscles. However, the end result is the same: impairment to voluntary movement. A highly knowledgeable team of health care providers is needed to work collaboratively to help isolate the location of the pathology and diagnose the disorder: electroneurophysiologists being such a provider. Similarly that team will include professionals such as orthotists to help create a workable management plan to help the patient maintain the best mobility and stability possible.

Credits

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Videoproducer: Lindsay Belloc (BCIT)

Post-test

JENNIFER KONG



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APPENDICES: CASE STUDY FOR HEART FAILURE

This case study is from another Open Education Resource "Health Case Studies" by Glynda Rees, Rob Kruger, and Janet Morrison. The following chapters follow the health journey fictional character Meryl Smith takes from her exacerbation of heart failure followed by her hospital admission.

Although the case study's pathology is heart failure in general (rather than our chapter on right- vs left-sided heart failure), there are many similarities in the diagnosis and treatment and interactions with health care team.

Learning Objectives

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Learning Objectives

In this case, learners have an opportunity to:

1. Review etiological factors (i.e., risk factors, prevalence, comorbidities) associated with HF
2. Build knowledge related to the patient's experience of HF
3. Continue to develop comprehensive assessment and monitoring skills and abilities (e.g., cardiac assessment, diagnostic studies, laboratory data)
4. Consider the links between evidence-based knowledge and practice in the care of patients with HF (e.g., CCS Guidelines for the Diagnosis and Management of Heart Failure)
5. Recommend interventions based on the risk factors, status, and progression of cardiac disease
6. Define the roles of healthcare professionals and the contributions they make to the healthcare team (or describe your own role and the roles of those in other professions)

This case describes a patient's experience with heart failure (HF) related to a post-pregnancy heart murmur.

Learners reviewing this case can consider how influenza affects chronic disease, how heart failure occurs, and treatment options. The same-sex family offers learning opportunities on what family means and explores the changes in societal norms. Interprofessional practice is role modelled between the healthcare professionals likely to care for a heart failure patient.

Patient: Meryl Smith

GLYNDA REES; ROB KRUGER; AND JANET MORRISON



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Patient: Meryl Smith

Date of Birth: 06/06/19xx

PERSONA

Meryl Smith is 44 years old and she lives in a small two bedroom home with her partner, Dorothy. They co-parent two children with Meryl's ex-husband. Her marriage to him ended four years ago. Meryl is a police officer with the Royal Canadian Mounted Police (RCMP). Meryl drinks occasionally, she has never smoked, and she is physically active. Meryl and Dorothy also have two cats at home with them.

Past medical history includes a heart murmur developed after her second pregnancy. She had a cholecystectomy three years ago and a laminectomy 14 years ago. She has recently been recovering from a severe flu.

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In the Supermarket

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 0

Time: 09h30

Place: Supermarket

Dorothy looked over her shoulder at Meryl, who seemed to be trailing with the shopping cart . *This is a bit unusual. Meryl hates food shopping and tries to complete it as quickly as possible*, she thought.

"Meryl, you doing ok dear? I think we are out of mayo. Can you grab the low fat, small jar as you walk past?"

Meryl looks up at Dorothy and smiles weakly. "I am feeling a bit tired, but I'm ok. Yes, I'll grab the mayo, but I'm getting the one that is on sale."

Meryl reaches up and grabs a small plastic jar of mayo and places it in the top part of the cart.*What the heck is going on? I really don't feel so well and Dorothy is walking so fast today. She usually likes to shop*, she thought.

Dorothy waits for Meryl at the end of the condiment row and rubs her back and gives her a quick peck on the cheek before moving off again down the next row. Meryl, taking a deep breath and leaning heavily on the cart, plods slowly forward.

Time: 10h00

"Meryl, where are you?" Dorothy does a 360 degree turn in the row and does not see her spouse anywhere. She quickly checks the next row only to see it empty. Feeling a bit panicked, like losing a child, Dorothy retraces her steps to the previous row to find Meryl, sitting on the floor with the partially full cart a few feet down the row.

Rushing up to Meryl, Dorothy quickly looks around and then bends down. "Did you fall? Are you ok?"

Meryl looks up slowly and Dorothy immediately recognizes that something is not right.

"Oh my, Meryl, you do not look good. You are pale and quite dusky looking. I'm not quite sure you are over the flu."

"Dorothy. I am not. Feeling good. Not the flu. Very dizzy." Meryl whispers breathlessly. "I think it's….My heart."

Dorothy goes into full panic mode on hearing 'heart'. She helps Meryl stand; Meryl wobbles a little bit before seeming to settle on her feet. Together they walk out like a coach guiding an injured player from the field.

"Dorothy… our cart!"

“Meryl, the least of my concerns is the cart. Someone can put the stuff back on the shelves. I am more concerned about you. We are going to the Emergency.”

Meryl places both hands on the roof of their small sports car and waits for Dorothy to open the door. “What if I. Don’t want to. Go to the Emergency?”

“Sorry, hon. Laying in the middle of Safeway examining the floor tiles closely, gets you one free express ticket to the Emergency. Don’t gripe. You are going to suck it up.”

Meryl allows Dorothy to help her into the passenger seat. Dorothy hears a bit of quiet grumbling from Meryl but chooses to ignore it.

Dorothy starts the car and backs out quickly. Driving faster than usual, Dorothy navigates the two of them through the back roads and into the parkade of the hospital.

Time: 10h30

“See, Meryl? This was meant to be. Someone left us a wheelchair to use.”

“You can’t be serious.”

“Try me, hon, you are riding until they tell me what is wrong with you.”

Dorothy guides Meryl out of the sports car and into the wheelchair. Pushing the wheelchair by the parking meter, Dorothy stops and pays for four hours of parking.

Emergency Room

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 0

Time: 11h15

Place: Emergency Triage

Nurse Jackie thinks to herself, *Wow, I finally get to sit for a minute. This flu season has been brutal. Fifteen patients before 10:30 in the morning*. She completes a number of stats forms behind the triage desk and adds some names to the whiteboard to keep track of where patients and staff are located.

Turning back to the desk, Jackie looks up to see two well-dressed, middle-aged women approaching, one in a wheelchair.

"I bet this is another flu case," Jackie says to herself.

"Good morning, can I help you?"

Dorothy pulls the wheelchair up to the triage desk. "That is why we are here, for you to help us or more specifically help Meryl!!"

Jackie looks at both women and attempts a smile. *Ok, this could be challenging*, she thinks.

"What seems to be the problem or what can I help with?"

"My name is Dorothy and this is my wife, Meryl, who happened to pass out at Safeway this morning while we were shopping."

"My name is Jackie and I am the triage nurse or the nurse that looks at you first to consider how serious your problem is. Ok, so you passed out? Did you lose conscious or did you become dizzy and just sink to the floor?"

Meryl looks over at both of them. "I think a little of both. I just remember coming to, sitting cross legged on the floor."

"Ok, seems you are a bit short of breath?"

Meryl tries to take a deep breath that only results in a weak cough. "Yes, getting over the flu. Thought I was over it."

Jackie steps out from behind the triage desk and brings the vital sign machine with her.

Hooking Meryl up to the blood pressure cuff and the pulse and temperature, she presses a button to initiate the machine to take Meryl's vital signs.

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 11h20	106	95/60	20	36.5°C	95%

Nurse Jackie looks over the results and sees the temperature is not elevated, but the blood pressure (BP) is down and the heart rate (HR) is up. “Doesn’t look like it’s the flu for you, but maybe something else. Ok, let’s get you to wait over there and I will see if we can get someone to see you shortly. It’s not too busy so it should not be long.”

Dorothy shakes her head. “Wonderful — our health system at work. Ok Meryl, we get to sit and wait.”

Meryl looks up at Dorothy. “I am ok to wait.”

“You might be but I am not.” Dorothy directs the chair over to where Jackie indicated.

Time: 11h30

Nurse Jackie approaches Meryl and Dorothy. “I need to take some more information and then we can get you seen by the doctor.”

Jackie takes a full health history from Meryl asking her about past history, medication, allergies, and contact information.

“So you have a heart murmur that didn’t go away after your last pregnancy?”

“Yes, they told me not to worry too much about it.”

“Did they tell you anything more?”

“No, I haven’t worried about it till now. Today my chest just feels different and I am short of breath.”

“Ok, thank you. I am going to talk with Dr. Smythe and we will move you to another area here so we can explore more fully what is going on.”

Jackie walks away to find Dr. Smythe.

Time: 12h15

Just as Jackie is finishing recording her findings, Dr. Smythe approaches the bedside.

“Hello, my name is Dr. Edward Smythe. I am one of the Emergency physicians and Jackie asked me to take a look at you.”

Both Meryl and Dorothy look up and smile at Dr. Smythe and nod their heads together.

Dr. Smythe begins to assess Meryl, turning her head back and forth looking at her neck. He then checks her fingers and then looks at her ankles and gives them a bit of a squeeze. “I need to listen to your heart and lungs.”

Meryl adjusts her blouse to allow Dr. Smthye to access her chest. Dr. Smythe listens carefully to heart and breath sounds.

After completing his assessment, he steps back and looks at both Meryl and Dorothy. “I don’t think it’s the flu. Your heart murmur is quite loud, much louder than I expected, and you have quite coarse breath sounds. I believe I am also hearing an extra heart sound. Now this could be nothing or it could be serious so I would like to do some blood work, and a chest X-ray. I am also going to ask for a pregnancy test since the heart murmur appeared with your last pregnancy.”

Dorothy laughs. “Doctor Smythe, I don’t think she is pregnant!”

“Still it did happen and we need to rule it out.”

Dr. Smythe turns to Jill. “Please place her on the monitor and take vital signs q 15 minutes for the next hour then q1h. I will order a CBC, lytes, BUN, creatinine, trops, 12 Lead, and a portable chest X-ray.” Also, glucose, urinalysis, and a pregnancy screen. For the time being you’re on bed rest, and I will ask Cardiology to come see you.”

Jill records all this to make sure nothing gets missed.

Dr. Smythe turns back to the two women. “Meryl, you are going to be spending the better part of the day with us, so I am going to admit you to the Emergency and after we have all the tests results back, I will come and discuss these with you and what our next steps are.”

“Thank you, Dr. Smythe.”

Time: 12h45

The phone rings beside Jill as she is charting another episode of atrial fib, “Hello, this is Jill.”

“Hi Jill. This is Gurpreet in Radiology. I have a requisition for a chest X-ray on a Mrs. Meryl Smith. Can she come to the department?”

“I am thinking not as I have her on the monitor, and she was admitted with a complaint of loss of consciousness. I am a bit concerned that if she goes out, something may happen. I or another nurse will need to go with her.”

“Ok Jill, I thought that might be the case but I thought I would ask. I’ll be down in a couple of minutes and will do her X-ray with the portable in Emergency.”

“Thanks.” Jill hangs up the phone, finishes scotch taping the rhythm change to the patient’s chart and moves to Meryl’s bedside.

“Hi, Mrs. Smith. They’re coming down to do a chest X-ray so I would like to help get you setup so you’re ready for it when Gurpreet arrives with the machine.”

Jill then helps Meryl sit up straight, moves the ECG leads off her chest, and explains the X-ray to both Dorothy and Meryl.

Just as she is finishing, Gurpreet comes around the corner pushing the portable x-ray.

“Man, these things never get any lighter! Even with the power drive they’re a challenge to move around without running on toes. Is this Mrs. Meryl Smith?”

Jill smiles and looks at Gurpreet, “Yes it is, and that was quick. Do I need to check the wheels for any toes?”

“No, heard a couple of screams but nothing else as I drove here. Thank you for getting everything setup for me.”

“No problem.”

Gurpreet moves to the bedside, and checks Meryl’s position. “My name is Gurpreet. I just need to double check who you are and then I’m going to place a very hard board behind your back and take a picture of your chest.”

Meryl nods her consent.

Gurpreet looks at the requisition, and compares the information to the ID band on Meryl's left wrist. "Can you tell me your birth date?"

"Yes it is June 6, 19xx."

"Ok, we are good to go."

Gurpreet returns to the portable X-ray and withdraws from the rear hidden compartment, a large board. Slipping the board into a special plastic bag, she returns to the bedside. With Jill's assistance they both lean Meryl forward and place the X-ray board behind her back.

"Oh, that is so uncomfortable."

"Its only for a couple of minutes. Relax against the board and try not to move."

Gurpreet maneuvers the X-ray machine into position at the end of the stretcher. She turns on a light on the camera head and adjusts the aperture for Meryl's chest size. Using the built-in tape measure, Gurpreet checks to make sure the X-ray is the proper distance away. Satisfied that everything is correct, Gurpreet nods to Jill and grabs a lead apron from the stanchion of the X-ray machine.

"X-ray ready in Bed 4.

"Stand clear, X-ray exposing Bed 4!" Gurpreet then presses a button which starts a whirring sound, ending with a dull click.

"Ok, all done Mrs. Smith." Gurpreet hangs up the lead apron on the stanchion and moves to the bedside to help Jill remove the board and reposition Meryl into a more comfortable position.

Gurpreet backs the portable X-ray machine out.

Dorothy returns at the same time from grabbing coffees for her and Meryl. "Hey, what did I miss?"

Jill turns and says "First of many tests we have to complete. That was the X-ray and I'm hoping the lab person will be by shortly as well for the other tests."

Time: 12h59

Alexa looks at the list of requisitions that have come into the lab. "Alright, there is a bunch from Emergency and two from the Family Birthing Unit. I can do the Emergency ones quickly. I should see if someone can do the FBU ones."

Looking up, she sees Harry at the desk. "Hey Harry, can you do me a favour? I am a bit swamped with reqs from Emergency and there are two from the FBU that I can't do as quickly as they would like. Do you mind?"

Harry smiles, "For you Alexa, anything, but it will cost you a coffee."

"A coffee I can handle, thank you."

Alexa grabs her lab cart and heads out the door to the Emergency Department. While waiting in the elevator she, looks over the reqs for Emergency. *Ok*, she thinks. *Nothing special. Appears to be more routine with no stats. Let's start with the oldest time stamp and work my way to the recents.*

Time: 13h14

Alexa: “Good day, are you Mrs. Meryl Smith?”

“Yes, why do you ask?”

“My name is Alexa and the Emergency physician ordered some lab work for you.”

“Ok.”

Alexa looks at the requisition, compares this to the labels and then attaches the labels to the appropriate tubes. That done, she approaches Meryl’s bedside. “I need to ask you some questions to ensure that I have the right patient and the right lab work ordered.” Alexa sees Meryl nod. “Ok, can you tell me your full legal name?”

“Meryl May Smith. My birth date is June 6, 19xx.”

“Oh, you have been practicing.”

“Not really, everyone seems to ask me the same questions.”

“True, we need to make sure we have the right patient and the right tests. We try to avoid making an error as much as possible.”

Alexa, prepares for the venipuncture by gathering all the correct equipment. She then wraps a tourniquet around Meryl’s left arm. Carefully examining her ACF she finds a large prominent vein. “You may feel a bit of a pinch.”

Alexa then slips the vacu-container needle quickly into the vein and seeing a flashback of blood pushes the first tube down into the vacu-container. She repeats this three more times to fill all four collection tubes.

“Ok, Mrs. Smith, please hold here.” Meryl does as requested. Alexa rechecks the labels against the requisition and then places the tubes in their racks for processing .

“Now, lets put a bit of a band-aid on that and then I will leave you be. I hope everything turns out ok for you, Mrs. Smith.” Alexa then pushes her cart out into the main part of the Emergency Department. *Ok, that’s all the patients*, she notes. *I’ll take these samples back for processing and then see if anyone needs help.*

Time: 13h20

Jill approaches Meryl’s bedside just as the ECG technician arrives. “Is this Mrs. Meryl Smith?”

Jill looks up and sees the 12 lead cart. “Yes it is.”

“Ok, thanks, it has been a bit hectic. Sorry, I’m running a bit late.”

Jill shrugs and checks the monitor and writes down the vital signs.

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 13h20	104	98/60	22	36.5°C	95%

“Hi Mrs. Smith, I’m Denis and I am going to place some wires on your chest, legs and arms. This will then give us a better view of your heart electrical function.”

“Ok, I guess.”

Denis pulls the curtains closed to give Meryl some privacy and then requests she lift her shirt up a bit so that he can place the wires on the left side of her chest. Efficiently he quickly places the leads on Meryl’s chest, legs, and arms. About a minute later the machines is printing out a 12 lead ECG.

“Now that you have all those squiggly lines on pink paper, who looks at it and what does it all mean?” asks Meryl.

Denis smiles, “Well I give one copy here to Jill for your chart and another copy goes with me for the heart doctor to look at. Whoever the heart doctor is, will then dictate a report that goes on your chart.”

“When will I know what it says?”

“I would guess pretty soon, but that is up to Jill and the Emergency doctor.”

Meryl sighs and lays back.

Denis pulls the curtains back and passes the 12 lead to Jill.

“Ok, Jill, here you go. I’ll let you discuss it with the Emergency doctors. I need to get up to the fifth floor for a stat.”

“Thanks Denis.”

Time: 14h30

Jill finds Dr. Smythe reviewing the chest X-ray, labs, and 12 lead of Meryl.

“What do you think, Dr. Smythe?”

“Well, it’s not great. Mrs. Smith has some congestion in her lungs, but has no fever, a little rise in WBC, and no signs of infection so I think the congestion is cardiac in nature. When I look at her 12 lead, I see some left ventricle enlargement. Her lab work is interesting as she has decreased kidney function according to her GFR and creatinine, plus, she has an elevated BNP. All other cardiac markers are normal. So, it appears she has exacerbation of heart failure.”

“Wow, she is very young to have HF.”

“Yes, but the valve issues she had when she was pregnant have not gotten better and it appears may have worsened over time. Is her wife here? I would like both of them to hear this.”

“Yes, Dorothy is with Meryl now.”

Jill leads Dr. Smythe to Meryl’s bedside.

Dr. Smythe looks at both women. *It just never gets easy to give bad news*; *I so wish there was another way*, he thinks.

“Ok, Mrs. Smith, I believe I know what is wrong with you and why you are not feeling well. I have reviewed all your lab tests and it points to a diagnosis of heart failure.”

“What, what is that, am I going to die?”

“Heart failure is a broad diagnosis indicating that your heart is not pumping as well as it should. For you, it is related to the valve issues you had when you were pregnant. The valve is not closing as well as it should and this is putting strain on your heart to meet your body’s need. No, you are not going to die right now. This is a serious diagnosis and needs to be managed well by you and a cardiologist.”

Dorothy begins to cry quietly at the bedside. Meryl reaches over and holds her hand. “Ok, Doctor, what happens now?”

“I am going to contact the cardiology team. I would like to admit you under their care so that they can get you on the right meds, provide some teaching for you and your spouse, and get you involved with some support groups to help you cope with this. I know it’s a lot to take in, but with proper management you should be ok.”

Meryl, looking overwhelmed, looks back at Dorothy then at Dr. Smythe and Jill. “I’ll do what ever you ask.”

Dr. Smythe backs away from the bedside and walks toward the main nursing station to call the cardiology team. Jill approaches both Meryl and Dorothy. “Do you have any questions?”

“No. Can you leaves us alone for a little bit?”

“I certainly can. I’ll draw the curtains to give you a bit of privacy. I’ll come back in 15 minutes and get you ready to go upstairs to the fifth floor.”

Time: 15h30

Jill looks up at Meryl’s monitor and sees that her oxygen saturation is decreasing, now reading 88% on room air.

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 15:30	106	96/60	22	36.5°C	88%

“Hi Meryl, are you feeling ok?” she asks.

“No, I feel short of breath, can’t catch my breath. Feels like I have been running.”

Jill notes that Meryl’s heart rate is also increasing but still sinus.

“Ok, I think I am going to have to put some oxygen on you.” Jill frees a set of nasal prongs from their plastic bag and plugs one end into the oxygen flowmeter. She wraps the other end around Meryl’s ears and places the prongs gently in her nose. Jill adjusts the oxygen flow to 4 LPM.

“Ok, Mrs. Smith. Take some deep breaths through your nose and blow out through your mouth.”

Meryl takes a half dozen breaths as instructed and Jill notes the sats improve to 93% and the heart rate beginning to decrease to 95 to 100 beats per minute.

“Thank you, I feel a bit better but not normal. Am I getting worse?”

“Maybe, but it is too early to tell. Let’s just say you need a bit of oxygen, but nothing else has changed.”

“All right.”

Jill leaves Meryl alone and goes to find Dr. Smythe

She finds Dr. Smythe coming out of the dictation room with a cup of tea in his hand.

“Dr. Smythe, Mrs Meryl Smith is now requiring oxygen and she is stating she is not feeling quite right and is short of breath.”

“I thought this might happen. Ok, I am going to order a transthoracic echo and I will call Cardiology to take her as soon as a bed is available. They said they are discharging eight patients today so there should be space for her.”

Jill watches Dr. Smythe fill out the stat requisition for a cardiac ultrasound.

Time: 16h00

Charlie reviews the requisitions on the computer screen. *What is this: stat echo in Emergency*? he wonders.

Reading the information on the echo requisition, he notes that a consult to Cardiology has also been requested.

Grabbing the phone, Charlie calls Emergency and asks for the nurse caring for Mrs. Meryl Smith.

“Hello this is Jill.”

“Hi Jill this is Charlie in Echo. I have a stat req for Mrs. Smith. Can she come to the department?”

“I am not comfortable sending her to you. She is on oxygen and is monitored. She is now experiencing shortness of breath and is not feeling quite right. This is her first experience with heart failure and we’re not sure how she is responding right now.”

“Ok, I will bring a portable machine down. It won’t be ideal, but I can help add to the information on the patient. Most likely she will need a second echo in the department to get better pictures, but I will leave that up to Cardiology. I will be there in about 10 minutes.”

“Thanks Charlie.”

Time: 16h10

Charlie, true to his word, arrives pushing a large ultrasound machine in front of him. Slightly out of breath from having to push the machine and avoid all the activity in the Emergency Department, he maneuvers the machine close to Meryl’s stretcher.

“Hi Mrs. Smith, my name is Charlie and I am an echo cardiology technician. I’m going to take some moving pictures of your heart. It won’t hurt, but may be a little cold as I have to use some gel.”

“I remember having one of these when I was pregnant.”

“Meryl, I’m going to step out and update the family while Charlie does his test thingy. There’s not much room for me and his machine. I will come back.” Dorothy moves around the echo machine and heads to the waiting area to make some phone calls.

Charlie pulls the curtains around Meryl’s bedside and turns off the lights by the bed so it’s a bit darker and easier to see the echo machine’s screen.

“Ok, Mrs. Smith. You are going to need to pull your gown up a bit so I can see the left side of your chest.”

Meryl exposes the left side of her chest and Charlie adjusts the gown to cover most of Meryl's breast.

"The gel is warm, but not really warm so it may feel a bit cold to you. I'm going to squirt some on your chest and on the probe. This helps us get a better picture."

Meryl shudders a bit as the gel is placed on her chest and then relaxes as Charlie places the probe over her tricuspid area.

"Ok, Mrs. Smith, I am done with the echo."

Charlie takes a towel and carefully removes as much of the gel as possible and then helps Meryl readjust her gown.

"What did you see? It looks like it was all shadows to me."

"I can tell that your heart is not pumping as well as it should and that you have a problem with one of your valves on the left side of your heart. Anything more will be up to the doctors as I cannot tell anymore than that."

"Not sure I needed this test as you just said the same thing as Dr. Smythe."

Charlie smiles, "Yeah? Well it confirms what he told you then."

Pulling back the curtains, Charlie navigates the ultrasound machine out of the space and waves goodbye to both Jill and Meryl.

Time: 16h30

Jill sees that Dr. Smythe is talking with Charlie and walks closer to hear what they are saying.

"Ok, Charlie tell me again what you saw on the ultrasound?"

"Right. The ejection fraction is estimated at about 30%. Her LV looks a bit dilated. The mitral valve is graded a moderate regurg. On the plus side, I did not see any vegetation."

Dr. Smythe looks over at Jill. "This is much worse than I expected. I am quite surprised she was managing so well in the community and this is her first time admitted with HF."

Jill nods, "There's a bed available for her on the fifth floor. They told me I could move her after 4pm."

"Well, given everything we know, that is the best place for her. Thanks Charlie. Say hello to your dad for me and tell him, when he wants another bowling lesson, I'm available."

"Thanks Dr. Smythe. I'm pretty sure my dad is still recovering from that perfect game you threw the last time you were out together. He may not want a lesson for awhile."

Charlie smiles at both Dr. Smythe and Jill and with a wave moves off to grab his ultrasound machine.

"Ok, Jill, I don't think I need to speak to Mrs. Smith again. Let's get her upstairs and let Cardiology manage her. That would be best. I'll finish writing the progress note and her orders to date. Cardiology will need to add their specific treatment."

"Right. I will phone up report to the fifth floor and then take her up after 4pm. Thanks, Dr. Smythe."

Time: 17h15

"Ok, Mrs. Smith," Jill says, "They are ready for you on the fifth floor and they have a real bed in an actual room for you. Dorothy can come with us. I'm going to attach your leads to a portable system and have Glen the porter help me with your stretcher."

Both Dorothy and Meryl look relieved that there is a real bed ready.

Jill grabs the portable monitor system and places it at the end of the bed. She then pulls out of the main monitor the cartridge with all of Meryl's leads and information, and slides it into the portable system. Looking at the smaller screen, Jill makes some adjustments and nods satisfactorily that everything looks good.

Jill calls the front desk and asks for Glen the porter to help her with Mrs. Smith.

Glen arrives a few minutes later and together, with Dorothy's help, they get Meryl up to her room on the fifth floor.

Day 0: Medical Ward

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 0

Time: 17h30

Place: Medical Ward

"Hi Jill, how are you doing? Is this Mrs. Smith?" asks Simone.

"Hi Simone, yes this is Mrs. Smith. Did someone pass on my phone report to you?"

"Yeah, I got the message. Do you have the transfer note and orders?"

"Here is the transfer note summarizing the care thus far and here is Dr. Smythe's transfer note and his orders," Jill says as she hands over the information. "He knows you will change them to support Mrs. Smith better."

Simone carefully reads through Jill's transfer note. "So she has had all her diagnostics but no cardiac meds?"

"That is correct."

"Ok, I'll get the team to see her as soon as we have her settled."

Simone, Jill, and Glen maneuver the stretcher into a semi-private room and help Meryl transfer to the bed near the window. Jill takes the cartridge out of the portable monitor and slips it into the monitor above the bed. Watching carefully, she sees the monitor boot-up and display Meryl's vital signs.

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 17h30	110	90/60	22	36.5°C	95% with 4 LPM

"Is this more comfortable than the stretcher?" Jill asks Meryl.

"Most definitely. Thank you."

"Glen, can you hook up the nasal prongs to oxygen at 4 LPM please? Great, thank you." Jill then turns to Dorothy and Meryl, "Mrs. Smith, it was a pleasure to meet you and I hope everything turns out well for you."

In unison both Dorothy and Meryl thank Jill for her assistance.

Glen and Jill reverse the stretcher and head out the door. Jill checks in with Simone before she leaves. "Simone, do you need any more information or are you good?"

"Family aware?" asks Simone.

"Yes, Dorothy is the wife and she has been updating siblings. I have had no contact with any other family. Dorothy was

stressed on admission, but seems to have settled right now. They seem to be good people with what appears to be bad luck."

"Ok Jill, thanks. If anything crops up before the end of the shift, I'll call you."

"Sounds good."

Both Glen and Jill wave and head to the elevators to get back to the Emergency Room.

Time: 17h45

Simone approaches the nursing station and sees the Cardiology team sitting at the small conference table in the middle of the nursing station.

"Hi Dr. Grant, Meryl Smith has just arrived from Emergency. She is the newly diagnosed heart failure patient."

"Yes, I was talking with Dr. Smythe about her. Have they started any cardiac meds?"

"No. They have left that to you and the team to start. Essentially she has had all her diagnostics done, but no interventions. She is stable right now. On 4 LPM nasal prongs. Sinus rhythm. I haven't done an assessment yet and wonder if we should all go in and talk with her and her wife."

"I think that's a great idea. We will be there in a couple of minutes. Simone, please go in and let her know she will have the team come and see her shortly."

"Excellent. Will do."

Simone heads to Meryl's room to let her know the plan.

"Hi Mrs. Smith, my name is Simone and I'm one of the cardiology nurses that will be caring for you while on the unit. In a few minutes, the cardiology team will be in to assess you and ask you a few questions. We are going to do our assessments together and this way we coordinate our care and plan the best approach for you, and you get to ask any questions you have. Does this sound ok?"

"It's a bit overwhelming."

"I understand that. It is a lot to take in. Remember we are here to help you get better."

"I realize that. It's just so new."

Dr. Grant then enters the room with the cardiology team.

"Good afternoon Mrs. Smith! My name is Dr. Neal Grant and these people behind me compose the cardiology team."

"I'm Dennis, a senior resident."

"I am Haley, the cardiology pharmacist."

"I'm Harjinder, the junior resident."

"I am Addy, the dietician for cardiology."

“Ok, now that is a lot of names right now. We would like to get to know you a bit better, have a listen to your heart and lungs, and then plan out the interventions that will make you feel better than you do right now. How does that sound?”

Both Meryl and Dorothy nod but look a bit shy with six people standing around the bedside.

Dorothy asks, “Do you need me here?”

Dr. Grant nods. “I would like you to stay here so you can get the same information and it helps us learn about your wife. You are integral to her care especially when we send her home which I hope is a couple of days from now.”

Dorothy smiles at that but stands up and moves away from the bedside to give the cardiology team more room.

Dr Grant begins by asking general health questions, about activity levels, and then steps forward to listen to Meryl’s chest. Haley asks about medications at home, both prescribed and over-the-counter. Addy inquires about diet and activity. The two residents follow Dr. Grant’s lead and perform a physical assessment.

After 30 minutes of questions and assessment, Dr. Grant steps to the end of the bed “Ok, I think that is all for now. What I would like to do is start you on some medications. A beta blocker to slow your heart beat a bit so that the heart can fill better, an ace-inhibitor to decrease your blood pressure and then a drug to make you urinate a bit more to get rid of the extra fluid you are carrying around. These are common medications for patients that have your type of disease. They are also powerful medications and can cause you to be dizzy or not feel like yourself which is why we are going to keep you here to monitor you and make sure you are stable on the meds before going home. You will know they are working when you do not need oxygen any more. Do you have any questions?”

“No, but it’s a bit much to take in right now. Dorothy?”

Dorothy nods. “I agree with Meryl. Let’s just sit with what you have told us and maybe we’ll have questions later.”

“That sounds good. I am on call all this week so you will see me each morning during rounds. Please ask any questions then or ask Simone here or another member of the team. We are all here to make sure you get better”

Dr. Grant then turns and leaves the room followed by the team and Simone.

In the nursing station, Dr. Grant facilitates a debrief of everyone, which leads to each making their own notes in Meryl’s chart and Dennis writing the orders for the medications that Dr. Grant talked about.

Day 1: Medical Ward

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 1

Time: 08h00

Place: Medical Ward

"Good morning, Mrs. Smith. Do you remember me from yesterday. I'm Simone?"

"Yes, Simone, I remember you from yesterday. I see you're back. This your second day shift?"

"Yes, this is my second. I am doing three days and a night shift this week so we will probably have one more day together. I have your meds here: a beta blocker, ace-inhibitor, and diuretic. But before you take these, I need to check your morning weight and your blood pressure. This is something you're going to have to do each day on your own."

"Ok, do you need me to do anything?"

"Nope, just lie back and relax while I take your BP and weight."

Simone then presses a button on the bed to get Meryl's weight and then presses the NIBP button on the monitor.

Day: 1	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O2 Saturation**
Time: 08h00	65	90/55	18	36.5°C	95% 3 LPM

"Your blood pressure is down to 90/55, which is what we expect. Your heart rate is around 65, which is also what we expected. You have lost 1 kg of fluid since we started the diuretic, which is a bit less than we expected. How are you feeling when you stand at the bedside or use the commode?"

"I feel a bit lightheaded but nothing really serious, I don't think."

"Your oxygen has been dialed back to 3 LPM, but is not really changed. I would like to listen to your chest, then I will give you your meds and morning tray."

Meryl adjusts her gown so that Simone can listen to her heart and lungs. Simone methodically moves through a head to toe assessment and records her findings.

"All done, Mrs. Smith. Here are your pills as we discussed and your breakfast."

"This is it for breakfast? Some cereal, skim milk, and a couple pieces of fruit?"

"Yes, Addy the dietician you met yesterday has ordered for you the cardiac diet low in sugar and salt. She will be coming

by later this AM to discuss diet with you and hopefully Dorothy. Diet is very important in heart failure and knowing more about how food affects your condition will help keep you out of the hospital."

"Ok, this will take some getting use to. I really like my sausage and eggs for breakfast."

"I can honestly say me too, but for you the rare sausage or eggs will be ok, just not every day. But Addy would be best to ask."

Simone heads out of the room to check on her other patients. Meanwhile, Meryl picks up her spoon and moves the cereal around but really does not eat anything other than the half apple and tea on her tray.

Time: 10h30

"Hello, Mrs. Smith. My name is Addy and I am the dietician for Cardiology. We met yesterday with the rest of the team. You are Dorothy right? Mrs. Smith's wife?"

Dorothy smiles. "Good memory, yes I am."

Meryl looks up, "You're probably here to discuss what I can or cannot eat?"

"That is correct. For you, diet and activity are going to be very important to maintaining good health and keeping you out of the hospital."

Dorothy looking unhappy and says: "I suppose I'm here to learn as well so that I keep her on the straight and narrow path."

"Yes, in my experience and in the research: when families are closely involved in the care of a loved one, the care is much more effective. The diet is not all bad, and you and Mrs. Smith will learn how to adapt it to your likes, but there are some things to consider."

Addy sits at the bedside and hands both Meryl and Dorothy a sheet of do's and don'ts for heart failure patients along with some sample menus and some links to recipes.

"It is really important that you consider low sodium foods and not adding any additional salt when cooking. Adding salt can lead to further water retention, which can stress your heart and make it not pump as well as it should."

"Look, Meryl, many of the menu items we already eat. I just need to not add salt."

"That is correct, Dorothy. Many patients find they are already cooking similar diets. I recommend that you not have a salt shaker on the counter or on the table. That way you're not tempted to add salt. Look for fresh herbs and spices to add that kick of flavor we all desire. Things like garlic, cilantro, or sage can add some additional flavor to something like a broiled chicken breast."

"Oh Meryl, we have always said we wanted a herb garden. I guess this will be the encouragement we need to start." Dorothy's eyes light up a bit more. "I can go shopping for the stuff we need and when you come home we can start planting."

"Dorothy, this is not an excuse to go shopping. You always get so excited about things. We need to take this slowly. A garden is a good idea, but let's start buying and cooking first."

Dorothy's eyes shine a bit less brightly, but she nods.

“Ok, you both look like you understand what I am asking you to do,” says Addy. “I would like you to look through the information I have given you. If you have any questions, write them on the sheets and I will come back tomorrow to see how you’re doing. The meal trays you get will be example meals that you should consider making at home. Dorothy, I need you not to bring anything extra in from home until Mrs. Smith is stabilized. Do you think you can do that?”

“I was just thinking of picking her up a milkshake, but I guess that’s out of the question?”

“Yes, until we have things more stabilized and the medications working well, that is for the best.”

Both women nod. Addy gets up and waves good bye to both Dorothy and Meryl, and heads out of the room to see the next patient on her list.

Time: 11h00

Simone stops Addy a couple of doors down from Meryl’s room. “How did your talk go?”

“Pretty well. They are both intelligent and are ready to learn. They seem less overwhelmed than yesterday. Meryl seems to be feeling better, but is still on oxygen. Dorothy was very excited about making a herb garden. All good signs.”

“Awesome, thanks. If they have any questions are you coming back today?”

“No, I think they will need to digest what I gave them. I said I would be back tomorrow to see how they are doing and to answer any questions.”

“Sounds good.”

Time: 11h15

“Mrs. Smith, how are you doing? I am back to do another ECG heart tracing on you.”

“Ok, and you are?”

“I’m Denis. I performed the test yesterday. Do you remember?”

“Oh, there was so much happening, I’m so sorry ,I can’t remember everyone’s name that is helping me.”

“That is quite all right. Ok, this test involves me placing some sticky tape on your arms, legs, and chest.”

“That I remember.” Meryl re-adjusts her gown so Denis can place the leads on her chest and arms. Denis pulls the covers up, leaving Meryl’s feet exposed so he can place the leads on each foot. “All done with that. I now need you to stay very still while we do the test.”

Denis pushes the button and the pink coloured paper is slowly pushed out of the machine with the squiggly lines from each of the 10 leads.

“All done.”

“Is there any change?”

“Mrs. Smith, I see lots of patients every day and my apologies. I cannot remember your test from yesterday. All I can say from looking at the ECG is that there is nothing to be done right away and you are not in danger right now.”

“I guess that’s a good thing, thanks.”

Denis prints out a second copy as an interim report for the chart, then removes the leads and stickies from Meryl’s body. “I’ll see you tomorrow.”

Meryl waves him goodbye.

As Denis is exiting the room, Simone pulls him aside. “You have the latest 12 lead?”

“Yes, I was going to place it in the chart.”

“Excellent, let’s do that and compare it to yesterday.”

Both go to the nursing station where Simone pulls up **y**esterday’s 12 lead and looks back and forth from today’s ECG to yesterdays.

“Do you see any differences Denis?”

“Nope, although it is quite a bit slower than yesterday’s. Did you start her on something?”

“Yes, we started her on a beta blocker to slow her rate down and to prevent any remodeling.”

“Well, it seems to be working. Heart rate is about 65, but other than that everything looks the same as yesterday.”

“Ok. Thanks Denis. See you tomorrow?”

“Yes, I’ll be here about the same time.” Denis then grabs his ECG cart and heads down the hallway to another patient.

Time: 14h00

“Good afternoon, Mrs. Smith.”

“Hello.”

Dorothy looks up to see a slightly stooped women enter the room and pull a chair up to the bedside. “Who are you?” she asks.

“My name is Stella and I am a social worker for the hospital. I come and see all the cardiac patients to make sure things are going well and to see if I can help at all.”

“Oh, not sure what you can offer.”

“Me neither, but lets have a conversation. Then I might have something a bit more definitive.”

Dorothy looks Stella over a bit more. “I guess that’s ok. Meryl has psych coverage as part of the RCMP so not sure what you can help with?”

“That’s good to know. If there’s something that needs to be shared, I can share it with the RCMP. It benefits people to ensure there is good coverage. I have a few set questions to ask, but please feel free to interrupt at any time. I do this to see if there are any gaps and where a social worker can assist you in your new journey to better health.”

Both Meryl and Dorothy nod.

“Ok, how long have you two been together?”

“We have been living together four years, but have dated for about eight years before moving in. I met Dorothy while I was having a coffee break and stretching my legs after being in the patrol car for 10 hours on a stake out. She was sitting in a booth by herself and the restaurant was completely jammed. I asked if she wouldn’t mind sharing her booth and she told me that it was ok and that I looked to be a safe person. We started talking and here we are 10 years later. She was the right person at the right time after my previous relationship dissolved due to him cheating with the teaching assistant.”

“You were previously married?”

“Yes, before Dorothy, I had a traditional family with a male husband. We were together for about six years. I never really felt comfortable in the relationship, but thought that that was what a woman should be when being a wife to a male. Anyway, he started cheating after I had our second child and then I just left.”

“How many kids?”

“Two. A boy, Roger, and a girl Jennie. Very lovely kids, but they’re growing up so quick. Roger is 16 and Jennie is 14. We share custody. Although Matt, my ex-husband, gets weird with me living with Dorothy.”

“Any issues with the coparenting or the kids?”

“No, the kids have adjusted nicely to having two moms and have really bonded with Dorothy.”

“How long have you been with the RCMP?”

“Twenty-four years—looking at retirement in about five or six, I think. Got a promotion three years ago that took me out of the patrol car and more desk duty. Been a little less active since that time, riding a desk.”

“Yes, physical activity is important. I think that is Addy’s day two talk after she gives you the news about your diet.”

All three women laugh.

“Oh, I am still active, just not the same level as when I was in a car. I like to walk, run a little, and really enjoy hiking on some of the trails we have around here when the weather is nice.”

“Sounds lovely. Good way to relieve stress in your type of job.”

“Yes, I guess so.”

“Do you smoke?”

Both women shake their heads no. “We both quit years ago. Never felt the need to take it up again.”

“How about alcohol?”

“Dorothy and I enjoy a glass of wine after work and the occasional martini when we go out, but I don’t think it’s excessive. What do you think, Dot?

Dorothy ponders this and a few seconds later answers. “Not sure we do drink every day, but only a glass, so I don’t feel it’s excessive.”

“Sounds quite normal to me. Ok, thank you for answering my questions. You are very normal people and look like you

have the coping skills and support needed to make the adjustment that heart failure requires. I don't think I need to be involved. With your permission, I would like to send a note to your HR benefits person in the RCMP to give them an update, and maybe they can follow up with any necessary assistance. "

"That would be fine." Meryl then gives Stella her division number and the contact information for benefits in her division.

"Thank you both. Have a great day."

Stella heads out of the room and to the nursing station to update her notes.

Simone comes by just as Stella is finishing up. "Anything I need to know?"

Stella looks up and smiles. "No, I think she is doing pretty good. I don't believe the diagnosis has really hit her or her partner yet. Right now they're still processing. On the plus side, good supportive family, and she has great support from the RCMP so things are setup well for her to be successful in this transition. The real question is: will she be allowed to continue to work or will the RCMP push for retirement? But that's not my decision and could add quite a bit of stress to Meryl and Dorothy."

"Thanks Stella. I have a good feeling about them. Will you check in with them again?"

"No. I'll see them in the healthy heart clinic, but I don't think I need to follow up beyond that."

Simone nods and moves over to complete her charting on the other patients she is caring for.

Time: 16h00

"Hello Mrs. Smith, how are you doing?" Simone asks as she looks over the monitor and does a primary sweep of her patient.

Meryl looks up with reddened eyes, "It's going ok I guess."

"Have you been crying, Mrs. Smith?"

"Just a little. I just. Why me?"

"I don't know why this has happened to you, but I can explain things a bit more to you if you would like?"

"That might help. I think it's suddenly hitting me that my body is changing and not for the better and I may have to retire and make so many changes. I, oh gawd. I just don't know what to do."

"This is perfectly normal. Let me pull up a chair and I can explain what is happening in your heart ,and what the plan is for you. Does that sound ok?"

"Yes, thank you."

Simone sits down beside Meryl's bed and explains how heart failure develops when a valve is not working, how valves become diseased, and the various treatments. She also carefully discusses some of the complications that can develop if Meryl does not follow doctor's orders.

"Oh, thank you. I think I understand a bit better now. It looks like I'm not going to die."

“Yes, Mrs. Smith, with the correct treatment, and you watching your diet and exercise you can live a very enjoyable life—maybe not the one you envisioned, but still quite enjoyable.”

“Yes, I think it’s all the changes I am facing that is overwhelming me. “

“Could very well be. Often facing one’s mortality can be a bit daunting. You need to give yourself time to grieve and recognize that this has happened to you and that it is not a punishment, but something that you need to deal with. Remember, there are many people here to help you and Dorothy make the best of this situation and diagnosis. You need to allow us to help you.”

“Thank you again. Yes, I will be asking for help now. What is the plan for tomorrow?”

“Much the same as today. You will have another chest X-ray, ECG, and lab work. I hope that I’ll be able to take you off oxygen, and then, if that happens we can introduce you to the heart failure clinic, which will begin an exercise routine with you to help strengthen your heart and your coping skills.”

“It would be nice to begin moving around again.”

“Let’s plan to do that tomorrow, shall we? I can hear the dinner trays being moved about in the hallway, so I’m going to get your meds and check on my other patients.”

Meryl smiles and pats Simone’s hand.

Simone moves the chair back to the corner and heads off to gather meds and check her other patients.

Day 2: Medical Ward

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 2

Time: 08h00

Place: Medical Ward

Simone looks over the MAR and double checks the meds she is pulling for Meryl Smith. *That all looks right*, she thinks to herself. *Beta blocker, ACE-I, and Lasix. Along with some vitamins and a proton pump inhibitor. Let's go see how she is doing this morning.*

Walking into the room, Simone can immediately see that things are not right. Looking up at the monitor she sees that Meryl's heart rate is 50 and that she looks a bit pale.

"Good morning, Mrs. Smith. How are you doing?"

"I don't feel quite right. I am not sure what is going on?"

"Ok, I am going to listen to your chest and take your blood pressure."

Simone carefully listens to Meryl's chest and hears a few less crackles than yesterday. Nodding to herself she thinks, *A bit better but let's check the BP.*

Pressing the NIBP button on the monitor, Simone waits a few seconds and sees the result displayed on the screen: 84/48. Placing her forefinger on Meryl's wrist, Simone double checks that the pulse is accurate when compared to the monitor.

Day: 2	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 08h00	50	84/48	18	36.5°C	95% on 3lpm

"Well, your heart rate is a bit slower than it was yesterday and your BP is a bit lower. All this can be caused by your medications, so before I give out your meds, I'm going to have Dr. Grant take a look."

"Sure sure." Meryl leans back against her pillow and closes her eyes.

Hmmm, a bit tired as well. Ok let's find Dr. Grant, thinks Simone.

Simone steps out of the room and sees Dr. Grant at the nurses' station.

"Dr. Grant, before you start rounds, can you quickly see Meryl Smith? Her heart rate is 50, BP 84/48, and she is a bit drowsy."

“Good morning, Simone. That sounds like she is having some issues with her meds. You know me by now: if they can keep their eyes open, I’m ok with whatever BP they have.”

“True enough, but it’s more the heart rate that is concerning me and her drowsiness.”

“Ok, let’s do a quick drive by and see how things are going.”

Dr. Grant and Simone head to Meryl’s room. They find her propped up in bed staring forlornly at her breakfast tray.

“Hello Mrs. Smith. How are you doing?” asks the doctor.

“Would be better with some sausages and pancakes, not the cardboard and watery milk that you’re feeding me here.”

“Ok. Do you mind if I have a listen to your chest and check you out before you dig into breakfast?”

Meryl pushes the bedside table away and adjusts her gown for Dr. Grant to listen to her heart and lungs.

After Dr. Grant finishes checking Meryl out, he steps back. “Ok, Simone, I am good with the BP, as that is not affecting her too much, so the ACE-I is good. She is down another ¾ of a kilo in weight. The heart rate is down a bit more than I would like. Let’s cut her dose of beta blockers in half and then go a bit more slowly up than we have been. Give her body a bit more time to adjust to the new drugs. How does that sound?”

“Great, thank you. Will you write that out as an order?”

“Yes. In the meantime cut the beta blocker pill in half. She needs to get on these drugs to get better.”

“I will do that and give her the half dose with breakfast along with the rest of the meds. Thanks again.”

Both professionals leave Meryl alone with her breakfast tray.

A few minutes later Simone comes in with the medications and explains everything to Meryl and the reason behind the changes. Meryl seems to understand but is still unhappy about her breakfast.

Time: 19h30

Dorothy peeks around the corner. “Up for a visitor?”

“Oh yes. Someone not dressed in those awful blue pajamas and who will talk to me about something other than my heart. What is that I smell, french fries?”

“Shhh the pajama police will hear!”

Both women share a laugh.

“You shouldn’t. It’s not on my diet!”

“You are doing so well, I thought we could celebrate. I brought a milkshake as well. I looked up on the web to see who had the healthiest French fries and I went there to pick some up to share.”

“Healthy fries? You are looking out for me, eh, or trying to get my life insurance payout?”

“Nothing of the sort. Just celebrating.”

The two women sit close and share what happened over the course of the day. For Meryl, it was a normal hospital day

with another ECG, chest X-ray, and lab work. But she did share that she was able to go for a walk with the physio, up and down the hallway. Dorothy shared about the kids' parent teacher interview and laughed at how awkward her ex-husband felt when he had to explain that Dorothy was not his wife but his wife's wife.

An hour later with visiting hours almost over, Dorothy cleans up the evidence of the celebration, kisses Meryl, and waves good bye. "Till tomorrow hon."

Time: 22h30

"Hello Mrs. Smith. Let's get you tucked in and taking your final meds of the evening."

"Ok Siri. Has Dr. Grant changed any meds again?"

"No, everything is the same as it was this morning. We are going a bit lighter on the beta blockers and allowing you to adjust a bit slower to them."

Siri then helps Meryl to the bedside commode and gives her the PM medications. Checking again with her that everything is fine, she turns the lights off in the room, leaving each patient with control of their own bedside lighting.

Day 3: Medical Ward

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 3

Time: 03h00

Place: Medical Ward

Meryl wakes up suddenly. *Something's not right*, she thinks to herself. *Oh my heart is beating so quick. I can't catch my breath. What the hell is going on? Where is that damn call bell?* Looking around her bedside in the dark, she finds the call bell and pushes it. A few minutes later she sees a flashlight waving around on the floor as it approaches her bedside.

Siri peeks around the corner of the curtain to find Mrs. Smith sitting upright in bed breathing rapidly and looking quite panicked.

"Well, Mrs. Smith, things don't look right. How are you feeling?"

"I don't feel good at all. Not sure why. I feel short of breath and I feel like my heart is just pounding."

"Ok, let me turn the lights on here and give you a good once over."

Siri turns the lights on over the bed, considers the monitor, and sees Meryl's heart rate at 100. Saturations are less than 88% on room air. *Something isn't right*, she says to herself. *I wonder what's going on?*

"I'm going to take your blood pressure and listen to your heart and lungs."

Siri listens to Meryl's chest and hears substantially more crackles than at the beginning of the night shift. The BP cuff beeps and the monitor shows 90/50.

Day: 3	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 03h00	100	90/50	24	36.5° C	88% RA

"Ok, something is not quite right Mrs. Smith. Let's put you on a bit of oxygen. I'm going to ask the RT to see you, along with Dennis the senior resident. I expect we are going to do a chest X-ray and another ECG and some labs to see what's going on."

"If you say so. Oh, why is this happening?"

Siri grabs the nasal prongs hanging on the flowmeter and places them on Meryl's nose. She turns the flowmeter on to 3 LPM. Not waiting to see what happens, Siri rushes out to the nursing station.

"Can you page the RT for me and find Dennis? I'd like both of them to see Meryl Smith in Room 23."

"Dennis is just seeing the patient that came in last night at 22:00. I think he's almost done, but I will let him know you need him. Jackson is the RT covering the floors and I'll page him now."

"Thanks."

Time: 03h20

"Hi, I'm Jackson the RT. You paged?"

Siri turns to see a very tall, smiling male dressed in bright blue scrubs. "Yes we did. Wow, are those the new RT scrubs?"

"Yeah, a bit bright, eh? They tell us they will fade with washing. Same colour as my grad suit was during the high school prom. Not a great colour then and less so today."

Siri laughs. "Ok. Mrs. Meryl Smith is a 44 year old woman who developed heart failure due to a heart murmur that occurred 16 years ago during her last pregnancy. She was doing fine and came off oxygen 24 hours ago. Just a few minutes ago, she rang and complained of distress and shortness of breath, and her sats were down. I put her on 3 LPM nasal prongs and have not had a chance to double check to see if that worked."

"Ok. Well, let's look now."

Day: 3	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 03h20	102	92/55	26	36.5° C	90% 3 LPM

Both Jackson and Siri head into Meryl's room to find not much of a change with saturation around 90% and HR around 100. Latest NIBP is 92/55.

"Hi Mrs. Smith, my name is Jackson and I am a respiratory therapist. I manage oxygen for patients and it seems you might need a bit more. I need to listen to your lungs. Is that ok?"

Meryl just nods.

Jackson listens quickly. "Wow, she is crackly everywhere. I'm going to get a mask and a water bottle. I'm probably going to put her on .5Fi02 and see how she does. Is the doc going to see her?"

"I've asked Dennis to come in and review, which I hope is soon."

Just then Dennis walks in. "How is this for soon?"

Siri smiles "Pretty good. Jackson is going to place her on oxygen. She woke up in distress about 15 minutes ago. HR is up, BP is up, and saturations are down. She is complaining of SOB and not feeling quite right."

"Ok. Jackson, what did you hear chest-wise?"

"She is crackly in all fields. I'm going to place her on .5 mask and see how she does. Resps are about 26 per minute right now."

"Thanks, I'll order a CXR and 12 Lead, with CBC, lytes, BUN, creatinine along with a troponin to see if this is an MI. After I look at the CXR, I may order some Lasix as she may be having an exacerbation of heart failure."

Siri stays with Meryl while Jackson gets the oxygen mask and Dennis writes the stat orders.

Over the course of the next hour, Meryl's saturations improve to 93% on .5 Fi02. A chest X-ray is complete, a 12 lead is done, and all morning lab work is completed.

Siri and Dennis are both looking at the CXR and the 12 Lead. "Ok, Siri what do you see on the CXR?" Dennis asks.

"Well, comparing it to yesterday, she seems to have a lot more infiltrates generally. There doesn't seem to be a pattern nor does she have a temperature or cough so I think, for some reason, she is retaining more fluid or her heart is not pumping very well."

"Excellent. I agree as well. Let's look at her 12 lead."

Both professionals compare the last two days' 12 leads with the one taken a few minutes ago.

"Same question, Siri. What do you see?"

"Well, comparing all three ECGs, they all look the same. If we are looking for an MI, I don't see any ST elevation nor Q waves on tonight's ECG. She could be having a NSTEMI I guess."

"That could be happening, but I'm suspecting it's something else. I wonder if the trop is back yet."

Dennis pulls up the computer and looks under Meryl Smith's lab work. "Awesome. Look here: no troponin detected. So, no MI. Let's give her 40 mg IV Lasix now and if she responds really well, just follow up with her normal AM dose. If she has a limited response, say less than 1500 cc urine in the next three hours, let's double the dose. But talk to me first before doing so. I'll write the order for the 40 mg direct IV."

"Ok, something happened here. I'll go see how she's doing and talk with her."

Time: 04h30

"How are you feeling now Mrs. Smith? I am going to give you some Lasix that will make you want to pee quite a bit for the next little while."

"Ok, is the commode close?"

"Yes it is, but I want you to call if you need to get up. Just want to make sure nothing happens or you slip. Ok, here goes the medication. Has to go in quite slowly."

Siri very slowly pushes the 40 mg IV over the next 5 minutes into Meryl's IV.

"So all those tests we did show you did not have a heart attack, but show that your heart is not pumping as well as it was yesterday. Anything different happen?"

Meryl sighs and looks sheepishly at Siri. "Dorothy and I celebrated just a little after dinner before you came on shift."

"What do you mean?"

"Well, Dorothy brought me fries and a large milkshake, you know one of the big ones."

"Oh my. Ok, I think I know what happened. Addy talked to you about salt and water, did she not?"

"Yes. I am not supposed to have too much of either."

"Yes, no extra salt and we're watching your fluids very carefully. So the extra salt from the fries caused your body to

hold onto fluid, then the extra big milkshake gave you more fluid than your heart could handle, causing your heart to be overstretched and not pump well. The Lasix that I'm giving you will help, but you can't do things like this."

"Yes, I know that now. Thank you. Are you going to talk with Dorothy?"

"Not tonight. But I think you both need to meet with Addy and Stella."

"Ok."

Time: 06h30

Siri helps Meryl back to bed for the eighth time since the Lasix has been given.

"Oh, I feel so thirsty."

"Yes, here is some water. Just take a sip and rinse it around your mouth before swallowing. That will help with some of the dryness." Siri removes the pan from the commode and measures the urine. *That gives us a total of 2200 cc since 0430. Not bad*, she says to herself.

"Ok, about two liters out. How are you feeling?" Siri checks the monitor and sees the heart rate below 90 and saturations sitting at 99% on the .5 $Fi0_2$.

Day: 4	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 06h30	88	110/75	20	36.5° C	99% .5 FIO_2

"Much better," Meryl says. "Feels like I'm back to where I was yesterday."

A few minutes later Jackson comes in to check on Meryl.

"How you doing now? Wow — 99%. Let's see if we can get you off the mask and onto something more comfortable or maybe even off oxygen." Jackson removes the mask and replaces it with nasal prongs at 3 LPM.

"I'll be back in 10 minutes to see how you are doing."

Time: 06h45

"Ok, Mrs. Smith, your sats are 96% on 3 LPM. Let's take you off the oxygen. I'll ask my day shift counterpart to check on you when they come in, but I think you don't need the oxygen anymore now that you got rid of all that fluid."

"Thank you. I feel so guilty. I did this to myself and I thought I knew better."

"Hey, now you know. Have a good morning Mrs. Smith."

Time: 07h30

"Hi Simone, back again?"

“Yeah, Philippa wanted to trade her day shift for a night. Something to do with a school outing, I think.”

“Very happy to see you. Should be an easy report.”

“Thanks Siri.”

“Ok, everyone had a good night except Meryl Smith, but will get to her in a minute. Beds 2 to 6 are ready for discharge as soon as the morning labs are back. Discharge orders are written. If labs are normal, they are good to go. I have phoned all the family and they are aware to come and pick them up. I have updated my charting and everything should be a go for them.”

“Thank you very much. Now what happened with Meryl?” Simone asks.

“The evening started out well. HS meds and care, she was doing fine. Did not need any assistance to commode. Then at 03:00 she wakes up not feeling right, SOB, sats down, chest sounding quite crackly throughout, and did not look exactly right. RT up, placed on FM at .5 Fi02, stat blood work, CXR, and the resident in to see her. Appeared to be having either an MI or acute exacerbation of HF. Labs came back with trop negative, 12 lead unchanged but CXR showed increased infiltrates. Had a bit of a discussion with her and it seems her and her partner celebrated how well she was doing with fries and an extra large milkshake. Looks like this tipped her over the edge. She received 40 mg IV Lasix. Diuresis of 1.5 L out and this morning is off oxygen with sats of about 93%. She feels pretty guilty. I think social work and Addy from dietary need to come and talk with both her and Dorothy to do some teaching.”

“I agree,” nods Simone. “When they were talking yesterday the conversation seemed a bit too easy. More teaching is definitely needed.”

“Ok, Simone, that’s it for me. This is my last night shift so maybe see you next week. Have a great shift.”

“Thanks Siri, I hope you get some sleep.”

Time: 08h10

The discharge patients are all up and dressed, Simone says to herself. *Breakfast trays delivered. So they should be good. Right. Let’s go see Meryl and see how she is doing.*

Simone double checks that she has the right meds, remembering yesterday that the beta blocker was adjusted.

Entering the room, she finds Meryl sitting up in bed looking much better than yesterday morning, despite the events of the night shift.

“How are you feeling Mrs Smith?”

“Much better thank you. I imagine you know what happened last night.”

“Yes I do. How do you feel about that?”

“Very embarrassed and a little scared.”

“I can believe that. Here are your meds for the morning. It looks like your heart rate is good at 65. Let’s do your blood pressure and then afterwards let’s talk about last night.”

“Ok. You aren’t mad, right?” says Meryl.

“Definitely not. I just want to help you develop a better understanding of your disease and see what we can put in place to prevent these sorts of things happening again.”

“Thank you.”

Over the course of the morning, Meryl discusses her feelings with Simone and seems to show a deeper understanding of heart failure and the implications. When Dorothy comes in, Addy and Stella meet with the two women and provide counseling and coping strategies.

The next three days show great improvement with Meryl. On the fourth day, she is discharged home, with appointments for follow up to the health heart clinic.

APPENDICES: CASE STUDY FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND PNEUMONIA

This case study is from another Open Education Resource "Health Case Studies" by Glynda Rees, Rob Kruger, and Janet Morrison. The following chapters follow the health journey fictional character Erin Johns takes from her exacerbation of COPD (asthma in this case) followed by her hospital admission for pneumonia.

Although Erin John's pathology is asthma (rather than our chapter on emphysema) and pneumonia, there are many similarities in the diagnosis and treatment and interactions with health care team.

In this case study, you will notice that Erin John's is an english-speaker who has no issues with being her own patient advocate. For a contrast, please view the subsequent case study of Miki Huang who is a non English-speaker and relies heavily on a patient advocate Appendices: Case study for Pneumonia (Miki Huang). Although the underlying pathology is the same (ie pneumonia causing an exacerbation of COPD), Miki and Erin's perspectives are quite different.

Patient: Erin Johns

GLYNDA REES; ROB KRUGER; AND JANET MORRISON



Erin Johns. Used under the creative commons license 3.0

Patient: Erin Johns

Date of Birth: 09/09/19xx

PERSONA

Erin Johns is 74 years old. She is widowed with four children, one of whom lives at home with her in their original family home in a small city in northern British Columbia. Two of Erin's children live within a one-hour drive from her, and one lives a three-hour flight away. She also has 10 grandchildren and one great grandchild. Erin communicates

with her grandchildren by telephone and Skype using her iPad. Erin describes herself as a non-smoker, but she smoked socially when she was in her early twenties for about five years. She is a retired hairdresser. Erin also has a small hairless Chihuahua named Trixie. Erin spends her time socializing at her local community centre with her friends, and she likes to play Bingo. At home, she enjoys watching Netflix and playing "Solitaire and Scrabble with friends" on her iPad. Erin tends to feel down when she thinks about her lower financial status and her advancing age, and how she is becoming more forgetful and less energetic. She often feels alone but is grateful to have the company of Trixie and the few friends she has left who are still alive. She worries about falling and not being able to alert anyone to come to her rescue. Driving is becoming hard for her, and she finds getting to the clinic and picking up her medications more and more challenging, especially now that she doesn't have her own doctor anymore and she needs to go to the walk-in clinic.

Media Attribution

Erin Johns: Photo by Pacian commonswiki is used under a CC BY-SA 3.0 Unported license.

Media Attributions

- Private: Erin Johns

At Home

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 0

Time: 16h00

Place: At home

"Trixie stop barking!" Erin calls. She gets up from the couch slowly. "I can't believe how tired I am."

Taking a few steps towards the back door to let Trixie out, Erin stops at the corner of the kitchen island and puts a hand out to steady herself on the counter.

"Oh my. Can't catch. My breath. Trixie. Stop barking."

Remembering it was her late husband who took care of the dog, her eyes tear up slightly.

I miss him so, she thinks.

Moving toward the back door, Erin reaches down and lifts Trixie up onto the washing machine to place the leash on her.

"You stink, Trixie. Your bath will have to wait till I feel better. Not sure what is happening."

Trixie, finally leashed, is lifted down and out they go through the back door into the cold winter air.

Erin gets down the steps and leans against the house to catch her breath. Meanwhile, Trixie relieves herself against a flower pot.

After about a minute, Erin begins to walk very slowly, with Trixie pulling on the leash. After about five minutes walking, Erin slows to a stop.

Looking back, Erin thinks to herself, "I have only walked about 50 meters. I am not sure I can even walk back to the house."

Erin takes out her cell phone and calls her son at work.

"Thomas, I don't feel well. You need to come home."

"Mom, I'm at work. What's up?" asks Thomas.

"I can't. Catch. My. Breath. I think. I need. To go. To the. Hospital."

"I will be there in 10 minutes, Mom."

Emergency Room

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 0

Time: 18h00

Place: Emergency Room Triage

Sitting back in her chair, Jackie sighs. “Wow, this has been a long shift. I’m exhausted.”

Looking up from the desk, she sees an old green Ford truck stop in front of the Emergency Room. From the passenger door, an elderly lady slowly emerges. Reaching back into the truck, she pulls out a very small dog and slowly places it on the ground.

The older lady makes her way slowly to the doors, with the dog trailing her on a leash. Once she is inside the doors, Jackie notes that the woman displays pursed lip breathing, has a slight blue tinge to her lips and a very slow gait.

Finally making it to the triage desk, the lady leans against the desk and sighs loudly.

Jackie comes out from behind the desk and moves a wheelchair close to Erin for her to sit in.

“Hi, my name is Jackie and I’m the triage nurse today. How can I help you?”

“Thank you. My name. Erin. I feel awful. Can’t catch. My breath.”

Jackie pulls the blood pressure and pulse oximetry machine close to Erin and wraps the cuff around her right arm. She presses a button and the cuff inflates. On Erin’s left index finger she places a pulse oximeter.

After about 30 seconds, the machine beeps and displays the following vital signs:

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 18h00	96	180/90	28	36.5° C	85%

Grabbing a clipboard with an emergency assessment record on it, Jackie fills out the initial vital signs.

Referring to the Triage and Acuity Scale along with the vital signs, Jackie grades Erin’s condition as “Triage Level III – Urgent”.

A tall middle-aged man in workman’s clothes approaches the triage desk. “How is my Mom doing?” asks Thomas.

“I think it would be best if Mrs. Johns stays with us awhile and has a doctor take a look at her. I will make arrangements for a spot for her to stay once we get her admission paperwork done. Can you and your Mom answer a few questions from Denise, the clerk who is just to the left of my desk?”

Denise, the admission clerk, comes over and introduces herself to Erin.

“Good evening. My name is Denise.”

“My name is. Erin. This is my son. Thomas,” Erin states breathlessly.

“Ok. Thomas, can you wheel your Mom close to my desk so I can input her information into the computer, please? That way we can get her a space in the ER quickly and have a doctor see her as well.”

Thomas pushes the wheelchair over to the admissions desk.

“Do you have your Care Card with you?” asks Denise.

Erin hands over her Care Card to Denise, who rapidly inputs the information into the system.

“I see, Mrs. Johns, that you were at a clinic last week. Is this correct?”

Erin nods ‘yes’. Thomas explains: “They changed her puffers and said to come back if there was any problem.”

Denise nods her head. “Make sure you tell the nurses that.”

Denise then asks, “Do you see anyone regularly at the clinic?”

“No. I see whoever is available. They change so often.”

Looking up at Thomas, Denise asks, “Can I have your contact information, Thomas, in case we need to contact you?”

Thomas recites his cell phone number and tells Denise that he currently lives with his Mom, due to a complicated divorce that has left him a bit depressed and short of cash.

Denise nods and inputs the contact information into the computer.

“Well, that is all I need right now. I have called for a porter and they will move you to a spot where the doctor can see you.”

Denise watches as the porter comes up to both Thomas and Erin and begins pushing the wheelchair through the doors into the back area of the Emergency Ward.

Denise shakes her head slightly and wiggles her nose. She thinks to herself, *That dog needs a bath. Poor thing.*

“Is this where. You are. Going to leave. Me. It’s a hallway!” Erin looks up at the porter pleadingly.

The porter looks at her. “You will need to wait here till there is a better spot for you,” and he walks away.

Erin pulls Trixie closer to her as she sits in the wheelchair. Thomas looks around at the chaos and sees people moving from curtained area to curtained area, all dressed alike in light blue scrubs. No one makes eye contact or even acknowledges them as the new arrivals.

Just as he is thinking this to himself, he feels a presence behind him. Turning around, he sees another nurse dressed in light blue holding a clipboard.

“Are you Mrs. Johns and her son, Thomas?”

Both nod affirmatively.

“My name is Jason. I’ve just come on shift. I see the triage nurse started your chart and that you have been admitted. What I need to do now is listen to your chest and ask you some questions. Is that ok?”

Jason watches both of them nod ‘yes’.

“Ok, then. Thomas, would you mind taking the dog outside so I can assess your mother?”

Thomas reaches down and gently extracts Trixie from Erin.

“Can you come get me after you’re done?” asks Erin.

Thomas: “Mom, I’ll walk Trixie and then put her in the truck. I have some biscuits that I can give her and she should be perfectly fine there.”

Thomas cradles the small dog, who begins to whimper quietly, and strides out through the doors to the emergency exit.

Jason pulls a chair closer to Erin. “I am going to ask you a few questions. This helps us to help you. Do you feel up to answering a few questions?”

“Yes.”

“When did you begin to feel short of breath?”

“About a week. Ago. I went. Clinic. Gave me new puffers. Seemed to help. Today. Walking Trixie. Cold out. Really short of breath. Called Thomas. Brought me here.”

Jason writes the information directly into the second page of the nursing record.

“The clinic notes indicate you have COPD. Is this correct?”

“Yes.”

“Do you have any other conditions?”

“No.” Erin smiles weakly. “Otherwise. Healthy.”

“Ok. That is enough right now. Let’s take your vital signs, and then I’m going to listen to your lungs and heart.”

Jason pulls the vital sign machine close to the wheelchair, attaches the BP cuff and the pulse oximeter, and presses the button.

As the cuff inflates, Jason looks carefully at Erin. He notes that her airway is patent and her breathing is rapid at 28/minute and appears shallow, with some nasal flaring.

The blood pressure cuff dings and the result appears on the screen.

“Ok, Mrs. Johns. Your blood pressure is higher than I would expect. Is this normal for you?”

Erin leans forward and peers closely at the numbers. “I think so. Top number. 150 to. 170. Normally.”

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 19h30	112	190/84	28	–	84% on RA

Jason nods. “Your oxygen saturation is a bit low, so I’m going to put you on a little oxygen. Is that ok with you?”

“Yes.”

Jason reaches over to draw in a cart from the hallway. He pulls out a set of nasal prongs and attaches them to an oxygen tank fitted at the back of the wheelchair. He thinks to himself and then sets the flow at 2 LPM.

"Let's see if that helps with your shortness of breath. I'm now going to listen to your heart and lungs. I know we are in the hallway and I'll do my best to not expose you. Are you ok with me examining you?"

"Yes. Not happy. In hallway."

"I can understand that, but we're very busy and I have no other place to give you. I hope this will only be for a couple of hours."

Jason then carefully slips his stethoscope between Erin's clothes and skin. Closing his eyes, he moves the stethoscope systematically first to the anterior chest then posterior chest. After listening, he quickly examines her abdomen and extremities.

"Ok, Mrs. Johns. I'm done right now. I see your oxygen levels appear to be a bit higher. Are you feeling a little less short of breath?"

"Yes, I feel a bit better."

"Great! I am going to find the doctor and see what the plan will be for you. If you need any help, just wave your arms."

Erin nods that she understands. Looking around, she shivers slightly at being sick and so exposed in the hallway. She watches Jason move towards the nursing station where there are two people who look like doctors. She thinks to herself, "They look so young. How can they be doctors? I'm stuck in a hallway, can't believe all the money we pay for taxes and this is the best they can do for me. When Thomas comes back, I'll ask him to take me and Trixie home. This is ridiculous."

Jason looks at the various people huddled around the nursing station.

He shakes his head slightly and mumbles, "Yeah, shift change for everyone."

He walks up to Dr. Singh, whom he is most familiar with. As he approaches he hears Dr. Singh announce, "I'll take the back rooms and the hallway patients. Stan, can you take the triage and trauma? I did that yesterday, and with that patient dying in the trauma room, I still have to sign off the chart and have a discussion with the coroner."

Stan looks up at his peer. "Ok, but if it gets really busy, we'll need to call someone in or you will need to help."

Dr. Singh sighs. "If you need help, I will stay."

Dr. Singh moves off to check the computer for emergency admissions and to start planning his shift.

Jason moves up beside him. "Can I interrupt?"

"Sure thing, Jason. What's up?

Trying to keep to SBAR, Jason says, "I just came on shift as well. New patient, Mrs. Johns, 72 years old, in Hallway B. Exacerbation of COPD, maybe pneumonia, no other medical history, quite short of breath with low sats. I placed her on 2 LPM prongs with some relief and better sats. Breath sounds are quite quiet to the lower fields and she has a slight wheeze in the upper fields. She's stable right now but I need some orders, please."

"Ok, Jason. I agree that she's stable right now, but with a big potential to deteriorate. I will follow the COPD protocol and write orders for a chest X-ray, some labs, puffers, spirometry, and an ABG. Let's hold off on antibiotics till we have a firmer picture of pneumonia. I don't want to overreact and prescribe something she doesn't need right now. With her diagnosis and potentially frequent antibiotic use, we could set her up for a superbug. How does that sound?"

"I agree, and thank you. I'll get the RT for the ABG and see if Medrad can do the X-ray portably."

Dr. Singh pulls out a doctor's order sheet. Jason places a sticker with Erin Johns's identification on the top right corner.

Jason takes the orders from Dr. Singh and goes over to the unit clerk, Sheila.

Sheila looks at him with raised eyebrows. “I just got here, so please don’t tell me this is a long order set! My commute was terrible and daycare was late opening up. I already feel behind before I’ve even started.”

Jason smiles. “Aww, Sheila. I hate when my day starts like that. I once had to bring little Jim in to work when my daycare was late as well. Cathy picked him up a half hour into the shift. The orders are really short, as you would expect from Dr. Singh. Just what you need, no extras. Since you are settling in, do you want me to enter them into the computer?”

“That would be awesome!! I see Dr. Greg’s admitted a patient to 7B and the order set for that patient is seven pages. I would rather get started on that set, if you don’t mind.”

“No problem.” Jason moves away from the nursing station and signs on to a computer located just a few feet from Erin.

He types in all the information and generates the requisitions for the orders Dr. Singh wrote: CBC, lytes, BUN, creatinine, spirometry, and a portable chest X-ray, and medications as per COPD protocol.

Jason quietly moves towards Erin and notes that she is sleeping in the chair.

“Wow, I wonder when she last had a good sleep.”Jason gently touches her arm to wake her and updates her on her tests. He tells her that Dr. Singh will come by in a little bit, after the tests are done, to check on her.

Erin nods and then closes her eyes.

Place: Medical Laboratory

Alexa has just started her shift. Smiling inwardly, she thinks, *This is my third shift by myself after orientation. Can’t believe it. School does a good job of preparing you for the job, but nothing can prepare you for the work. It’s so busy. My feet already hurt.*

Straightening her scrub top, she leans over and double-checks her cart to make sure she has enough supplies to last the majority of the shift.

The lab supervisor approaches her. “Emergency is really busy right now. Would you mind going down there first before heading to the rest of the hospital? Sheila, the clerk down there, says there are about 20 lab reqs waiting.”

“Ok, I haven’t been there since I was a student.”

“No worries. James is already down there and he can help you out. He thoroughly enjoys the atmosphere of the Emergency.”

Alexa pushes her cart out of the lab area and heads to the elevator that goes to Emergency. She pushes the button for the Emergency floor and watches the buttons slowly creep towards that floor. Exiting, she pushes her cart up to the emergency staff doors, and taking a deep breath she pushes the button. As soon as the doors open, she sways back from the noise and the smells and the overwhelming sense of chaos.

“Oh my. Yep, school did not prepare me for this. Wow.”

Navigating her cart through the Emergency Department, she thinks to herself, *It’s just like driving in rush hour in a foreign country. There are rules but no one sticks to the lines.*

She quickly finds herself at the nursing station and moves towards the desk area where all the requisitions are waiting.

She notes that James has taken all the stat ones, as there is not one in the pile. Looking through requisitions, she notes that they are all pretty similar and all the reqs have close to the same time on them.

“Ok, let’s start with this one,” she says as she places Erin Johns’s req on the top of her board. Looking at the req, she pulls out the appropriate lab tubes and labels them with Erin Johns’ stickers.

That done, she looks up. A frown creases her forehead, and she mumbles, “Hallway B. Where the heck is that?”

Jason, walking by, hears Alexa mumble and stops. “Hi, I’m Jason and Hallway B is my assignment. Who are you looking for?”

Alexa, looking somewhat sheepish, says, “I didn’t think anyone would hear me mumble in this noise.”

“It’s not so noisy and you do get used to it.”

“I’m looking for Erin Johns.”

“Erin is my patient. Let’s walk over here and down this corridor. I’ll introduce you. I haven’t seen you before. Are you new?”

“Yes, this is my third shift by myself after orientation. I’ve mainly been in the lab department or on the medical floors. I was in Emergency for some of my final preceptorship.”

“Excellent. This is a great place to work. Busy, but the people are knowledgeable and quite caring.”

As they move down the hallway, Alexa sees an elderly lady, still in her normal clothes and with a light blanket wrapped around her shoulders, sleeping in a wheelchair.

“Is that…?”

“Yes. That is Erin Johns.”

Jason moves confidently up to Erin and lightly touches her on the arm. Alexa notes that Erin’s eyes open quickly and they appear sharp and not withdrawn, like some of the patients she has seen.

“Mrs. Johns, this is Alexa, one of our lab technicians. She’s here to take some blood from you. Is that ok?

Erin nods ‘yes’.

Alexa moves her cart closer. Looking at the req and then at Mrs. Johns, she says, “Can you tell me your name?”

“Erin Johns.”

“Your birthday?”

“06/06/19xx.”

“Excellent, thank you.” Alexa checks the identification band on Erin’s right wrist against the information on the requisition. Satisfied, she gathers the tubes, double-checks them, and picks up the venipuncture equipment and tourniquet. Following the World Health Organization guidelines, Alexa prepares to take the required blood specimens.

Alexa first asks Erin to roll her sleeve up a bit more. Carefully putting the tourniquet around Erin’s right upper arm, Alexa then swabs her inner antecubital space.

“Ok, this will pinch a bit.”

Carefully sliding the needle under the skin, Alexa quickly finds the vein and pushes the first of three tubes into the vacutainer.

Once all the tubes are full, Alexa shakes them slowly and carefully to mix the blood and the anticoagulant. After that, she carefully places the tubes in the holder in the front of her cart.

“I’m all done, Mrs. Johns. I hope you feel better soon.”

Alexa moves away and heads towards the nursing station. She looks down at the next req on her list and notes that it’s not a hallway but a number. Looking around, she quickly finds number 12 and heads towards the next patient.

Place: Medical Radiography

Gurpreet checks the list of patients requisitions that need to be done. Looking at the list, she sees there are a number of emergency patients and floor patients. No requisitions are marked as stat.

“Ok, looks like we need a porter.”

Glen looks across the lobby from where he is sitting. “What’s that, Gurpreet? Do you need me?”

“Sorry, Glen, didn’t see you there. Yes, can you go pick up Mrs. Erin Johns from Hallway B in Emergency, please?”

“Yes, no problem.”

Glen pulls himself out of the chair and strides through the double doors of the Radiology Department. Looking quickly up and down the hallway, Glen makes his way down the back stairs to the Emergency Department.

Glen has been working in the hospital for about 15 years and knows every short cut there is. Taking the stairs two at a time, he arrives at a little used doorway into Hallway B of the Emergency Department.

Walking up to the nursing station at the far end of the hallway, he looks at Sheila, the unit clerk. “Hi ya, Sheila.”

“Oh, hi Glen. What can I do for you?”

“Oi, how about dinner?”

“That’s not what I meant!” Sheila smiles at her boyfriend and winks at him.

“I’m here to escort Mrs. Erin Johns to the Radiology Department for a picture.”

Sheila looks at her assignment list and finds that Jason is the nurse. “Ok, Jason is caring for her. And there he is talking with Mrs. Johns.”

“Thanks. See you after work?”

“I’m done at seven. Come down here when you’re finished. We can share a bus seat home.”

Glen smiles and walks towards Erin and Jason.

“Hi, my name is Glen and I’ve been asked to escort Mrs. Johns here to the X-ray Department.”

Jason frowns. “Can’t that be done portably?”

Glen shakes his head. “Not my call. Gurpreet asked me to escort her to the department.”

Jason leans down and explains to Erin that she needs a chest X-ray to help them figure out why she is short of breath.

Erin, looking a bit more tired, says, “I’ve had quite a few of those. I’d be glad to get out of this hallway. It’s so noisy.”

Glen grabs the back of the wheelchair, quickly turns her around and points the chair out the door. Striding to the elevator, Glen recaps for Erin the weather outside, the hockey game, and recent city events. Erin sits in her chair and pretends to listen.

Glen and Erin roll through the doors of the Radiology Department to see Gurpreet standing at the desk.

“Here is Mrs. Erin Johns, from Hallway B in the Emergency Department.”

“Thank you, Glen. Can you place her in Room 2, please? I’ll be right behind you.”

Time: 11h30

Place: Emergency Room, Hallway B

“When will I get my results?”

Glen looks at Erin. “I’m not the one to ask, I’ll let Sheila know you are back, so the doctor and Jason can look at your picture.”

“Thank you.”

Glen walks quickly away to the nursing station to inform Sheila that the chest X-ray is completed.

Erin looks up and down the hallway and sees less activity and some empty stretcher bays.

I do hope I can get a bed to lie down in, she thinks to herself. *My backside is getting sore*.

Without realizing it, Erin closes her eyes. Suddenly she feels a touch on her hand. Startled, she gives a little shout.

“Oh oh oh, it’s ok. My name is Matt. I had no intention of scaring you. Wow. Really sorry, Mrs. Johns.”

“It’s ok. I didn’t realize I had fallen asleep.”

“I’m a respiratory therapist and a couple of tests have been ordered for you. One is spirometry, which I think you have had before, from the results in your chart, and the second one is a blood gas.”

“Spirometry is the blowing test, right?”

“Yes, that’s the one. Shall we do that one first?”

“Ok.”

Matt opens a small plastic bag to retrieve a freshly sterilized kit tube with a gauge on it. He quickly describes what he wants Erin to do.

“Mrs. Johns, I’m going to ask you to take a deep breath and then blow it out as hard as you can through this tube. We’re going to do this three times to make sure we get an accurate measurement.”

Erin sits a bit straighter in her wheelchair and nods. “I’ll try my best.”

Matt hands Erin the device. “Good. Ok, take a deep breath, then blow through the tube.”

Erin does as instructed, three times. After each time, Jason records the results on the requisition for spirometry.

“Ok, that is now done. You did a great job, Mrs. Johns.”

Erin nods her head and smiles slightly.

“Next, I need to do an Arterial Blood Gas or ABG, so I must draw a small sample of blood from your wrist. This is a bit more uncomfortable than having your lab work done.”

Erin looks up questioningly. “Is it necessary? I had a blood gas done before and it really hurt!”

“I’ll try my best to not hurt you, but it is uncomfortable. Which hand do you use the most?”

“I am right-handed.”

Matt gently grabs Erin’s left hand and bends her elbow 90 degrees. He then performs the Allen test.

“Ok, ok, everything looks good, Mrs. Johns.”

Matt then rubs an alcohol swab vigorously across Mrs. Johns’ wrist. Then he waves his hand back and forth to disperse the smell.

“I need you to relax and stay still while I do this, ok?”

Erin nods nervously.

Matt, holding the syringe at a 45 degree angle, slips the needle under Erin’s skin. Quickly the syringe fills with red fluid. Matt then withdraws the syringe and holds a gauze over the site.

“That wasn’t too bad. You are very good at this.”

“I’ve had a bit of practice, Mrs. Johns.” While holding pressure on her left wrist, Matt deftly removes the needle from the sample and caps the syringe. After a couple of minutes, he asks Erin to hold pressure but not to peek and not to let go until he comes back.

Taking the sample, Matt goes to the back area of the Emergency Department and runs the sample through the blood gas machine. The machine quickly prints out the result.

Matt goes back to Erin.

“Ok, let’s look under the gauze.”

Matt see no bleeding but notes a small bruise at the puncture site. He places a small gauze over the site and wraps a small dressing right around Erin’s wrist.

“Please leave this dressing on. We can take it off later tonight, but I want to make sure you don’t get left with a big bruise.”

Erin nods.

Matt steps away to find Jason and show him the results from spirometry and the blood gas.

Matt finds Jason at the computer in the nursing station.

“Hi, Jason. I have the results from spirometry and blood gases for Mrs. Johns.”

Jason looks up, smiles and says, “Ok, anything special?”

“Spirometry shows a decrease in vital capacity from what was taken at the clinic a couple of months ago. That’s not surprising, given that she’s back here. The ABG shows a rise in CO_2 and just normal PaO_2 on 2 LPM oxygen. She’s a bit compromised right now. I took a listen to her chest a little while ago. She sounds typically COPD-like, with nothing I didn’t expect.”

“Ok. Are the results on the clipboard?”

“Yes, and I hope you don’t mind I wrote the ABG in the chart as well.”

“You are awesome. I’ll go find Dr. Singh when I’m done here and see what he would like to do, but my guess is she is staying the night.”

Thirty minutes later, Jason says: “Dr. Singh, here are the spirometry results and ABG on Erin Johns.”

“Thanks.”

Dr. Singh reviews the results and comes to the same conclusions as Matt and Jason. “Let’s look at her chest X-ray.”

Dr. Singh pulls up the X-ray film onto the computer and both lean in to view the black and white picture. Jason looks at the picture and then at Dr. Singh, thinking to himself that it looks like a normal X-ray, except the lungs look a bit long.

Dr. Singh sighs. “Ok, the X-ray shows a bit of infiltrates at the bases and your typical COPD hyper-inflation. Nothing that I would consider abnormal itself, but when we consider the ABG and the spirometry all together, I’d like to keep her overnight to see if she is going to get better or going to get worse. If it’s pneumonia, she will get worse overnight and the next day. If it’s just the cool weather we’re having and nothing infective, she should get a bit better with some care and attention. What do you think?”

“Matt and I were having the same discussion. I’m pretty sure I can find a bay for her to stay. Question is, will she want to stay?”

“I’ll go talk to her.”

“Hello, Mrs. Johns. My name is Dr. Amir Singh. I am one of the many people here taking care of you.”

“Not sure about taking care of me. First I’ve seen of you.”

Dr. Singh smiles. “So true. I’ve been more in the shadows than caring for you directly like Jason here. Both Jason and I have reviewed your tests and we believe you should stay overnight with us. I don’t think it’s serious, and if you are able to get a reasonable sleep and a few more puffs of the meds I’ve ordered, along with some oxygen, you may look better in the morning.”

“I’m feeling better. Not perfect. Can I have a bed? Can my dog visit me? Will someone call my son?”

Dr. Singh smiles. “Yes to all. I’ll call your son and let him know, and Jason here will find you one of our finest beds in the Emergency.”

“Thank you.”

Dr. Singh then nods to both Erin and Jason and walks over to where a nurse is gesturing for him at Bed 3.

Jason bends down to be eye level with Erin and says, “Give me a couple of minutes and I’ll find you a more private location.”

Erin nods and smiles. She grabs Jason’s hand and pats it kindly, like all the old ladies do with Jason.

After a discussion with the charge nurse and getting housekeeping to clean an area from a recent discharge, Jason moves Erin into the last stretcher bed furthest from the nursing station and the doors, the most private location they have and a coveted location for staff to take their breaks.

“This should be a lot better for you. You need to let me know if you need to use the washroom, as I’ll get another oxygen tank on wheels for you to use when you are up.”

“Thank you. What about my son and Trixie?”

“Dr. Singh and I updated Thomas. He’s not going to come in tonight but will in the morning. He says not to worry about Trixie. Thomas said he was going to give her a bath and a meal and they were going to chill with some Netflix.”

“Oh, she really needs a bath. Been feeling awful not to be able to do even that small task. Trixie likes to watch Mad Men. That Mr. Draper is such a scamp!”

“Ok, Mrs. Johns. If you need anything, please push the call button.”

Day: 1

Time: 07h00

Dr. Notley is reviewing the list of patients to see this morning when he is approached by the charge nurse with a list of overnight patients that potentially could be sent home if everything is well.

“Can you look at these patients first? Let me know which ones can be sent home.”

Dr. Notley notes the first patient is Erin Johns, exacerbation of COPD, on 2 LPM nasal prongs, ABG shows higher than normal CO_2 and drop in PaO_2 with maybe something on the CXR.

Dr. Notley walks quickly down the hall to the last stretcher in the row of twenty. Seeing the curtain partially open, he announces himself. “Good morning. I’m Dr. Notley.”

Jackie, the nurse taking care of Erin, waves him in.

“Hello, Jackie. How are you doing?”

“Doing good right now. Mrs. Johns is doing quite well. I was at the triage desk yesterday when she came in. She didn’t look very happy nor well. This morning, I’ve taken her O_2 off and her sats have stayed 90-91% on room air. No cyanosis noted and her breath sounds have no wheezes and she is not coughing anything up.”

“Excellent. How are you feeling, Mrs. Johns?”

Erin looks at Dr. Notley and thinks to herself that he looks exactly how a doctor should look, with nice grey hair, pressed lab coat, and a stethoscope around his neck. Dr. Welby’s brother. “I’m much better. I feel a bit short of breath but not

worse than usual. I can go to the washroom without stopping for breath. The food here is terrible and I would love something better."

"Ok, good appetite and able to move around. Not sure we're doing anything for you now, Mrs. Johns. I'd like to send you home with follow-up in the clinic tomorrow and the next day. I want to make sure that you are well followed and that this does not happen to you again."

"Will you make the appointments? Can someone phone my son to pick me up?"

"That won't be necessary, Mom. Trixie and I are already here."

Dr. Notley nods and asks Thomas to come closer. He then goes on to explain what probably happened, with the cold weather, stress and not taking her puffers regularly, leading to her coming to the Emergency. He then goes on to explain the importance of the medications and the follow-up appointments.

Thomas shakes his head and reaches out for his mother's hand. "Thank you, doctor. I'll make sure she gets to the appointments. Are there any new prescriptions for her?"

"I'm going to send you home with the puffers she is using here, and I'm going to send a note to the clinic with our recommendations for meds for Mrs. Johns. That's why it's important to go to the clinic tomorrow."

Mother and son both promise to go to the clinic.

Thomas moves Trixie from inside his coat onto Erin's lap. The little dog excitedly jumps around and then curls up in the covers on Erin's lap.

"Cute dog, Mrs. Johns," Dr. Notley exclaims as he walks away to finish the discharge list and begin the paperwork to discharge Mrs. Johns.

Jackie then explains that they will have to wait until the paperwork is done for discharge and the clinic appointment. "Do you have any questions?"

Both shake their heads 'no'.

"Ok, I'll come back in a few minutes with your meds and the paperwork to sign for your discharge."

APPENDICES: INTRODUCTION TO HISTOLOGY FOR FIRST-TIME LEARNERS

Histology Summary and Credits

JENNIFER KONG

Learning histology is similar to learning how to read. But instead of learning the shapes of your "a, b, c's", new learners in histology needs to recognize shapes in cellular morphology (squamous, cuboidal, columnar). And like in certain languages there are variations of a letter like an accent. In histology the columnar shape has variations dependent on their function (transitional, pseudostratified). And like learning how words fit in a sentence, the distribution of cells gives meaning to the function of the tissue (simple vs stratified vs pseudostratified). As with learning how to read, the learner needs to practice practice practice – ideally with a more experienced 'reader' by your side.

Perspective of the reading frame is also important in both reading and histology. Can you read a book upside down? Yes – if you have mastered your letter and pattern recognition. In histology, imagining what a tissue structure looks like in 3D based on the 2D plane of the tissue slice is not an easy task. However, that 3D recognition in 2D will develop with practice and eventual mastery.

Layers of cells also helps determine function. Using reading as an analogy, a paragraph with a lot of detail has more info to communicate than a single line. Likewise, in histology, a simple single layer of cells has just one function (e.g absorption) whereas multiple layers of cell have multiple possible functions (e.g. protection by built up layers, protection by sloughing/shedding, etc)

The most common histological stain allows for easy visualization of the nucleus and amount of protein in the cytoplasm. Thus, a nucleus:cytoplasm ratio can be visualized to help determine the cellular morphology and viability. For example, there is more cytoplasm than nuclei in squamous whereas there is more nucleus to cytoplasm with cuboidal. But if no nucleus isn't present, then that cell is not alive, regardless of size of cytoplasm.

In summary, histology requires 'visual literacy' which recall, symbol/pattern recognition, critical thinking and lots of practice is needed.

Credits

Author: Willie Wu (UBC Graduate Student in Interdisciplinary Oncology Program), Athena Li (UBC undergraduate student in BMLSc program), and Dr. Jennifer Kong (BCIT & UBC)

Illustrations: Athena Li (UBC undergraduate student in BMLSc program) and Sarah Pinault (UBC-O undergraduate student)

APPENDICES: ADDITIONAL EXERCISES FOR CRITICAL THINKING AND CLINICAL REASONING

Introduction to Recall, Critical Thinking, and Clinical Reasoning

GHAZAL SOKHANRAN; KRISTEN DANIELLE GO; SAMUEL LAM; AND JENNIFER KONG

Learning Objectives

By the end of this section, you will be able to:

- Describe what is critical thinking and give some examples of real life use
- Explain the reasoning behind critical reasoning and differentiate it from recall & clinical reasoning
- Describe the critical thinking skills and how to develop and enhance them
- Practice and understand the difference between knowledge based thinking, critical thinking and clinical reasoning questions

"The important thing is not to stop questioning. Curiosity has its own reason for existing" -Albert Einstein

When a patient visits a doctor, a diagnosis is rarely immediately obvious, which means that the answer does not simply come from real life interactions with patients. Instead, a diagnosis is reached by combining information from a variety of sources. After recalling what he or she knows about how the body works and recognizing the physiology behind the patient's condition, the doctor will need to focus on the appropriate organ system based on the patient's complaints as well as results from lab testing and imaging. Now, the doctor will need to use critical thinking to apply all of the available information to discern what is normal or abnormal, and the reasoning behind any abnormalities. This is why **critical thinking** is important — critical thinking leads us to approach problems from different angles, and to reach unique solutions that exhibit deeper understanding of a subject. This section will introduce you to strategies to help you think critically as well as define critical thinking.

Getting Started with Critical Thinking

Let us start by asking ourselves — what is critical thinking? Some things that come to mind when you hear critical thinking might be puzzles, analyzing data or written works, or even having a debate or an argument. These activities all share the need for **logical reasoning**. Critical thinking is a method that requires you to apply prior knowledge from related concepts in order to reach a solution. For example, in order to solve a jigsaw puzzle, you would need to combine what you know about what the finished puzzle looks like together with spatial perception — that is, how the pieces and different portions of images fit together.

Examples of everyday uses of critical thinking

You might not have noticed, but you use critical thinking in daily life, here are some examples

- Identifying fake news vs real news
- Making purchases
- Giving recommendations or advice to a friend
- Planning a vacation
- Driving

The following video attempts to put critical thinking into perspective

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6201#h5p-346

Differentiation between Recall and Critical Thinking

Traditional studying such as listening to lectures, taking notes, and revision prompt students to mostly practice recall skills. Recall is simply repeating previously gained knowledge from memory, such as when you match a term to a definition on an exam. Recall questions have one definitive answer, while critical thinking questions may have many possible correct answers and are more open-ended. Critical thinking actually takes place in a different region of the brain than the region used for recall — critical thinking takes place in the prefrontal cortex, while recall takes place in the temporal lobe. Because of this, critical thinking may not come naturally to students who are not accustomed to innervating the neuron pathways in the critical thinking centres of the brain.

Critical thinking may be complex and require outside-the-box thinking. This skill also requires you to be organized in order to combine what you know about a variety of topics to come up with a solution for a problem. As you approach critical thinking questions, highlight important details and ask yourself what else you know regarding the topic, and what other concepts may be related. You will be able to apply your critical thinking abilities for problem-solving in almost any real world scenario, making it a truly invaluable skill.

The following video demonstrates an example of using information from other concepts to work a practice question.

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Differentiation between Thinking, Critical Thinking, Clinical Reasoning, and Clinical Judgement

One doesn't need an introduction to 'thinking' as it is a skill we have been doing since birth: it's the mental processes needed to gain and recall information and apply it for the appropriate scenario (e.g. recalled skills to drive a car in real life vs a video game). Critical thinking is thinking with both purpose and control: one has a purpose (i.e. a problem) which the thinker controls the logic of what to recall and apply to get the solution needed. As mentioned earlier, critical thinking is challenging because learners often don't get much practice with controlling their learning for a specific purpose.

Clinical Reasoning is a process where you apply critical thinking to the purpose of a patient's current context. Although a patient's medical history requires recall, the patient's current context (i.e. their current signs and symptoms) are dynamic which requires both critical thinking (e.g. "Why did the patient's symptoms change suddenly?") and forward thinking (e.g. "what else will change for the worse and how can I prevent it?"). Clinical Reasoning is the logical process needed for actions to take place in the clinical setting (i.e. Clinical Judgement) which outcomes can be measured (e.g. "Did the patient's vital signs stabilize?")

To highlight the similarities and differences between Critical Thinking and Clinical reasoning, refer to the Table 1

Critical Thinking in Everyday Life	Clinical Reasoning (Critical Thinking in a Clinical Setting)	Clinical Judgement (Actions taken after clinical reasoning)
Problem Solving, decision-making	Prioritization of which clinical problem needs to be addressed first	assess the patient for vital signs, collect blood test samples
Teaching-Learning (in classroom, online, simulation)	Patient-centered care & risk management with patient's needs guiding the process	communication with patient and health care team about options for interventions
Test-Taking	Applying evidence-based practice	initiating interventions such as medications and diagnostic tests
using and creating electronic data (studying)	Using and creating electronical medical data (informatics, recommended guidelines)	Refer to and initiate treatment algorithm, update patient's medical record

Table 1 – modified from Figure 1.2 of "*Critical Thinking, clinical reasoning, and clinical judgement*: A *Practical Approach*" by R. Alfaro-LeFevre.[1]

Clinical Reasoning in a Classroom Setting

In a classroom setting, clinical reasoning skills are developed in a safe setting where patient safety isn't in question. This can be in the form of a case study, clinical skills simulation, or even a examination question. Generally a clinical reasoning question contains a patient history with or without a story illustrating the patient's context. Patient data is included (e.g. labs or physical examination findings) with the expectation of the learner to recognize what is normal and abnormal physiology. Clinical reasoning still gets the learner to control their logical process of specific recall, critical thinking with a purpose (i.e. a solution), but now the patient context now has to be taken into consideration.

Steps to Critical Thinking and Clinical Reasoning in the Classroom

The steps to approach critical thinking and clinical reasoning overlap. Overall, the process can be broken into steps

1. If this is a multiple choice question, immediately cover the multiple choice options. Often, too many options distract or confuse the critical thinking process.
2. Read the patient's story/history and underline key words that catch your attention. Identify what the current problem is – or at least, the abnormal data.
3. What is the question asking you? It is often helpful to either highlight the question or write it out into a very simple version that a child can understand.
4. On scrap paper, jot down everything you recall about the normal physiology associated with the patient's problem
5. Using critical thinking, identify where interruptions in the normal physiology (i.e. pathophysiology) can occur and what they would look like clinically.
6. Look back at the underlined data. Does any of the data match with the pathophysiology in Step 4?
7. Go to the highlighted question. Answer only the question posed with the data you have on hand: do not add "what if's" when choosing your answer.

Read the next section for demonstrations and strategies on how to apply clinical reasoning skills.

Notes

1. Critical Thinking, clinical reasoning and clinical judgement: A Practical Approach 7th Ed. by Rosalinda Alfaro-LeFevre, Elsevier 2020.

Demonstration of How to Work Through Clinical Reasoning Exercises

JENNIFER KONG

Clinical reasoning is the culmination of knowledge of anatomy, physiology, & pathology being applied in a logical process, taking into consideration the current context. To achieve clinical reasoning one must consider:

1. The current context. Usually thought of as, "Why this change, now?" To answer this question, one must do a logical process starting with… of all things… recall
2. Recall what you DO know. This will involve knowledge of the normal anatomy & physiology to identify what has gone wrong. Once identifying the part that is wrong, one must use logic and critical thinking
3. Critical thinking is when one can problem solve why there is a sudden change from normal physiology to abnormal pathophysiology (or normal anatomy to abnormal pathology). When one can critically think of the sudden change, this lays the groundwork for interventions.
4. Interventions, or treatment, must take the current context into precedence. If the current context demands immediate attention because airway, breathing, circulation, and/or cognition is in danger – then the intervention must address these life saving functions first. If the current context allows for time to treat, then contextual factors (albeit, less immediate) need to be considered. For example, how invasive is the intervention (e.g. do I have to make the patient bleed where they weren't bleeding before?) or accessible a treatment (e.g. an easily accessible X-ray with instantaneous results vs a lengthy wait for an MRI scan that takes time to interpret)

Watch this demonstration video of how to approach a clinical reasoning question. After watching, consider practicing on the clinical reasoning exercises following this chapter.



An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6203#h5p-347

Extra Critical Thinking Questions

GHAZAL SOKHANRAN; SAMUEL LAM; KRISTEN DANIELLE GO; AND JENNIFER KONG

In this appendix you will find a series of extra critical thinking questions that relate back to all the knowledge you have learned till this point, and they require you to apply the critical thinking skills and methods to solve them

Heart Failure Chapter

1. Compare the anatomy and function of the right and left sides of the heart. Speculate on some possible defects in the heart that could lead to diseases. Hint: they don't have to be actual disease, don't even name disease, just speculate. Eg. Hypertrophy on the left side of heart (the muscle tissue gets too large on the left side)

2.

Pathophysiology	Physiological manifestations (e.g. chamber volume, cardiac output)
EXAMPLE: LV is abnormally thick	Reduced LV filling volume –> decr ejection fraction
1	Reduced volume in pulmonary circulation & left heart
LA is enlarged with abnormally thin walls	2
3	Superior & Inferior Vena Cava are distended with excess volume, low cardiac output
4	LV is enlarged with thin walls & decr CO, murmur is heard during systole

3. What do you think would happen if the aortic valve doesn't work properly? For each of the following scenarios, explain what: i) would would the effect be on cardiac output (i.e. volume ejected into the aorta)? ii) leftover volume after systole (i.e. end systolic volume)? iii) preload (i.e. volume filling the ventricle).

    - a. Aortic Valve has problem opening fully [5]
    - b. Aortic Valve doesn't close fully, allowing for leakage [6]
    - c. Aortic Valve opening is abnormally narrow[7]

4. What respiratory changes (if any) would someone with L-sided heart failure experience? How does this compare with R-sided heart failure? Are these difference enough for you to make a "diagnosis"?[8]
5. Which would have a greater impact on overall perfusion of the body: concentric vs eccentric hypertrophy? [9]

Acute Kidney Injury Chapter

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Metastatic Melanoma Chapter

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An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6322#h5p-355

Diabetes Mellitus Chapter

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https://pressbooks.bccampus.ca/pathology/?p=6322#h5p-358

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://pressbooks.bccampus.ca/pathology/?p=6322#h5p-360

Emphysema & Pneumonia Chapters

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https://pressbooks.bccampus.ca/pathology/?p=6322#h5p-406

Cirrhosis Chapter

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://pressbooks.bccampus.ca/pathology/?p=6322#h5p-405

Notes

1. RV has reduced contractility or pulmonary valve won't open fully
2. pulmonary circulation will be overfilled with fluid in alveolar space
3. right heart can't contract and eject
4. aortic valve can't close fully and volume falls back into LV
5. ai.reduced ejection fraction (i.e. less volume ejected); aii) incr end systolic volume in LV' aiii) reduced filling volume entering LV
6. bi.reduced ejection fraction (i.e. less volume ejected); bii) incr end systolic volume in LV' biii) reduced filling volume entering LV
7. ci.reduced ejection fraction (i.e. less volume ejected); cii) incr end systolic volume in LV' ciii) reduced filling volume entering LV
8. 4. L-sided heart failure has blood backed up to pulmonary circulation which the fluid will push into the alveoli (pulmonary edema) causing coughing and dyspnea. Right sided heart failure will have less blood going to the pulmonary circulation and a backup of

blood going to the SVC & IVC

9. The key here is how the hypertrophy affects ejection fraction (EF). If there is reduced filling volume, as with concentric hypertrophy, there would be reduced EF. However, eccentric hypertrophy will preserve filling volume but will have decreased contractile function as the walls thinning causing loss of function. So concentric hypertrophy with reduced EF has a greater impact on cardiac output until eccentric hypertrophy loses its contractile function.

Extra Clinical Reasoning Exercises

MEIHUA E. SU; MENA BURR; AND JENNIFER KONG

These extra exercises in clinical reasoning are of different levels of difficulty, depending on the amount of training the learner has experienced. Thus, when possible, the authors have tried to introduce the clinical reasoning process in a logical order to help with learners' development, regardless of their starting point!

A. Meet 78 years old Jeanette with sudden appearance of blurry vision and fast HR

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B. Meet 5 years old Kevin in the Emergency Dept with sudden complaints of vomiting and abdominal pain

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6529#h5p-399

C. Meet 25 years old Serena with sudden headache, confusion, and fever

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6529#h5p-344

D. Meet 47 years old Braxton with nausea, abdominal pain, swollen feet, and jaundice after a morning jog

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6529#h5p-345

E. Meet 21 years old Rosario with abnormal discolouration on their back

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6529#h5p-341

F. Interventions for complaints of short of breath

Recall the exercise where you matched respiratory disorders with the pathophysiology of gas exchange (below).

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6529#h5p-406

Now, work out which interventions would be appropriate for each condition.

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.bccampus.ca/pathology/?p=6529#h5p-407

APPENDICES: CASE STUDY FOR PNEUMONIA

This case study was written by UBC student Annabelle Liao in 2022. The following chapters follow the health journey fictional character Miki Huang takes from an infection of pneumonia leading to an exacerbation of her COPD, causing her to be admitted into hospital.

Although Miki's pathology of pneumonia and ensuing exacerbation of COPD is different than patients with just pneumonia, there are many similarities in the diagnosis and treatment and interactions with health care team.

In this case study, Miki Huang is a non English-speaker and relies heavily on her daughter as her translator and patient advocate. Contrast this with the previous case study of Erin John who is an english-speaker and has no problem being her own patient advocate Patient: Erin Johns. Although the underlying pathology is the same (ie pneumonia causing an exacerbation of COPD), Miki and Erin's perspectives are quite different.

Learning Objectives

JENNIFER KONG

Learning Objectives

In this case, learners have an opportunity to:

1. Review etiological factors (i.e., risk factors, prevalence, comorbidities) associated with respiratory disease and pneumonia.
2. Build knowledge related to the patient's experience of respiratory disease
3. Continue to develop comprehensive assessment, monitoring skills, and abilities (e.g., respiratory assessment, diagnostic studies, laboratory data)
4. Develop and justify optimal therapy based on the current understanding of the pathophysiology of COPD and pneumonia, based on available clinical evidence
5. List the roles of healthcare professionals and the contributions they make to the healthcare team (or describe your own role and the roles of those in other professions)
6. Define the roles of translator and patient advocate and explain the persons who can fulfill that role.

This case describes a patient's experience of chronic obstructive pulmonary disease (COPD) with a new diagnosis of pneumonia. The interprofessional collaboration is role modelled between nursing, medical radiology, medical laboratory, respiratory therapist, physiotherapist, and healthcare workers in the emergency department and medical units.

Note: The core story told here is used in both Erin Johns and Miki Huang case studies. Erin Johns is a simpler version with the patient being a native English speaker and her own patient advocate. The Miki Huang case reintroduces the storyline but expands her story – as a non-English speaker and relying on family to be her advocate – along with more details for more advanced study in health sciences.

Adaptation

This case study is adapted by Annabelle Liao from the following text:

Case Study #2: Pneumonia in Health Case Studies: Toward Closing the Healthcare Communication Gap licensed under a Creative Commons Attribution-ShareAlike 4.0 International License

Patient: Miki Huang

ANNABELLE LIAO

Patient: Miki Huang



Miki Huang. Image created by Sarah Pinault using CC BY NC license.

Date of Birth: 09/05/1926

PERSONA

Miki Huang is 96 years old. She is widowed with three children, and the eldest daughter (Linda) lives at home with her in their townhouse in Metro Vancouver. Immigrating from Taiwan 27 years ago, her other two children moved back home to Taichung for work. She has seven grandchildren and nine great grandchildren. Miki communicates with her family by telephone and video calls using her large-format flip phone. Miki describes herself as a non-smoker and social drinker, and is also a retired math teacher, although she studied fashion in school. She spends a lot of her time calling her lifelong friends back in Taiwan, but even more time is dedicated to singing familiar old Taiwanese and Japanese tunes, a common passion in the family. At home, she has a karaoke machine connected to the television, set up for her by her son who visited years ago. There is nothing she enjoys more than an afternoon with all her favourite songs queued up. Sometimes, she looks back with nostalgia on the years that have flown by in this new country, and a part of her feels gloomy because she knows she would get out of the house more if only her English skills were more advanced. Ever since her fall 6 years ago, which resulted in a hip fracture, she constantly worries about falling again while Linda is working; however, due to her larger ego, she actively tries to maintain an image of independence and autonomy. Miki never learned to drive even back in Taiwan, and since her English skills are very limited, her daughter picks up her high blood pressure medication for her and drives her to the walk-in clinic when needed (although Miki hates going).

Media Attributions

- Patient_Narrative_-_Pneumonia 1

At Home

ANNABELLE LIAO

Day: 0

Time: 15h00

Place: At home

Miki sighs and slowly sinks back into her wheelchair. Even though she had skipped the last family karaoke session, her lungs still ached a bit, and that persistent cough, albeit minor at the moment, bothers her more than she would like to admit. Although she is someone who prides herself on being able to walk everywhere, she had stayed in her wheelchair for the majority of that day, which incites the slightest tinge of distress. “Don’t worry,” Miki whispers hoarsely to herself, “it’s wintertime, the cold’s just getting to your joints.”

She glances over at the black television screen, before turning to look at the time. She thinks that maybe some hot tea will help her tight chest. “Linda,” she calls weakly to her daughter working at the computer upstairs.

A minute passes, but there is no response. Miki tries to clear her throat, but that in itself seemed to bring about exhaustion. Perhaps she had better call her daughter with her phone.

She slowly scrolls through her call history until she sees her daughter’s name. “Mom?” her daughter’s voice immediately sounds after the second ring, full of concern, “Why are you calling me? I’m just upstairs, remember?”

Suddenly it occurs to Miki that she feels too weak to even speak at her regular volume, and all she can do is stare blankly at the blinking numbers on her screen indicating the time elapsed in the call. She vaguely realizes that Linda’s anxious voice is coming through the speaker but can’t seem to formulate a response. In the silence, she hears tiny popping sounds somewhere in her chest when inhaling and exhaling.

“Mom?” This time, the voice comes from in front of her, and she looks up to see her daughter looking distraught. Although Miki eventually catches her breath after a minute and persistently waves off any concern to put Linda at ease, she soon finds herself in the car driven by her unsettled daughter and on the way to the hospital.

Day 0: Emergency Department

ANNABELLE LIAO

Day 0

Time: 15h30

Place: Emergency Room Triage

Sitting back in her chair, Jackie sighs. “Wow, this has been a long shift. I’m exhausted.”

Looking up from the desk, she sees a shiny Lexus stop in front of the Emergency Room. A middle-aged woman leaps from the driver’s seat and rushes around to open the passenger door. She unfolds a wheelchair and places it on the ground, and an elderly lady slowly eases her way into it.

The woman urgently pushes the wheelchair to the doors, leaving her car where it is parked. Once inside, Jackie notices that the woman displays pursed lip breathing and has a slight blue tinge to her lips. By this time, the duo is at the triage desk.

Day 0 – Miki arrives in the Emergency Room. Image created by Sarah Perkins using a CC-BY-NC license.Jackie comes out from behind the desk. “Hi, my name is Jackie and I’m the triage nurse today. How can I help you?”

“Thank you so much, this is my mother Miki Huang and she started having trouble breathing before we rushed over here. She also has been coughing a bit and it sounds wet, like there may be phlegm?”

Jackie pulls the blood pressure monitor and pulse oximetry machine close to Miki and wraps the cuff around her right arm. She presses a button, and the cuff inflates. On Miki’s left index finger, she places a pulse oximeter.

After about 30 seconds, the machine beeps and displays the following vital signs:

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 15h30	96	180/90	28	36.5° C	85%

Grabbing a clipboard with an emergency assessment record on it, Jackie fills out the initial vital signs.



Day 0 – Miki and Linda arrive at the Emergency Room. Image created by Sarah Pinault using a CC-BY-NC license.

Referring to the Triage and Acuity Scale along with the vital signs, Jackie grades Miki's condition as "Triage Level III – Urgent."

"Is she going to be okay?" asks Linda, breathlessly.

"I think it would be best if Ms. Huang stays with us for a while and has a doctor take a look at her. I will make arrangements for a spot for her to stay once we get admission paperwork done. Can you and your mom answer a few questions from Denise, the admission clerk who is just to the left of my desk?"

Denise comes over and introduces herself to Miki.

“Good afternoon. My name is Denise.”

Miki stares at her and nods out of politeness, but nothing really registers.

“Her name is Miki and mine is Linda,” Linda interjects. “My mother doesn’t really speak English.”

Denise pauses. “Ok. Linda, can you wheel your mom close to my desk so I can input her information into the computer, please? That way we can get her a space in the ER quickly and have a doctor see her as well.”

Linda pushes the wheelchair over to the admissions desk.

“Do you have your Care Card with you?” asks Denise.

Miki continues to just focus on her breathing, but Linda nods ‘yes’ and quickly rummages through her purse for it. She hands it over to Denise, who rapidly inputs the information into the system.

“I see that she was at the clinic last week. Is this correct?”

Linda explains: “They changed her puffers- I mean, her inhalers, and said to come back if there was any problem.”

Denise nods her head. “Make sure you tell the nurses that….do you see anyone regularly at the clinic?”

“No, usually we just see the first doctor available. They change so often, and my mother doesn’t like going, so usually we only visit if it is absolutely necessary.”

Looking up at Linda, Denise asks, “Can I have your contact information, Linda, in case we need to contact you?”

Linda looks bewildered. “But who will tell my mom what the doctors are saying? She doesn’t speak English, remember?”

“We have remote interpreters available for many languages,” Denise explained. “Family members are good support, but they shouldn’t be the main translator.”

Linda looked doubtful, “Well…I would still feel more comfortable staying with my mom though. I’m the one who takes care of her. Would it be fine if I just stayed anyways?”

Denise hesitated, “Sure, that’s fine. It may take a while though, just warning you. I have called for a porter, and they will move to a spot where the doctor can see you.”

Denise watches as the porter comes up to both Linda and Miki and begins pushing the wheelchair through the doors into the back area of the Emergency Ward.

The mother and daughter pair are abruptly left in the hallway. Linda reaches around to grasp her mother’s hand, who grips it tightly. She looks around the chaos and sees people moving from curtained area to curtained area, all dressed in identical blue scrubs. No one makes eye contact or even acknowledges them as new arrivals.

She didn’t want her mother to know, but Linda secretly worried about the whole situation. “If only we were back in Taiwan,” she secretly fretted. “What if I say something wrong or don’t understand something? What if I don’t know the right words?”

Just then, she feels a presence behind her. Turning around, she sees another nurse dressed in light blue holding a clipboard.

“Are you Ms. Huang and her daughter?”

Linda nods for the both of them while Miki remains passive.

“My name is Jason. I’ve just come on shift. I see the triage nurse started your chart and that you have been admitted. What I need to do now is listen to your chest and ask you some questions. Is that ok?”

“Yes,” Linda blurts out. “My mother only speaks Taiwanese and Japanese, so I will answer for her.”

“Ok then. Linda, why don’t you sit by the side over here,” Jason says, gesturing as he pulls up a chair closer to Miki.

“When did you begin to feel short of breath?” He watches the younger relay the question to the older.

“She said before we got her new inhalers she would sometime feel out of breath, but today she suddenly couldn’t breathe again. She felt pretty weak all day,” Linda states.

Jason writes the information directly onto the second page of the nursing record.

“The clinic notes indicate you have COPD. Is that correct?”

“Yes, she does.”

“And do you have any other conditions?”

“No,” Linda says. “She’s overall pretty healthy.”

“Okay, that’s all the questions for now. Let’s take your vital signs, and then I’m going to listen to your lungs and heart.”

Jason pulls the vital sign machine closer to the wheelchair, but as he starts to attach the blood pressure (BP) cuff and the pulse oximeter, Miki seems to startle.

Jason notices this and hesitates, but Linda is quick to reassure her in their native language that the doctor is simply checking her vitals.

He presses the button and as the cuff inflates, Jason observes Miki carefully. He notes that her airway is patent, and her breathing is rapid at 28 breaths/minutes and appears shallow, with some nasal flaring. Periodically, she coughs with great effort, and it sounds like there is phlegm in her system.

The blood pressure cuff dings and the results appear on the screen.

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O_2 Saturation**
Time: 20h00	92	170/90	26	36.4° C	84%

“Ok, Ms. Huang. Your blood pressure is higher than I would expect. Is this normal for you?”

Linda leans forward. “I think so? I remember it being in the higher range, but it’s also been a while since she last got her blood pressure taken.”

Worried, Miki pulls on Linda’s sleeve, wondering where the conversation is going. She cannot understand anything that is happening at the moment and worries that something is wrong with her.

“Don’t worry Mom. I was just telling the doctor I think your blood pressure has always been a bit higher” Linda explains.

Relieved, Miki eases back into her wheelchair. “Hopefully I’ll be home by tonight,” she thinks to herself. “The new episode of that singing show is coming out soon.”

Jason continues. “Your oxygen saturation is also a bit low, so I’m going to put you on a little oxygen. Is that okay with you?”

“Of course!” Linda exclaims.

“Sorry, if I could get an affirmative from Miki herself that would be great,” Jason says.

“Oh, sorry, of course,” Linda says. She turns to her mother and explains, and Jason sees Miki nod, although it comes with some frowning and hesitancy.

“My mother’s wondering how long she has to stay here for?”

Jason pauses. “The doctor will be able to give you a better answer. Why don’t we wait and see what they say?” He reaches over to draw in a cart from the hallway. He pulls out a set of nasal prongs and attaches them to an oxygen tank fitted at the back of the wheelchair. He thinks to himself, then sets the flow at 2 Litres Per Minute (LPM).”

“Let’s see if that helps with your shortness of breath. I’m not going to listen to your heart and lungs. I know we are in the hallway, and I’ll do my best to not expose you. Are you okay with me examining you?”

Linda starts translating to Miki, whose brows furrow deeper and deeper. Jason notices that even with her shortness of breath she can convey great objection and dissatisfaction. Linda and Miki both seem to forget that he is there, and the conversation starts to escalate, with Linda seemingly trying to persuade her mother. They both sigh before Linda turns to face Jason again.

"She's not happy in this hallway and scared that she'll be accidentally exposed."

"I totally understand, but we're super busy right now and I have no other place to offer you at the moment. Hopefully this will only be for a couple of hours. So do I have permission to examine her?"

"Yes, she agreed, but she also warned you to be careful," Linda says tiredly.

Jason nods and carefully slips his stethoscope between Miki's clothes and skin. Closing his eyes, he moves the stethoscope systematically first to the anterior chest, then to the posterior chest. After listening, he quickly examines her abdomen and extremities.

"Ok, Miki. I just finished. I see your oxygen levels appear to be a bit higher. Are you feeling a little less short of breath?"

Linda quickly starts speaking, and Miki begins to nod.

"Yes, she said she feels a bit better."

"Great! I am going to find the doctor and see what the plan will be for you. If you need any help, just wave your arms."

Linda nods and shifts her feet around. Miki peers around with trepidation and shivers slightly. Linda immediately notices and wonders if she should tell Jason that her mother is cold, but watches as he moves toward the nursing station where there are two people who look like doctors. She thinks to herself, "They look so young. How can they be doctors? I can't believe my mother has to sit here in this hallway to wait. Can't they see how old she is? Is this what we pay taxes for? I wonder if they treat all their patients like this. I can't wait to get out of here; I still have work tomorrow."

Jason looks at the various people huddled around the nursing station.

Jason shakes his head slightly and mumbles, "Yeah, shift change for everyone."

He walks up to Dr. Singh, whom he is most familiar with. As he approaches, he hears Dr. Singh announce: “I’ll take the back rooms and the hallway patients. Stan, can you take the triage and trauma? I did that yesterday, and with that patient dying in the trauma room, I still have to sign off the chart and have a discussion with the coroner.”

Stan looks up at his peer. “Okay, but if it gets really busy, we’ll need to call someone in or you will need to help.”

Dr. Singh sighs, “If you need help, I will stay.”

Dr. Singh moves off to check the computer for emergency admissions and to start planning his shift.

Jason moves up beside him. “Can I interrupt?”

“Sure thing, Jason. What’s up?”

Jason summarizes his findings with Miki’s report and explains, “I just came on shift as well. New patient, Ms. Huang, 96 years old, in Hallway B. Exacerbation of COPD, maybe pneumonia, no other medical history, quite short of breath with low sats. I placed her on 2 LPM prongs with some relief and better sats, otherwise known as oxygen saturation. Breath sounds are quite quiet to the lower fields, and she has a slight wheeze in the upper fields. She’s stable right now but I need some orders, please.”

“Okay, Jason. I agree that she’s stable right now, but with a big potential to deteriorate. I will follow the COPD protocol and write orders for a chest X-ray, some labs, puffers, spirometry, and an ABG. Let’s hold off on antibiotics till we have a firmer picture of pneumonia. I don’t want to overreact and prescribe something she doesn’t need yet. With her diagnosis and potentially frequent antibiotic use, it could set her up for a superbug. How does that sound?”

“I agree, and thank you. I’ll get the RT for the arterial blood gases (ABG) and see if medical radiography can do the X-ray portably.”

Dr. Singh pulls out a doctor’s order sheet. Jason places a sticker with Miki Huang’s identification on the top right corner.

Jason takes the orders from Dr. Singh and goes over to the unit clerk, Sheila.

Sheila looks at him with raised eyebrows. “I just got here, so please don’t tell me this is a long order set! My commute was terrible, and daycare was late opening up. I already feel behind before I’ve even started.”

Jason smiles. “Aww, Sheila. I hate it when my day starts like that. I once had to bring little Kim to work when my daycare was late as well. Cathy picked him up half an hour into the shift. The orders are really short, as you would expect from Dr. Singh. Just what you need, no extras. Since you are settling in, do you want me to enter them into the computer?”

“That would be awesome! I see Dr. Greg’s admitted a patient to 7B and the order set for that patient is seven pages. I would rather get started on that set, if you don’t mind.”

“No problem.” Jason moves away from the nursing station and signs onto a computer located just a few feet from Miki.

He types in all the information and generates the requisitions for the orders Dr. Singh wrote: CBC, Lytes, BUN, creatinine, spirometry, and a portable chest X-ray, and medications as per COPD protocol.

Jason quietly moves towards Miki and notes that she is sleeping in the chair.

“Wow, I wonder when she last had a good sleep.” Jason decides not to disturb her and instead gently touches Linda’s arm to update her on her tests. He tells her that Dr. Singh will come by in a little bit, after the tests are done, to check on her.

Linda nods, looking exhausted and frantic.

Place: Medical Laboratory

Alexa has just started her shift. Smiling inwardly, she thinks, “This is my third shift by myself after orientation. Can’t believe it. School prepares you for the job, but nothing can prepare you for the endless work. It’s so busy; my feet already hurt.”

Straightening her scrub top, she leans over and double-checks her cart to make sure she has enough supplies to last most of the shift.

The lab supervisor approaches her. “Emergency is super busy right now. Would you mind going down there first before heading to the rest of the hospital? Sheila, the clerk down there, says there are about 20 lab requisitions waiting.”

“Okay, I haven’t been there since I was a student.”

“No worries. James is already down there, and he can help you out. He thoroughly enjoys the atmosphere of the Emergency.”

Alexa pushes her cart out of the lab area and heads to the elevator that goes to Emergency. She pushes the button for the Emergency Department and watches the buttons slowly creep towards that floor. Exiting, she pushes her cart up to the emergency staff doors, and taking a deep breath, pushes the button. As soon as the doors open, she instinctively leans back from the noise and smells and overwhelming sense of chaos.

“Oh wow…school definitely did not prepare me for this…”

Navigating her cart through the Emergency Department, she thinks to herself, “It’s just like driving during rush hour in a foreign country. There are rules but no one sticks to the lines.”

She quickly finds herself at the nursing station and moves towards the desk area where all the requisitions are waiting. She notes that James has taken all the urgent request (STAT) ones, as there is not a single one in the pile. Looking through requisitions, she observes that they are all pretty similar and all the requisitions have close to the same time on them.

“Okay, let’s start with this one,” she says as she places Miki Huang’s requisition on the top of her board. Looking at the req, she pulls out the appropriate lab tubes and labels them with Miki Huang’s stickers.

That done, she looks up. A frown creases her forehead, and she mumbles, “Hallway B. Where the heck is that?”

Jason, walking by, hears Alexa mumble and stops. “Hi, I’m Jason and Hallway B is my assignment. Who are you looking for?”

Alexa, looking somewhat sheepish, says, “I didn’t think anyone would hear me mumble in this noise.”

“It’s not so noisy and you do get used to it after a while I guess.”

“I’m looking for a Miki Huang?”

“Miki is my patient. Let’s walk over here and down this corridor. I’ll introduce you to both her and her daughter Linda. Unfortunately, the patient can’t speak English, which is why Linda is still here. She seems really worried.... say, I haven’t seen you before, are you new?”

“Yep, this is my third shift by myself after orientation. I’ve mainly been in the lab department or on the medical floors. I was in Emergency for some of my final preceptorship.”

“Excellent. This is a great place to work. Busy, but the people are all knowledgeable and quite caring.”

As they move down the hallway, Alexa sees an elderly lady, still in her normal clothes with a light blanket wrapped around her shoulders, sleeping in a wheelchair. Beside her, a middle-aged woman fidgeted and shuffled her feet, eyes darting up and down the hallway. Alexa could feel that she was protective of the older woman.

“Is that...?”

“Yes, that is Miki Huang.”

Jason moves confidently up to the pair and briefly speaks to Linda, before lightly touching Miki’s arm. Alexa notes that Miki’s eyes snap open quickly and appear sharp, not withdrawn, like some of the patients she has seen.

“Ms. Huang, this is Alexa, one of our lab technicians. She’s here to take some blood from you. Is that okay?”

Linda speaks rapidly in a language Alexa can’t place, and then Miki nods slowly.

Alexa moves her cart closer. Looking at the requisition and then at Ms. Huang , she says, “Can you tell me your name?”

Linda answers, “Miki Huang.”

“Birthday?”

“September fifth, nineteen twenty-six.”

“Excellent, thank you.” Alexa checks the identification band on Miki’s right wrist against the information on the requisition. Satisfied, she gathers the tubes, double-checks them, and picks up the venipuncture equipment and tourniquet. Following the World Health Organization (WHO) guidelines, Alexa prepares to take the blood specimens.

Alexa first asks Linda to help Miki roll her sleeve up a bit more, but this seems to irritate Miki, who insists that she can do it herself. Carefully putting the tourniquet around Miki’s right upper arm, Alexa then swabs her inner ante-cubital space.

“Ok, this will pinch a bit.”

Carefully sliding the needle under the skin, Alexa quickly finds the vein and pushes the first of three tubes into the vacutainer.

Once all the tubes are full, Alexa shakes them slowly and carefully to mix the blood and anticoagulant. After that, she carefully places the tubes in the holder in the front of her cart.

“I’m all done, Ms. Huang. I hope you feel better soon.” She smiles reassuringly to convey what words cannot.

Alexa moves away and heads towards the nursing station. She looks down at the next requisition on her list and notes that it’s not a hallway but a number. Looking around, she quickly finds number 12 and heads towards the next patient.

Place: Medical Radiography

Gurpreet checks the list of patients’ requisitions that need to be done. Looking at the list, she sees several emergency patients and floor patients. No requisitions are marked as stat.

“Okay, looks like we need a porter.”

Glen looks across the lobby from where he is sitting. “What’s that, Gurpreet? Do you need me?”

“Sorry, Glen, didn’t see you there. Yes, can you go pick up Ms. Miki Huang from Hallway B in Emergency, please?”

“Yes, no problem!”

Glen pulls himself out of the chair and strides through the double doors of the Radiology Department. Looking quickly up and down the hallway, Glen makes his way down the back stairs to the Emergency Department.

Glen has been working in the hospital for about 15 years and knows every short cut there is. Taking the stairs two at a time, he arrives at a little-used doorway into Hallway B of the Emergency Department.

Walking up to the nursing stations at the far end of the hallway, he looks at Sheila, the unit clerk. “Hiya, Sheila.”

“Oh, hi Glen. What can I do for you?”

“Oi, how about dinner?”

“That’s not what I meant!” Sheila smiles at her boyfriend and winks.

“I’m here to escort Ms. Miki Huang to the Radiology Department for a picture.”

Sheila looks at her assignment list and finds that Jason is the nurse. “Okay, Jason is caring for her. And there he is, talking to the patient’s daughter.”

“Huh, wonder why she stuck around. Thanks, though. See you after work?”

“I’m done at seven. Come down here when you’re finished. We can share a bus seat home.”

Glen smiles and walks towards the trio huddled in the hallway.

“Hi, my name is Glen and I’ve been asked to escort Ms. Huang here to X-ray Department.”

Jason frowns. “Can’t that be done portably?”

Glen shakes his head. “Not my call. Gurpreet asked me to escort her to the department.”

Jason explains to Linda that Miki needs a chest X-ray to help them figure out why she is short of breath. Miki, impatient, leans forward in her seat, yearning to understand. Was she going to be okay? What was going on?

Linda looked down at her frail mother. “Don’t worry Mom, they just need a few X-rays, okay?”

“Alright, I guess. At least I’ll be out of this noisy hallway,” Miki sighed.

Glen grabs the back of the wheelchair, quickly turns her around, and points the chair out the door. Striding to the elevator, Glen recaps for Miki the weather outside, the hockey game, and recent city events. Miki sits in her chair and wonders why the man won’t stop talking. And although she would never show it, she is secretly relieved to hear the pattering of her daughter’s feet hurrying after them.

Glen and Miki roll through the doors of the Radiology Department after taking the X-ray to see Gurpreet standing at the desk.

“Here is Ms. Miki Huang, from Hallway B in the Emergency Department.”

“Thank you, Glen. Can you place her in Room 2, please? I’ll be right behind you.”

Time: 19h30

Place: Emergency Room, Hallway B

Having come back from radiology, Miki and Linda once again find themselves in the hallway.

“Linda, can you ask when we’ll get the results?” Miki whispers impatiently.

Reluctant and afraid to be a bother, Linda asks Glen, who looks down at Miki. “Tell her I’m not the one to ask. I can let Sheila know that you’re back, so the doctor and Jason can look at your X-ray images.”

Linda thanks Glen profusely as he walks away to the nursing station to inform Sheila that the chest X-ray is completed.

Miki looks up and down the hallway and sees less activity and some empty stretcher bays.

“I do hope I can get a bed to lie down in,” she thinks to herself. “I can’t believe they know how old I am and haven’t even offered me a bed yet. My backside is getting sore. This would never be happening back home.”

Without realizing it, Miki’s eyes slowly shut. Suddenly, she feels a touch on her hand. Startled, she gives a little shout.

“Oh oh oh, it’s okay. My name is Matt. I had no intention of scaring you. Wow, I’m really sorry Ms. Huang.”

Miki turns to look at Linda, wondering why she didn’t interject.

“He said he’s sorry, Mom.” Turning to Matt, she continued, “Don’t worry about it, my mother’s had a tiring day. We’re all pretty tired, actually.”

“Completely understandable. Well, I’m a respiratory therapist and a couple of tests have been ordered for you. One is spirometry, which I think you have had before looking at the results in your chart. And the second one is a blood gas.”

The word “test” vaguely registers in Miki’s head, and her brows furrow with concern.

Matt looks between mother and daughter. “Shall we do the spirometry first?”

He opens a small plastic bag to retrieve a freshly sterilized kit tube with a gauge on it. He quickly describes what he wants Miki to do. “Ms. Huang, I’m going to ask you to take a deep breath and then blow it out as hard as you can through this tube. We’re going to do this three times to make sure we get an accurate measurement.”

At this point, Linda is extremely worried about saying the wrong thing or giving the wrong directions and messing up the test. She translates with some hesitancy in her voice, and Matt, picking up on this, also feels a tinge of worry that he tries to brush off.

Miki, however, sits up a but straighter in her wheelchair and nods, ready to do her best.

Matt hands Miki the device. “Please tell your mom to take a deep breath, then blow through the tube.”

Miki does as instructed, three times. After each time, Jason records the results on the requisition for spirometry.

“Okay, we’re done for now. You did a great job, Miki.”

Miki, understanding that they are finished, pats Matt’s hand gratefully.

“Next, I need to do an Arterial Blood Gas or ABG, so I must draw a small sample of blood from your wrist. This is a bit more uncomfortable than having your lab work done.”

“Wait, aren’t those painful?” Linda interrupted. “I think she’s done one before, and I remember her complaining endlessly.”

“I’ll try my best not to hurt her, but it is uncomfortable. Which hand does she use the most?”

“She is right-handed.”

Matt gently takes Miki’s left hand and bends her elbow 90 degrees. He then performs the Allen test, which is a standard test used to assess the arterial blood supply of the hand, prior to doing arterial blood gases.

“Okay, everything looks good, Ms. Huang.”

Matt then rubs an alcohol swab vigorously across Ms. Huang's wrist. Then, he waves his hand back and forth to disperse the smell.

"I need her to relax and stay still while I do this, okay?"

Linda relays the message to Miki, who sighs with displeasure. This day could not get any worse.

Matt, holding the syringe at a 45-degree angle, slips the needle under Miki's skin. Quickly, the syringe fills with red fluid. Matt then withdraws the syringe and holds a gauze over the site.

"That was pretty good! You're doing great, Miki."

While holding pressure on her left wrist, Matt deftly removes the needle from the sample and caps the syringe. After a couple of minutes, he asks Linda to tell Miki to hold pressure but not to peek and not to let go until he comes back.

Taking the sample, Matt goes to the back area of the Emergency Department and runs the sample through the blood gas machine. The machine quickly prints out the result. Matt goes back to Miki, and gestures for her to take away the gauze.

Matt sees no bleeding but notes a small bruise at the puncture site. He places a small gauze over the site and wraps a small dressing right around Miki's wrist.

"Please leave this dressing on. We can take it off later tonight, but I want to make sure you don't end up with a big bruise."

Matt steps away to find Jason and show him the results from spirometry and the blood gas. He finds Jason at the computer in the nursing station.

"Hi Jason. I have the results from spirometry and blood gases for Ms. Huang."

Jason looks up, smiles and says, "Okay, anything special?"

"Spirometry shows a decrease in vital capacity from what was taken at the clinic a couple of months ago. That's not surprising, given that she's back here. The ABG shows a rise in CO2 and just normal partial pressure of oxygen (PaO2)

on 2 LPM oxygen. She's a bit compromised right now. I took a listen to her chest a little while ago. She sounds typically COPD-like, with nothing I didn't expect."

"Hmm. Are the results on the clipboard?"

"Yes, and I hope you don't mind I wrote the ABG in the chart as well."

"You're awesome. I'll go find Dr. Singh when I'm done here and see what he would like to do, but my guess is she's going to have to stay the night."

"Matt and I were having the same discussion. I'm pretty sure I can find a bay for her to stay. Question is, will she want to stay?"

"I'll go talk to her."

"Actually, you'll have to go talk to the daughter. I didn't mention before, but the patient actually doesn't speak English at all."

Dr. Singh stares at Jason. "Okay, then…"

Adaptations

This section has been from Health Case Studies by Glynda Rees, Rob Kruger, and Janet Morrison.

Media Attributions

- Day_0_ER 1

Day 1 Emergency Department & Medical Unit

ANNABELLE LIAO

Day 1

Time: 02h00

Place: Emergency Room

Jason decides to take another set of vital signs:

Day: 1	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	O_2 Saturation
Time: 02h00	86	160/90	22	36.5°C	90%

Time: 02h30

"Dr. Singh, here are the spirometry and ABG results on Miki Huang."

"Thanks." Dr. Singh reviews the results and comes to the same conclusions as Matt and Jason. "Let's look at her chest X-ray."

Dr. Singh pulls up the X-ray film onto the computer and both lean in to view the black and white image. Jason looks at the image and then at Dr. Singh, thinking to himself that it looks like a normal X-ray except that the lungs look a bit long.

Dr. Singh sighs, "Okay, the X-ray shows a small number of infiltrates at the bases and typical COPD hyperinflation. Nothing that I would consider abnormal in itself, but when we consider the ABG and the spirometry all together, I would like to keep her overnight to see if she is going to get better or worse. If it's pneumonia, she will get worse overnight and the next day. If it's just the cool weather we are having and nothing infective, she should get a bit better with some care and attention. What do you think?"

"Matt and I were having the same discussion. I am pretty sure I can find a bay for her to stay in. Question is, will she want to stay?"

“I’ll go talk to her.”

“Hello, Ms. Huang, My name is Dr. Amir Singh. I am one of the many people here taking care of you.”

Ms. Huang stares back, brows furrowed.

Dr. Singh smiles reassuringly and continues, “Both Jason and I have reviewed your tests and we believe you should stay overnight with us. I don’t think it’s serious, and if you are able to get a reasonable sleep, and a few more puffs of the meds I have ordered along with some oxygen, you may feel better in the morning.”

Still Ms. Huang remains silent. Just then, Jason comes running up from behind.

“Sorry Dr. Singh, our patient doesn’t speak English, remember? Her daughter Linda has been translating this entire time, but it seems that she went home briefly to get some matters sorted.”



Day 1 in ER – Miki is visited by hospital staff while Linda is absent. Image created by Sarah Pinault using a CC-BY-NC license.

Dr. Singh nods, "Yes, I can't believe that slipped my mind. Perhaps we had better get Linda on the line and update her."

Throughout this entire exchange, Miki sits in her wheelchair and coughs occasionally, growing increasingly impatient. Jason bends down to meet her eye level.

"Hi Ms. Huang," he slowly enunciates with big gestures, "I am going to call Linda and tell her you need to stay overnight. Give me a few minutes."

Miki glares back and wonders if he realizes that even if he speaks slower, she still cannot understand English.

Time: 02h35

Place: Home

Linda collapses on the couch, thoroughly exhausted. She tells herself that she's just resting for a quick minute and no more. So much has happened and her head is still spinning. It briefly crosses her mind that she still needs to work tomorrow. Her eyes flicker to the blaring television, which wasn't turned off in their rush to the hospital. Although she's trying her best, Linda cannot stop thinking about her poor mother alone in the hospital and imagining every worst possible outcome.



Day 1 in ER – Linda is home, resting briefly. Image created by Sarah Pinault using a CC-BY-NC license

Just then, her phone rings and she lunges for it. It is the hospital.

"Hello?" she answers breathlessly.

"Hi Linda, this is Jason from the hospital. I'm just calling to inform you that myself and Dr. Singh have reviewed Miki's tests and think that it's best if she stays overnight with us. It shouldn't be too serious; we would just like to observe her symptoms for a bit longer to see if she gets worse."

Linda's head starts racing. "But is that really necessary? Who is going to help my mother? How is she going to ask for help or answer your questions?"

Jason tries to reassure her, "Not to worry at all, Linda. We have interpreters available in many languages and I can arrange one for your mother. The interpreters are all highly qualified and certified medical interpreters and I'm confident they can help."

"But how long are they going to take to get there? And how do you know they'll understand? My mother is so old. I should be there for her," Linda protests.

"Linda, you need to take care of yourself too. I will make sure your mother receives the best care possible. We're arranging a bed for her right now. I'll also call the interpreting services right after."

Linda hesitates briefly, then makes up her mind. "I'm calling in sick to work and then I'll be right there to be with my mother. There's no need to call interpreting services," she states resolutely.

After hanging up, she immediately lets her work know she won't be available for the next few days, splashes cold water on her face, and is promptly in her car on the way to the hospital again.

Time: 03h00

Place: Emergency Room

Reunited with her mother, both mother and daughter feel more at ease again. Jason has already updated Linda on her mother's situation, and now Dr. Singh is speaking to her.

“Hello, Linda. I just want to preface this conversation by reminding you that we have excellent interpreters available. It’s actually recommended that these interpreters be used instead of family members, because they’re very well versed in medical terminology.”

“No, thank you. They may know more medical terms, but they don’t know my mother like I do.”

Dr. Singh nods. “Alright, but make sure you take care of yourself. It’s not going to be super comfortable for you given the spaces available at the moment. You can only take care of your mother if your own wellbeing is maintained too.”

“Thank you Dr. Singh; I’m sure I will be fine.”

Just then, a nurse gestures to Dr. Singh from Bed 3.

Jason tells the pair, “Give me a couple of minutes and I will find you two a more private location.”

Linda nods gratefully, and quickly relays this message to Miki, whose mouth turns upwards ever so slightly.

After a discussion with the charge nurse and getting housekeeping to clean an area from a recent discharge, Jason is able to move Miki into the last stretcher bed farthest from the nursing station and the doors. It’s the most private location they have and a coveted location for staff to take their breaks.

“This should be a lot better for Miki. You need to let me know if she needs to use the washroom as I will get another oxygen tank on wheels for her to use when she’s up.”

“Thank you so much again. And is there room for me here too, or where should I go?”

Jason hesitates, “Well, we wouldn’t be able to arrange a bed for you…”

“That’s okay. I’ll be right next to my mom. I’m pretty sure I have a little stool in my car somewhere.”

“Okay, Linda. I’m just going to take one more set of vitals and then your mother can sleep. If she needs anything, please push the call button.”

Day: 1	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	O2 Saturation
Time: 02h00	86	160/90	22	36.5°C	90%

Time: 07h00

Place: Emergency Room

Dr. Notley is reviewing the list of patients to see this morning when he is approached by the charge nurse with a list of overnight patients that potentially could be sent home if everything is well.

“Can you look at these patients first? Let me know which ones can be sent home. Ms. Miki Huang in the far room appears to be a little worse. We may need to find her a bed.”

Dr. Notley nods. “I’ll see her quickly and then take a look at the potential discharges. I trust your judgement so start drawing up the paperwork on those patients so that when I agree we can move them quickly.”

Dr. Notley pulls up Miki Huang’s electronic record: Exacerbation of Chronic Obstructive Pulmonary Disease (COPD), on 2 LPM nasal prongs, ABG shows higher than normal CO2 and drop in PaO2 with maybe something on the Chest X-ray (CXR).

Dr. Notley walks quickly down the hall to the last stretcher in the row of 20. Seeing the curtain partially open, he announces himself, “Good morning, I’m Dr. Notley. You must be the nurse taking care of Miki?”

“Yes, my name is Jackie; it’s very nice to meet you. “

Jackie waves him in. Dr. Notley also notices a middle-aged woman on a little stool in the corner just as Jackie speaks up.

“Right now, Ms. Huang is not doing as well as expected. I was at the triage desk yesterday when she came in. This morning, I have increased her O2 to 5 LPM and I’m asking the RT to come by and assess her for face mask or Optiflow. I am not sure which option is best.

Her sats have stayed at 90-91% on 5 LPM, work on breathing appears increased, and her breath sounds have expiratory wheezes in upper fields with coarse crackles in lower fields."

"That is a bit disappointing. How are you feeling, Ms. Huang?"

Miki, gauging the newcomer, notices his neat hair, unwrinkled lab coat, and stethoscope. "Now this looks like a proper doctor," she thinks approvingly.

Linda, now alert, answers for her mother: "Hi Dr. Notley, I'm Linda her daughter. My mother can't speak English so I will be translating for her."

She quickly confers with Miki, then looks back up at Dr. Notley. "She said she's tired and can't catch her breath. She also couldn't get out of bed herself. What's happening to her?"

"Well, Linda, that is a very good question. We anticipated that your mother would get better with additional inhalers and a good night's sleep, but obviously that has not happened. I am going to listen to her chest and then order some tests to help find out why she's not feeling like herself. I expect that we're going to have to start her on some antibiotics and admit her to the medical floor for additional treatment."

Linda's looks simultaneously frantic and exhausted. "But my mother doesn't want to stay here. And I'm already behind on work too. I need to be here for her."

"Linda, I would like your mother to stay. Whether you stay is completely optional and up to you. I know that it's challenging being away from family…"

"How can you tell me staying is optional? Am I supposed to just let my mother fend for herself here? At least I could take care of her while working if we both went home."

"Your mother has a long-term condition called COPD (Chronic Obstructive Pulmonary Disease). I suspect that she also has pneumonia as well. If you both go home, she will likely get worse."

"You mean die?!"

“Yes, that could happen. I don’t ask my patients to stay without a good reason. Do you trust me?”

Linda looks down and rubs her hands together. “Yes, of course. You’re the expert here. But I will be staying here with my mother until she gets better.”

Miki, who has been observing from the bed during the entire exchange, grows increasingly frustrated. Nobody was telling her anything even though it was her body that there was something wrong with. She’s not used to feeling powerless or not being in charge, and she absolutely hates it. She clears her throat as loudly as she can. “Linda, tell me what they’re saying,” she demands.

Linda relays the doctor’s words to her mother as quickly as she can, and Dr. Notley watches the older woman’s face become visibly upset. The pair seem to be arguing, although he cannot really tell.

“Mom, I’m telling you, it’s the doctors who are saying you have to stay.”

“Nonsense. I know my body best. They won’t even know how to treat me here; I have my own treatments at home. There’s one that can clear my airways, you know.”

Linda can barely contain her frustration. “Mom! You have something called COPD; the doctor said it’s very serious. You could die!”

“Don’t even say that!” Miki answers sharply. “I know my body best, not these people I met 5 minutes ago. Besides, my own stuff at home is just as good as this Western medicine, and more natural too.”

Linda seethes, “Well, guess what? I’m not driving either of us home until the doctors clear you, so too bad.”

Miki is shocked. What is happening? Her daughter never spoke to her like this. Linda interprets her mother’s silence as compliance and stares her down.

Finally, Linda looks back to Dr. Notley. “Okay,” she says wearily, “We’ll both stay, although my mother’s pretty torn up about the situation. She said you better heal her fast.”

Dr. Notley smiles. “Thank you. I am going to listen to her chest and then write some orders for tests and talk with the

medical team to get her a bed as soon as possible. Her stay with us may not be as long if we can get the right treatment." Dr. Notley lifts his stethoscope off his neck, places the earpieces in his ears and gently places the bell on Miki's chest. He listens methodically, anteriorly and posteriorly.

"Thank you, Ms. Huang. Jackie and I are just going to step out now and see a couple of other patients, but we will be back."

Jackie and Dr. Notley step through the curtain and make their way to an alcove to have a more private discussion.

"What do you think, Dr. Notley?"

"I agree with you Jackie, Ms. Huang looks a lot worse. Her chest sounds very congested and wheezy. O2 requirements are going up. I expect she has community acquired pneumonia. I would like to order another CXR, CBC, ABG, and a sputum sample. I'll see if the lab has the gram stain on the earlier sputum sample which may help guide us. I will also order some antibiotics but will check with the pharmacy to make sure I order the correct one. I will admit her and let the medical admit team know they have a new patient. Anything else you need?"

"That sounds good. I will have the RT get the ABG now so we can get the right O2 therapy." "Excellent. Your other two patients are on my discharge list. How are they doing?"

"Both are fantastic. No complaints and both are already dressed and have called for a ride. They both need prescriptions for the meds that were ordered last night. Once you have seen them, I will move them to the waiting room so we can get the areas clean and ready for a couple of the hallway patients that need a spot."

"Okay. Let me quickly see them. I'll write the scripts and discharge orders so you can move them. Thank you."

Jackie hesitates, "Actually, I would probably also recommend bringing a translator in for Miki…I can see how dedicated Linda is to taking care of her mother, but I'm thinking with both her and her mother's best interests in mind right now. From what I've seen, having a family member act as translator could get a bit messy. It's also just not as efficient in my opinion, but obviously I've never had personal experience with this. However, I do know that there is on-demand phone interpreting here at the Vancouver hospitals, or a professional translator can be dispatched to us within a few hours…and I think some places even offer remote video interpreting now."

Dr. Notley thinks, "Yes, I can see what you're saying. It's also commonly taught that the role of family is to support only for fear of becoming too involved or making decisions on behalf of the patient. Well, we can't force Linda to leave, but I can bring it up again. I know that we can have professional interpreters here immediately with on-demand phone

interpreting, or book one to be here in a couple of hours. Let me double check to make sure this information is accurate, and I will speak to the two again."

Dr. Notley heads over to Beds 18 and 19 to talk to the patients ready for discharge. Jackie waits for a bit in case he needs something, and then moves off to the nursing station to page the RT.

Time: 07h30

Jackie sees Alexa, the respiratory therapist, come into the unit and quickly walks over to her.

"Hi Alexa, do you have a minute to check a patient with me and draw an ABG?"

"Oh, hi Jackie, just give me a minute to finish running this blood gas and gather some stuff. I can meet you at the bedside. Which patient?"

"It's Ms. Huang in the back room."

Alexa nods and rapidly walks over to the ABG machine to run the blood gas. Jackie turns and goes to Ms. Huang's stretcher.

"Ms. Huang, Alexa, a respiratory therapist, will be here shortly to assess you and draw a blood gas which will help us help you."

Linda quickly interjects, "Oh, she had one yesterday too I think."

"Yes, that's correct. And here is Alexa."

Alexa places her hand lightly on Miki's wrist to feel for a pulse and introduces herself. "Hi Ms. Huang, I am Alexa, a respiratory therapist. I am going to listen to your chest, poke your wrist here for a blood test, and depending on the result, make some adjustments to your oxygen therapy before you head upstairs to the ward. Are you okay with that plan?

Miki's head spins, exhausted of being overwhelmed with words and syllables that were so familiar yet so incomprehensible still. She shuts her eyes and wishes she could just go home and sleep, and a deeper part of her is worried about her daughter's job and guilty about being such a burden.

"Yes, she's fine with that" Linda interjects.

"Okay. She appears quite short of breath, so I won't ask her to move around a whole lot."

Although Miki doesn't understand the uttered words, she comprehends that Linda agreed to something based on her tone of voice. She feels a twinge of annoyance at her daughter consenting to something on her behalf without consulting her first, even if it was something small. Ever since arriving at the hospital, she has felt nothing but powerlessness and vulnerability. Besides physically being too weak to plan and carry out any of her usual activities and having to submit to the orders of all those doctors, she completely had to rely on Linda because of the language barrier. This instance literally proves her absolute dependency, and she is hating every minute of it.

Alexa checks the oxygen flow, the position of the nasal prongs, and listens to Miki's chest. Taking her right wrist, Alexa performs the Allen test.

"Everything looks good. I am going to go ahead and do the test now."

Alexa efficiently obtains the ABG. Miki does not even flinch and is just lying back in her bed breathing rapidly.

"You did great, Ms. Huang. I am going to have Jackie hold your wrist for a few more minutes while I go and run this sample through a special machine."

Jackie comes over and holds Miki's wrist firmly to prevent bruising. Alexa moves off quickly to the blood gas machine. Her services temporarily not needed, Linda allows herself a few moments to space out and think about nothing.

A few minutes later Alexa comes back. She takes a look at Miki's wrist and puts a light pressure dressing on it. She then shows Jackie the ABG results.

Day: 1	**pH**	**O_2**	**CO_2**	**HCO_3**	**SaO_2**
Time: 08h30	7.3	65	52	27	89

“Thanks Alexa, the blood CO2 level is about normal for Ms. Huang with the COPD but the oxygen levels are much lower which is a bit concerning.”

“I agree, I think I will place her on Optiflow right now, and when she goes up to the floor ask whoever is covering up there to take another look. I think we can follow just with monitoring her on the pulse oximeter and not require another blood gas until maybe tomorrow.”

“Sounds good to me.”

Jackie leans down and explains the plan to Linda, who wearily tells Miki, who weakly nods her head.

Alexa moves off quickly to gather the Optiflow equipment and returns a couple minutes later. She sets up the humidifier and places the high flow nasal prongs in Miki’s nose. Making some adjustments to the flow, Alexa leans in. “How does that feel, Ms. Huang?”

Miki looks at Linda, who is staring off into space. Feeling eyes upon her, Linda startles. “Oh! She’s asking you how that feels, Mom.”

Miki tells her daughter that she feels fine as Alexa leans in. Looking up at the oxygen saturation (SaO2) displayed on the screen, both Jackie and Alexa can see the number increase to 93%.

Alexa listens to Miki’s breath sounds and finds no real changes.

“Okay Jackie, I think she is fine right now. Dr. Notley ordered a CXR, and I think we should do it portably. I will call the department to ask them to do so. I think the transport to X-ray and back may be too much activity at this time.”

“I agree. I can call them if you want?”

“Not, I’ve got this. You probably have other things to do this morning.” Alexa indicates the two patients that need to be moved to the waiting room and have their discharge forms completed.

"Yeah…it's been pretty busy but not too bad. Almost feels slow given how it was the last couple of days."

Alexa smiles and moves towards the nursing station to call the X-ray department. Jackie walks over to the two patients waiting in chairs for their paperwork to be completed so they can leave.

Alexa calls X-Ray Department

"Hi, this is Alexa. I am the respiratory therapist in the Emergency department. I think you have a requisition for a CXR for Ms. Miki Huang?"

"Just a minute, let me check."

Alexa hums a Drake tune to herself as she waits. Smiling, she remembers his concert from last week.

"Yes, we have the requisition for Ms. Huang. I was about to call for a porter for her as we are ready to take her picture."

"We would prefer that it is done portably. I have just placed her on high flow, and she is really short of breath. I am concerned that if we move her that she may deteriorate or worse."

"Now, we don't want 'or worse'. I will mark that she is unstable and will ask the tech to perform the X-ray portably."

"Awesome. Thank you!"

Alexa hangs up the phone and moves off to find Jackie and let her know.

Place: Medical Radiography

Serge, an X-ray technician, looks at Emily, the unit coordinator for X-ray and frowns. "She can't come to the department?"

"Yes, that's correct. The respiratory therapist (RT) says she is unstable and is concerned that she won't do well being moved about."

“Okay, I hope there is someone to help me out down there.”

“I am sure there is, Serge. Your back will be fine. You might want to think about a different sport to do on your days off. I saw the YouTube video of your rugby game that you posted. That game is violent; you took some pretty good hits.”

Serge smiles. “Yeah. My partner says the same thing, yet he comes to every game and cheers us on. I think he gets a kick out of seeing me being flattened on the field!”

Emily laughs. “I also like to see you flattened. Your expression after being run over is one of pure confusion, as in ‘How could this happen to me?’”

Serge chuckles. “Okay, I can only take so much ribbing here. I’m off to Emergency. Sharon and Preeti are the only ones in the department right now. They are in the back helping out in Room 2 with a chest tube insertion. You can page me if anything comes in. They will probably be busy for another 30 minutes or so.”

Emily nods her head and goes back to the computer.

Serge quickly heads out the doors and takes the back stairs to the Emergency Department. In the alcove by the back stairs in Emergency is the portable X-ray machine. He grabs an unexposed plate and places it in the cassette bin on the back of the machine. He then checks the charge and pre-sets a chest technique of 85 kvp (kilovoltage peak, the maximum high voltage applied to an X-ray tube in order to produce the X-rays) and 5 mAs (milliampere-second, a unit to measure the amount of radiation produced for an X-ray, over a second) before unplugging the machine. He navigates the X-ray machine to Miki’s stretcher. Looking at the requisition for the reason of the exam, he thinks to himself, “SOB. Not much of a history.” Driving the X-ray machine to the end of the bed, he pulls out the X-ray tube to point towards his client.

“Good morning, Ms. Huang.” While reaching to read her name band, he continues. “My name is Serge, and I am going to take a picture of your chest today.” Serge notes the large nasal prong Optiflow and then looks at the SaO2 on the screen and sees the number in the low 90s. “Okay, that is not bad, but not great,” he thinks to himself, “I can see why they asked for a portable.”

Miki weakly opens her eyes to see a very large man with a jet-black beard holding what looks to be a rectangular metal board. Panicked to see this stranger towering over her, her eyes dart around the room before she remembers that Linda left to use the restroom. “What is he here for? What is he going to do to me?” she thinks, mind racing.

Noting the patient's wariness, Serge smiles broadly to reassure her. "Ms. Huang, I am going to take an X-ray of your chest. Dr. Notley has requested this test to help us help you."

Still groggy and unsure of what is happening, Miki blurts out one of the only English words she knows: "No."

Serge stops, a bit confused. "Don't worry Miki, there is nothing to be worried about. This procedure is completely painless and super quick, too."

"...No." Miki tries to gesture towards where Linda headed, but Serge does not understand.

Just then, Linda barrels back into the room. "Hi hi! I'm here now I'm her daughter and translator oh my goodness I'm so sorry what did I miss?" she asks, breathless.

"This strange man is trying to do something to me, and I want him out right now," Miki says to her daughter sternly.

Serge steps forward. "Hi, my name is Serge, and I'm here to take an X-ray of your mother's chest as requested by Dr. Notley."

"Oh, yes, of course, that makes sense. My apologies for my mother; she doesn't speak English at all."

"No problem...oh look, here is Jackie the nurse coming now. Jackie, can you help position Ms. Huang so we can get the best picture possible?"

Jackie smiles, "Would be happy to do so. Thanks for doing this portable. I am not sure that she would have tolerated going to the department."

"We are a bit short-staffed today so it's a bit of a stretch for us, but yes, I can see why you asked."

Turning his attention back to Ms. Huang and Linda, he says to the pair, "We are going to get you sitting up straight in your stretcher. Looks like you're high enough on the bed that we don't need to boost you. Linda, I need you to tell your mom to breathe when I yell, and you just follow Jackie's lead later, okay?"

Serge and Jackie position Miki into high fowlers and place the X-ray plate behind her back. “This is a hard board, but it won’t be for too long.” From the side of the stretcher, Serge reaches around Miki to make sure there is enough of the Imaging Plate (IP) on both sides of her and above her shoulders. “Please tell your mother to try her best to hold still.”

Serge walks back to the portable X-ray machine to adjust his pre-set technique to 90 kVp at 3.2 mAs to hopefully compensate for her SOB. “That should give a faster exposure,” he thinks. Meanwhile, Miki wiggles from the discomfort of the plate, and the IP slips down from where Serge had placed it. He does not notice.

“Okay, Ms. Huang, I’m going to take that X-ray now. Hold still.” Serge reaches for the lead apron hanging on the portable machine. He opens the collimation wide and adjusts the tube head to match his IP. Speaking very loudly, he calls out, “X-ray, Bed 3!” On cue, Jackie and all the other personnel scatter, with Linda in hot pursuit.

“Breathe in. Ms. Huang, take a breath in!” Serge watches her chest fall and rise and takes the X-ray on what he hopes is inspiration. “X-ray clear!” He pulls Miki forward on his own and slips out his plate. “I’ll sit you back a little. Let me know when…” He starts to bring her head down until she clenches his arm out of discomfort.

“Thanks Miki. I am all done now. Dr. Notley should have the result in a few minutes. Thanks to you too, Nurse Jackie.” Miki understands that they are finished for now and pats Serge’s arm gratefully. Jackie scowls at Serge and lightly punches him. “Be careful now. I saw that YouTube video of you playing rugby. I could see me cheering-on the opposite team.”

Serge rolls his eyes. “Who hasn’t seen that video? It’s going to haunt me for a long time.”

“Ah, I’m sure one day it will fade into irrelevancy.”

Serge smiles and backs the portable X-ray machine away from the bedside table and navigates it back to the alcove. He plugs it in and readies it for the next use.

Opening the back stairwell door, he takes the stairs two at a time back to the department.

Place: Medical Laboratory

Jennifer, who was the lab tech on duty yesterday, checks the list of patients she was just handed by the unit coordinator. “Wow, I got Emergency again,” she notes to herself. “This is either going to be a good day or not.” Looking through the list, she sees the familiar name of Miki Huang. “I wonder how she is doing? I think I will go see her first.”

Jennifer pushes her white cart to the elevator and makes her way to the Emergency Department. Checking in at the nurses' station, she confirms that Miki Huang is still in Emergency and that she is in the back area.

Jennifer proceeds to Miki's bedside and looks behind the curtain to see the elderly woman sleeping. She is slightly surprised to see Linda still there, huddled on a stool and eyes filled with concern. Moving towards her, she touches Linda's hand gently. "Linda?"

Startled, Linda looks up. "Oh, hi. I think I remember you. Sorry, I was lost in thought. Is S everything okay?"

"Yes, my name is Jennifer in case you have forgotten. Dr. Notley ordered some lab tests for you and I am here to draw them."

"Oh, you're the girl from yesterday, right?"

"That is correct. But what are you still doing here? You look so exhausted. Has nobody offered a translator? They should be here by now."

Linda hesitates. "To tell you the truth, I'm just so used to always taking care of my mother that I don't trust anyone but me to get the job done," she says. "Especially where we're from, children are always expected to care for their parents in old age. And I don't mind it, it's just that there's going to be a lot of work for me to catch up on later."

"Okay, Linda, I see. Well, you are more than welcome to stay and watch over your mother, and we certainly appreciate having someone so attentive and understanding of your mother's needs," Jennifer replies soothingly. "Now, I just need to check her ID band and ask a few quick questions."

Jennifer checks the ID band against the requisition and the blood tube labels and sees that everything is correct. Miki, awakened by the conversation, lies back and observes silently.

"Can you tell me your birth date?"

Linda translates the question, before quickly conveying the answer back to Jennifer.

“Excellent. Can you tell me your middle name?”

Confused, Linda translates the question for her anyways and looks back to Jennifer. “She says she doesn’t have one, just like I thought?”

“Yes, that was a trick question. I need to confirm that you are who you are and not someone else. This makes sure that the test is done on the right person.”

Relieved, Linda nods her head. Jennifer wraps a tourniquet around Miki’s upper right arm. She assesses the brachial vein and sees it stand out after a few seconds. Nodding to herself, she reaches back into her cart and gathers the correct tubes. “This is going to feel like a pinch. Are you ready?” Jennifer quickly inserts the needle into the vein and fills each of the tubes. Releasing the tourniquet, she places a cotton swab on Miki’s puncture wound. “Linda, please tell her to hold it here. I just need to label these tubes.”

After labelling the tubes, Jennifer checks the site and sees no further bleeding. She places a small round band-aid on the site. “All good. You okay?”

“She says she’s doing fine for being locked up in this prison.”

Jennifer chuckles and nods, then turns to the cart and leaves Miki.

Time: 09h30

Dr. Notley approaches Jackie. “Okay, the medical team has accepted Miki Huang. Can you get her ready to go to the 7th floor? She will be under Dr. Honicutt’s team.”

“She is pretty well ready to go. I need to fill out her transfer assessment information and gather any belongings. She has been asking when she can get out of this noisy place.”

Dr. Notley smiles and turns to the unit coordinator. “Can you ask for a porter to help Jackie take Miki Huang to the floor please?”

“Glen will be back from Diagnostics shortly and he knows to check with Jackie about the next transfer.”

“Excellent. Okay, I am off to the triage desk to see who will fill that stretcher.”

“Thanks.” Looking at the unit coordinator, Jackie asks, “Can you hand me up one of those transfer assessment forms please?”

“Sure thing.”

Jacki takes the form handed to her, reviews the notes and Miki’s chart, and fills it out quickly, remembering to include the daughter Linda’s cell phone number and a quick note about the patient’s language barrier. “I will have to include that Linda is acting as translator at the moment too. Oh, and almost forgot- better find Alexa the RT so she can get the O2 tank.”

Jackie walks back to Miki’s stretcher to find Alexa already with a portable tank and setting it up.

“I was just going to page you to see if you knew about the transfer.”

“A little bird by the name of Glen let me know that this may be happening. I will go up with Glen and transfer my notes over to the floor RT so they know to check in on Ms. Huang often.”

Jackie smiles. “Glen always seems to know when things are happening. He’s the one who showed me the video with Serge taking that hit.”

“Ms. Huang, in a few minutes, Glen and Alexa are going to take you up to the 7th floor. You will be in a semi-private room, meaning that you will have one other person with you.”

Linda frowns, “Is there no way for her to get a private room? Will it be too cramped if I’m there too?”

“I don’t think that’s possible at the moment. Of course, I am aware that you’ll still be staying with her, and I’ll do my best to make sure that your mother’s stay runs as smoothly as possible.”

Just then, Glen comes around the corner. “All ready to go?”

“Yes, here is the transfer assessment, and Alexa will report to the floor RT. Let them know all the latest results are in the system. Here is her bag of meds. I have started the antibiotic, and it’s infusing on the pump.”

“Okay, sounds good. Leave her to us, she is in good hands.”

“Take care, you two.” Jackie watches as Glen pushes the stretcher out of the Emergency Room towards the patient elevator, with Linda scurrying behind. She notes to herself, “Ms. Huang doesn’t look too happy, but does look slightly better with some oxygen on. Okay, I wonder who will be taking her place?”

Jackie turns around and heads to the nursing station to find out who will be filling the stretcher.

Time: 10h30

Place: Medical Unit (Seventh Floor)

As the elevator doors open, Miki and Linda are greeted with a view that overlooks the city. Miki thinks to herself, “I haven’t seen the outside world in so long. My room better have a view like this.” Glen grunts as he pushes the stretcher over the gap between the elevator and the door. Alexa follows him as he weaves past visitors and other professionals waiting for the elevators.

At the nurses’ station, Glen announces that Miki is the patient from Emergency., Tracie, a new Bachelor of Science in Nursing (BSN) graduate, stands up from the computer screen. This is just her tenth shift on the seventh floor. “Hi Glen. Ms. Huang is going to be my patient. I have prepared Room 712 for her, and she will be next to the window in Bed 1.”

“Awesome. Okay Ms. Huang, let’s get you into your room.” Tracie assumes that the woman following near them is a family member.

Glen, with Alexa, Tracie, and Linda following him, pushes the stretcher part-way down the hall to Room 712. Sliding it easily past the patient in Bed 2, he maneuvers the stretcher right beside the bed and locks the wheels. Alexa and Tracie go to the other side of the bed and all three assist Miki to move across to her new bed.

Miki becomes breathless and keeps gasping for air. “Oh my god,” she panics silently, “I can’t catch my breath and I have no way of telling them.” It suddenly strikes her all at once how helpless she really is, which only intensifies her anxiety.

Since arriving at the hospital, Linda feels like she has not once taken her eyes off her frail mother. This is probably why she quickly notices Miki's widened eyes and rapidly fluttering chest. "Hey, I think she's having trouble breathing!" Linda yells from the side.

Although the English words don't make sense to her, Miki is flooded with relief because she is reminded of her daughter's presence. In the midst of her wheezing fit, she makes up her mind to buy Linda a present after this whole ordeal is over. Perhaps that phone Linda had been eyeing earlier in the month.

Alexa steps toward the bed and moves the oxygen tubing from the portable tank to the wall outlet. "Ms. Huang, I want you to try to take some deep breaths through your nose and blow out through your mouth. Slightly close your lips together like you are whistling."

Linda quickly translates, voice trembling just the slightest at the sight of her mother struggling to breathe. Miki takes a deep breath in through her nose and breathes out through her partially closed mouth.

"Very good, Ms. Huang. Keep going. Another breath. Excellent." Alexa watches the oximeter move from an SpO2 of 88% to 93% with Miki taking slow deep breaths.

"How do you feel now?"

Linda touches her mother's arm gently, and Alexa watches the two of them converse with each other in their native language.

"She said she's really tired but can catch her breath now. Thank you." Miki reaches her hand out and pats Alexa's gratefully. Alexa smiles back and pats Miki's hand a couple of times.

"Ms. Huang, my name is Tracie, and I will be the nurse caring for you. I am going to step outside and review your chart so I can plan your care and then I will be back in a few minutes. Do you need anything right now?"

"She said her karaoke machine," Linda says, rolling her eyes. Secretly though, she is thrilled that her mother is feeling well enough to joke around again.

Everyone in the room chuckles, then Tracie and Alexa step outside the room. Glen follows, pulling the stretcher out, only banging the wall lightly as he pulls it around the corner of Bed 2.

Alexa speaks. “Tracie? I have placed Ms. Huang on opti-flow and her Sats are pretty good when she does not exert herself. Orders are to keep Sats above 93%. I will talk with the RT covering this flow so they can come by and see her frequently.”

Tracie flips through the papers from Emergency including the transfer form. “Looks good. I do have one question though: why did you ask her to breathe through closed lips like whistling?”

“That is called pursed lip breathing. Some patients with COPD do it naturally. It helps keep the alveoli open and prevents them from collapsing and making her oxygenation worse.”

“Oh, I sort of remember that from school. I will have to look that up. Thank you.”

“Okay, if you need anything, please call the floor RT and they will come and help out.”

“Will do.” Tracie moves back to the desk to review the chart, lab work, and other tests. She notes that the antibiotics have started and the next dose according to the transfer form is in four hours.

“Okay, everything looks fine right now. I need to start the admission assessment.”

Tracie gathers the vital sign machine and her stethoscope, before heading to Miki’s room.

“Hi Ms. Huang, I would like to have a closer look at you and take your vital signs. Is that okay?”

“Mom, she’s just going to do a quick check up again, alright?”

Miki nods passively, and Tracie attaches the blood pressure cuff to Miki’s arm, places the pulse oximeter on her finger, and then inserts the temperature probe under her tongue. While the machine is humming, she looks critically at Miki and thinks to herself: “I*t looks like she is breathing a bit faster than normal, chest expansion seems symmetrical, and she has a bit of nasal flaring.*”

The vital signs machine beeps and Tracie records all the vitals onto the admission assessment.

Day: 1	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	O_2 Saturation
Time: 18h00	96	180/90	28	36.5° C	85% on Optiflow

“Ms. Huang, I need to lift up your gown a bit and listen to your heart and lungs.”

Linda gestures to her mother, who understands. She sighs and pulls her gown out from under her. Tracie systematically listens to Miki’s heart and lungs and records her findings along with the respiratory rate onto the admission assessment form.

“Thank you, Ms. Huang. I am almost done. Can you tell me your birth date, day of the week and who is prime minister?”

Miki answers each question in Taiwanese, and Linda conveys them back to Tracie in English. Tracie goes on to fully assess Miki and record her findings on the admission assessment form.

“Okay, thank you. I’m all done for now. Do you need anything?”

“She’s asking when lunch will be?”

“It should be coming up anytime now. I think I heard the lunch cart in the hallway so you should be getting it soon.”

“Thank you so much. She doesn’t need anything else at the moment.”

Around 15 minutes later, lunch is dropped off. Eyeing it, Miki is speechless. A plate featuring a single chicken breast is crowned with steamed corn and broccoli, along with a garden salad and yogurt on the side. Even in her weak state, Miki musters up the energy to complain.

“What is all this? How cheap do they have to be, serving breast meat? I don’t even have to taste it to tell you it’s dry.”

Linda cracks a smile. “Mom, this isn’t Taiwan. People love chicken breasts here and they’re actually more expensive than the thigh believe it or not. Plus, there’s lots of protein which is good for you.”

Miki rolls her eyes. “Yeah, sure. And I suppose they got too lazy to cook the vegetables? How dumb is this hospital, everyone knows that eating cold things aren’t good for organs. I swear they’re trying to make me sicker.”

“Um, I’m not sure if they have the same concepts as Chinese medicine about cooling foods but I can eat your salad for you?”

“Not a chance, are you trying to get pneumonia too? Neither of us will be touching this salad.”

Linda sighs, mentally preparing herself for a challenging (and hungry) few days.

Adaptations

This section has been from Health Case Studies by Glynda Rees, Rob Kruger, and Janet Morrison.

Media Attributions

- Day_1_ER 1
- Day_1__Side_Panel_Of_Linda_Resting 1

Day 2: Medical unit

ANNABELLE LIAO

Day 2

Time: 07h00

Place: Medical Unit

Tracie walks into the nursing station and heads to her usual chair. She moves the assignment book towards her and sees that she has the same assignment as yesterday. "That's okay," she thinks, "At least I know the patients." She looks up at the patient board and sees that there have only been two admissions since yesterday and one discharge. "Looks like it could be a busy discharge and admissions day."

Jim comes down and pulls his chair close to Tracie's. "Hi Tracie, how's it going?"

"So far so good, how was your night?"

"Night was quiet. Ms. Huang required some adjustments in her Optiflow which the RTs took care of. Mr. Alex had a bit of sundowner syndrome and was quite restless, but otherwise the night was pretty quiet."

"Great. Okay, let's do the report so you can get home."

"Yeah, I have to get out of here quick. I'm taking the kids on a field trip later in the afternoon. Twenty-six Grade 2 kids. I can't believe I volunteered to chaperone after a night shift."

Tracie laughs, "Lucky you."

Jim then walks Tracie through the night and updates her on changes to her patients. After reporting, Jim heads out,

while Tracie quickly looks through the charts to plan her morning. Tracie notes that she has a lot of 08h00 medications so she decides to prepare these meds and then do her patient checks at the same time.

Tracie makes her rounds and drops off all her medications. With that done, she notes to herself, "Everyone seems all right now, having breakfast. I didn't see any issues off the top. I'll give everyone a few minutes and then do vitals, assessments, and discharges."

Tracie sits down to check the RT's note on Miki Huang when Miki's call bell rings. She gets up from her chair and walks down the hallway to her room.

"Hi, Ms. Huang. Hi Linda. How can I help?" She notices Linda's disheveled appearance and dark moons under her eyes with slight concern.

Linda herself is frantic. "My mother said she couldn't catch her breath shortly after we took off her oxygen to eat. Can you help us put it back on please?"

"I want Miki to take some deep breaths. Tell her in through her nose and out her mouth. Remember to close the lips slightly as she breathes out. I'm going to get the vitals machine and be right back."

Miki watches Tracie walk briskly out of the room and is annoyed. What good is she if she's not going to help? She then hears her daughter speaking to her and turns around to realize that she's telling her how to breathe. "What's the point of staying in the hospital if I'm just going to breathe on my own without the oxygen?" She thinks to herself. "I can literally do this at home."

Miki reluctantly follows Linda's instructions and continues to take deep breaths, although she makes it a point to glare at her daughter throughout the entire process. Linda, weary and frustrated herself, glares back.

Tracie grabs a vital signs machine from the hallway charger and brings it into Miki's room to take her vital signs.

"Okay, let's start checking you out." Tracie wraps the blood pressure cuff around Miki's left arm, pulse oximeter on the right forefinger, and temperature probe under the tongue. About 30 seconds later, she notes that the blood pressure is up a bit, and the oxygen saturation is down. Temperature is unchanged with the same low-grade fever. Respiratory rate is up as well, and heart rate is above 110 bpm. "This is not going in the right direction," she thinks, "I may need the RT to come see her."

Day: 2	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	O_2 Saturation
Time: 07h30	112	165/90	22	36.5°C	83% on RA

“Okay, Ms. Huang, let’s listen to your heart and lungs.”

Tracie systematically auscultates, thinking, “Not any change from what I remember yesterday.”

“How are you feeling now?”

Linda conveys the question to her mother, who answers: “Not great, but maybe a bit better.”

“Alright, I’m going to ask the RT to come and see you right away.”

Linda instantly becomes alert. “Why? Is she okay? Is she…dying?”

“Gosh no, Linda. The respiratory therapist is here to help both your mother and me. They manage the oxygen and help with breathing.”

“Oh,” Linda replies. “Good.”

“I will be right back.” Tracie moves quickly again out to the main hallway to the nursing station. She then asks for the RT to be paged and to come to Miki Huang’s room.

The unit coordinator looks up. “What should I tell them.”

“Ms. Huang is quite short of breath and has low sats on Optiflow. I’m not sure what to do next.”

“Done. If they have any further questions, I’ll transfer their call to the phone outside the room.”

“Thank you.”

Tracie heads back to Miki's room.

Tracie has the vitals machine to another cycle of vital signs but not the temperature. She reads the machine, thinking, "Heart rate is down to slightly less than 100 bpm. Respiratory rate is still up and sats have only improved slightly." Tracie records all this information and her assessment into Miki's chart. Just then, Alexa, the RT, enters the room.

Day: 2	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O2 Saturation**
Time: 07h45	98	165/90	22	–	85% on Optiflow

"Hi…Tracie, right?"

"Yes, you remembered! So, you must also remember Ms. Huang then. And her daughter too?"

"Yes, I do. Have her sats not improved? You asked her to breathe deep like yesterday?"

"Yes. She has improved slightly but not very much with the deep breathing."

"Okay, let's take a look. Hi Ms. Huang and Linda, do you remember me?"

Linda, too tired to process, stares back. Miki, obviously not understanding, also stares back.

Alexa chuckles awkwardly. "I was in Emergency yesterday. Anyways, I'm going to listen to your chest and then I may have to take some blood from your wrist again."

Linda snaps out of it and tells her mother that they're going to check up on her again, and Miki nods solemnly. Alexa methodically assesses Miki's respiratory system.

"Okay, Ms. Huang. Your breath sounds don't seem much different than they did in Emergency, but obviously you are not feeling your best. I think I am going to have to change your oxygen treatment to a face mask. Have you had a face mask before?"

Linda shakes her head, “I don’t think so.”

“It’s a mask that covers both your mouth and nose. It allows me to give you a bit more oxygen than the system you are currently on. I am going to get the equipment to do so, and we will see how you do with the new oxygen treatment and whether you need another needle poke in your wrist.”

Alexa steps out to the storeroom and selects a high flow mask with humidifier. Back in Miki’s room, she sets up the equipment and turns the flow meter up as high as it goes. Looking at the humidifier bottle, Alexa notes a good amount of bubbling.

“Ms. Huang, I’m going to take away those nasal prongs and place a mask on your face.”

Before Linda can translate, Alexa confidently changes the therapy and places the high flow mask on Miki.

“Now, take some deep breaths slowly and blow out through your mouth. How does that feel now?”

Miki turns to Linda, “Well at least I don’t think I’m going to die anymore,” she says sarcastically.

Linda sighs. “She says she feels a bit better, thanks.”

Turning to Tracie, Alexa states: “I have placed her on 65Fi02 high flow face mask. Can you do another set of vitals for me?” Tracie hits start on the vitals machine.

Both health professionals, along with Miki, and Linda, turn to look at the numbers as they appear on the screen.

Day: 2	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O2 Saturation**
Time: 08h05	98	165/90	22	–	092% on High Flow FM

“Okay, Ms. Huang, your oxygen level is better, and your other vitals look the same as they did when I first came on shift. I have another patient to see next door, but before I leave, I will come back and see how Ms. Huang is doing.”

Tracie nods and follows Alexa out of the room. “What do you think is going on? Why did her saturations drop, Alexa?”

“Her pneumonia might be progressing a bit. Sometimes that happens even with antibiotics. Antibiotics take about three days to really work well. In the meantime, if she could stand it, we should see if Physio can see her and maybe get her moving, which will help with chest expansion. One of the worst things to do is just lie about. Is she due for a Chest X-ray (CXR)?”

“Yes, I saw that she will be getting one around 2pm this afternoon. Can she go down with that mask on?”

“No problem. I will make sure that there is a full tank available. Tony is the RT in Emergency and he also covers X-ray if need be. I will let him know in case there is an issue while she is down there.”

“Okay, I will talk with the doctor about a physio order and let him know you have adjusted her O2.”

“Thanks. I will look in on her after I see my other patients on this floor. If her sats stay up where they are, I don’t believe she needs a blood gas.”

“Awesome. Okay, see you later.”

Time: 09h00

“Hi Dr. Hunicutt, I’m Tracie. One of my patients, Miki Huang, is under your care.”

“Aw, yes, the older lady with COPD and pneumonia. How was her night?”

“Night was pretty good, needed some adjustment on her Optiflow but otherwise slept well. My concern is what happened this morning. She became quite short of breath and anxious; I called the RT, and we made some adjustments and moved her to high flow face mask at .65. Sats responded and she improved to 93% and has stayed there for the past hour. Appears quite relaxed now. No other changes in breath sounds or temperature. Very little sputum production.”

“Very good. Let’s go and see her now and see if I need to make any further adjustments.”

Both Tracie and Dr. Hunicutt walk down the hall to Miki's room. As they enter, they see Miki sitting in bed with a green oxygen mask on, flicking through the TV channels. Linda is also sitting in the corner of the room, eyes fixed on the TV and occasionally making comments on the programs.

Linda notices the pair enter the room and immediately stands up out of formality. "HiI everyone. My mother keeps complaining about the mask blocking her view. Do you know how much longer she needs to keep it on for?"

"Hi Ms. Huang, and you must be her daughter. My name is Dr. Hunicutt, and I am a doctor helping to care for you. I see you are less short of breath right now. Would you mind if I listen to your chest?"

He gestured towards Miki as he spoke, and Miki, understanding, nodded but sighed.

Dr. Hunicutt takes his stethoscope out and systematically listens to Miki's heart and lungs. Then he proceeds to examine the rest of Miki.

"Very good. Thank you, Ms. Huang."

"It can't be too good, otherwise we wouldn't be stuck here," Linda muttered under her breath.

"My apologies. It is okay. Your mother's lungs are not the healthiest due to the COPD, and by listening to your chest I can see that she does have lots of consolidation in both lower lobes." Dr. Hunicutt points to where he heard the bronchial breath sounds.

Linda's face flushes red. "I'm so sorry, doc. I didn't know you would hear what I just said. I don't know what came over me, I'm just so tired."

"It's okay, Linda, I understand. I do believe that Miki is on the right antibiotics. We are still waiting for the sputum test to tell me that, and we will also do a chest X-ray today to confirm that the pneumonia is not spreading more. Tracie, is there anything you would like to add?"

"I would like to have Physio come over to see her and get her moving a bit more."

“I think that is a very good idea. I will write the order. They may not come today, but that doesn’t mean Ms. Huang cannot sit in a chair or stand at the bedside. I don’t want her doing too much, but she does need to move a bit more.”

“We can do the chair. What about the bathroom?”

“Commode at bedside until she is below 50% oxygen. Anything else?”

“Alexa the RT said she would wait to do another blood gas as her sats are okay right now.”

“I agree. But I will write an order for another blood gas tomorrow morning to see how we stand with CO2 and PaO2. I want to ensure that her COPD does not get worse as well. At this point, our other option is BiPAP (a non-invasive ventilation device which applies different levels of positive pressure in the airways during inhalation and exhalation to allow for easier ventilation), which I’m pretty sure Ms. Huang will not be happy with, so let’s see if we can manage her without going to intensive care.”

“Thank you. I think that will do. Ms. Huang and Linda, do you have any questions?”

“No, I think we’re good for now,” Linda answers. Miki, who hadn’t been translated for this entire time, remains silent. She was trying hard not to be irritated as she knew that her daughter was already trying her best, but it was not easy constantly being out of the loop especially when she was the topic of discussion.

Both Dr. Hunicutt and Tracie smile, nod at the mother-daughter duo, and then leave the room.

Outside the room, Dr. Hunicutt asks if anything else needs to be done. Tracie points to a couple of other rooms where she has patients and explains that two patients need discharge orders, and two others need lab work looked at, as pharmacy is stating that antibiotic coverage may not be appropriate. Dr. Hunicutt nods his head and gives her the thumbs up sign as he heads to the chart rack to begin the process of discharge and looking at labs.

Tracie begins the process of recording the interaction with Dr. Hunicutt and Miki, making sure to include Linda’s role and presence.

Over the course of the day, Tracie was able to get Miki up twice to the bedside commode and twice to a chair for 30 minutes each time. Miki’s saturation stayed stable along with her other vitals signs.

When the shift change rolled around, Tracie was very happy to see Jim come into the unit. “Wow, I did not think I would see you tonight.”

“Me either. They called me for overtime during my chaperoning of a school trip.”

“Man, you must be exhausted.”

“Yeah, but no more than usual. Got some shuteye before coming in. Anyway, how was your day?”

Tracie gives an overall report of two discharges and two new admissions. She updates Jim on changes to Miki’s oxygen levels and her increased orders for activity.

“Awesome, thanks. Will I see you in the morning?”

“I believe you will. I’m doing four days in a row. I traded my night shifts so I could attend a play with my husband. We have had so little time together with him finishing his PhD, and my shift work. He promised not to talk research and take me out on a real date if I would change my night shifts.”

“Wow, I am so jealous. Well, have a good sleep and we will see you in the morning.”

“Good night!”

While this exchange was happening, Miki and Linda are having their own conversation, or rather, altercation, back in the room.



Day 2 – While wearing a breathing mask, Miki is arguing with Linda. Image created by Sarah Pinault under a CC-BY-NC license

"What's the point of having you here if you're not going to tell me anything they're saying?" Miki says in an accusatory tone.

Linda throws up her hands, "I don't know what you want me to say! You can't actually expect me to translate word for word every single thing that's going on. It's too much, you should know that."

"The very least you could do is not act like I'm not even here. Would an actual translator do that?"

"Maybe we should just get you an actual translator then. You think I'm having fun right now?" Linda snaps back. "I have missed how many days of work now and you haven't even uttered a single 'thank you'."

“Works for me. At least an actual translator wouldn’t consent to things on my behalf without consulting me first.” Miki answers scornfully.

“That wasn’t even that big of a deal!” Linda cries out. “That was literally just to take your blood. If you want to be involved so bad, maybe you should’ve learned English then!”

Taken aback by the volume of her normally quiet daughter’s voice, Miki pauses. “I don’t know. I’m sorry. Everything is just so different here, but I know how tired you must be. I miss home.”

Somehow, Linda knew that the home her mother was referring to was Taiwan and not their townhouse a few blocks away. “I’m sorry too. I shouldn’t have said that. I know you’re doing your best to adjust to this new environment. I’ll try to keep you in the loop more from now on. Say, even the food is making it difficult, huh?”

Miki cracked a small smile. “Oh god. What is it with these people and their Jell-O. Don’t they know the perfect desserts shouldn’t be too sweet?”

Smiling herself, Linda reaches out to pat her mother’s wrinkled hand. “Don’t worry, Mom, we’ll be home before you know it.”

Adaptations

This section has been from Health Case Studies by Glynda Rees, Rob Kruger, and Janet Morrison.

Media Attributions

- Day_2_Medical_Unit 1

Day 3: Medical unit

ANNABELLE LIAO

Day 3

Time: 07h00

Place: Medical Unit

Tracie walks slowly up the walkway behind a patient in a walker entering the hospital. She remarks to herself, "Wow. My third dayshift. I didn't think I would miss the changeover time to nights."

"Here, let me get the door for you," Tracie says as she opens the door for an elderly patient who then asks directions to the Ultrasound Department. Tracie points him in the direction of the Diagnostics Department and explains that he can follow the blue line right to the check-in desk.

Tracie turns in the opposite direction and enters the elevator that takes her to the seventh floor. The doors open, and she is greeted with the familiar disinfectant smells. Walking quickly to the staff room, she shrugs out of her coat and puts on her duty clogs. Looking in the mirror, she moves errant strands of hair behind her ears and runs her hands over her uniform. "I guess I'm ready. Let's go see if anything has changed overnight."

Walking out of the staff room to the main nursing station, Tracie finds Jim finishing off his night's charting.

Jim looks up. "Wow, I am glad to see you."

"Okay, that answers my first question. I have the same assignment as yesterday?"

Jim smiles. "Yes, you do. I asked specifically to keep you with the same group of patients as you know then and it will provide some consistency."

"Are you ready to hand over to me?"

“Just give me a minute to finish this last note and chart my meds that I just gave to Room 5. It has been very busy, and I have not really had a chance to sit down all night.”

“Ok, I am going to grab a glass of water. I’ll be right back.”

A few minutes later, Tracie sits down beside an obviously exhausted Jim to get the handover report.

“Where to start? Let’s start with Ms. Miki Huang if that is okay?”

“Sure. I am hoping she had a quiet night.”

“Yes, she had a better night than her roommate and some of the other patients on the floor. Last night we needed to adjust her oxygen up as her sats went to 90% and even dropped further with movement. The RTs saw her a number of times but elected not to do an ABG at this time.” Jim points at the vital signs flow sheet. “Her heart rate, temp, and BP are up slightly from what you recorded yesterday. Ins and outs are even balance. She is due for lab work this morning, a CXR and potentially an ABG, especially if you can’t decrease her oxygen.”

“If I remember correctly, the Physio will also assess her. Is she still on IV antibiotics?”

“Yes, it’s only day two and we have no results from the sputum sample in the system. We could be changing them tomorrow if we get the culture/sensitivities then. Her next antibiotic is due at 10h00 and she has some other meds at 08h00.”

“Great, who is next?”

Jim then goes through the rest of the patient assignment.

Leaning back in his chair, Jim rubs his hair through his closely cropped hair. “That’s it for me. I’m going to change into my gear and cycle home in time to take the kids to school. Any questions?”

“Nope. Have a good sleep.”

“See you tonight. I’m scheduled to come in.”

“Awesome.”

Jim walks quickly to the staff room and then disappears through the door. Meanwhile, Tracie takes a quick look through her patient chart to plan her priorities for the day.

“Bed 5 is ready for discharge, so should be okay for the next little bit. Beds 6 and 7 had a rough night. I will see them and then be off to check on Ms. Huang.”

Sighing a little as she stands, Tracie heads off to Bed 6.

Time: 08h15

“Good morning Ms. Huang, how are you doing? Good to see you too, Linda.”

Tracie looks towards Miki and sees a very sleepy elderly woman. “Wow, she looks like she has aged even more since yesterday,” she thinks to herself.

Miki looks up and attempts to say something, but it comes out as “Argg argg.” Her voice is muffled by the mask and the sound of the bubbling from the humidifier.

Linda frowns, “What’s that, Mom?”

Tracie also furrows her brow. “Hmm, that doesn’t sound right,” she mutters to herself.

She pulls the vital sign machine up to the bedside and hooks Miki up. Immediately, she notes that Miki’s oxygen saturation is down again to 90%, then thinks to herself, “Okay, I am going to have to call the RT. May need to adjust her FiO2.” About a minute later, the machine beeps and the vitals are displayed on the small screen. Tracie records them on the vital sign flow sheet.

Day: 3	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	O2 Saturation
Time: 08h00	96	170/90	22	36.5°C	90% on FM

“Ms. Huang, I am going to listen to your lungs and heart.”

“Mom, she’s just going to check your lungs and heart, okay?” Linda translates.

Miki nods her head, “I do feel really tired though.”

Tracie places the stethoscope in her ears and bell against Miki’s chest. She quickly moves the bell around her chest in a systematic manner. Standing up straight and stretching her arms out after leaning over the bed, she thinks, “There seems to be slightly coarser sounds mid to lower field bilaterally. A few wheezes on expiration. Heart sounds are normal.”

“Ms. Huang, I am going to give you some Ventolin and ask the RT to come and see you to make sure you are on the right oxygen setting.”

Miki doesn’t react to this, but Linda nods worriedly and tells Tracie that her mother is very tired.

Tracie heads over to the nursing station and asks the unit coordinator to page the RT for her.

A few minutes later, the RT, Herman, calls back.

“Hey, this is Herman; I am the RT covering the floors today.”

“Thank you for calling back so quickly. Did you get the report on Ms. Miki Huang?”

“She’s the lady on the seventh floor with pneumonia and COPD, and on high flow face mask?”

“Yes, that is Ms. Huang. This morning when I assessed her, she mentioned being pretty tired. Sats are around 90%, RR is up slightly along with HR and blood pressure (BP). Breath sounds are a bit coarser in the lower fields with wheezes on expiration in the upper. I have just started her on some Ventolin. I am not sure about adjusting her FiO2 further or

whether her COPD is getting worse which is causing her to feel tired. There is an order for an ABG if there is a change in patient's condition. I would like you to come and see her."

"Sounds like I should pop up there. I am seeing a patient on the fourth floor right now and titrating his oxygen. Can you wait about 10 minutes?"

"I can. I am pretty sure Ms. Huang will be okay as well. I will recheck her saturations after the Ventolin treatment."

"That's an excellent idea, I will be up as soon as I can."

"Thanks." Tracie hangs up the phone. Pushing back the loose strands of hair behind her ears, she stands up and heads down the hallway again to Ms. Huang's room. Entering the room, she finds a very tall, fit, woman leaning over the bedside of Ms. Huang.

"Can I help you?" Tracie asks.

"Hi, my name is Gladys. I am a Physio student doing a preceptorship, and Ms. Huang's name is on our list of patients to see today. I thought I would come by and see Ms. Huang to see what physio she needs and then plan a time to come back to do physio with her."

"Oh, okay. Sorry, I didn't see your name tag. My name is Tracie, and I am the nurse caring for her. I don't think this morning is a good time. Ms. Huang's oxygen saturations are down a bit and her breath sounds are a bit coarser than yesterday. Last night she required an increase in her FiO2. She has been complaining of feeling tired and seems a bit sleepier than usual."

Gladys looks down at Miki, who is propped up with a few pillows at 45 degrees.

"Tracie, would you have a few minutes to help me reposition Ms. Huang? I think I can help improve her saturations with better position for expansion and maybe lead her to do some deep breathing exercises and coughing exercises to help move her secretions out."

"I can help."

“Okay, I am just going to get a bolster. Can you find a couple more pillows for me?”

“Yes, I think so. There is always a shortage of pillows. Most are like placemats, and patients are always hoarding them as one is never fluffy enough.”

Gladys smiles and moves out the door to the storeroom to find a bolster.

A few minutes later, both Gladys and Tracie are standing together at the end of the bed looking at Miki, who stares back cautious.

“Okay Gladys, what are we going to do?”

“I would like to position Ms. Huang more upright in bed with her arms resting on pillows on the overbed table. I am not familiar with these beds, but I believe we can move the foot of the bed, so Ms. Huang is in more of a sitting position?”

“Sounds good; let’s get started.”

Throughout this exchange, Linda is not present, and Miki is growing increasingly anxious. As much as she hates admitting it, she is reliant on her daughter now more than ever. Sure, at home Linda took care of Miki’s physical needs, but ever since they got to the hospital, Linda also took over anything related to communication. “If only I had tried harder to learn English in the past,” Miki thinks to herself wistfully, and not for the first time since she arrived either.

Now, in bed, she feels completely in the dark about what the doctors want to do with her. What if it hurt? What if something went wrong? Where was Linda when she needed her most? Miki notices Gladys gesturing towards her, seemingly trying to demonstrate what they wanted to do. Miki only grips the bed railing tighter.

Both Gladys and Tracie work together to move Miki into a chair-like position while in bed. They place the bolster at Miki’s back to ensure correct body alignment. After positioning Miki, both step back to admire their work, but Miki’s heart is pounding rapidly. Was that it? Did they only need to adjust her position?



Day 3 – While wearing a breathing mask, Miki is placed in a position by the respiratory therapist and nurse. Image created by Sarah Pinault under a CC-BY-NC license

Just then, Linda returns from the bathroom. “Oh, hi there. What’s happening?”

“I’m going to check Ms. Huang’s vitals again to see if this movement helped. I’ll go get the machine to do that.”

“I am going to see if I can get her to deep-breathe and cough. Maybe moving or clearing those secretions will help.”

Gladys moves closer to Miki. “Okay, Ms. Huang, I want you to take a deep breath.”

“Take a deep breath, Mom,” Linda instructed.

Miki takes a week breath in through her mouth. “That’s great. And now breathe out.” Miki coughs weakly.

“That is very good Ms. Huang. I want you to take a slow deep breath to the count of three, then breathe out to the count of three.” Gladys demonstrates what she is asking.

Miki understands that she’s imitating what she wants and nods her head. “Okay, breathe in, 1, 2, 3. Hold. Breathe out 1, 2, 3. Very good.” Miki begins coughing and makes frantic motions with her hands to remove the O2 mask. Gladys removes the mask and hands a tissue to Miki. Miki coughs a moderate amount of green sputum into the tissue.

Behind them, Linda winces, but Gladys is happy. “This is exactly what we want to see! Let’s do the breathing and coughing exercises some more and see if we can clear your lungs a bit.” Gladys then leads Miki through five more deep breathing and coughing exercises with Linda’s assistance. At the end of each deep breath, Miki coughs out more greenish/yellow sputum.

At the end of the fifth attempt, Tracie walks into the room with the vital sign machine. “Sorry, I had to answer Bed 6’s call bell. Did I miss anything?” Tracie walks to Miki and attaches the machine to her arm and finger.

Gladys smiles, “Do we need a sputum sample? Ms. Huang has coughed out quite a bit of stuff.”

“No, I don’t think so. One was sent from Emergency that we are still waiting on. If she is coughing now, we can always have you come back and assist us to get another specimen.”

The vital sign machine beeps and displays the vital signs on the screen. Saturations are up quite a bit and HR and BP are back to normal for Miki. Temperature is still low-grade fever. Tracie records the vital signs.

Day: 3	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O2 Saturation**
Time: 09h00	86	150/85	18	36.5°C	95% on FM

“Wow, great improvement Ms. Huang. Getting you up in bed and breathing better has certainly helped.” Miki smiles weakly at the encouraging tones.

Tracie stares at Miki for a moment longer and thinks, “She looks more alert, eyes are open, better eye contact…overall she looks much better than when I first came on shift.”

The RT, Herman, arrives in the room and looks at Ms. Huang, Linda, Gladys, and Tracie. “Hi, I’m Herman. You paged me earlier to come and see Ms. Huang.”

“Hi Herman. I’m Tracie and this is Gladys, a physiotherapist. And this here is Linda, Ms. Huang’s daughter. Since Ms. Huang cannot speak English, she’s helping out as a translator.”

“Happy to meet you all. So, what can I do to help Ms. Huang here?” Herman moves closer to Miki, checks her mask, and then works his way back to the humidifier and checks the flow meter on the wall. He nods his head, thinking, “Exactly like I was told. No real changes in therapy.”

Tracie then gives a quick report including changes overnight and what happened thus far this morning.

Herman rubs his chin. “Okay, she has improved with physio but is still on high flow. We know she is a CO2 retainer which may explain her being sleepy this morning, and she has not had an ABG since being in Emergency. Doctor orders give me some leeway on taking an ABG. I would like to do an ABG and see where we are and if there are really any changes since Emergency. From her saturations here it looks like we could drop her FiO2 a bit. So, let’s do this: I will drop her FiO2 a bit to bring her sats to 93% and then go gather the stuff for an ABG radial stab. We will let her rest for a few more minutes and then I will do a gas.” Herman adjusts the FiO2 while keeping an eye on the saturations displayed on the vital sign machine. He makes a couple of more adjustments and sees the sats stabilize at 93%. He gives the FiO2 to Tracie who records it in the nurses’ notes and flow sheet.

Herman leans closer in. “Linda, can you please ask your mother how that feels with the oxygen decreased a little?”

Linda smiles. “She says she’s a little better than earlier, although still short of breath.”

“Okay, that may not change very quickly. I’m going to listen to her lungs now. Is that okay?”

Linda starts to nod, then remembers. “Wait a minute, let me ask. Mom, is it okay if the doctor listens to your lungs?”

Miki rolls her eyes and answers, “Yes, of course. Isn’t that what he’s here for?” Secretly, though, she’s glad Linda confirmed with her first before consenting on her behalf.

Herman pulls his stethoscope out and systematically auscultates Ms. Huang's chest. "Not too bad. A bit decreased to the bases with coarse sounds and no wheezes."

Traci smiles at Gladys. "That does sound better than what I heard this morning."

Herman says, "Okay, she seems okay right now. I am going to get my stuff to do the ABG and will be back in about 10 minutes."

Both Tracie and Gladys nods. Tracie nods towards Miki. "Linda, does your mother need anything right now?"

"No, we'll probably just keep watching TV to be honest."

Gladys pats her hand. "I will come back in about 30 minutes and see if she needs to be repositioned or feels strong enough to get into a chair then."

Linda and Miki wave to both of them before focusing their attention on the TV.

Tracie and Gladys move out of the room.

"Thank you, Gladys, for your help. You did a great job in there."

"Thanks Tracie. It was really nice to see that I made a difference. I'm going to talk with my preceptor about what I did and see another patient. I will come back in about 30 minutes to see how Ms. Huang is doing."

"Awesome. Let me know if you need my help. I am going to see my other patients and hand out my 10am meds and antibiotics."

Back in the room, both mother and daughter's eyes are still fixed on the television, but Miki speaks up.

"When you were in the bathroom, and they came in to move me I was a little scared."

“I’m sorry, but you really cannot expect me to be here 24/7. That’s just not possible.”

“I know, I’m not blaming you. I just wish I could have known what was going on and what they wanted to do to me.”

Linda sighs, “I’m sorry Mom. I don’t know what to say. You’ll be better soon enough, and we can get out of this place.”

Miki finds it hard to express her frustration; as kind and sympathetic as her daughter tried to be, there was just know way to truly know how frightening it was to be so physically vulnerable in an environment where you also could not understand a single word.

Across the room in her chair, all Linda wants to do is lock herself in her room and sob. It pains her to see her mother so on edge and anxious, but ever since her mother got sick Linda has constantly been feeling suffocating pressure. Besides constantly being by her mother’s side and acting as the primary liaison, she also hasn’t slept well in days and is worried about all the work she’s missing. Deep in her heart, she knows that this is not a sustainable arrangement and wonders if she made the wrong call in turning down the designated translator. Although there are so many things happening at once, the only thing Linda can’t stop obsessing over is the fact that she is almost out of allotted sick days for her job.

Time: 10h00

Herman comes up to the desk and sees Tracie charting. “Hi Tracie, I’ve done the ABG on Ms. Huang and have sent it to the lab. We should be getting the results in about 30 minutes or less. I’m going to see a patient on the tenth floor. I will check the system for the results, and I may come back and make additional changes to her FiO2.”

“Thank you, Herman. I really appreciate your help.”

Time: 11h00

Tracie logs into the clinical system in the hallway outside Miki’s room. “Okay, let’s find the ABG result. Wow, that ABG result looks much better, O2 and sats better, CO2 is high but looks normal for her. Nice. Looks like Herman can bring her FiO2 down.” Next Tracie checks to see if the culture and sensitivity is back. “C&S is still pending. Gram stain shows gram positive cocci. Okay, not sure what that means; I will have to ask Dr. Hunicutt.”

Tracie signs off the system, turns around, and runs directly into Herman. “Oh, I am so sorry!”

“No problem. Did you see the ABG result?”

“Yes, it looks better than it did even in Emergency.”

“Yes, it is, but you have to remember she is on a higher amount of O2.”

“Yes, I never considered that. Good point.”

“I am going to go in and adjust her FiO2 down a bit more. If she continues to improve, we can probably move her later today or tomorrow to Optiflow again.”

“Excellent. I will come in with you and do a focus assessment.”

“Sure, no problem.”

Both Herman and Tracie enter Miki’s room to find her and Linda still watching TV intently.

Miki notices the two of them entering her room out of the corner of her eye and groans inwardly. “Ugh, they literally just left. What do these two want again? Will I never get peace and quiet?”

“Hi, Ms. Huang. Herman here is going to make some adjustments to your oxygen level. And with the test we did earlier, we may be able to move you to a more comfortable type of mask.”

Tracie moves the vital sign machine to Miki’s bedside and attaches it to her left arm and right finger.

Herman checks the pulse ox saturation and then begins to adjust the FiO2. He thinks, “It’s not below the toxic level of oxygen, which should help.”

The oxygen saturation stays stable. Tracie listens to Miki’s chest and finds that the air entry is decreased to her bases, with a few crackles, and no wheezes noted. Vital signs are unchanged from the morning.

“You are looking pretty good, Ms. Huang.”

Linda jabs her mom excitedly, “Hey, they said you’re looking pretty good!”

Miki rolled her eyes. “Then why am I still here? Tell them not to waste their time lying to me and heal me instead.”

Linda smiles at the doctors, “Um, my mom said thanks.”

Herman smiles back. “Dr. Hunicutt will also be coming by today to update you>”

“Okay Tracie, I have decreased the FiO2 below .50 and she looks to be holding her saturations really well at 93%. I will come by towards the end of the shift and if things are good, move to Optiflow.”

“Thanks, Herman.”

Just then, Gladys enters the room. “Hi Tracie. Hi Ms. Huang and Linda! Would you like to sit in a chair or move to a different position?”

Linda translates, then turns to Gladys, “She said a chair sounds much better.”

Gladys then directs both Tracie and Herman to assist her to move Miki to a bedside chair. Miki transfers easily and feels much more comfortable.

Gladys explains, “We need to be careful that you do not get any bed sores. Plus, moving around helps your lungs out. Tomorrow I will come by and get you walking the hallways.”

Suddenly more cheerful, Linda is pleased with the progress and the prospect of her mother moving around. She thinks that perhaps she should run home later and grab her laptop so she can get some work done when her mom’s walking tomorrow.

Tracie leans forward and adjusts the blanket on Miki. “All good. Need anything right now?”

Linda asks her mom, who shakes her head. Tracie heads to the nursing station to complete her charting, and Gladys heads off to find her preceptor.

Time: 19h00-shift change

"Hi Jim, how are you this lovely evening?"

"Hi Tracie, I am doing well. I had a great sleep."

"Awesome. You should have the same patients as last night."

"Cool. Should be a quick report."

Tracie then describes the status of each of the patients. Coming to Miki's chart, Tracie explains, "Ms. Huang is doing much better, up in a chair today. Deep breathing exercises cleared a lot of sputum. FiO2 less than .5 gram stain came back gram positive, but Dr. Hunicutt says it is not too helpful for adjusting her antibiotics. C&S should be available tomorrow. The RT did not want to move quite yet to Optiflow and they may do so tomorrow. She is still comfortable on the mask, and the humidity may help clear secretions." Tracie then goes through the rest of the assessment.

"Looks good, thanks, Tracie. I guess tomorrow is your last day shift?"

"Yes, see you in the morning."

Adaptations

This section has been from Health Case Studies by Glynda Rees, Rob Kruger, and Janet Morrison.

Media Attributions

- Day_3_Medical_Unit

Day 4: Medical unit

ANNABELLE LIAO

Day 4

Time: 10h30

Place: Medical Unit

“Hi Tracie, I’m here to review a couple of patients for discharge.”

“Hi Dr. Hunicutt, I would also like to talk about Ms. Miki Huang.”

“Oh, the lady with pneumonia and COPD. She is doing better, yes?”

“Much better it seems, her C&S (culture and sensitivity) results are in along with the rest of her morning lab work. I have her assessment here to review. The RT has moved her to Optiflow again and Physio is seeing her daily and ambulating her in the hallway starting today.”

“That sounds good. Big improvement. Okay, the discharges I will get to. Let’s look together at the C&S results.”

Dr. Hunicutt pulls up the lab results for Miki and immediately goes to the C&S.

“Okay Tracie, what antibiotic is Ms. Huang on?”

Tracie pulls up the MAR. “She is on ceftriaxone 1 gram IV q 24 hours, and azithromycin 500mg IV q 24 hours.”

“Excellent. That is the recommended coverage. Now let’s look at her C&S.”

On the computer screen, Tracie sees a list of about 10 antibiotics with either R or S beside each. R represents antibiotic resistant, while S stands for antibiotic sensitive. For the antibiotics that Miki is on, she sees an S beside each one. Tracie understands that this means the bacteria in her patient's lungs are sensitive to ceftriaxone and azithromycin. "The antibiotics Ms. Huang is on are appropriate for her as the bacteria is sensitive to them," says Tracie.

"Correct," states the doctor. "And since Ms. Huang is doing well and you are mobilizing her, I would like to get rid of her IV to make that job easier."

"How are you going to do that? I know azithromycin comes in PO form, but ceftriaxone is only IV."

"Take a look at the list and see if there is another antibiotic that you recognize that can be given PO."

Tracie considers the list again, thinking, "No, gentamycin is IV, cefotaxime is IV…Oh wait, here is levofloxacin. She speaks up, "Okay, Dr. Hunicutt, I think levofloxacin can be given PO."

"That's correct, and since the two antibiotics are different classes and work slightly differently, we are cross-covering Ms. Huang so she should continue to get better."

"I think she will be happy to have the IV capped."

"Most patients are. So, I am going to write the orders for levofloxacin 750mg PO q 24 hours and azithromycin 250mg PO daily. Has she had her antibiotics today?"

"Yes. She should just be finishing now on the IV pump."

"Great. I will state to start these with breakfast tomorrow. Now let's go see her and then I'll see the discharge patients and write their orders."

Both Dr. Hunicutt and Tracie get up and move towards Miki's room. As they get closer to the room, they can hear Linda and Miki talking quietly, and the occasional chuckle. Coming into the room, they see the mother and daughter duo sitting and chatting together.

Tracie observes and thinks to herself, “I guess it’s good for Miki to have at least one person she can speak to here. If I was her, I would want a daughter like Linda too.”

“Hi Ms. Huang, hi Linda, do you remember me?”

Miki and Linda both look up from their conversation and consider the man standing before them. “You’re my mom’s doctor, right?”

“That is correct, at least for the time that she is in the hospital. I don’t have an office, but the whole hospital could be considered my office. Tracie and I have reviewed your chart and your treatment regimen, and we will be making some adjustments to your IV. With your improvement and walking, it looks like we can cap your IV and start you on oral antibiotics.”

Linda speaks up. “Oh, I think she’s had oral antibiotics before, and they upset her stomach.”

“Well, if her stomach is not upset now with the IV antibiotics, I don’t expect that it will be upset with the oral ones because it’s the same medication. Let’s try it and see.”

“Will you get rid of this then?” Linda indicates the IV in her mother’s left arm.

Tracie shakes her head. “I will remove the tubing, but we will leave the rest in your arm in case something changes. I am sure you don’t want another IV started. I will wrap it up with a dressing, and it will be less bothersome without the tubing attached.”

Linda looks up at Dr. Hunicutt. “When can she come home?”

“That’s a good question. I would like to do another chest X-ray today. Your mom needs a couple of more days of antibiotics and to be completely off any oxygen therapy for 24 hours. Once that is met, I would be pleased to see her go home with you.”

“And how long will that be?”

“Oral antibiotics start tomorrow so the earliest for home would be three days from now, maybe two, if your mom tolerates no oxygen starting tomorrow. I don’t think we need to rush. She is getting great care here.”

“True, it’s just that I don’t want to miss more work than necessary, and I know that my mom feels a lot more comfortable at home too. Nothing in this environment feels like home for her, even the food and television.”

“That may be, but your mom is pretty sick.”

Linda looks down at her feet and seems resigned to what Dr. Hunicutt says. Dr. Hunicutt looks at the both of them. “Any questions?”

When neither of them makes eye contact or speaks, the doctor adds, “All right then, I will order the chest X-ray and let Tracie cap off your IV. I will see you tomorrow.”

Dr. Hunicutt leaves, and Linda drops into her chair, thoroughly exhausted.

“Linda, tell me what the doctor said,” Miki demands.

Linda drops her face into her hands. “Ugh, please Mom, just give me a second. My head is spinning.”

“Your job is to translate! You can’t even do that correctly, the least you could do is tell me what happened afterwards.”

Linda groans, “Mom, I will! Give me a break, you don’t know how it feels to be relied on 24/7 to translate everything.”

“And you have no idea how it feels to not know what people are talking about even though you’re the topic of discussion,” Miki replied reproachfully. “I would just like to know what is going to happen with me and when I can go home, is that too much to ask?”

Meanwhile, Tracie has gone outside and grabs supplies to cap off Miki’s IV. Just as she is finishing, Gladys comes in and says, “Ready for a walk, Ms. Huang?”

Linda cracks a smile and turns to her mom. “Mom, time for a walk.”

Miki shifts her position apprehensively. She hates exercising and is not ready to showcase her athletic abilities in front of all these doctors and nurses. “Linda,” she whispers urgently. “Tell them I’ll walk on my own at home.”

“What? No way, Mom,” Linda replies. “You have to start walking now so you can get better faster. The doctors know what they’re saying.”

The two glare at each other, and Gladys and Tracie reposition Miki to get her standing. Tracie follows behind with the oxygen tank as Gladys encourages Miki to walk, which she does reluctantly.

Miki looks around the hallway as she leaves the room, finding it unbelievable that she now needs two people to help her walk.

Tracie and Gladys navigate Miki to the lounge and back to her room. Just as they get her back, Glen, the X-ray porter, comes in with a wheelchair. “Hey, it’s picture time!”

Miki smiles politely but groans inwardly. “Oh god, it’s the man who drives the wheelchair like a race car.”

Gladys helps Glen get Miki into the wheelchair. Glen hangs the oxygen tank on the back of the chair, and then maneuvers the wheelchair out into the hallway and to the elevators. They take the elevator to the second floor which opens directly facing the doors of the Radiology Department.



Day 4 – Miki is having an X-ray performed. Image created by Sarah Pinault under a CC-BY-NC license.

Glen pushes Miki in and around to X-ray Room 2. “Hey Gurpreet, Ms. Huang is here.” Her chest X-ray is completed, after which Glen wheels Miki to the elevator and back to the seventh floor.

Tracie sees Glen and Miki coming down the hallway and meets them in Miki’s room. Tracie helps Miki from the wheelchair to a chair at the bedside and covers her with a blanket. “Do you need anything else right now?”

Miki shuts her eyes, and Tracie looks uncertainly at Linda who smiles reassuringly. “Don’t worry, she should be good for now.”

Glen and Tracie leave the room.

Linda and Miki settle back into their chair and bed, and Linda decides to speak up. “Hey, Mom, I think the doctors are going to be thinking about letting you go home soon! What do you think?”

“Hmfph. I could have gone home ages ago if I wanted to.”

Linda sighs. “Mom, I know that you are aware of how sick you are so just stop pretending. I think even once we get home you will still need to recover. I already spoke to my manager and I’m going to be working 2 hours less each day so I can continue to take care of you; there is no room for discussion.”

“Don’t worry, I’m going to be a model patient until I get discharged. You said the doctors told you I have to be off oxygen for how long?”

“Just 24 hours! And then we can both go home and get on with our lives, won’t that be fun?”

Both women sit in silence for a moment, contemplating.

Miki spoke up hesitantly. “Linda…I know I don’t say this often, but I do appreciate everything you’ve done to take care of me. Not even just my time in the hospital, but in general. And I’m sorry for things I’ve said out of frustration.”

Linda scoffed, “No need to thank me Mom, there’s obviously nothing I want to see more than my mother being strong and healthy.” However, Linda was secretly touched and pleased that her mother truly recognized all the sacrifices she had made.

Miki reaches out to pat Linda’s hand, and the two of them continue to talk about their plans at home.

Adaptations

This section has been from Health Case Studies by Glynda Rees, Rob Kruger, and Janet Morrison.

Media Attributions

- Day_4_Medical_Unit

Discharge

ANNABELLE LIAO

Day 5

Time: 1ohoo

Place: Medical Unit

Jim, the registered nurse (RN), walks with Dr. Hunicutt to Miki's room.

"Hi Ms. Huang. This is Dr. Hunicutt and he has some great news for you."

Dr. Hunicutt nods towards Linda as well. "Ms. Huang, you have been off oxygen for 24 hours, and your X-ray from a couple of days ago improved from where you were first admitted, so I think you are ready to go home."

Linda is ecstatic. Obviously, she is thrilled that her mother is better and healthy again, but a part of her is even happier that she can have her life back and get on track with her normal routine. She never thought she would miss the mundane nature of her normal workday, but now she craves it. The past few days of being a patient advocate and translator has thoroughly exhausted her and she is more than ready to go home.

Miki is also equally excited to be going home. Home is where the familiar food, comprehensible television shows, and peace and quiet are. And of course, her prized karaoke machine. Although welcomed and respected for the most part of the hospital, there was never truly a moment where she felt as if she belonged, but at least the doctors were able to heal her. Her mind is racing thinking about all the good, recognizable things at home, and it takes her a moment to realize that the doctor is still speaking to Linda.

"Now, this does not mean resuming normal activities yet. You are still going to be tired, and I still want you to take the antibiotics for another week to ensure that we have fully cleared up your pneumonia. If you stop taking them, you will be back here and much worse off."

"Okay, you hear that, Mom? No karaoke for a while and don't forget about your medicine."

Nurse Jim turns to Linda. "Now, as the registered nurse, I have a few more strategies and tips to give you to make

sure that your mom doesn't wind up here again anytime soon, as much as we will miss her." He provides discharge instructions to Linda, who diligently notes them down.



Day 5 Miki is discharged from hospital and embraces Linda. Image created by Sarah Pinault using a CC-BY-NC- ND license.

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Media Attributions

- Day_5__Discharge 1

APPENDICES - HEALTHCARE DISPARITIES: EXPLORING INEQUITIES ACROSS THE SPECTRUM

Introduction to Healthcare Disparities

Introduction to Healthcare Disparities

LUCY OGOKE

Although their names have been changed for privacy purposes, the narratives presented in this appendix are stories of real people in Canada, who have faced the consequences of health disparities – often at a critical point. Reading these narratives can help give you, the health care professional, some insight and changes that need to be made – to do right by them.

These true stories are representations of how socio-economic disparities show up in healthcare in Canada and and their immediate affects on the lives of these individuals. These disparities cause tremendous difficult to people who are in need of care resulting in lower quality care, in comparison to their more privileged counter parts. In the long run, these disparities place a huge strain on the healthcare system directly and on the economy, both directly in indirectly.

As a community we need to work hard to close the gaps in healthcare to make sure everyone is treated equally as it is both the right of the patient as a human being and the duty of every health care professional.

Although systematic change is required, we – as individuals – need to hold ourselves accountable and make changes in our daily lives that will positively impact disadvantaged communities. Becoming educated about this disparities through literature or person:person interaction is the first step to being able to make those changes. However, it is also important to share and have discussions so the knowledge can be shared: to raise awareness about injustices allowing us to each be advocates for change.

As healthcare professionals one of most essential skills is to be able to be able to put yourselves in the shoes of your patients. This no longer means just symptomatically. Individual health is multifactorial with stigma, biases and socioeconomic status as part of health and healthcare. Reading these narratives can help give you some insight into the struggles marginalized people in our society face.

Amaka Zeiden's Birth Story: How Ignored Complaints Nearly Cost Her Her Life.

Amaka Zeiden's Birth Story

LUCY OGOKE



***Fictional Amaka Zeiden a few days before giving birth to her child Olympia**. Licensed with Creative Commons Zero (No Rights Reserved)*

Disclaimer: All names in this production are **fictitious**. No identification with actual persons (living or deceased), should be inferred

Panic set in as my baby Olympia's heartbeat dropped, making my heart beat rapidly as the contractions continued. It was a moment of fear, but thanks to the swift actions of the medical team, I underwent an emergency cesarean section (C-section) and safely delivered my precious child. C-sections are not uncommon and overall mine went well. I can vividly recall the incredible moment when my partner cut the umbilical cord, and our daughter was gently placed on my chest. I felt pure joy and relief, knowing that my daughter and I were both safe and healthy.

However, shortly after that blissful moment, everything took a turn for the worse. I have a history of thrombocytosis, or

forming excessive blood clots. These clots, which can form in veins or arteries, pose a serious threat to the circulatory system and organs by blocking off blood flow to vital organs or tissue. To prevent clots from forming, I take blood thinners on a daily basis. After my C-section, the doctors advised that I temporarily stop taking them to allow my surgical wound to heal. I trusted their advice because I believed they would keep my medical history in mind; however this was not the case.

The day after stopping the blood thinners, I started experiencing breathing difficulties while recovering in my hospital room. Despite not wanting to worry my visiting mother, I asked my mother to find a nearby nurse. When the nurse arrived I asked if it was possible that I was forming clots in my lungs; but the nurse did not seem too concerned about the possibility after listening to my breath sounds with her stethoscope. Feeling concerned because of my medical history, I insisted on receiving an IV with heparin, a blood thinner, and a CT scan to check for clots. Unfortunately, the nurse dismissed my health concerns, attributing them to the post-surgical healing process. However, after my continued insistence, a doctor arrived but only performed an ultrasound, not the CT scan I believed was necessary. The ultrasound did not reveal anything concerning, but I remained adamant: repeating that I needed a CT scan and a heparin drip. I remember feeling concerned that the doctors would interpret my firm insistence as aggression and take unilateral action to pacify me, such as sedation. Finally, the doctor granted my request, and the CT scan revealed the truth: several small blood clots in my lungs. The medical team immediately began administering the necessary medication.

How are Disparities Affecting Black Pregnant People?

Black women like Amaka are about three to four times more likely to die of pregnancy or delivery complications than white women. There are economic, social, environmental, biological, genetic, behavioral and health care factors that all contribute to disparities. The experience of black women during childbirth is further impacted by factors such as stereotyping by medical professionals, and implicit biases within the medical system. Many black women report feeling unheard and dismissed by healthcare providers, leading to concerns being overlooked and important medical decisions not being made in their best interest. This experience is a result of historical and ongoing racial biases that have permeated medical practices.[1]

My intuition had proved right, but the ordeal was far from over. Over the next six days, I faced a series of medical crises. First, my C-section wound reopened due to a coughing spell triggered by the clots in my lungs. It was a setback, but the medical team swiftly took action to address it. Soon after, I had to undergo another surgery, this time to treat the pulmonary embolism—a blood clot that was blocking a vessel in my right lung. To add to the complications, they discovered a large hematoma, in my abdomen which could present further adverse effects for my healing. It seemed like a never- ending cycle of challenges, but I remained determined to overcome them for my daughter.

In yet another operation, a surgeon inserted a filter into a major vein to prevent further clots from dislodging and

traveling to my lungs. Finally, after a week filled with uncertainty and pain, I was able to return home to be with my daughter and family.

Key Takeaways

This scenario highlights several areas where healthcare workers can make a difference in addressing disparities and improving outcomes for patients, particularly Black women. Here are some things that healthcare workers could do differently in this situation:

Listen and take patient concerns seriously: in this scenario, the patient was insistent about her symptoms and the need for a CT scan and heparin based on her own medical history, but her concerns were initially dismissed. As doctors who have spent years studying the body, it can be easy to think you know better than the patient. However, it is important to address the concerns of patients and take complaints seriously. Especially after being reminded of Amaka's history of blood clots the possibility pulmonary emboli should have been explored fully. The healthcare professions need to ask themselves why they believed it would be okay to dismiss this concern even with her medical history.

Address systemic and structural issues: healthcare workers should educate themselves on and advocate for systemic changes to address the social, economic, and environmental factors that contribute to disparities. This includes working towards equitable access to healthcare, improving communication and coordination among healthcare providers, and promoting policies that support better outcomes for marginalized communities. The case of Amaka should be brought up in department meetings to discuss why certain patients concerns are ignored and to prevent it moving forward factoring in these systemic issues.

Improve health literacy and education: enhancing health literacy among patients, particularly in underserved communities, can empower them to be active participants in their own healthcare. Healthcare professionals should provide clear and accessible information about health conditions, treatment options, and prevention strategies, ensuring that patients have the knowledge to make informed decisions. Additionally, it has been shown that black women giving birth displayed better outcomes when they had more knowledge regarding the diagnosis and complications. This can look like a nurse or physician making sure to speak with the patients about risks which are specific to them and their condition taking into account all factors that could impact the patients outcome.

By implementing these changes, healthcare professionals can help reduce disparities, improve patient outcomes, and ensure that all individuals receive equitable and quality care, regardless of their racial or ethnic background. [2]

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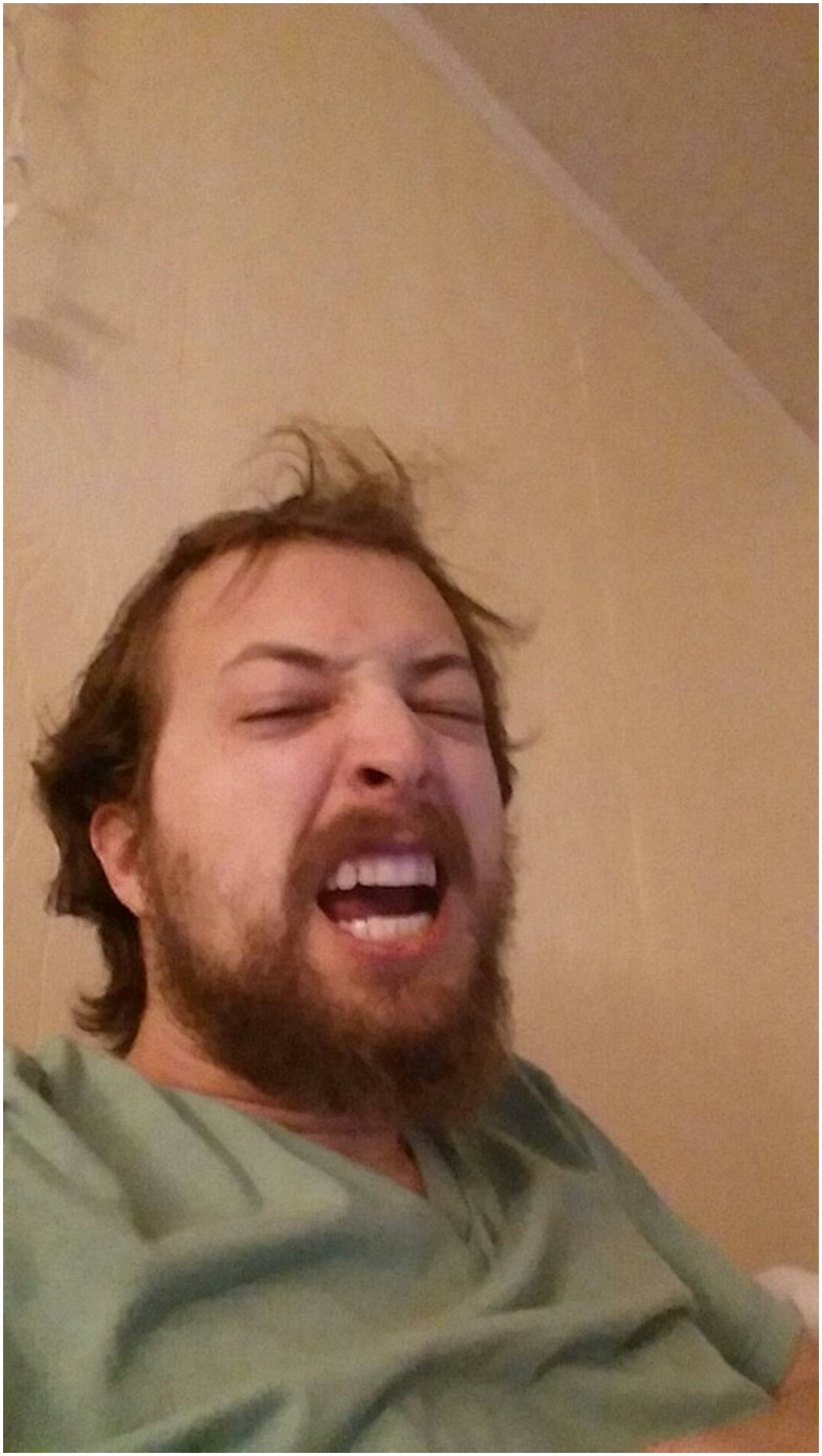
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Kidney Infection? These Stretches Should Help: The Effects of Weight Bias in Healthcare

Kidney Infection? These Stretches Should Help: The effects of weight bias in healthcare

LUCY OGOKE



Fictional patient Mr. Bromini is experiencing pain. *Licensed under Creative commons* 2.0 CC SA

Disclaimer: All names portrayed in this production are **fictitious**. No identification with actual persons (living or deceased), should be inferred

This was the first time I had experienced such excruciating pain, and it was beginning to worry me. As an overweight man, I was no stranger to the occasional aches and pains, but this was different. This was something I could not ignore. As I walked into the clinic's waiting room, I peered around the room to see if there was a chair I would be able to sit and wait on. However, as I scanned the room, I saw only narrow chairs with stiff arms at the side. Now, I am a pretty big guy, tall and fairly wide. I knew just by looking at these chairs that I would not be able to sit and fit comfortably. I opted to stand in the corner feeling the eyes of other patrons in the waiting room turn my way as I found myself a space to lean against the wall in the waiting room. Already feeling unwelcome, I pulled out my phone, and kept my head down as I waited for my name to be called. At least the fact that I maintained an active lifestyle hiking and swimming as well as other activities made it so that it was not too difficult for me to stand for long periods of time.

Finally, my name was called, and I entered the examination room, hopeful that the doctor would provide some answers. The doctor, a middle-aged woman with a clinical demeanor, glanced at my chart, and immediately honed in on my weight. She peered at me up and down as I pushed myself off the wall, placing my right hand at my lower back, where I felt a sharp pain at the movement.

"Hello Mr. Bromini, Please follow me into the exam room." She stepped aside, allowing me to enter the room in front of her before she entered herself, closing the door, taking a seat at the desk, and pulling up my file. I sat down gingerly, using the step stool to allow me to reach the exam table.

"So, you're here because of back pain?" she asked, her tone tinged with skepticism.

"Yes," I replied, trying to convey the seriousness of my discomfort. "It came on suddenly, and it's been getting worse. I've never experienced anything like this before."

The doctor's gaze shifted back to the screen, as she seemed to lose interest. "Well, it's not uncommon for people with your body size to experience back pain," she remarked casually.

I attempted to interject. "I have been active all my life and, barring athletic injuries, I have never had–"

"I would suggest losing weight and exercising more. That should help alleviate the strain on your back," the doctor replied, cutting me off. She handed me her card and a pamphlet displaying exercises and stretches that can alleviate back pain, and instructed me to do them twice a day before grabbing her clipboard, and leaving the room.

How is Weight Bias Affecting Patients?

Plus-size individuals often face significant disadvantages within the healthcare system. Doctors frequently dismiss or overlook the concerns of larger patients, attributing health issues solely to weight without thorough investigation. This approach not only fails to address the root causes of health problems, but also undermines the trust between patient and provider. From entering the clinic Johannes felt unwelcome beginning from being unable to fit in the waiting room chairs. Following this, the health care provider immediately made assumptions about patient's lifestyle based on his appearance. She did not take the time to dive deeper and gave him a surface level diagnosis without doing her due-diligence. Advocating for yourself, and asking your doctor to document denied requests for further investigation, can help to persuade doctors to take certain concerns more seriously. Addressing fatphobia should commence with the recognition that obesity is a matter of social justice not a medical or public health emergency. It's important to note that implementing solutions won't be straightforward, especially given the global history of stigmatizing larger bodies over many years. Nevertheless, resolving the issue of fatphobia is within reach if we are ready to muster the political determination and allocate the required resources.[1]

I felt a pang of frustration and defeat. She had dismissed my concerns without truly listening; but I knew something was not right. The pain was too severe, too persistent, to be attributed solely to my weight, especially given its very sudden onset. Days turned into a week, and the pain continued to worsen. I was also running a fever, and had incredible fatigue. A few days later, I saw blood in my urine. Alarmed, I made my way back to the doctor's office, determined to make her take my pain seriously.

This time, the doctor seemed slightly more attentive as I recounted my new symptom. Reluctantly, she agreed to run further tests. Four days later, I received a call from the doctor's office. It was not the call I expected. "Sir, we've reviewed your test results," the voice on the other end of the line said. "You have a kidney infection that requires immediate treatment with antibiotics. Please come in as soon as possible to collect your prescription."

Relief washed over me, knowing that I had finally found the cause of my pain, but along with that relief came a sense of frustration. Why had the doctor not taken me seriously from the beginning? Why had my symptoms been attributed solely to my size?

As I reflected on my experience, I could not help but think about the countless overweight individuals who might face similar dismissals from healthcare professionals. Our symptoms are often attributed to our size, leading to delayed diagnoses and inadequate treatment. It was a sobering realization, one that highlighted the urgent need for healthcare providers to look beyond weight and listen to their patients, regardless of their size.

Key Takeaways

Instead of immediately attributing health issues to weight, healthcare professionals can serve patients better by conducting comprehensive assessments to identify potential underlying factors. Healthcare professionals need to be open to engaging in open and non-judgmental discussions about health concerns, while acknowledging the unique experiences of plus-size individuals.

Medical practitioners could also offer evidence-based recommendations that are tailored to the individual's needs, accounting for factors beyond weight, such as genetics, medical history, and lifestyle. When addressing health issues it is best to focus on improving overall well-being, rather than solely pursuing weight loss. By promoting healthy habits and discussing achievable goals, doctors can empower patients to take charge of their health without feeling marginalized or stigmatized.

Furthermore, healthcare professionals could also undergo training to recognize and confront their own biases, ensuring that they provide unbiased and respectful care to all patients, regardless of their size. Implementing these changes can create a more inclusive and effective healthcare experience for plus-size individuals, ultimately leading to improved health outcomes, and a stronger healthcare professional-patient partnership. [2]

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Navigating Healthcare as a Transgender Patient

Navigating Healthcare as a Transgender Patient

LUCY OGOKE



Fictional patient Xander experiencing jaw pain *– licensed under Creative commons 2.0 CC BY NC ND*

Disclaimer: All names portrayed in this production are **fictitious**. No identification with actual persons (living or deceased), should be inferred

Walking into the local clinic, I immediately felt overwhelmed. The waiting area was packed with people, and the receptionists seemed stressed and rushed. As I sat there, anxieties about being treated differently because of my gender identity swirled in my mind. Accessing healthcare has always been a daunting task. As a transgender man, the fear of discrimination and judgment often kept me from seeking the help I needed. Would the doctors dismiss me? Would they understand my unique healthcare needs? Accessing healthcare always felt like an uphill battle; however when I started experiencing persistent jaw pain, I knew it was time to confront my fears and reach out for medical attention.

I walk over to a chair between a mother and her child, and another middle aged man. I felt my heart rate increase as I

wondered if those who had turned their attention to me had done so simply because I was newly entering the waiting room, or if they were trying to figure out if or why my facial features seem at odds with my overall presentation.

Finally, it was my turn to see a doctor. I entered the examination room, my heart pounding in my chest. The doctor, an older man with salt and pepper hair, barely looked up from the computer screen as I entered. “Hello Alexandria, how are you doing today?” I wince and cringe at the sound of my legal name leaving his mouth. I could have sworn I wrote my preferred name on the patient intake form.

Before he goes on, I interject. “Um, actually doctor, I go by Xander. I think I wrote it on the form there.” He peers back down at his clipboard, seeing where I had written it, and mumbles off a quick apology before continuing where he left off. He asked me to describe my symptoms, so I explained the persistent jaw pain, and added that I had been experiencing debilitating headaches and blurred vision.

He responded as soon as I finished speaking. “It’s probably just anxiety,” he said, barely making eye contact. “I see here it says you’re on a testosterone regimen for gender affirmation reasons. You’re undergoing hormonal changes, so it’s not unusual to experience these symptoms.”

Feeling frustrated and unheard, I gathered my courage and spoke up. “I understand that hormonal changes can cause symptoms, but I feel like there’s something more going on. I need help finding the root cause of my pain and discomfort.”

To my surprise, the doctor paused and looked at me. He seemed to recognize the determination in my eyes. “Alright,” he said, his tone changing slightly. “Let’s explore other possibilities. We could consider taking you off of testosterone for some time and see if that makes any changes.”

My head snaps up to meet his eyes. “What happens to my body if I am taken off the testosterone?”

He continues to look at me. “Well, currently the regimen you are on is blocking female puberty, as well as driving male puberty in your body. Should you come off testosterone, your body would return to its normal state, and likely your pain will subside.”

The world around me spun as I was catapulted back in memories from a terrible time, when my body was not my own and I felt so uncomfortable in my own skin. The thought of this made my skin crawl, and I shivered, asking in response if this is the only option.

He ordered some tests before referring me to a specialist. The specialist, a dentist specializing in temporomandibular

joint disorders, listened attentively as I described my symptoms and concerns. She took the time to understand my gender identity and the potential impact it could have on my healthcare.

Are Transgender Patients at Greater risk in Healthcare settings?

A common saying in health care is, "When you hear hoofbeats, think horses not zebras." In many cases the most obvious conclusion is what is wrong with the patient. However, this can compromise care when there is actually something more going on. Without proper investigation, the physician would never know. Especially in newly emerging medical sectors, such as those related to transgender care, where there is limited research into the effects of hormones and other related conditions or complications of gender affirming care. Physicians need to stay up-to-date on transgender healthcare. Stay informed about current research, guidelines, and the best practices. Not everything can be chalked up to hormones.

Additionally, physicians should be conscious of the language they use when interacting with transgender patients. When recommending Xander to forgo hormone therapy, the doctor said, "Their body should go back to normal." This can insinuate that the current state is abnormal and can incite tension in the interaction if the patient does not feel accepted for who they are. The physicians body language can also go a long way in setting the tone for the interaction. Throughout their communications, the doctor did not make sufficient eye contact with Xander. Making eye contact is crucial in healthcare interactions as it establishes trust, conveys empathy, and fosters a strong patient-provider connection, ensuring patients feel heard, respected, and valued. Finally, use of the patient's legal name, as opposed to the patient's preferred name, can be extremely triggering for these individuals. [1]

After a thorough examination, the dentist confirmed that I had temporomandibular joint disorder, or TMJD, which was causing my jaw pain and related symptoms. She discussed treatment options with me, including therapy, medication, and lifestyle changes. She also addressed my concerns about any potential impact on my transition and offered resources for transgender- friendly healthcare providers. She explained that male hormones may have a part to play, as they could be causing a growth spurt further contributing to my condition; but this couldn't be known without some more investigation and examination.

I left the dental clinic feeling a mix of relief and frustration. Relief, because I finally had a diagnosis and a plan for treatment. Frustration, because it had taken so much effort to be heard and taken seriously. This experience served as a painful reminder for how gender identity disparities can lead to inadequate care and put transgender individuals at risk.

Key Takeaways

While TMJD is more commonly associated with younger individuals, it is not limited to any specific age group. The condition can develop or become more pronounced due to various factors, such as changes in bite alignment, trauma or injury to the jaw, arthritis, stress, teeth grinding or clenching.

Transgender patients encounter a range of challenges within the healthcare system, stemming from both systemic and individual factors. Discrimination and lack of understanding from healthcare providers can lead to inadequate or inappropriate care. Misgendering and deadnaming, using the patient's birth name instead of their chosen name, can cause emotional distress and erode trust

Transgender individuals may face difficulties accessing gender-affirming treatments (e.g. hormone therapy, gender-affirming surgeries) due to insurance barriers, lack of coverage, or gatekeeping by medical professionals. Mental health support tailored to their unique experiences is often lacking, contributing to higher rates of depression, anxiety, and suicide within the transgender community. Additionally, confidentiality concerns and fear of disclosure can hinder open communication, preventing patients from seeking the care they need. To address these challenges, comprehensive training for healthcare providers, inclusive policies, increased awareness, and improved access to gender-affirming care are essential steps toward creating a more equitable and supportive healthcare environment for transgender individuals.

Medical professionals can significantly enhance their interactions with transgender patients by cultivating an environment of respect, empathy, and understanding. To begin with, practitioners should prioritize the use of correct gender pronouns and names, demonstrating their commitment to acknowledging and validating the patient's identity. If one is unsure of someone's gender identity, one can ask "What name/pronoun would you like me to use, when addressing you?" Additionally, when faced with complex or unfamiliar cases, don't hesitate to refer patients to specialists who have experience and knowledge in transgender healthcare. Consultations and collaborations can lead to more accurate diagnoses and effective treatment plans, especially in multifactorial conditions.

Healthcare providers should educate themselves on transgender health issues, staying informed about the latest research and guidelines to offer informed and affirming care. Sensitivity to potential dysphoria and discomfort during physical exams and procedures is essential, as is involving the patient in discussions about their preferences and comfort levels. Lastly, fostering an open dialogue about treatment options, potential side effects, and the patient's healthcare goals will empower transgender individuals to actively participate in their care decisions, ultimately leading to more positive health outcomes and a more inclusive healthcare experience. [2]

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Self Advocacy in the Face of Dismissal

Self Advocacy in the face of Dismissal

LUCY OGOKE



Fictional patient Giselle interacting with physician after fainting on the train. *Licensed under Creative Commons Zero (No rights reserved)*

Disclaimer: All names portrayed in this production are **fictitious**. No identification with actual persons (living or deceased), should be inferred

I had fainted on the subway station, overwhelmed by the sudden wave of pain and dizziness. Now, I was in the emergency room, hoping for some answers. The doctor, a middle-aged man with an air of indifference, entered the room. He glanced at my chart briefly before meeting my eyes. “Well Giselle, according to your blood tests, there does not seem to be anything wrong,” he said matter-of-factly, his tone suggesting that he was settled in his assessment that I was fine.

I cleared my throat, and with my voice barely above a whisper, I responded. “But I’ve been bleeding excessively for eleven days now,” I said, my words carrying the weight of my frustration. “The pain is unbearable, and I can’t go on like this.”

The doctor seemed unfazed by my plea. He leaned against the wall, crossing his arms. “Sometimes, periods can be heavy and painful. It’s nothing out of the ordinary. All women are different, and it is normal to see some variation. You probably fainted from anemia caused by the blood loss. I’ll give you some ibuprofen to help with the cramps, but there’s not much else we can do.”

My friend, who had been by my side throughout this ordeal, could not contain herself, and spoke up. “Doctor, you haven’t even done a proper workup. How can you be so sure it’s just her period?” she interjected, her voice filled with disbelief.

The doctor’s expression grew slightly irritated. “Look, we’ve taken blood samples, and the results are clear. There’s no need for unnecessary tests.” His jaw was set, quite obviously wanting to be done with this interaction. “I assure you, it’s just a heavy period. Women tend to exaggerate their symptoms sometimes to get pain medication. Are you one of those?” He eyed me suspiciously. “The hospital does not make a habit of supporting the drug problems of our patients.”

Combating Biases in Healthcare

People of color and women have historically faced systemic biases and stereotypes within healthcare. These biases can unconsciously influence healthcare providers’ perceptions and decisions, potentially resulting in inadequate care. Due to the historical and ongoing disparities in healthcare, patients need to be professional yet assertive, thus strengthening patient autonomy and empowers patients to actively participate in their healthcare decisions.

Advocating for oneself can be crucial due to the pervasive oppressive biases that may downplay or disregard a patient’s concerns- especially for POC women. However, for POC women must conduct their spoken and body language intentionally, yet not be deemed to aggressive or uncooperative. By communicating assertively and professionally, individuals can counteract these biases and insist on the level of care everyone deserves. However it is extremely taxing on these patients to have to advocate for themselves repeatedly in order to receive optimal care. [1]

My heart sank. It felt as if he did not believe me, as if my pain was inconsequential. Tears welled up in my eyes as I struggled to make him understand. “Please, I can’t live like this. It’s not normal,” I pleaded, my voice trembling with a mix of frustration and desperation. After a moment of silence, my friend spoke up again, her voice steady, but determined. “Doctor, I kindly request that you note the ignored complaints and perform further investigations. Something is clearly wrong, and it’s important to find out what it is.”

Reluctantly, the doctor sighed and agreed to perform an ultrasound. As the gel touched my abdomen and the doctor placed the probe on my abdomen, I prayed for answers: for validation of the pain I had been enduring for far too long. Moments later, the monitor came to life, displaying the image of my uterus. The doctor's indifferent expression changed to one of surprise. "It seems you have uterine fibroids Giselle," he finally admitted, his voice filled with reluctant acknowledgement. "They're likely causing your symptoms." Relief washed over me, mixed with frustration and a sense of vindication. I was not imagining things. There was a tangible reason for my pain, and it could have been missed. I would have suffered longer, if not for my friend.

As the doctor left the room to discuss the next steps, I clung to my friend's hand, grateful for her unwavering support. It was a reminder that our voices matter, that we should never settle for being dismissed or misunderstood.

Key Takeaways

By requesting documentation and additional tests, the patient and their advocate can ensure that their concerns are properly recorded and addressed. This approach can help to substantiate the need for further investigation, and prompt the healthcare professional to take the patient's symptoms seriously. The doctor both dismissed her pain and symptoms before accusing her of trolling for pain medication, an experience which is quite common for patients of colour or of lower socioeconomic status.

For healthcare professionals, be mindful of how you are communicating: both verbally and with body language. In this story, the attitude of the doctor was dismissive: he still did not apologize for his behavior and sentiments during the interaction. Often healthcare professionals may be ashamed to have fallen short of the high expectations set for themselves, or fearful of the legal and social consequences. Many doctors can feel hesitant to issue apologies to patients because they believe it can open themselves up to liability. Although this is a common sentiment, it has not been proven. Studies have shown that in cases where physicians did give a genuine apology there was no litigation or payouts were significantly smaller. In this scenario and similar ones, an apology can go a long way in letting the patient know that they are heard, understood what was done and the potential outcomes. And the professional will strive to do better in future interactions. Not only do apologies serve the patient well, but it often serves the physician who may feel guilt or remorse at potentially or having caused harm. [23]

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- male-healthcare-worker-making-reports-clipboard-while-standing-by-female-patient-lying-bed-hospital (1) © Tonodiaz is licensed under a CC0 (Creative Commons Zero) license

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APPENDICES: CASE STUDY OF UNSTABLE ANGINA AND ATHEROSCLEROSIS

This case study is from another Open Education Resource "Health Case Studies" by Glynda Rees, Rob Kruger, and Janet Morrison. The following chapters follow the health journey fictional character Harj Singh takes from his unstable angina to a possible cardiac event.

Although the case study's pathology is unstable angina (rather than our chapter on atherosclerotic development to symptoms of angina), there are many similarities in the diagnosis and treatment and interactions with health care team.

Learning Objectives

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Learning Objectives

In this case, learners have an opportunity to:

1. Review etiological factors (i.e., risk factors, prevalence, comorbidities) associated with acute coronary syndrome
2. Build knowledge related to the patient's experience of chest pain (including the experience of chest pain and sudden critical illness)
3. Continue to develop comprehensive assessment and monitoring skills and abilities (i.e., chest pain assessment, risk analysis, ECG changes, laboratory data)
4. Consider the links between evidence-based knowledge and practice in the care of patients with chest pain (e.g., chest pain guidelines)
5. Recommend interventions based on the risk factors, status, and progression of cardiac disease
6. Define the roles of healthcare professionals and the contributions they make to the healthcare team (or describe your own role and the roles of those in other professions)

This case describes a patient's experience with unstable angina and potential myocardial infarction (MI). The interprofessional collaboration is between physician, medical laboratory and medical radiology health professionals.

Learners reviewing this case can consider the pathophysiology of heart disease and how ethnicity, employment, and family may play a role in this common disease process. Interprofessional collaboration is ideal in this case and presents opportunities for discussion on what makes the interactions presented ideal.

Patient: Harj Singh

GLYNDA REES; ROB KRUGER; AND JANET MORRISON



Harj Singh, used under the Creative Commons license 1.0

Patient: Harj Singh

Date of Birth: 03/03/19xx

PERSONA

Harj Sing is a 59 year old male. He lives with his wife in a small town in the interior of British Columbia. He is a short haul truck driver and owns his own vehicle. He finds the long hours, slow business, and his truck, which constantly gives him mechanical trouble, stressful.

His wife, Priya Singh, is 56 years old; she manages the books for their trucking business. She is constantly worrying about the stress she sees in Harj despite his denial of feeling stressed or worried about their financial situation.

They have two adult children, one boy and one girl, who live locally. They have four grandchildren.

Harj smokes one pack if cigarettes per day and is trying to quit. He drinks moderately, his favorite drink being Crown Royal.

He leads a fairly sedentary lifestyle and is carrying extra weight. He loves fries and soda, and frequently gives into this weakness whenever he passes by fast food vendors.

Harj does not have a primary care physician. Instead, he uses the local walk-in clinic to manage his hypertension and other medical concerns. His surgical history includes an appendectomy as a child. He takes hydrochlorothiazide for hypertension and over-the-counter antacids to manage his heartburn.

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Harj Singh: Photo by AFRINIC is in the public domain.

Media Attributions

- Sim_Harj_Singh

At Home

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 0

Time: 8:30pm

Place: At home

Priya looks out the window to see her husband Harj working on the truck again.

"He's always out there doing something to that thing. I swear it hasn't worked well for any of the time we've owned it," she mutters.

Cleaning up the kitchen just before dinner, she glances at the half full bottle of Crown Royal. "He's drinking way too much again. I know he'll be grumpy and sad at the dinner table."

Again Priya looks out the window and sees Harj taking a smoke break from working under the hood of the truck. "He's also smoking way too much. We probably could make ends meet better if he didn't smoke and drink so much."

She moves to the stove and stirs some aloo gobi, then turns the heat off on the stove. "Ok, it's done. Now it's time to see if he will come in to eat or if he says he's too busy."

She turns around to find Harj staring at her. "You talking to yourself or are the kids here for dinner, too?"

"No, Harj. Just thinking out loud. Are you going to stop and have something to eat?"

"Yes, I think I'm almost done. It's the fuel pump this time. That's the last time I'm buying gas from your brother-in-law. The price was right, but I'm thinking the quality wasn't."

"It may not have been Gurr's fault. The truck is old, and have you ever replaced the fuel filter?"

"No." Harj steps closer to the kitchen island and, lifting his large abdomen on top of the island, reaches for the cupboard with the small glasses. He pours himself a half glass of Crown Royal. "I remember when we only used these glasses for the kids when they were growing up. Now that they're gone, I use them for my drink. Do you want one, Priya?"

Priya shakes her head. "Maybe you should move to even smaller glasses or drink less."

"Not again and not today. I've been up before dawn, driving all over the bloody county, and now its 7:30 at night. I deserve a drink for how hard I've been working."

"Well, I just looked at the books. All that driving doesn't mean we are making money. We're going to have to cut some expenses: maybe your drinking and smoking."

Harj shakes his head. "This is the only enjoyment and stress reliever I have. I'll look for more jobs so we're not driving empty any time this week."

Harj sits at the head of the table with a view out the patio doors to his beloved truck. *Not quite a semi, but not one of those UPS vans, either*, he thinks.

"I just have to attach the electrics and I should be done for the night and ready to go tomorrow early," he tells Priya.

Priya brings dinner to the table and ladles the steamy and fragrant potatoes and vegetables into Harj's bowl. She gives him one piece of naan but watches in disgust as he reaches and takes hers. He looks at her and shrugs his shoulders. "What? I'm hungry."

"You haven't even eaten it and you are taking more. I remember when I could put my arms around your waist."

Harj looks down at his quite large abdomen and smiles at Priya. "Probably the only thing I own that is fully paid for."

Priya smiles at his joke and sits at the table.

The two share stories of their day and what the kids have been up to. "It's really different without the kids here, Priya. The last one moved out over a year ago, but it still seems strange. It's too quiet."

Priya nods. "Yes, I know what you mean. They'll be here on the weekend. You need to take some time off to visit when they come. Last time you worked the whole weekend through and never saw them. That isn't good for you or the kids."

Harj stops eating and just looks at his food. Priya hears a quiet, "I know."

Harj quickly finishes his meal, pushes himself away from the table and begins the motion to bring a cigarette out of his pocket. "No, Harj. We agreed no smoking in the house."

Harj grimaces at her and walks out the patio doors to the truck, lighting his cigarette as he goes.

Pryia cleans up the kitchen and makes Harj a lunch for tomorrow. She sees him come in. "All done?"

"Not quite. About five minutes more. Got brutal heartburn. Your cooking is killing me. Where are the antacid tablets?"

"By your bedside, like always."

Harj goes to the bedroom and takes four tablets. Then he walks quickly out to the truck.

Completing the last of the connections, he says to himself, "Finally done. Let's start this up to double-check." Slamming the hood down, Harj moves around to the driver side of the cab and lifts himself inside, grunting numerous times. The truck starts up on the first try. Harj revs the engine a couple of times and looks at the dashboard to confirm everything is sound. Turning the key off, he steps out of the cab, locks it, and heads to the house.

After washing up, Harj plops down in the lazy boy chair and lets out a long sigh. Flicking through the channels, he finds the Punjabi Hockey Night in Canada broadcast. Smiling, he says to himself, *These guys are hilarious. Much better than the CBC version.*

About 20 minutes later, Priya comes out of her sewing room to find Harj leaning forward. "Everything ok?"

"Yeah, yeah, fine."

Priya moves closer to Harj and sees the top of his bald head glistening with sweat. She notes that he is rubbing his left shoulder and upper arm. "Did you hurt you arm working on the truck?"

"What, what? No, no. I'm fine."

"You don't look fine. In fact, you look pale for a brown guy." Priya leans closer to see if he heard her little joke.

“Ok, ok. Your dinner is killing my guts. It’s just sitting right here.” Harj moves his arm from his left shoulder to indicate his whole chest is sore.

“Not my dinner. You love that meal. Something else is wrong.”

“No, it’s your dinner.”

Priya moves around to look Harj right in the eyes and get a better read on him. Looking closer, she can see he is in a lot of discomfort.

“Ok, Harj, you are not doing well. I think you’re having heart problems.”

“No.”

“Yes. At the mosque, they told us the signs of a heart attack. You must remember that. Chest pain, arm and jaw pain, indigestion that does not go away, shortness of breath.”

“I am not having a heart attack. Leave me alone.”

“No, I’m not leaving you alone. I’m going to call an ambulance.”

“No, you’re not. We can’t afford that.”

“Your life is worth a small bill. Preeti’s dad used an ambulance when he broke his hip. It was about $80.”

“No ambulance. That’s final.”

“Well, then you are going in my car and going to have to put up with me driving. I will take you to the hospital.”

Harj looks down at his feet. “Ok.”

Now Priya knows for certain he is not feeling well. *He hates my driving. For him to be willing to go with me really means something is wrong*, she thinks.

“I’m going to grab your coat and wallet along with my purse. Meet me at the front door.”

Priya gathers everything up, including her cell phone so she can call the kids to let them know their dad is going to the hospital.

Moving to the front door, Priya notices that Harj is out of breath just getting out of his chair and walking to the front door.

Opening the door, she holds Harj’s right arm and feels him lean on her, thinking, *Looks like he can barely walk now, as well. Better not slip or we are both going to have broken hips.*

Priya gets him in the front seat of the car and runs back to the house to lock the door.

Sliding into the driver’s seat, she starts her small Corolla and carefully moves out of the driveway and onto the main street.

“Ok, the hospital is about 20 minutes away.”

“The way you drive, woman, it’s about 30 minutes.”

“No, I’m going to drive a little over the speed limit. Might make it there in 15, even.”

Harj leans back in his seat and shakes his head.

Emergency Room

GLYNDA REES; ROB KRUGER; AND JANET MORRISON

Day: 0

Time: 22h30

Place: Emergency Room

Nurse Jackie, on the triage desk tonight, let's out a long sigh, and says to herself, "Been a quiet evening so far." Jackie has her back to the waiting room and is updating the census when she hears, "Excuse me, can you help my husband? I think he's having a heart attack!"

Jackie immediately turns around and looks at the two people standing at the triage desk. She sees two middle-aged East Asian individuals: one, a woman who looks about to burst into tears and a man, quite overweight, hair a bit messed up, and rubbing his left shoulder.

"Can you say that again? Your husband is having chest pain?"

Priya, looking a bit exasperated and tired at the same time, says, "Yes, he thinks it's nothing but indigestion, but since dinner he has been rubbing his shoulder and complaining of not feeling well. He took some Tums but that didn't help. He blames my cooking, but we've been married for over 25 years. If my cooking was a problem, he would be slimmer."

Jackie looks at both of them again and nods. She quickly comes out from the triage desk and grabs a nearby wheelchair. "Mr…?"

"My name is Harj Singh and I don't need a wheelchair."

"Please have a seat, Mr. Singh, and let's humour your wife and me. It looks to me like you're having some difficulty breathing. You are rubbing your arm and upper chest, and you look a bit paler than I would expect."

Harj plops down into the wheelchair with a huff, looking quite unhappy with the whole situation. Priya reaches down and squeezes his hand.

Jackie squats down to talk directly to Harj and Priya. "We take chest pain very seriously, so a lot of things are going to happen real quick. I am going to take you back in behind my desk to a special room. We're going to take your blood pressure and other vitals and have a doctor look quickly at you. We'll probably give you some medications to see if we can relieve the pain in your arm and chest. Your wife can stay with you, as we'll need to understand more of how this started. But then I'll ask her to step away to the admitting desk to give them some information. Are you ready?"

Harj and Priya now both look quite scared, but nod affirmative.

Jackie moves behind the wheelchair, rapidly pushes it to the acute side of the Emergency Room, and enters Trauma Room 1. As she enters the trauma room, she nods to two other emergency nurses who come over. "Hey, Jackie, anything we can do to help?"

“Yes, can you let Dr. Smythe know that we have a patient with chest pain in Trauma 1. Can you also get me ASA and some nitrospray. I’ll also need someone to start an IV on Mr. Singh.”

One of the nurses moves quickly over to the unit coordinator to page Dr. Smythe and the other nurse, Carrie, assists Jackie to get Mr. Singh onto the trauma room stretcher.

“Ok, Mr. Singh. Carrie here is going to help you remove your shirt. She is also going to start an IV in your left arm, in case we need to give you some fluids. I am going to take your vital signs.”

Jackie wraps the blood pressure cuff around Harj’s right arm, places an SpO_2 probe on his left forefinger, and puts a temperature probe under his tongue. Carrie grabs the monitor leads and places five leads on Harj’s chest. She turns the monitor on.

Looking at the vital sign machine, Jackie records the vital signs onto the Emergency Record.

Day: 0	**Pulse Rate**	**Blood Pressure**	**Respiratory Rate**	**Temperature**	**O2 Saturation**
Time: 22:00	96	180/90	28	36.5°C	95%

Looking up at the monitor, she notes that Harj is in normal sinus tachy with some ST depression noted on leads II and III.

“Now that is done, are you having pain in your chest?”

Harj nods ‘yes’.

“Have you had this type of pain before?”

Priya looks anxiously at her husband. Harj, looking down at his belly, says, “Yes, but only for a short time. When I sat down it went away.”

Priya looks horrified. “You never told me! What am I to do with you?”

“It’s ok, Mrs. Singh. This is quite usual. Denial is quite common. Mr. Singh, if you were to rate your pain on a scale of 1 to 10, with 1 being barely able to feel any discomfort and 10 being the worse pain you have ever felt, what would you say your pain is right now?”

“It’s about 5 out of 10.”

“Right, I am going to give you an aspirin and spray some medication under your tongue. It tastes terrible and may give you a bit of a headache as well. Do you have any drug allergies? What medications are you currently taking?”

Priya looks at Jackie. “He is on HCTZ. Sorry, I can’t say the whole name. One tablet in the morning for high blood pressure.”

Jackie looks at them both. “Do you take any Viagra or Cialis?”

Both Harj and Priya look at each other and shake their heads ‘no’.

“The reason I asked is that those drugs can cause a very low blood pressure with the medication I am going to spray under your tongue.”

Jackie hands Harj a small med cup with a tiny blue 81 mg ASA in the bottom of the cup.

“I want you to chew this aspirin. It will taste awful, so here is a cup of water to rinse and swallow after.”

Harj takes the ASA and chews the medication, making a sour looking face, and drinks all the water from the cup in one swallow.

“Ok, I am going to now spray some medication under your tongue. Please open your mouth and put the tip of your tongue on the roof of your mouth.”

Harj does as he is told and Jackie sprays nitro twice under his tongue. “Let’s give that a couple of minutes to see if that helps your chest pain.”

“Jackie, the IV is in Mr. Singh’s left ACF. I have NS running at 25 cc/hour on the pump right now. Are you ok?”

“Thanks, Carrie. I should be fine. Mr. Singh doesn’t look critical right now. I will call if we need help. Can you cover the triage desk for a little bit while we get Mr. Singh settled?”

“Yes, no problem. I’ve done that before. I’ll call you if I need help. Then maybe we can switch?”

“Sure thing. Thanks.” Jackie reaches over and pushes the NIBP button again to see how Harj’s blood pressure is after the nitro sprays. She then enters the number in the emergency record.

“Good evening, I’m Dr. Smythe. Can you give me an update here, Jackie?”

Jackie looks up at the doctor who has entered the trauma room. “Hello, Dr. Smythe. This is Mr. and Mrs. Singh. Mr. Singh came in with a complaint of chest pain radiating to left arm and jaw. We have given him two sprays of nitro, 81 mg of ASA, and oxygen saturations are above 93%, so I have not given him oxygen. I was just about to inquire as to his chest pain and call you about additional orders.”

“Thank you, Jackie. Mr. Singh, how do you feel right now?”

Harj looks up and sees a well-dressed, bow-tied traditional looking doctor in a short, white coat. “I am doing ok right now. I think everyone is making a bigger deal about this than is necessary. I need to get to work in the morning or I don’t get paid.”

“Let’s deal with one issue at a time here. Can you tell me about your chest pain?”

Harj rolls his eyes, then begins to explain that he had this type of chest pain a couple of weeks ago, but it went away when he rested in the cab of his truck. Today, after dinner, it came back. He took some antacids, but it did not go away.

“It felt like dull heavy pressure, with some numbness to my left arm.”

Priya adds, “He complained of feeling tired, and I had to help him walk to the car, as he was so short of breath and tired. He also looks pale.”

“Do you smoke, Mr. Singh?”

Pryia says, “Way too much. At least a pack a day.”

“Oh, come on! I don’t smoke that much.”

“Yes, you do. I see the empty packs in the recycling box.”

“Do you drink alcohol?”

“Yes, I have a drink after work.”

“More like two or three drinks after work. Harj, they are trying to help you, not criticize you. Tell them the truth!”

“Ok, I have two to three drinks per evening of Crown Royal.”

Dr. Smythe and Jackie write the information down. “Thank you, Mr. Singh. What about your work? Is it stressful?”

“Not really. I run a small trucking delivery company. Things have been tight, but not especially so.”

Priya rolls her eyes. “We are barely making ends meet. Everyday Harj is out fixing the truck. He is up at 5am and doesn’t usually come home till after 6pm.”

“That sounds a bit stressful. Do you have any activities other than work, Mr. Singh?”

“If you are asking, do I exercise, no.”

“Right, how would you describe your chest pain now?”

“A bit less than when I came in. Oh, right, you want a number. Three out of 10. The sprays helped, but it has really made my head ache.”

Dr. Symth looks at Jackie. “How long since the last spray of nitro?”

Jackie consults the emergency record. “A little over five minutes.”

“Ok, give him two more sprays of nitro, and if the chest pain doesn’t go away, try morphine, 1-2 mg IV, till the pain is gone. I’ll write that down for you. Plus, let’s get some lab work, including CBC, lytes, BUN, creatinine, Trops, 12 lead, and a portable chest X-ray.”

Jackie nods her head and makes note of what Dr. Smythe has stated.

Dr. Smythe moves over to the same side of bed that Priya is on. “I’m not positive that your husband is having a heart attack. We need to do some tests, then we will know more. I’m going to keep him here until we have those results.”

“Aww, Doc,” Harj says, “You are going to cost me money to do this.”

Pryia grabs his hand. “Better a day’s pay than a dead husband.”

Harj rolls his eyes and leans back into his pillow with a sigh of exasperation.

“Mrs. Singh, why don’t you follow me out to the admitting desk so we can get all of your contact information, and then you can call any other family. Jackie will take good care of your husband.”

Dr. Smythe leads Priya out to the admitting desk and introduces her to the clerk there. “You can give your contact information to the clerk. When you’re done, just go to the desk where you came in and ask to see your husband. They will guide you to him.”

Priya thanks Dr. Smythe.

Dr. Smythe returns to the unit clerk’s desk and asks her to have the lab and X-ray come to see Mr. Singh in Trauma 1.

She looks up at him. “Jackie already called me to let me know that she put the order into the computer as stat. They should be coming shortly. Do you want to add anything?”

“No, that’s a good start. Let’s see what the results are and go from there. He may not need to be admitted if it’s just angina.”

Time: 21h55

Jackie confirms with Mr. Singh that his chest pain is still three out of 10 and sprays two more doses of nitro under his tongue.

Place: Medical Laboratory

Alexa, just about to leave the Emergency Department and head to the lab to drop off some specimens and restock her cart, looks down at her buzzing pager, and thinks, *Stat lab work in Trauma 1. That takes precedence over going to the lab. Looks like my break will be a bit later than usual.*

Turning around her white cart, Alexa walks quickly to Trauma 1.

Entering Trauma 1, Alexa sees an overweight middle-aged East Asian male and Jackie, the nurse that is usually at the triage desk.

"Hi, Jackie. I'm here from the lab. You requested some stat blood work?"

Jackie turns around and smiles. "Hi, Alexa. Thank you for coming so quick. Yes, this is Mr. Harj Singh. We are investigating him for unstable angina, possible MI."

"Ok, do you have the labels?"

"Yes, they're over there on the printer."

Alexa walks over to the label printer and pulls off three labels for Mr. Harj Singh.

Walking back to Harj's bedside, Alexa begins the routine of checking identity. "Hi, Mr. Singh. My name is Alexa and I'm going to draw some blood for testing. I need to ask you some questions to confirm that you are the right person and that the labels all match up."

"Really, here is my ID band. Is that not good enough?"

"No, we really want to make sure we are taking blood from the right patient, as many treatments are based on the results, and you would not want to receive the wrong treatment."

"Ah, yes, you guessed right. I want no mistakes. Ask your questions."

Alexa goes through the process of confirming name, date of birth, and Mr Singh's ID number.

Once satisfied, she efficiently draws the blood from Harj's right antecubital fossa.

"All done, Mr. Singh. Please hold pressure here for another couple of minutes. Jackie, I will take the blood back to the lab and you should have the results for the troponin very quickly."

"Thanks, Alexa."

"Ok, Mr. Singh, can you tell me how your chest pain is right now?

Harj looks up at her. "I think it's gone."

"That's excellent. We'll do all of these tests and make sure nothing else is happening, but this is a good sign."

Time: 22h10

Gurpreet checks the list of patient requests and sees that the top request is a portable chest X-ray in Trauma 1. Pulling up the patient data she sees that the patient was admitted with potential MI. "Ok," she says to herself. "I can understand them not wanting to transport to the department. Looks like I will do this with the portable machine."

Gurpreet pulls the requisition off the printer and heads straight out the department doors and down the stairs that lead directly to the Emergency Department. At the bottom of the stairs she pulls an imaging plate out of the rack and places it in the rear door of the portable X-ray machine. Unplugging the machine, she pushes the portable down the hallway and navigates it through the chaos of people moving around in the Emergency Department into Trauma 1.

"Hi, I'm Gurpreet from Medrad here to do a chest X-ray on Mr. Singh."

"Hi, Gurpreet. I'm Jackie and this is Mr. Harj Singh."

"Hello, Mr. Singh. Do you think you can sit straight up and have a very hard board behind you?"

"I think so. Depends on how straight." Harj points at his belly as he says this.

"We can work around it. Let's see."

Both Jackie and Gurpreet help Harj to sit up in bed, and they place the hard cassette behind his back.

Gurpreet moves to the end of the bed and looks at Mr. Singh. "Can you move a little to your right, that's it. Hold right there."

Gurpreet moves the machine into position. She pulls the tape measure out of the camera and confirms that it is the appropriate distance away. Looking at Mr. Singh she adjusts the technique settings for exposure. *That should work on someone his size*, she thinks to herself. Pushing a button to bring up the positioning lighting, Gurpreet makes adjustments to capture the chest correctly.

"Ok, ready to shoot."

Jackie steps quickly out of the room as Gurpreet grabs the lead shield to cover her neck and chest and pulls the exposure button out as far as the cord goes. "Ok, Mr. Singh, take a deep breath and let it out. Ok, ready to shoot. Take a deep breath and hold it … X-ray! Trauma 1."

Gurpreet presses the exposure button and the portable machine whines up and makes a clicking noise.

"Ok, all clear, Mr. Singh. Great job. Let's get that hard cassette out."

Both Jackie and Gurpreet remove the cassette and reposition Harj. "How is that?"

"I am good, thank you."

"Thanks, Gurpreet. How long till I can see the results?"

"I'll run it through now and should have it on the system in less than 10 minutes."

"Excellent."

Gurpreet pushes the machine out and places it back in its special niche. Grabbing the exposed cassette she heads back to the department to process the chest X-ray of Mr. Singh.

Just as Gurpreet is leaving, Dennis from Cardiology pushes his cart in. “I have a req for a 12 lead for one Mr. H. Singh with complaint of chest pain. Am I in the right place?”

“Yes, you are. I’m Jackie, taking care of Mr. Harj Singh. Please do the 12 lead.”

“Awesome. Hey, Mr. Singh. Can I ask you a couple of questions?”

Harj looks at Dennis and nods ‘yes’.

Dennis goes through the same routine as Alexa of confirming Harj’s identity.

“Ok, you are you. I am going to place 10 little sticky patches on you, Mr. Singh. One for each leg and arm and six on your chest. This test won’t hurt, but I will need you to stay very still. Have you had one of these before?”

“Yes, about four years ago when they determined I had high blood pressure. I’ve no idea if it showed anything.”

“Well, if we do find anything today, Dr. Smythe will discuss that with you.”

Dennis proceeds to place all the leads on Harj, and after a few minutes is ready to take the test.

“Ok, this is where you need to stay still. Ready. Excellent.” Dennis presses the record button and, a few seconds later, a pink 8 x 11 paper with multiple black lines is printed out. Dennis hits the print button a second time and gives the copy to Jackie. “Here is the preliminary result for you to discuss with Dr. Smythe. I’ll take the original with me for analysis by the cardiologist-on-call. If you have any questions, please call them.”

“Thanks, Dennis.”

“Ok, Mr. Singh. Looks like you’ve had all your tests done. We will need to wait for some of the results, and then Dr. Smythe will come and talk to you and your wife. I’m going to step out for a minute and get your wife to come in. Is that ok?”

Harj nods ‘yes’.

Time: 22h30

Jackie approaches Dr. Smythe at the nursing station. “Have you got a minute to look up the results of Mr. Singh in Trauma 1?”

“Yes, I was just about to check to see what’s back.”

Both Jackie and Dr. Smythe step closer to the computer screen. Dr. Smythe pulls up the X-ray first.

“The chest X-ray looks clear, so does not look like he has ventricle dysfunction or a low LVEF. Heart is a bit enlarged. He may be developing heart failure or is on the cusp of doing so.”

Next Dr. Smythe pulls up the lab work. “The WBC are normal. Not really helpful, but at least we know there is no inflammation. HGB is normal. BUN and creatinine are higher than I would expect but within normal range. Ah, here is what I am looking for. The troponin is normal, so no MI for Mr. Singh. All good news. You have his 12 lead, Jackie?”

“Yes, I don’t see any depression or elevation in any of his leads, so, looking at the 12 lead with the trops, he appears to have unstable angina, not an MI.” Jackie hands the 12 lead to Dr. Smythe.

“Completely agree. UA not MI. Ok. Let’s repeat and keep him until morning. But if everything stays the same and he has no chest pain, he can be discharged. I see he has no doctor on file. Is there a way we can have him followed?”

“I will talk with social work in the morning. Maybe they can arrange a GP for him so he can be followed.”

“Thanks, I’ll go talk to him and his wife.”

Conclusion

We hope that you have benefited from this book that seeks to tie together the changes that occur at the cellular and tissue level during the disease process with both the clinical presentation (signs and symptoms) and the health care workers that will assist a patient on their journey from determining what is going on (diagnosis) to helping to manage living with these changes.

Glossary

avidity

total binding strength of a multivalent antibody with antigen

affinities

attraction of molecular complementarity between antigen and antibody molecules

allergy

immune reaction that results from immediate hypersensitivities in which an antibody-mediated immune response occurs within minutes of exposure to a harmless antigen

antibody

protein that is produced by plasma cells after stimulation by an antigen; also known as an immunoglobulin

autoantibodies

antibody that incorrectly marks "self" components as foreign and stimulates the immune response

basophil

leukocyte that releases chemicals usually involved in the inflammatory response

Cross reactivity

binding of an antibody to an epitope corresponding to an antigen that is different from the one the antibody was raised against

hypersensitivities

spectrum of maladaptive immune responses toward harmless foreign particles or self antigens; occurs after tissue sensitization and includes immediate-type (allergy), delayed-type, and autoimmunity

passive immunity

transfer of antibodies from one individual to another to provide temporary protection against pathogens

hyperplasia

tissue that is enlarged due to an increased number of new cells

Physiology

Physiology is the study of the function of cells, tissues and organs

acute inflammation

inflammatory response that occurs from the time of injury to infection up to a few days

Adaptive immunity

immunity that has memory and occurs after exposure to an antigen either from a pathogen or a vaccination

afterload

the pressure/resistance against which the heart must work in order to eject blood for each contraction

albinism

Genetic disorder that affects the skin, in which there is no melanin production.

alpha cell

pancreatic islet cell type that produces the hormone glucagon

alpha-1-antitrypsin

A protease inhibitor that protects tissues from proteases released by inflammatory cells

Alveolar dead space

Air space within alveoli that are unable to participate in gas exchange.

alveolar duct

Small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli.

alveolar macrophages

Immune system cell of the alveolus that removes debris and pathogens.

alveolar pores

Opening that allows airflow between neighboring alveoli.

alveolar sac

Cluster of alveoli.

alveolus

Small, grape-like sac that performs gas exchange in the lungs.

amount of force

Amount of force that is exerted by gases in the air surrounding any given surface.

anaphase

Third stage of mitosis (and meiosis), during which sister chromatids separate into two new nuclear regions of a dividing cell.

anastomosis

(plural = anastomoses) area where vessels unite to allow blood to circulate even if there may be partial blockage in another branch

Anatomic Pathologists

Pathology specialty that looks at organs and tissues to determine what changes, if any, are occurring that might lead to an explanation for the signs and symptoms.

anatomical dead space

Air space present in the airway that never reaches the alveoli and therefore never participates in gas exchange.

anchoring junctions

Mechanically attaches adjacent cells to each other or to the basement membrane.

aneurysm

abnormal ballooning/ widening of the blood vessel wall cause by it's weakness. Aneurysm rupture is very dangerous and often fatal

angiogenesis

process in which new blood vessels form from existing ones

anterior cardiac veins

vessels that parallel the small cardiac arteries and drain the anterior surface of the right ventricle; bypass the coronary sinus and drain directly into the right atrium

anterior interventricular artery

(also, left anterior descending artery or LAD) major branch of the left coronary artery that follows the anterior interventricular sulcus

anterior interventricular sulcus

sulcus located between the left and right ventricles on the anterior surface of the heart

anti-nuclear antibodies

Antibody that the immune system makes to mistakenly attack the nucleus of its own cells

antigen

foreign or “non-self” protein that triggers the immune response

antigen-presenting cell

immune cell that detects, engulfs, and informs the adaptive immune response about an infection by presenting the processed antigen on the cell surface

antigen-presenting cell (APC)

immune cell that detects, engulfs, and informs the adaptive immune response about an infection by presenting the processed antigen on the cell surface

aortic valve

(also, aortic semilunar valve) valve located at the base of the aorta

apical

The part of a cell or tissue which, in general, faces an open space.

apneustic center

Network of neurons within the pons that stimulate the neurons in the dorsal respiratory group; controls the depth of inspiration.

apocrine secretion

Release of a substance along with the apical portion of the cell.

apoptosis

"programmed" cells death that eliminates abnormal cells

apoptotic bodies

small membrane-bound vesicles released from cells undergoing apoptosis

arterioles

(also, resistance vessel) very small artery that leads to a capillary

arteriovenous anastomosis

short vessel connecting an arteriole directly to a venule and bypassing the capillary beds

artery

blood vessel that conducts blood away from the heart; may be a conducting or distributing vessel

ascending aorta

part of the aorta that originates from the heart; total length - around 5 cm

ascites

abnormal collection of fluid in the abdominal cavity

ASCVD

acute atherosclerotic cardiovascular disease

atheroma

same as atherosclerotic plaque

atrioventricular septum

cardiac septum located between the atria and ventricles; atrioventricular valves are located here

atrioventricular valves

one-way valves located between the atria and ventricles; the valve on the right is called the tricuspid valve, and the one on the left is the mitral or bicuspid valve

atrium

(plural = atria) upper or receiving chamber of the heart that pumps blood into the lower chambers just prior to their contraction; the right atrium receives blood from the systemic circuit that flows into the right ventricle; the left atrium receives blood from the pulmonary circuit that flows into the left ventricle

auricle

extension of an atrium visible on the superior surface of the heart

auscultation

listening with a stethoscope for changes in sounds produced by movement of air, blood, food digestion, etc.

autoantigens

normal components of an individual's own body that are mistakenly targeted by the immune system

autoimmune response

inappropriate immune response to host cells or self-antigens

Autoimmunity

class of hypersensitivity reactions to self antigens

autorhythmicity

heart's ability to control its own contractions

B cells

lymphocytes that mature in the bone marrow and differentiate into antibody-secreting plasma cells

basal cells

Type of stem cell found in the stratum basale and in the hair matrix that continually undergoes cell division, producing the keratinocytes of the epidermis.

basal lamina

Thin extracellular layer that lies underneath epithelial cells and separates them from other tissues.

basement membrane

In epithelial tissue, a thin layer of fibrous material that anchors the epithelial tissue to the underlying connective tissue; made up of the basal lamina and reticular lamina.

beta cell

pancreatic islet cell type that produces the hormone insulin

bicuspid valve

(also, mitral valve or left atrioventricular valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

bifurcation

part of the blood vessel where it splits in 2 branches

bifurcations

separation

bile

alkaline solution produced by the liver and important for the emulsification of lipids

bile canaliculus

small ducts between hepatocytes that collects bile

bilirubin

main bile pigment, which is responsible for the brown color of feces

biopsy

Eextraction of sample cells or tissues for examination to determine the presence or extent of a disease. The tissue is examined under a microscope by a pathologist for histological changes

blood flow

movement of blood through a vessel, tissue, or organ that is usually expressed in terms of volume per unit of time

blood pressure

force exerted by the blood against the wall of a vessel or heart chamber; can be described with the more generic term hydrostatic pressure

Bowman's capsule

cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

Bowman's Space

The space surrounding the glomerulus that the filtrate initially passes into.

Boyle's law

Relationship between volume and pressure as described by the formula: P1V1 = P2V2

bradykinin

a pro-inflammatory peptide with many vasoactive and inflammatory effects

bronchial tree

Collective name for the multiple branches of the bronchi and bronchioles of the respiratory system.

bronchiole

branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

Bronchioles

Branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs.

bronchoconstriction

decrease in the size of the bronchiole due to contraction of the muscular wall

bronchodilation

increase in the size of the bronchiole due to contraction of the muscular wall

Brush Border

A feature of the cells of the proximal convoluted tubule that creates increased surface area for absorption.

calyces

cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

capacitance

ability of a vein to distend and store blood

capacitance vessels

veins

capillary

smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

capillary bed

network of 10–100 capillaries connecting arterioles to venules

cardiac notch

depression in the medial surface of the inferior lobe of the left lung where the apex of the heart is located

Cardiac output

measurement of blood flow from the heart through the ventricles, is usually measured in liters per minute

cardiac skeleton

(also, skeleton of the heart) reinforced connective tissue located within the atrioventricular septum; includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta; the point of attachment for the heart valves

cardiomyocyte

muscle cell of the heart

cell cycle

Life cycle of a single cell, from its birth until its division into two new daughter cells.

cell junctions

Point of cell-to-cell contact that connects one cell to another in a tissue.

cell-mediated immune response

adaptive immune response that is carried out by T cells

central chemoreceptor

One of the specialized receptors that are located in the brain that sense changes in hydrogen ion, oxygen, or carbon dioxide concentrations in the brain.

central vein

vein that receives blood from hepatic sinusoids

centromere

Region of attachment for two sister chromatids.

centrosome

Cellular structure that organizes microtubules during cell division.

checkpoint

Progress point in the cell cycle during which certain conditions must be met in order for the cell to proceed to a subsequence phase.

chordae tendineae

string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

chronic inflammation

a slow, long-term inflammation, in response to repeated injury, lasting for weeks, months to years.

circumflex artery

branch of the left coronary artery that follows coronary sulcus

cleavage furrow

Contractile ring that forms around a cell during cytokinesis that pinches the cell into two halves.

Clinical Chemists

Specialty that works with Medical Biochemists and Medical Laboratory Technologists to run laboratory services and equipment for the testing of chemicals in specimens such as blood, and urine.

clinical manifestations

symptoms that a person experiences because they have a disease

clinical reasoning

the process which information (e.g. lab findings, physical exam results, previous clinical experience) AND the patient's context results in an understanding of a patient's
problem or disease; thus aiding with treatment plan and interventions.

clonal selection

activation of B cells corresponding to one specific BCR variant and the dramatic proliferation of that variant

common bile duct

structure formed by the union of the common hepatic duct and the gallbladder's cystic duct

common hepatic duct

duct formed by the merger of the two hepatic ducts

common iliac artery

a large artery that carries oxydenated blood to lower limbs, pelvis, and reproductive organs

complement system

array of approximately 20 soluble proteins of the innate immune system that enhance phagocytosis, bore holes in pathogens, and recruit lymphocytes; enhances the adaptive response when antibodies are produced

compliance

degree to which a blood vessel can stretch as opposed to being rigid

conducting zone

Region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange.

congestive heart failure (CHF)

heart is too weak or damaged to fill and pump efficiently resulting in blood pooling upstream (i.e. into lungs for left-sided and venous system for right-sided)

continuous capillary

most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

COPD

Chronic Obstructive Pulmonary Disease is an umbrella term for chronic pulmonary diseases that progressively narrows & obstructs the airways - especially during exhalation. This makes it progressively harder to breathe. Emphysema and chronic bronchitis are the most common examples of COPD

cor pulmonale

alteration in the structure and function of the right ventricle caused by pulmonary hypertension

coronary

arteries that supply heart muscle

Coronary arteries

branches of the ascending aorta that supply blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

coronary sinus

large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium

coronary sulcus

sulcus that marks the boundary between the atria and ventricles

coronary veins

vessels that drain the heart and generally parallel the large surface arteries

critical thinking

analysis of a problem/situation and the data or evidence related to it

cyanosis

blue/purple colour of the skin or mucous membranes due to the blood & tissues near the skin surface having low oxygen.

cyclin

One of a group of proteins that function in the progression of the cell cycle.

cyclin-dependent kinase

One of a group of enzymes associated with cyclins that help them perform their functions.

cystic duct

duct through which bile drains and enters the gallbladder

cytokine

chemical messenger that regulates cell differentiation, proliferation, gene expression, and cell trafficking to effect immune responses

cytokines

small proteins released by cells; allow for communication between the cells involved in the same type of immune response/reaction

cytokinesis

Final stage in cell division, where the cytoplasm divides to form two separate daughter cells.

cytotoxic T lymphocytes

adaptive immune cell that directly kills infected cells via perforin and granzymes, and releases cytokines to enhance the immune response

delta cell

minor cell type in the pancreas that secretes the hormone somatostatin

Dendritic cells

immune cell that processes antigen material and presents it on the surface of other cells to induce an immune response

dermal papilla

(plural = dermal papillae) extension of the papillary layer of the dermis that increases surface contact between the epidermis and dermis.

dermal papilla (plural = dermal papillae)

Extension of the papillary layer of the dermis that increases surface contact between the epidermis and dermis.

dermis

Layer of skin between the epidermis and hypodermis, composed mainly of connective tissue and containing blood vessels, hair follicles, sweat glands, and other structures.

desmosome

Structure that forms an impermeable junction between cells.

desmosomes

cell structure that anchors the ends of cardiac muscle fibers to allow contraction to occur

detrusor muscle

smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

diabetes mellitus

a condition caused by destruction or dysfunction of the beta cells of the pancreas or cellular resistance to insulin that results in abnormally high blood glucose levels

diapedesis

movement of blood cells through the blood vessel wall

diastole

relaxation of ventricles during the cardiac cycle

diastolic failure

The left ventricle can't fill well during diastole because the ventricular walls can't relax well and/or the ventricular lumen size is reduced

diastolic pressure

lower number recorded when measuring arterial blood pressure; represents the minimal value corresponding to the pressure that remains during ventricular relaxation

dilatation

widening

diploid

condition marked by the Presence of a double complement of genetic material (two sets of chromosomes, one set inherited from each of two parents).

disease

A disorder of structure and function that may produce specific signs and symptoms but is not caused by a direct injury.

diseases

dissection

injury to the inner layer of the vessel, separation (tear) of blood vessel wall that allows for blood to flow between the layers; a medical emergency

distal convoluted tubule

portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

Dorsal respiratory group (DRG)

Region of the medulla oblongata that stimulates the contraction of the diaphragm and intercostal muscles to induce inspiration.

dyspnea

a feeling of not being able to breathe well enough; short of breath

Ecchymoses

bleeds under the skin, greater than 1 cm
Ecchymosis (singular)

edema

'swelling' of tissue, most often due to increased fluid in the interstitial spaces

effector cells

lymphocyte that has differentiated, such as a B cell, plasma cell, or cytotoxic T lymphocyte

efferent arteriole

arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

elastic artery

(also, conducting artery) artery with abundant elastic fibers located closer to the heart, which maintains the pressure gradient and conducts blood to smaller branches

elastin fibers

Fibers made of the protein elastin that increase the elasticity of the dermis.

eleiden

Clear protein-bound lipid found in the stratum lucidum that is derived from keratohyalin and helps to prevent water loss.

embolus

unattached mass that travels through the bloodstream and can create blockages, resulting in acute vascular events

Emphysema

a chronic obstructive pulmonary disease. Continual injury to lung tissue causes chronic inflammation and remodeling resulting in a loss of lung elasticity that is key to passive exhalation. This causes an 'obstruction' during exhalation.

emulsifier

a substtance that helps mix two liquids

endocardium

innermost layer of the heart lining the heart chambers and heart valves; composed of endothelium reinforced with a thin layer of connective tissue that binds to the myocardium

endocrine gland

Groups of cells that release chemical signals into the intercellular fluid to be picked up and transported to their target organs by blood.

endothelium

Tissue that lines vessels of the lymphatic and cardiovascular system, made up of a simple squamous epithelium.

enterohepatic circulation

recycling mechanism that conserves bile salts

enzyme

protein(s) that accelerate chemical reactions and transform substrate(s) into product(s)

Eosin

Eosin is a pink acidic dye that stains basic elements such as most proteins in the tissue pink or red

eosinophil

leukocyte that responds to parasites and is involved in the allergic response

epicardial coronary arteries

surface arteries of the heart that generally follow the sulci

epicardium

innermost layer of the serous pericardium and the outermost layer of the heart wall

epidermis

Outermost tissue layer of the skin.

epigastric

upper abdomen, below the ribs

Epithelium

The layer of cells that covers all internal and external surfaces of the body

epitope

small component of an antigen that is specifically recognized by antibodies, B cells, and T cells; the antigenic determinant

erythema

increased blood in tissue, resulting in visible redness and increased heat

exacerbation

a sudden worsening of a disease or an increase in its symptoms

exocrine gland

Group of epithelial cells that secrete substances through ducts that open to the skin or to internal body surfaces that lead to the exterior of the body.

expiration

Also, exhalation, process that causes the air to leave the lungs.

Expiratory reserve volume

Amount of air that can be forcefully exhaled after a normal tidal exhalation.

external elastic membrane

membrane composed of elastic fibers that separates the tunica media from the tunica externa; seen in larger arteries

fenestrated capillary

type of capillary with pores or fenestrations in the endothelium that allow for rapid passage of certain small materials

FEV1

The percentage of the total volume of air that can forcibly be blown out in first second, after full inhalation. FEV1 in healthy people is >80%, depending on age, sex, height, mass and ethnicity

fever

a systemic inflammatory response that extends beyond the site of infection and affects the entire body, resulting in an overall increase in body temperature

Fibroblasts

Cell type found in connective tissue, responsible for producing and maintaining the extracellular matrix

fibroelastic membrane

Specialized membrane that connects the ends of the C-shape cartilage in the trachea; contains smooth muscle fibers.

foramen ovale

opening in the fetal heart that allows blood to flow directly from the right atrium to the left atrium, bypassing the fetal pulmonary circuit

forced breathing

Also, hyperpnea, mode of breathing that occurs during exercise or by active thought that requires muscle contraction for both inspiration and expiration.

Forensic Pathologists

Definition

fossa ovalis

oval-shaped depression in the interatrial septum that marks the former location of the foramen ovale

functional residual capacity (FRC)

Sum of ERV and RV, which is the amount of air that remains in the lungs after a tidal expiration.

G0 phase

Phase of the cell cycle, usually entered from the G1 phase; characterized by long or permanent periods where the cell does not move forward into the DNA synthesis phase.

G1 phase

First phase of the cell cycle, after a new cell is born.

G2 phase

Third phase of the cell cycle, after the DNA synthesis phase.

gallbladder

accessory digestive organ that stores and concentrates bile

gap junctions

Allows cytoplasmic communications to occur between cells.

glomerular filtration rate

rate of renal filtration

glomerulus

tuft or cluster of capillaries surrounded by Bowman's capsule; filters the blood based on molecular size

glucagon

pancreatic hormone that stimulates the catabolism of glycogen to glucose, thereby increasing blood glucose levels

goblet cell

Unicellular gland found in columnar epithelium that secretes mucous.

granulomas

pockets of infected tissue walled off and surrounded by white blood cells

granzyme

protease that enters target cells through perforin and induces apoptosis in the target cells; used by NK cells and killer T cells

great cardiac vein

vessel that follows the interventricular sulcus on the anterior surface of the heart and flows along the coronary sulcus into the coronary sinus on the posterior surface; parallels the anterior interventricular artery and drains the areas supplied by this vessel

gut microbiota

collection of microorganisms (bacteria, fungi, viruses, and other) in person's gastrointestinal system

H. pylori

Gram-negative, flagellated, helical bacterium that may cause stomach infection

HDL

high-density lipoproteins, responsible for carrying cholesterol out of the bloodstream and into the liver; commonly referred to as "good cholesterol"

helper T lymphocytes

cell of the adaptive immune system that binds APCs via MHC II molecules and stimulates B cells or secretes cytokines to initiate the immune response

Hematopathologists

Definition

Hematoxylin

A blue basic dye that is used to stain tissues. It turns acidic elements such as RNA and DNA in the tissue blue.

hemorrhage

bleeding

hepatic artery

artery that supplies oxygenated blood to the liver

hepatic lobule

hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein

hepatic portal vein

vein that supplies deoxygenated nutrient-rich blood to the liver

hepatic sinusoids

blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery

hepatic vein

vein that drains into the inferior vena cava

hepatocytes

major functional cells of the liver

hilum

concave structure on the mediastinal surface of the lungs where blood vessels, lymphatic vessels, nerves, and a bronchus enter the lung

Histopathology

Histopathology is the study of the tissues to identify changes at the cellular or microscopic level.

holocrine secretion

Release of a substance caused by the rupture of a gland cell, which becomes part of the secretion.

homogenous

uniform in composition or character (i.e. color, shape, size, texture, etc.)

homologous

Describes two copies of the same chromosome (not identical), one inherited from each parent.

host

an organism that is invaded by a pathogen or parasite

human leukocyte antigen

genes part of the major histocompatibility complex

humoral immune response

adaptive immune response that is controlled by activated B cells and antibodies

hyperplasia

An enlargement of a tissue or organ caused by an abnormal increase in the number of cells in a tissue or organ

hypertension

elevated blood pressure

hypertrophic cardiomyopathy

pathological enlargement of the heart, generally for no known reason

hypertrophy

tissue is enlarged due to each individual cell becoming larger, often with an increase of cytoplasmic contents such as contractile proteins as in the case with muscle tissue

hypervolemia

abnormally high levels of fluid and blood within the body

hypodermis

Connective tissue connecting the integument to the underlying bone and muscle.

hypothalamus

part of the brain below the thalamus that is an important interface between the central nervous system and vasculature. Amongst its many functions, it plays a major role in hormonal secretion, temperature and fluid homeostasis, and emotional regulation.

hypovolemia

decrease in blood volume

hypoxia

lack of oxygen supply to the tissues

IgA

antibody crucial for mucosal immunity

immune tolerance

acquired ability to prevent an unnecessary or harmful immune response to a detected foreign body known not to cause disease or to self-antigens

Immunodeficiency

failure, insufficiency, or delay at any level of the immune system, which may be acquired or inherited

immunoglobulin

Proteins produced by the immune system which recognize and neutralize antigens. Also known as antibodies

Infectious Disease

Definition

inferior vena cava

large systemic vein that returns blood to the heart from the inferior portion of the body

inflammasomes

multiprotein complexes that activate inflammatory responses

inflammation

a necessary process that recruits the cellular defenses needed to eliminate pathogens, remove damaged and dead cells, and initiate repair mechanisms

Innate immunity

immunity that occurs naturally because of genetic factors or physiology, and is not induced by infection or vaccination

inspiration

Also, inhalation, process that causes air to enter the lungs.

Inspiratory capacity (IC)

Sum of the TV and IRV, which is the amount of air that can maximally be inhaled past a tidal expiration.

Inspiratory reserve volume (IRV)

Amount of air that enters the lungs due to deep inhalation past the tidal volume.

insulin

pancreatic hormone that enhances the cellular uptake and utilization of glucose, thereby decreasing blood glucose levels

integumentary system

Skin and its accessory structures.

interatrial septum

cardiac septum located between the two atria; contains the fossa ovalis after birth

intercalated discs

part of the sarcolemma that connects cardiac tissue, and contains gap junctions and desmosomes

interferon

cytokine that inhibits viral replication and modulates the immune response

internal elastic membrane

membrane composed of elastic fibers that separates the tunica intima from the tunica media; seen in larger arteries

interphase

Entire life cycle of a cell, excluding mitosis.

interventricular septum

cardiac septum located between the two ventricles

intestinal microvillus

finger-like projection of the lining of the small intestine; a primary surface of nutrient absorption in the digestive system

intra-alveolar pressure

Intrapulmonary pressure, pressure of the air within the alveoli.

intrapleural pressure

Pressure of the air within the pleural cavity.

ischemia

insufficient blood flow to the tissues

keratin

Type of structural protein that gives skin, hair, and nails its hard, water-resistant properties.

keratinocytes

Cell that produces keratin and is the most predominant type of cell found in the epidermis.

keratohyalin

Granulated protein found in the stratum granulosum.

kinetochore

Region of a centromere where microtubules attach to a pair of sister chromatids.

Korotkoff sounds

noises created by turbulent blood flow through the vessels

lamina propria

Connective tissue found under the thin layer of surface epithelium covering a mucous membrane

laminar

type of fluid flow in which fluid travels smoothly

Langerhans cell

Specialized dendritic cell found in the stratum spinosum that functions as a macrophage.

laryngopharynx

Portion of the pharynx bordered by the oropharynx superiorly and esophagus and trachea inferiorly; serves as a route for both air and food.

larynx

Cartilaginous structure that produces the voice, prevents food and beverages from entering the trachea, and regulates the volume of air that enters and leaves the lungs.

LDL

low-density lipoprotein, "bad cholesterol" , the form that carries lipids from the liver to various body tissue; increased levels of LDL can accumulate within the blood vessel wall and cause atherosclerosis

left atrioventricular valve

(also, mitral valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

leukocyte

cellular component of blood, also known as white blood cells; part of the immune system

lipase

an enzyme that breaks down fat

Lipids

A family of organic compounds composed of carbon, hydrogen, and oxygen. They are insoluble in water. The three main types of lipids are triglycerides, phospholipids, and sterols.

Lipoprotein

a particle that consists a protein and a lipid (triglyceride or cholesterol). The main function of lipoproteins is to transport lipids through the bloodstream to various body tissues/organs

liver

largest gland in the body whose main digestive function is the production of bile

loop of Henle

descending and ascending portions between the proximal and distal convoluted tubules

loose connective tissue

a type of connective tissue that consists of fibroblasts, a large amount of extracellular matrix (also called ground substance), and space connective tissue fibers (collagen, elastin). Loose connective tissue often contains cappillaries, arterioles, and venules that supply epithelium on top of it

lumen

interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

lung

organ of the respiratory system that performs gas exchange

Lymph

watery fluid that bathes tissues and organs with protective white blood cells and does not contain erythrocytes

lymphatic filariasis

parasitic worms that live in the lymphatic vessels causing a chronic inflammatory response. This results in blockage of lymph flow causing edema, repeated infections, skin thickening and fibrosis.

Lymphocytes

leukocyte that is histologically identifiable by its large nuclei; it is a small cell with very little cytoplasm

macrophage

large phagocytic cell that engulfs foreign particles and pathogens

marginal arteries

branches of the right coronary artery that supply blood to the superficial portions of the right ventricle

mast cell

leukocyte that produces inflammatory molecules, such as histamine, in response to large pathogens and allergens

mean arterial pressure (MAP)

average driving force of blood to the tissues; approximated by taking diastolic pressure and adding 1/3 of pulse pressure

meatuses

One of three recesses (superior, middle, and inferior) in the nasal cavity attached to the conchae that increase the surface area of the nasal cavity.

Medical Biochemists

Definition

Medical Microbiologists

Definition

medulla

inner region of kidney containing the renal pyramids

melanin

Pigment that determines the color of hair and skin.

melanocyte

Cell found in the stratum basale of the epidermis that produces the pigment melanin.

melanocytes

Cells that produce the brown/black pigment melanin. They are located in select parts of the body, but most visible at the bottom layer (the stratum basale) of the skin's epidermis and the middle layer of the eye (the uvea)

melanosome

Intercellular vesicle that transfers melanin from melanocytes into keratinocytes of the epidermis.

memory cell

antigen-specific B or T lymphocyte that does not differentiate into effector cells during the primary immune response but that can immediately become an effector cell upon re-exposure to the same pathogen

Merkel cell

Receptor cell in the stratum basale of the epidermis that responds to the sense of touch.

Merocrine secretion

Release of a substance from a gland via exocytosis.

mesothelium

Simple squamous epithelial tissue which covers the major body cavities and is the epithelial portion of serous membranes.

metaphase

Second stage of mitosis (and meiosis), characterized by the linear alignment of sister chromatids in the center of the cell.

metaphase plate

Linear alignment of sister chromatids in the center of the cell, which takes place during metaphase.

metarteriole

short vessel arising from a terminal arteriole that branches to supply a capillary bed

Metastasis

cancerous growth spreads beyond its original site - often breaching the basement membrane and invading nearby tissues or entering lymphatic/blood circulation

MHC I

protein found on the surface of all nucleated cells that signals to immune cells whether the cell is healthy/normal or is infected/cancerous; it provides the appropriate template into which antigens can be loaded for recognition by lymphocytes

MHC II

protein found on the surface of antigen-presenting cells that signals to immune cells whether the cell is healthy/

normal or is infected/cancerous; it provides the appropriate template into which antigens can be loaded for recognition by lymphocytes

microbiome

a term that encompasses not only microorganisms that inhabit certain environments, but also their genomes and surronding environmental conditions

microbiota

microorganisms (bacteria, fungi, viruses) that inhabit multicellular organisms (including humans) and affect immunological, hormonal, and metabolic health of the host

microcirculation

blood flow through the capillaries

middle cardiac vein

vessel that parallels and drains the areas supplied by the posterior interventricular artery; drains into the great cardiac vein

mitosis

Division of genetic material, during which the cell nucleus breaks down and two new, fully functional, nuclei are formed.

mitotic phase

Network of microtubules, originating from centrioles, that arranges and pulls apart chromosomes during mitosis.

mitral valve

(also, left atrioventricular valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

moderator band

band of myocardium covered by endocardium that arises from the inferior portion of the interventricular septum in the right ventricle and crosses to the anterior papillary muscle; contains conductile fibers that carry electrical signals followed by contraction of the heart

monocyte

a type of white blood cell that can further differentiate in macrophages and is involved in adaptive immunity and inflammation

Mucosa-associated lymphoid tissue

collection of lymphatic tissue that combines with epithelial tissue lining the mucosa throughout the body

mucous gland

A group of cells that secrete mucous, a thick, slippery substance that keeps tissues moist and acts as a lubricant.

multipotent

Describes the condition of being able to differentiate into different types of cells within a given cell lineage or small number of lineages, such as a red blood cell or white blood cell.

muscular artery

(also, distributing artery) artery with abundant smooth muscle in the tunica media that branches to distribute blood to the arteriole network

Mutualistic

a type of relationship between two organisms, species, where both parties benefit from the relationship

myocardium

thickest layer of the heart composed of cardiac muscle cells built upon a framework of primarily collagenous fibers and blood vessels that supply it and the nervous fibers that help to regulate it

nasal cells

Type of stem cell found in the stratum basale and in the hair matrix that continually undergoes cell division, producing the keratinocytes of the epidermis.

nasopharynx

Portion of the pharynx flanked by the conchae and oropharynx that serves as an airway.

natural killer cells

lymphocyte that can kill cells infected with viruses or tumor cells

Nephrons

functional units of the kidney that carry out filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

nervi vasorum

small nerve fibers found in arteries and veins that trigger contraction of the smooth muscle in their walls

net filtration pressure

pressure of fluid across the glomerulus; calculated by taking the hydrostatic pressure of the capillary and subtracting the colloid osmotic pressure of the blood and the hydrostatic pressure of Bowman's capsule

Neuropathologists

Definition

neutrophil

phagocytic leukocyte that engulfs and digests pathogens

oligopotent

Describes the condition of being more specialized than multipotency; the condition of being able to differentiate into one of a few possible cell types.

oncogenes

Mutated version of a normal gene involved in the positive regulation of the cell cycle.

opsonins

extracellular proteins that mark it to be be phagocytosed

opsonization

process that enhances phagocytosis using proteins to indicate the presence of a pathogen to phagocytic cells

oropharynx

Portion of the pharynx flanked by the nasopharynx, oral cavity, and laryngopharynx that is a passageway for both air and food.

pagetoid

"upward" direction. Growth towards the outer, epidermal surface

palpation

care provider feels (tactile sensation) a part of the body for changes in firmness, size, location, etc

PAMPs

Pathogen-associated molecular patterns are small molecular motifs conserved within a class of microbes.

pancreas

organ with both exocrine and endocrine functions located posterior to the stomach that is important for digestion and the regulation of blood glucose

pancreatic islets

specialized clusters of pancreatic cells that have endocrine functions; also called islets of Langerhans

pancreatic juice

secretion of the pancreas containing digestive enzymes and bicarbonate

pannus

abnormal layer of fibrous and granular tissue, often formed in the joints, cornea, or heart valves

papillary layer

Superficial layer of the dermis, made of loose, areolar connective tissue.

papillary muscle

extension of the myocardium in the ventricles to which the chordae tendineae attach

parietal pleura

outermost layer of the pleura that connects to the thoracic wall, mediastinum, and diaphragm

pathogen-associated molecular patterns

carbohydrate, polypeptide, and nucleic acid "signature" that is expressed by viruses, bacteria, and parasites but differs from molecules on host cells

pathogens

an agent, usually a microbe, that causes disease in the organisms they invade

Pathologists

Specialized doctors who are able to identify abnormal changes in tissues and organs.

Pathology

Pathology is the study of abnormal changes to cells, tissues and organs that negatively impacts their structure or function

Pathophysiology

Pathophysiology is the study of the changes in function that are detrimental.

pattern recognition receptors

molecules on macrophages and dendritic cells that bind molecular signatures of pathogens and promotes pathogen engulfment and destruction

pectinate muscles

muscular ridges seen on the anterior surface of the right atrium

perforin

destructive protein that creates a pore in the target cell; used by NK cells and killer T cells

perfusion

distribution of blood into the capillaries so the tissues can be supplied

pericardial cavity

cavity surrounding the heart filled with a lubricating serous fluid that reduces friction as the heart contracts

pericardial sac

(also, pericardium) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

pericardium

(also, pericardial sac) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

periosteum

Dense layer of connective tissue enclosing the bones except at the surface of joints

peripheral artery disease

the narrowing or blockage of arteries that supply upper/lower limbs

peripheral chemoreceptor

One of the specialized receptors located in the aortic arch and carotid arteries that sense changes in pH, carbon dioxide, or oxygen blood levels.

peritubular capillary

second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

petechiae

tiny pinpoint bleeds

pharynx

Region of the conducting zone that forms a tube of skeletal muscle lined with respiratory epithelium; located between the nasal conchae and the esophagus and trachea.

plasma cell

an immune cell that secrets antibodies; these cells arise from B cells that were stimulated by antigens

pleural cavity

space between the visceral and parietal pleurae

pleural fluid

substance that acts as a lubricant for the visceral and parietal layers of the pleura during the movement of breathing

pluripotent

Describes the condition of being able to differentiate into a large variety of cell types.

pneumotaxic centers

Network of neurons within the pons that inhibit the activity of the neurons in the dorsal respiratory group; controls rate of breathing.

Podocytes

Specialized cells present in the glomeruli of the kidneys that create the filtration barrier, allowing fluid and small molecules to pass through while keeping larger proteins and cells in the blood.

porta hepatis

"gateway to the liver" where the hepatic artery and hepatic portal vein enter the liver

portal triad

bile duct, hepatic artery branch, and hepatic portal vein branch

posterior cardiac vein

vessel that parallels and drains the areas supplied by the marginal artery branch of the circumflex artery; drains into the great cardiac vein

posterior interventricular artery

(also, posterior descending artery) branch of the right coronary artery that runs along the posterior portion of the interventricular sulcus toward the apex of the heart and gives rise to branches that supply the interventricular septum and portions of both ventricles

posterior interventricular sulcus

sulcus located between the left and right ventricles on the anterior surface of the heart

PP cell

minor cell type in the pancreas that secretes the hormone pancreatic polypeptide

precapillary sphincters

circular rings of smooth muscle that surround the entrance to a capillary and regulate blood flow into that capillary

prognosis

long term health outcome

prophase

First stage of mitosis (and meiosis), characterized by breakdown of the nuclear envelope and condensing of the chromatin to form chromosomes.

proteases

A general term for an enzyme that the breaks down proteins into smaller polypeptides or amino acids.

proto-oncogenes

Normal gene that when mutated becomes an oncogene.

proximal convoluted tubule

twisted tubules receiving filtrate from Bowman's capsule; most active part of the nephron in reabsorption and secretion

Pseudostratified columnar epithelium

Tissue that consists of a single layer of irregularly shaped and sized cells that give the appearance of multiple layers; found in ducts of certain glands and the upper respiratory tract.

pulmonary arteries

left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs

pulmonary artery

artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli

pulmonary capillaries

capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters

pulmonary circuit

blood flow to and from the lungs

pulmonary plexus

network of autonomic nervous system fibers found near the hilum of the lung

pulmonary surfactant

Substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells.

pulmonary trunk

large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

pulmonary valve

(also, pulmonary semilunar valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps

pulmonary veins

veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

Pulmonary ventilation

Exchange of gases between the lungs and the atmosphere; breathing.

pulse

alternating expansion and recoil of an artery as blood moves through the vessel; an indicator of heart rate

pulse pressure

difference between the systolic and diastolic pressures

purpura

sign of bleeding under the skin, up to 1cm

pus

a protein-rich fluid formed at the site of inflammation during bacterial or fungal infection. Filled with dead cells and leukocytes, pus is typically white-yellow, yellow, or yellow-brown.

pyrogens

chemicals that effect the temperature set point in the hypothalamus, thus elevating body temperature and causing fever.

Quiet breathing

Also, eupnea, mode of breathing that occurs at rest and does not require the cognitive thought of the individual.

Rank-Ligand

Protein involved in bone metabolism, and key regulator of osteoclast formation, activation, and survival

regulatory T (Treg) cells

specialized lymphocyte that suppresses local inflammation and inhibits the secretion of cytokines, antibodies, and other stimulatory immune factors; involved in immune tolerance

renal columns

extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

renal corpuscle

consists of the glomerulus and Bowman's capsule

renal cortex

outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

renal hilum

medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

renal papillae

medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

renal pyramids

six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of some nephrons

Residual volume (RV)

Amount of air that remains in the lungs after maximum exhalation.

resistance

any condition or parameter that slows or counteracts the flow of blood

respiratory bronchiole

Specific type of bronchiole that leads to alveolar sacs.

respiratory cycle

One sequence of inspiration and expiration.

respiratory epithelium

Ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus.

respiratory membrane

Alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases.

respiratory pump

increase in the volume of the thorax during inhalation that decreases air pressure, enabling venous blood to flow into the thoracic region, then exhalation increases pressure, moving blood into the atria

respiratory rate

Total number of breaths taken each minute.

Respiratory volume

Varying amounts of air within the lung at a given time.

respiratory zone

Includes structures of the respiratory system that are directly involved in gas exchange.

reticular lamina

A matrix containing collagen and elastin secreted by connective tissue; a component of the basement membrane.

reticular layer

Deeper layer of the dermis; it has a reticulated appearance due to the presence of abundant collagen and elastin fibers/

reticuloendothelial cells

(also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

right atrioventricular valve

(also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of tissue

S phase

Stage of the cell cycle during which DNA replication occurs.

semilunar valves

valves located at the base of the pulmonary trunk and at the base of the aorta

septum

(plural = septa) walls or partitions that divide the heart into chambers

septum primum

flap of tissue in the fetus that covers the foramen ovale within a few seconds after birth

serology

Scientific examination or study of blood serum

serous glands

A group of cells within the serous membrane that secrete a lubricating substance onto the surface.

short-chain fatty acids

a metabolite that's produced by gut microbiota as a result of dietary fiber fermentation

signs

changes in one's health that can be observed or measured objectively (eg. change in body temperature)

simple columnar epithelium

Tissue that consists of a single layer of column-like cells; promotes secretion and absorption in tissues and organs.

simple cuboidal epithelium

Tissue that consists of a single layer of cube-shaped cells; promotes secretion and absorption in ducts and tubules.

simple squamous epithelium

Tissue that consists of a single layer of flat scale-like cells; promotes diffusion and filtration across surface.

sinusoid capillary

rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

sister chromatid

One of a pair of identical chromosomes, formed during DNA replication.

skeletal muscle pump

effect on increasing blood pressure within veins by compression of the vessel caused by the contraction of nearby skeletal muscle

small cardiac vein

parallels the right coronary artery and drains blood from the posterior surfaces of the right atrium and ventricle; drains into the great cardiac vein

somatic cells

All cells of the body excluding gamete cells.

sphygmomanometer

blood pressure cuff attached to a device that measures blood pressure

stained

chemicals with dyes are added to tissues and attach to cellular components based on their chemical characteristic (e.g. acidic, basic, hydrophobic)

stem cell

Cell that is oligo-, multi-, or pleuripotent that has the ability to produce additional stem cells rather than becoming further specialized.

stratified columnar epithelium

Tissue that consists of two or more layers of column-like cells, contains glands and is found in some ducts.

Stratified cuboidal epithelium

Tissue that consists of two or more layers of cube-shaped cells, found in some ducts.

stratified squamous epithelium

Tissue that consists of multiple layers of cells with the most apical being flat scale-like cells; protects surfaces from abrasion.

stratum basale

Deepest layer of the epidermis, made of epidermal stem cells.

stratum corneum

Most superficial layer of the epidermis.

stratum granulosum

Most superficial layer of the epidermis.

stratum lucidum

Layer of the epidermis between the stratum granulosum and stratum corneum, found only in thick skin covering the palms, soles of the feet, and digits.

stratum spinosum

Layer of the epidermis superficial to the stratum basale, characterized by the presence of desmosomes.

stroke volume

amount of blood ejected from the ventricle with each cardiac cycle

sulcus

(plural = sulci) fat-filled groove visible on the surface of the heart; coronary vessels are also located in these areas

superantigens

bacterial or viral proteins that can cause an excessive inflammatory response

superior vena cava

large systemic vein that returns blood to the heart from the superior portion of the body

symptoms

changes in health which are subjectively felt and can not be objectively measured (eg. feeling nauseous)

systemic circuits

blood flow to and from virtually all of the tissues of the body

systemic edema

increased fluid retention in the interstitial spaces and cells of the body; can be seen as swelling over large areas of the body, particularly the lower extremities

Systemic lupus erythematosus

Autoimmune disease in which the immune system mistakenly attacks a wide variety of organs and tissues.

systole

a part of the heart cycle; contraction of the heart ventricles that ejects blood out of the heart

systolic failure

The left ventricle is unable to contract strongly enough during systole. As a result, not enough blood leaves the heart to nourish the rest of the body

systolic pressure

larger number recorded when measuring arterial blood pressure; represents the maximum value following ventricular contraction

T cells

lymphocytes that mature in the thymus gland; one of the main cells involved in the adaptive immune system

tachycardia

abnormally high heart rate. In a resting adult, it is >100 beats per minute

tachypnea

rapid and shallow breathing; respiratory rate is >21 breaths per minute in adults

telophase

Final stage of mitosis (and meiosis), preceding cytokinesis, characterized by the formation of two new daughter nuclei.

Thoracic wall compliance

Ability of the thoracic wall to stretch while under pressure.

thoroughfare channel

continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

thyroid stimulating hormone

hormone produced by the anterior pituitary gland that stimulates the thyroid gland to produce thyroid hormones

thyroid storm

occurs when the thyroid gland releases excessive amounts of thyroid hormones into the bloodstream. Can lead to dramatic increase in hyperthyroidism and its symptoms.

thyrotropin releasing hormone

hormone produced in the hypothalamus that stimulates the release of thyroid-stimulating hormone in the anterior pituitary gland

thyroxine

primary hormone produced by the thyroid gland. Is the pro hormone form of the more active form thyroid hormone triiodothyronine.

Tidal volume (TV)

Amount of air that normally enters the lungs during quiet breathing.

tight junctions

Forms an impermeable barrier between cells.

Total dead space

Sum of the anatomical dead space and alveolar dead space.

total lung capacity (TLC)

Total amount of air that can be held in the lungs; sum of TV, ERV, IRV, and RV.

totipotent

Embryonic cells that have the ability to differentiate into any type of cell and organ in the body.

trabeculae carneae

ridges of muscle covered by endocardium located in the ventricles

trachea

Tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung.

trachealis muscle

Smooth muscle located in the fibroelastic membrane of the trachea.

transcription factors

One of the proteins that regulate the transcription of genes.

Transfusion medicine

Definition

transitional epithelium

Form of stratified epithelium found in the urinary tract, characterized by an apical layer of cells that change shape in response to the presence of urine.

Transpulmonary pressure

Pressure difference between the intrapleural and intra-alveolar pressures.

tricuspid valves

term used most often in clinical settings for the right atrioventricular valve

triglycerides

The most common of the three basic classes of lipids and the main form fat takes in both diet and the human body. A triacylglycerol is made up of three molecules of fatty acids and one molecule of glycerol.

triiodothyronine

thyroid hormone that has many regulating effects in the body such as metabolism, growth, body temperature, and heart rate.

tuberculosis

an infectious bacterial disease (usually caused by Mycobacterium tuberculosis bacteria) that generally affects the lungs, but can also affect other parts of the body

Tumor suppressor

Segment of DNA that codes for regulator proteins that prevent the cell from undergoing uncontrolled division.

tumour

abnormal and excessive growth of cells, creating a mass of tissue

tunica externa

(also, tunica adventitia) outermost layer or tunic of a vessel (except capillaries)

tunica intima

(also, tunica interna) innermost lining or tunic of a vessel

tunica media

middle layer or tunic of a vessel (except capillaries)

turbulent

type of fluid flow in which fluid undergoes irregular fluctuations and mixing

tympanic

sounds like a ringing akin to striking a typmani drum. indicative of a lot of air trapped in a hollow vessel

type I alveolar cells

Squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases.

type II alveolar cells

Cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant.

type II hypersensitivity reaction

type of hypersensitivity reaction in which antibodies bind to antigens on the surface of cells or extracellular materials, triggering an immune response that damages or destroys those cells or tissues

type III hypersensitivity reaction

Immune reaction where circulating antigen-antibody complexes deposit in tissues, leading to inflammation and tissue damage

unipotent

Describes the condition of being committed to a single specialized cell type.

urethra

transports urine from the bladder to the outside environment

valves

in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

vasa vasorum

small blood vessels located within the walls or tunics of larger vessels that supply nourishment to and remove wastes from the cells of the vessels

vascular shunt

continuation of the metarteriole and thoroughfare channel that allows blood to bypass the capillary beds to flow directly from the arterial to the venous circulation

vascular tone

contractile state of smooth muscle in a blood vessel

vasoconstriction

constriction of the smooth muscle of a blood vessel, resulting in a decreased vascular diameter

vasodilation

relaxation of the smooth muscle in the wall of a blood vessel, resulting in an increased vascular diameter

vasomotion

irregular, pulsating flow of blood through capillaries and related structures

vein

blood vessel that conducts blood toward the heart

Vena cava

large vein that brings deoxygenated blood from the organs in the body back to the heart

venous reserve

volume of blood contained within systemic veins in the integument, bone marrow, and liver that can be returned to the heart for circulation, if needed

ventral respiratory group (VRG)

Region of the medulla oblongata that stimulates the contraction of the accessory muscles involved in respiration to induce forced inspiration and expiration.

ventricle

one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side

of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium

venules

small vessel leading from the capillaries to veins

visceral pleura

innermost layer of the pleura that is superficial to the lungs and extends into the lung fissures

Viscosity

thickness of fluids that affects their ability to flow

Vital capacity (VC)

Sum of TV, ERV, and IRV, which is all the volumes that participate in gas exchange.

vitiligo

skin condition in which Melanocytes in certain areas lose the ability to produce melanin, possibly due an autoimmune reaction that leads to loss of color in patches.

VSMC

vascular smooth muscle cells

wheezes

continuous, coarse, whistling sound produced in a narrowed or obstructed airway causing an increase airflow velocity

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UBC-V Students

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Annabelle Liao – Annabelle is a fourth year student majoring in English with a Language and Literature emphasis with two main passions: writing and sustainability. Her passion for sustainability stems from leading marine conservation youth camps at the Vancouver Aquarium in high school, and her diversified experience has led her to develop and manage various projects relating to capacity-building, waste reduction, and greenhouse gas management on campus at UBC. As for writing, Annabelle believes that effective communication is one of the greatest assets in catalyzing high quality education, and continues to seek out various avenues of collaboration in creating digestible educational content for a diversity of audiences.

Tetiana Povshedna – Tetiana is a PhD student in Pathology and Laboratory Medicine at UBC who contributed to the content of the "Atherosclerosis and Angina" chapter. She believes that integrated educational resources that highlight all the aspects of a certain condition at once (including a very important patient lens!) are the key to a genuine holistic understanding of health by everyone working in healthcare. A chance to work on such a resource has been an amazing opportunity to contribute to this idea.

Noah Stewart – Noah is a graduate from the Bachelor of Medical Laboratory Science program at UBC. He is interested in the pathophysiology of different diseases and how they relate to what can be seen under the microscope. He has contributed to the writing of the chapters on pneumonia, the filming of the normal histology/histopathology videos of the lung, and has created practice exercises for the pneumonia and emphysema chapters. For Noah, playing a part in the Pressbook has been a great opportunity to learn, and he hopes it will be equally as valuable as a resource for other learners!

Meihua E. Su (Eva) – Eva is a graduate from the Bachelor of Medical Laboratory Science program at UBC. The topics in this textbook that she has helped out with are the topics of metastatic melanoma, acute kidney injury, and diabetes. Eva loves to explore and learn about the different diseases and how it affects different organs. She believes that by promoting a better understanding of the different diseases and making this knowledge more accessible, we are one step closer to finding new treatments to help patients. Perhaps the next person to find a treatment for one of these diseases is you, a reader of our textbook. Eva is extremely grateful to have had the opportunity to be part of a supportive team that encourages lifelong learning and curiosity.

Yimei Qin – Yimei is a graduate from the Bachelor of Medical Laboratory Science program at UBC. She has contributed to adding closed captions and practice questions to the instructional videos throughout the textbook, as well as the writing and filming of the normal liver and cirrhosis histology videos. Helping to create a resource that will make learning about various diseases more accessible and interactive has been a rewarding and fulfilling task!

Ghazal Sokhanran – Ghazal is an undergraduate student in the Bachelor of Medical Laboratory Science program at UBC. She is interested in understanding and learning more about the pathophysiology of many different diseases and how they affect the body as a whole each and every day. She has contributed to writing the chapter on "Blood, Anemia, Leukemia, and Blood Tests" and appendix section on "Additional exercises for critical thinking and clinical reasoning". Furthermore, she was also involved in creating critical thinking questions for the "Acute Kidney Injury" and "Heart Failure" chapters. She is extremely grateful to have been part of a great team of individuals with different backgrounds, coming together to create an amazing resource for other learners.

Samuel Lam – Sam is an undergraduate student in the Bachelor of Medical Laboratory Science Program in UBC. He has profound interest in studying the mechanism of which diseases affect individuals, especially cancer. He has contributed

to writing the chapters on Metastatic Melanoma, Diabetes, Leukemia as a well as creating critical thinking questions and related guides. Sam is extremely grateful to have the opportunity to be part of this amazing team with talented individuals, he has learnt a lot throughout the process and glad that his effort will benefit many learners in the future.

Kristen Danielle Go – Dana is an undergraduate student in the Bachelor of Medical Laboratory Science Program at UBC. Her experience as a Medical Office Assistant during the COVID-19 pandemic led her to pursue further studies in healthcare and human pathology. In September, she will be starting a position as a Directed Studies student to research neurological blood biomarkers with the Wellington Laboratory at Djavad Mowafaghian Centre for Brain Health. Dana contributed to writing chapters on Leukemia, as well as creating critical thinking exercises and related guides. She is truly grateful for the opportunity to work alongside the wonderful team behind this Pressbook resource, and to be able to share her passion for learning about the pathophysiology of human disease.

Lucy Ogoke – Lucy is a Nigerian Canadian Undergraduate student studying Medical Laboratory Science at the University of British Columbia Vancouver campus coming from Calgary, Alberta. Lucy enjoys singing and various athletics including rugby and powerbuilding. Lucy and her family immigrated to Canada when she was 5 years old. As a result of growing up in a first generation immigrant, Nigerian household and attending predominantly white, Canadian institutions her whole life, Lucy was able to find herself immersed in both cultures and grew to love both. However in attending these institutions Lucy had experienced and witnessed first hand the inequalities that are still ingrained in many aspects of our society and their affects on BIPOC individuals in her community: some systematically perpetuated while others stemming from people projecting biases onto others. Once she had discovered her passion for healthcare, Lucy saw how these same biases are built into our healthcare systems. Through volunteering and personal experience, she saw evidence of these biases significantly affecting the quality of care these individuals receive.

Mena Burr – Mena is a Doctor of Medicine student at UBC with a undergraduate background in neuroscience from the University of Alberta. She created the multiple sclerosis subchapter and contributed to the clinical reasoning exercises for the diabetes chapter. She has a strong interest in neurological diseases. In particular, she is fascinated by how clearly the underlying neuropathology translates into the clinical picture of many neurological conditions. She is also passionate about medical education, and hopes to continue to find ways to communicate medical concepts in clear and accessible ways.

Athena Li – Athena is an undergraduate student in the Bachelor of Medical Laboratory Science program at UBC. She has an interest in immunology and is currently doing an undergraduate thesis in tumour cell sociology and its implication for patient prognosis. She contributed to the Accessible Histology chapter in the appendices and is grateful for this opportunity to help visually decode the various tissues in histology for new learners. In her spare time she likes to draw, write and play her accordion.

Carter Allen – Carter is a Bachelor of Nursing student UBC. He has had a life long interest in pathology, and the clinical manifestations of disease processes. He has an undergraduate background in microbiology. Carter has volunteered extensively on the DTES doing outreach and overdose prevention and hopes to serve marginalized populations in canada once he finishes his schooling. He was incredibly grateful for the opportunity to contribute to this book, and hopes to continue learning about pathology throughout his career.

Dylan Mann – Dylan is an undergraduate student in the Bachelor of Biological Science program at UBC. He is particularly interested autoimmunity, drug mechanisms, and patient-professional relationships. He has contributed to writing the Autoimmunity and Diabetes Mellitus chapters, as well as creating review questions for both. Additionally, He has also made instructor review videos for the Diabetes Mellitus chapter. Dylan is exceptionally grateful for the opportunity to contribute and work alongside the entire team creating this resource. He is excited for this textbook to be a free resource for students, and hopes it will be a valuable tool in their learning.

Max Yang – Max is a student in the Doctor of Dental Medicine program at UBC who has contributed to the development

of the instructor guides and hematology case studies. He is interested in understanding how different diseases can manifest to become clinically recognizable. He hopes the information within OpenPatho is utilized by other learners who are just as passionate about understanding how the human body adapts, interacts, and heals; creating the connection between text and real-world disease.

Willie Wu – Willie is a graduate student in the Interdisciplinary Oncology program at UBC, with a keen interest in cancer pathophysiology and histology. Willie authored the Histology chapter for first-time learners and developed high-yield visual summaries, critical thinking case studies, and interactive review questions for the Acute Kidney Injury and Cirrhosis chapters. He also collaborated with UBC librarians to format existing content to meet accessibility standards for BC Campus adoption. Willie is truly grateful for the opportunity to contribute to this open educational resource and remains committed to advancing Open Education initiatives that make learning more accessible for all students.

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Adrian Marcuzzi (Yr 1 Undergraduate Medical Program in 2020): video recording and editing for Introduction and Preface

Sebastian Swic (Yr 3 Undergraduate Medical Program in 2020): video editing for Introduction and Preface

Theodore Lam (Pathology, Graduate Studies): acting and script development for Introduction and Preface

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