Explanation

This document is my distillation of the textbook *Fundamentals of Anatomy & Physiology,* Tenth Edition (2015), by Frederic H. Martini et al. (a.k.a. "the 10th Martini"), and associated slides prepared by Lee Ann Frederick. While this textbook is a valuable resource, I believe that it is too dense to be read successfully by many undergraduate students. I offer *Crowther's Tenth Martini* so that students who have purchased the Martini textbook may benefit more fully from it. No copyright infringement is intended and, to the best of my knowledge, none has been committed. Any errors in *Crowther's Tenth Martini* are my fault.

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Table of Contents	15: Sensory Pathways and the Somatic Nervous System
1: An Introduction to Anatomy and Physiology	16: The Autonomic Nervous System and Higher-Order Functions
2: The Chemical Level of Organization	17: The Special Senses
3: The Cellular Level of Organization	18: The Endocrine System
4: The Tissue Level of Organization	19: Blood
5: The Integumentary System	20: The Heart
6: Osseous Tissue and Bone Structure	21: Blood Vessels and Circulation
7: The Axial Skeleton	22: The Lymphatic System and Immunity
8: The Appendicular Skeleton	23: The Respiratory System
9: Joints	24: The Digestive System
10: Muscle Tissue	25: Metabolism and Energetics
11: The Muscular System	26: The Urinary System
12: Neural Tissue	27: Fluid, Electrolyte, and Acid-Base Balance
13: The Spinal Cord, Spinal Nerves, and Spinal Reflexes	28: The Reproductive System
14: The Brain and Cranial Nerves	29: Development and Inheritance

Chapter 1: An Introduction to Anatomy and Physiology

Let's get started!

1.0: Outline

1.1: What are anatomy and physiology?
- Anatomy and physiology cover structure and function, respectively. The two go hand in hand.

1.2: What levels of organization are included in anatomy and physiology?
- One can study A&P at the level of molecules, cells, tissues, organs, and organ systems (of which there are 11).

1.3: What are homeostasis and negative feedback?
- Homeostasis is a near-constant state.
- Negative feedback maintains homeostasis by negating (counteracting) changes away from setpoints. Negative feedback systems also include receptors/sensors, integrators, and effectors.

1.4: How do we describe anatomy clearly?
- The anatomical position is a standard reference position.
- There about 40 common anatomical surface landmarks, seven standard pairs of anatomical directions, and three standard types of anatomical sections.

1.5: What are body cavities?
- The trunk is subdivided into membrane-lined cavities.
- The ventral interior is divided into the thoracic and abdominopelvic cavities, separated by the diaphragm.

1.6: Recommended review questions

1.7: Appendix: word roots, prefixes, and suffixes

1.1: What are anatomy and physiology?

Anatomy describes the structures of the body: what they are made of, where they are located, and which structures are associated with which. Physiology is the study of the functions of these structures.

Anatomy and physiology – often abbreviated A&P – can be approached separately but usually are presented together because structure and function are so closely interconnected. It is often said that "form follows function"; in other words, the specific structure of a given molecule, cell, organ, or organ system must suit its specific function(s).

As an example, consider the structural differences between skeletal muscle cells and cardiac (heart) muscle cells. The job of both types of cells is to contract, so they both contain lots of the proteins that make the cells shorter (actin and myosin and other associated proteins – to be covered in Chapters 4 and 10). However, cardiac cells must do this day and night without a rest, so their structure must be a bit different from that of skeletal muscle cells. In particular, a large

fraction of cardiac cells' volume (25-30%) is taken up by mitochondria, which produce ATP in a sustained aerobic manner that helps the cells contract over and over and over. In contrast, skeletal muscle cells are only used intermittently and only devote a small fraction of their volume (1-5%) to mitochondria. Therefore we can say that structural differences between cardiac and skeletal muscle cells – the fraction of cellular space taken up by mitochondria – reflect their functional differences – continuous versus intermittent contraction.

1.2: What levels of organization are included in anatomy and physiology?

Anatomy and physiology span all of the levels shown in the top half of 10th Martini Figure 1-1 (Levels of Organization). Starting at the atomic level, we note that atoms are combined to make molecules such as the proteins actin, troponin, and tropomyosin – components of muscle cells that are pictured under the label "Chemical Level" in 10th Martini Figure 1-1. Proteins and other molecules such as lipids, polysaccharides, and nucleic acids are contained in and organized by cells (e.g., heart muscle cells), the fundamental unit of life. A tissue (e.g., cardiac muscle tissue) can be defined as cells working together; an organ (e.g., the heart) is two or more tissues working together; and an organ system (e.g., the cardiovascular system) is two or more organs working together.

Subsequent chapters will cover basic information about atoms and molecules (Chapter 2), cells (Chapter 3), and tissues (Chapter 4).

The body may be divided into 11 organ systems (also pictured in 10th Martini Figure 1-1): integumentary, skeletal, muscular, nervous, endocrine, cardiovascular, lymphatic, respiratory, digestive, urinary, and reproductive. In many two-quarter anatomy & physiology courses, the first quarter (e.g., Biology 241) focuses on the first four of these: integumentary (Chapter 5), skeletal (Chapters 6-9), muscular (Chapters 10-11), and nervous (Chapters 12-17). They are summarized in CTM Table 1.1. Most of the remaining organ systems are covered in the second quarter (e.g., Biology 242).

CTM Table 1.1: Overview of organ systems covered in the first "half" of 10th Martini

Organ system	Major organs	Major functions
Integumentary	• skin • hair • sweat glands • nails	• protection • temperature control (cooling, insulation) • sensing the environment
Skeletal	• bones • cartilage • ligaments • bone marrow	• shape and support • makes blood cells • stores calcium and other minerals
Muscular	• skeletal muscles • tendons	• movement • heat production • structure and support
Nervous	• brain • spinal cord • peripheral nerves • sense organs	• senses environment • responds to stimuli • communicates with other organs

1.3: What are homeostasis and negative feedback?

This first chapter does not include much physiology. However, two concepts are so central to physiology that they are included here: homeostasis and negative feedback.

The word homeostasis can be understood in terms of its roots. "Homeo" means "similar or unchanging" and "stasis" means "state," so homeostasis indicates a near-constant state.

For organisms such as humans to survive, we must maintain the homeostasis of our internal environment despite frequent changes in the external environment. 10th Martini Table 1-1 lists many of the variables that we try to keep constant: body temperature, oxygen and carbon dioxide levels, body fluid volume, blood pressure, and so on. Failure to keep these variables within healthy ranges leads to disease and sometimes death.

The general mechanism for maintaining the homeostasis of a given variable is called negative feedback. This is a term that physiologists have borrowed from engineers. In general, feedback is a response to a stimulus or input. Negative feedback is called *negative* because the response counteracts (negates) the stimulus. For example, in the control of room temperature (10th Martini Figure 1-2), a rising temperature will cause an air conditioner to lower the temperature, thus counteracting the initial stimulus.

If we look at negative feedback systems in a bit more detail, we can say that they include four key components (with control-of-room-temperature examples in parentheses):
• *Receptors (or Sensors):* report the current level of a variable (e.g., thermometer)
• *Setpoint:* the default or "ideal" level of the variable (e.g., 70 °F – set by resident of house)
• *Integrator:* compares the actual level to the setpoint (e.g., is actual temperature higher or lower than 70 °F?)
• *Effectors:* move the actual level back toward the setpoint (e.g., air conditioner or heater)

Now let's find these four components in the biological regulation of temperature (10th Martini Figure 1-3):
• *Receptors (or Sensors):* temperature sensors in skin and hypothalamus
• *Setpoint:* the preferred core temperature is 98 °F, which equals 37 °C
• *Integrator:* the thermoregulatory center in the brain (the hypothalamus, specifically) compares the actual temperature to the setpoint
• *Effectors:* sweating by glands in the skin and dilation of blood vessels in the skin increase heat loss from the skin and reduce body temperature toward the setpoint

We will return frequently to the concept of negative feedback throughout this course.

1.4: How do we describe anatomy clearly?

The language of anatomy is intimidating to many students, and for good reason: there are a lot of terms to be understood and memorized. While we cannot avoid this jargon, we will try to cover it in an organized and sensible manner.

One useful starting point is the list of word roots, prefixes, and suffixes inside the back cover of your book. Examples that we will encounter in 10th Martini are highlighted in an Appendix below (section 1.7).

Another starting point is what is called the anatomical position. Many anatomical questions (e.g., "Which is closer to your head, your hand or your elbow?") are ambiguous unless an exact body pose is specified. The anatomical position, pictured in 10th Martini Figure 1-5 (Anatomical Landmarks), provides a standard reference position to use. The anatomical position is defined by Martini as follows: "the hands are at the sides with the palms facing forward, and the feet are together."

Chapter 1 covers three aspects of superficial anatomy (the anatomy of structures at or near the surface of the body: anatomical landmarks, anatomical regions, and anatomical directions.

Anatomical landmarks are shown in 10th Martini Figure 1-5 (Anatomical Landmarks).

Anatomical regions for the surface of the abdomen and pelvis are shown in 10th Martini Figure 1-6 (Anatomical relationships). This surface can be divided into four quadrants (upper left, lower left, upper right, and lower right – note that the center of the grid is the belly button, and that left and right are from the perspective of the subject, not the observer!), or into the nine regions shown in the figure.

Anatomical directions, pictured in 10th Martini Figure 1-7 (Directional References), may be learned most easily as a set of opposites:
• *Superior* (toward the head) versus *Inferior* (toward the feet)
• *Cranial/Cephalic* (toward the head) versus *Caudal* (toward the tailbone)
• *Proximal* (toward the trunk of the body) versus *Distal* (away from the trunk)
• *Lateral* (away from the midline) versus *Medial* (toward the midline)
• *Superficial* (toward the body's surface) versus *Deep* (toward the body's interior)
• *Anterior* (toward the front) versus *Posterior* (toward the back)
• *Ventral* (toward the belly) versus *Dorsal* (toward the back)

You will receive additional practice on anatomical landmarks, regions, and directions in lab (Exercise 1).

Finally, we must move away from purely superficial anatomy to talk about anatomical sections. These are three-dimensional slices of the body – obtained either from physically cutting the body, or from an imaging technique (CT scan, MRI, X-ray, ultrasound, etc.) that can scan the body noninvasively. Anatomical sections can be frontal/coronal (coronal means "crown"), sagittal, or transverse, as pictured in 10th Martini Figure 1-8 (Sectional Planes):
• A *frontal* or *coronal* plane divides the body into anterior and posterior portions (not necessarily equal in volume or weight).
• A *sagittal* plane divides the body into left and right portions.
• A *transverse* plane divides the body into superior and inferior portions.

1.5: What are body cavities?

As our final bit of anatomy in this introductory chapter, we'll continue burrowing into the body's interior. Can you imagine what it would be like if all of the organs of the trunk (heart, lungs, gastrointestinal tract, bladder, etc.) were all thrown together in a single giant compartment? There would be at least a couple of problems. First, organs that expand and contract would have trouble undergoing such movements, as they would be crammed up against all of the other organs. Second, any movements by one organ might rub against and irritate or damage adjacent organs.

These potential problems are avoided through the subdivision of the trunk of the body into fluid-filled body cavities. Each cavity keeps its organs separate from those of other cavities, thus protecting the organs and giving them some room to expand and contract. Each cavity is lined by a thin, moist serous membrane. The serous membrane includes both a visceral layer, which covers each organ, and a parietal layer, which lines the cavity itself.

The ventral interior of the body's trunk is divided into the thoracic cavity (thoracic is the adjective form of thorax), which contains the heart and lungs, and the abdominopelvic cavity, which contains the digestive/excretory and reproductive organs. Between these two cavities is the diaphragm, a flat oval-shaped muscle that helps the lungs inflate. See 10th Martini Figure 1-9 (Relationships among the Subdivisions of the Body Cavities of the Trunk).

The thoracic cavity is further subdivided into the left and right pleural cavities, which contain the left and right lungs, and the pericardial cavity, which contains the heart.

1.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 1: #1, #21, #22, #25, #27, #28, #29, #30, and #31. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

1.7: Appendix: word roots, prefixes, and suffixes

Below is a table of word roots, prefixes, and suffixes adapted from the inside back cover of the 10th Martini. When you know the meanings listed in this table, you will often be able to guess the meaning of unfamiliar words. Consider this a preview of upcoming jargon!

Root/ prefix/ suffix	Meaning	Examples (Martini chapter)
Ad-	Toward	• adduction: movement of a limb toward the midline of the body (Ch. 9) • adrenal gland: located near or "toward" the kidney (renal = kidney) (Ch. 18)
Angio-	Vessel	• angiogenesis: the production of blood vessels (Ch. 21) • angiotensin: a hormone that maintains blood pressure (tension) (Ch. 18)

Anti-	Against	• antibodies: fight invaders of the body (Ch. 22) • antidiuretic hormone: a hormone that prevents dehydration (diuresis) (Ch. 26) • antihistamines: prevent inflammation triggered by histamine (Ch. 22)
Auto-	Self	• autoimmune disease: the body attacks itself (Ch. 22) • autonomic nervous system: works automatically (doesn't require conscious input) (Ch. 16) • autoregulation: a physiological entity adjusts itself without needing control by the nervous or endocrine systems (Ch. 21/26)
Cardi-, Cardio-	Heart	• cardiac output: the blood flow delivered by the heart per unit time (Ch. 20) • cardiomyocyte: a muscle cell in the heart (myo = muscle; cyte = cell) (Ch. 10/20) • cardiovascular system: organ system consisting of the heart and blood vessels (Ch. 20-21)
Cep-, Cephal-	Head	• biceps, triceps, quadriceps: muscles with 2, 3, and 4 "heads," respectively (Ch. 11) • brachiocephalic vein: collects blood from the head and arm (brachio = arm) (Ch. 21)
Cerebr-, Cerebro-	Brain	• cerebral hemispheres: halves of the brain (Ch. 14) • cerebrospinal fluid: fluid surrounding and bathing the brain (Ch. 14)
Cervic-	Neck	• cervical vertebrae: found in/near the neck (Ch. 7) • cervix: a narrowing or "neck" of the uterus (Ch. 28)
Chondro-	Cartilage	• chondrocyte: a cartilage cell (cyte = cell) (Ch. 4) • endochondral ossification: process by which cartilage is replaced by bone (os = bone) (Ch. 6)
Cortic-	Cortex (outer layer)	• cortical nephron: found in the outer layer (cortex) of the kidney (Ch. 26) • corticospinal neuron: connects the cerebral cortex to the spinal cord (Ch. 13)
Cost-	Rib	• costal cartilage: cartilage making up the ribs (Ch. 7) • intercostal muscles: connect the ribs to each other (Ch. 23)
Cranio-	Skull	• cranium: the skull (Ch. 7) • cranial nerves: go into and out of the skull (Ch. 14)
Cyte-	Cell	• chondrocyte: cartilage cell (Ch. 4) • keratinocyte: keratin-producing cell (Ch. 5) • melanocyte: melanin-producing cell (Ch. 5) • myocyte: muscle cell (myo = muscle) (Ch. 10) • osteocyte: bone cell (os = bone) (Ch. 4)
Derm-	Skin	• epidermis: outer layer of skin (epi = outer) (Ch. 5) • dermatome: section of skin corresponding to one spinal nerve (Ch. 13)
Di-	Two	• disaccharide: two sugar molecules joined together (Ch. 24) • dizygotic twins: formed from two eggs (Ch. 29)
End-, Endo-	Within	• endocytosis: substances are imported into the cell (Ch. 3) • endometrium: inner membrane lining the uterus (Ch. 28) • endoplasmic reticulum: a network within the cell (reticulum = network) (Ch. 3)
Epi-	Around or upon	• epidermis: outer layer of skin (Ch. 5) • epigastric abdominopelvic region: near the stomach (Ch. 1) • epiphyses: the ends of long bones (Ch. 6)
-Gen-, -Genic	To produce	• angiogenesis: production of blood vessels (Ch. 21) • carcinogen: something that causes cancer (Ch. 3)

Glosso-, -Glossus	Tongue	• glossopharyngeal nerve (cranial nerve IX) innervates the tongue and pharynx (Ch. 14) • hypoglossal nerve (cranial nerve XII) controls the tongue (Ch. 14)
Glyco-	Sugar	• glycogen: storage form of sugar (Ch. 18/25) • glycolysis: breakdown of sugar (lysis = break) (Ch. 25) • glycosylation: addition of sugar groups to lipids or proteins (Ch. 3)
Hem-, Hemo-	Blood	• hematocrit: the fraction of your blood that is red blood cells (Ch. 21) • hemoglobin: oxygen-carrying protein in red blood cells (Ch. 21)
Hemi-	Half	• cerebral hemisphere: half of the brain (Ch. 14) • hemidesmosome: "half-desmosome" (a desmosome links two adjacent cells, while a hemidesmosome links a cell to extracellular structures) (Ch. 4)
Hydro-	Water	• hydrophilic/hydrophobic: "water-loving" and "water-fearing" molecules (Ch. 3) • hydrostatic pressure: pressure exerted by a liquid (Ch. 21)
Hyper-	Greater or higher	• hyperpolarized: when a neuron is more polarized than normal (Ch. 12) • hypertension: high blood pressure (Ch. 21) • hyperthyroidism: excessive release of thyroid hormone (Ch. 18)
Hypo-	Below or lower	• hypochondriac and hypogastric abdominopelvic regions: below the ribs (cartilage) and stomach, respectively (Ch. 1) • hypothalamus: brain structure that is under the thalamus (Ch. 14)
Iso-	Equal	• isometric: a muscle contraction in which the muscle is kept at a constant length (Ch. 10) • isotonic: having a concentration equal to something else (Ch. 3)
Lact-, Lacto-, -Lactin	Milk	• lactation: milk production by the breast (Ch. 28) • lactose: a sugar found in milk (Ch. 24) • prolactin: a hormone controlling development of the (milk-producing) mammary glands (Ch. 18)
Liga-	Bind together	• ligament: a tissue that connects two bones (Ch. 9) • ligase: an enzyme that joins two pieces of DNA (Ch. 3)
Melan-	Black	• melanin: a dark pigment (Ch. 5) • melanocytes: cells that make melanin (Ch. 5)
Meta-	Middle	• metaphase: a middle stage of mitosis in which chromosomes line up across the middle of the cell (Ch. 3) • metaphysis: a region of bone between the diaphysis and epiphysis (Ch. 6)
Mono-	Single	• monosynaptic reflex: only involves one synapse between neurons (Ch. 13) • monozygotic twins: come from one egg (Ch. 29)
Myo-	Muscle	• myocyte: muscle cell (Ch. 10) • myofibrils: bundles of muscle proteins (Ch. 10) • myofilaments: thick and thin filaments found in muscle (Ch. 10) • myosin, tropomyosin: muscle proteins (Ch. 10)
Ost-, Oste-, Osteo-	Bone	• osteoblast, osteoclast, osteocyte: types of bone cells (Ch. 6) • osteogenesis: bone production (Ch. 6)
Poly-	Many	• polysaccharide: many sugar molecules linked together (Ch. 24) • polysynaptic reflex: involves more than one synapse (Ch. 13)
Sarco-	Muscle	• sarcomere: unit of muscle contraction (Ch. 10) • sarcoplasmic reticulum: the endoplasmic reticulum in muscle cells (Ch. 10)
Sub-	Below	• subarachnoid space: below the arachnoid mater, the middle meningeal layer (Ch. 13) • subcutaneous: below the skin (Ch. 5)

Super-	Above or beyond	• superficial: toward the surface of the body (Ch. 1) • superior colliculus: brain structure above the inferior colliculus (Ch. 14)
Telo-	End	• telomere: end of a chromosome (Ch. 3) • telophase: last stage of mitosis (Ch. 3)
Vas-	Vessel	• vas deferens: vessel through which sperm pass (Ch. 28) • vascular: relating to blood vessels (Ch. 21) • vasopressin: alternate name for antidiuretic hormone, which helps maintain blood pressure (Ch. 26)

Chapter 2: The Chemical Level of Organization

With this chapter we begin our march through the body's levels of organization (recall the top of 10th Martini Figure 1-1). Here in Chapter 2 we will discuss the body at the chemical level; Chapters 3 and 4 will cover the cellular level and tissue level, respectively.

2.0: Outline

2.1: Elements, atoms, ions, bonds, and molecules
- Living things are mostly made up of a few elements from the periodic table.
- Atoms of these elements may gain or lose electrons, forming ions, or may share electrons with other atoms, forming covalent bonds.

2.2: Concentrations and moles
- A concentration is the amount of a solute present in a given volume of solvent (usually water).
- Concentrations are often expressed in M (moles per liter), mM, or μM.

2.3: Chemical reactions and enzymes
- Chemical reactions in the body are organized into catabolic pathways (which break down complex molecules into simpler ones) and anabolic pathways (which make simple molecules into more complex ones).
- Individual chemical reactions are sped up by specific proteins called enzymes.

2.4: Water: the body's solvent
- Hydrophilic (charged and highly polar) molecules mix readily in water, whereas hydrophobic molecules do not.
- pH is the negative exponent of the Molar hydrogen ion (H^+) concentration.
- Buffers prevent large deviations in pH.

2.5: What types of compounds are found in the body?
- 10th Martini lists five main types of organic molecules: carbohydrates, lipids, proteins, nucleic acids, and "high-energy molecules" like ATP.
- Breakdown of carbohydrates and lipids provides energy, often captured in the form of ATP.
- Proteins are the machines of the cell.
- Nucleic acids include DNA, which stores genetic information, and RNA, which helps use that information to produce proteins.

2.6: Recommended review questions

2.1: Elements, atoms, ions, bonds, and molecules

Even if you haven't had chemistry recently, you probably have some memory of the periodic table – the chart representing all ~118 chemical elements in the universe. (Google "periodic table" if this doesn't sound familiar.)

Living things are made up mostly of a few of these elements, as listed in 10th Martini Table 2-1 (Principal Elements in the Human Body): oxygen (O), carbon (C), hydrogen (H), nitrogen (N), and so on. In this chapter we will look at how these elements can be combined into molecules found in biology.

An atom is the smallest possible unit of a given element. If we're talking about the element of oxygen, one atom of oxygen is the smallest amount of oxygen that you can have. If you split an atom of oxygen into its subatomic particles, it's no longer oxygen.

Speaking of subatomic particles, you should recall that atoms are made up of protons (positively charged), neutrons (uncharged), and electrons (negatively charged). For our purposes, electrons are the most important of these, for two reasons:

- *Electrons may be gained or lost from atoms, thus creating ions*. An ion is defined as any atom or group of atoms with an electric charge. Examples of biologically important ions are Na^+, K^+, Ca^{2+}, and Cl^-. In each case, the atom is no longer electrically neutral because one or more electrons have been gained or lost. For example, when an atom of sodium (abbreviated Na after the Latin word natrium) loses one of its electrons, it becomes a sodium ion with a net charge of +1 (positive 1). Conversely, an atom of chlorine (Cl) can gain an additional electron, which gives it a net charge of -1 (negative 1).
- *Electrons may be shared between atoms as covalent bonds*, *thus creating molecules*. A covalent bond is defined as the sharing of electrons between atoms; a molecule is defined as any atoms held together by covalent bonds. You are probably familiar with molecules such as H_2O (water), CO_2 (carbon dioxide), and $C_6H_{12}O_6$ (glucose). These molecules' chemical formulas specify which elements they contain in what ratios; for example, a molecule of glucose contains 6 carbon (C) atoms, 12 hydrogen (H) atoms, and 6 oxygen (O) atoms.

2.2: Concentrations and moles

In clinical and research samples, it is usually not enough to know which ions or molecules are present – we also need to know their concentrations, i.e., how prevalent they are in the watery environment inside or outside cells. Concentrations are defined as the amount of solute (dissolved ion or molecule) present in a given volume of solvent (generally water, for biological samples). For example, blood glucose levels are often reported in milligrams per deciliter; typical values are 70-100 mg/dl after an overnight fast. However, other concentrations are often reported as molar (M, or moles per liter), millimolar (mM = millimoles per liter = thousandths of a mole per liter), micromolar (μM = micromoles per liter = millionths of a mole per liter), or nanomolar (nM = nanomoles per liter = billionths of a mole per liter). So what is a mole?

A mole of Na^+ ions is 6.02×10^{23} Na^+ ions. (6.02×10^{23} is a very large number known as Avogadro's number.) A mole of glucose molecules is 6.02×10^{23} glucose molecules. And so on. A mole of anything is 6.02×10^{23} copies of that thing.

Why is the concept of moles useful? As stated in 10th Martini (p. 30), "Expressing relationships in moles rather than in grams makes it easier to keep track of the relative numbers of atoms in chemical samples and processes. For example, if a report stated that a sample contains 0.5 mol of hydrogen atoms and 0.5 mol of oxygen atoms, you would know immediately that the two atoms were present in equal numbers. That would not be so evident if the report stated that there were 0.505 g of hydrogen atoms and 8.00 g of oxygen atoms."

An example of concentrations expressed in terms of molarity are the intracellular (inside-the-cell) and extracellular (outside-the-cell) concentrations of ions such as sodium (Na^+) and potassium (K^+). We will see in Chapter 12 that Na^+ is more concentrated outside cells and K^+ is more concentrated inside cells. If we want to be more precise, we can say that Na^+ is about 145 mM outside nerve cells and about 10 mM inside nerve cells, and that the concentrations for K^+ are nearly reversed: 140 mM inside nerve cells and 4.4 mM outside nerve cells.

2.3: Chemical reactions and enzymes

Living things build and maintain their bodies out of the nutrients they take in. This requires many chemical reactions in which molecules are broken down, combined, and altered in other ways. These chemical reactions can be grouped into metabolic pathways with specific purposes; for example, glycolysis is a pathway of about 10 reactions in which glucose is converted into pyruvate and lactate.

We will not focus on the details of such pathways. Very generally, however, we can distinguish between catabolic and anabolic pathways. Catabolic pathways break down complex molecules into simpler ones (glycolysis is an example of this), whereas anabolic pathways do the opposite, making simple molecules into more complex ones (an example would be making glucose out of pyruvate in the pathway of gluconeogenesis). Catabolic pathways recapture some of the chemical energy of their starting materials, often by making ATP, which can then be used to power the anabolic pathways, which require the input of chemical energy. All of the catabolic and anabolic pathways together constitute metabolism – all of the chemical reactions of the body.

Most chemical reactions inside living things do not occur spontaneously at high rates. For these reactions to occur at rates that are useful to the body, they must be expedited by proteins known as enzymes. It is often said that enzymes lower the activation energy of chemical reactions (10th Martini Figure 2-8 [Enzymes Lower Activation Energy]). What this means in practical terms is the following. For a reaction to occur, the reacting molecules need to collide in just the right way, which rarely happens spontaneously. Enzymes make these unlikely reactions more likely by grabbing onto the molecules and orienting them in such a way that they tend to react with each other. Enzymes thus play the role of a chemical matchmaker, introducing molecules who would not otherwise meet each other. More precisely, enzymes are called catalysts; they speed up reactions without themselves being altered in the process.

2.4: Water: the body's solvent

As a crude approximation, our bodies can be considered a whole lot of water with a bunch of solutes dissolved in it.

Some ("hydrophilic") molecules mix readily in water, whereas other ("hydrophobic") molecules do not. Ions and polar molecules (the latter of which have covalent bonds in which electrons are not shared equally) are hydrophilic, whereas lipids (i.e., fats) are hydrophobic molecules that do not mix well with water. Cells, the fundamental units of life, are surrounded by cell membranes made out of lipids. Therefore, hydrophilic molecules that pass easily through water cannot necessarily get in or out of cells easily. We will return to this point in Chapter 3.

Water includes hydrogen ions (H^+), whose concentration affects biological processes such as enzyme-catalyzed reactions, and which therefore needs to be regulated.

We quantify H^+ concentration using the pH scale, which is logarithmic (like the Richter scale for earthquake intensities and the decibel scale for sound intensities). In particular, pH is defined as the negative exponent of the H^+ concentration written in base 10. The following example may help. A H^+ concentration of 0.0000001 Molar can be written in base 10 as 10^{-7} Molar. Since pH is the negative exponent of the H^+ concentration, and since -7 is the exponent, the pH is -(-7), or just 7. If the $[H^+]$ were 10^{-6} Molar, the pH would be 6. Note the following:

- A *lower* pH represents a *higher* concentration of H^+ ions.
- A pH change of 1 unit (e.g., from 7 to 6) represents a 10-fold change in H^+ concentration.

10th Martini Figure 2-10 (The pH Scale Indicates Hydrogen Ion Concentration) shows the pH's of various fluids. Within the body, a wide range of pH's can be found, from stomach acid (pH = 1) to urine (pH = 4.5 to 8) and blood (pH = 7.4).

To control pH in any given compartment, the body has various buffers, which are defined as any substances that minimize pH changes. Also, the kidney can correct pH changes by excreting excess acids, which lower pH by releasing H^+ into the body fluids, or by excreting bases, which raise pH by removing H^+ from the body fluids. The wide range of possible urine pH's reflects the fact that, at any given time, the body may need to get rid of acids (acids in the urine lower the pH of the urine) or may need to get rid of bases (bases in the urine raise the pH of the urine).

2.5: What types of compounds are found in the body?

With all of the above as background, we are now ready to view and understand 10th Martini Table 2-7 (Classes of Inorganic and Organic Compounds).

This table distinguishes between organic compounds and inorganic compounds. The precise distinction is a bit tricky and not that important for our purposes, but "organic" generally means "containing carbon atoms" and "inorganic" generally means "not containing carbon atoms." (CO_2 is an exception because it contains carbon but is considered inorganic.)

Water is the first inorganic compound listed in the table. As shown in the Functions column, water does more than just serve as a solvent for other molecules. In the form of blood, it delivers materials and heat; in the form of sweat, it cools the body via evaporation.

Now let's look at the types of *organic* compounds listed in the table. There are five types shown: carbohydrates, lipids, proteins, nucleic acids, and "high-energy compounds." You may recognize the first three as the main components of food, which can be catabolized (broken down via catabolic pathways – see above) for their chemical energy. Thus they too could be considered "high-energy compounds," though Martini uses this term only in reference to ATP and similar molecules.

Let us make a few additional points about these types of compounds without dwelling too much on their structural details.

Carbohydrates: Look at (but do not memorize) the structure of glucose, a sugar molecule, as shown in 10th Martini Figure 2-11b (The Structures of Glucose). Note the hexagonal shape. Count up the carbon, hydrogen, and oxygen atoms and confirm that there are the numbers of each specified in the chemical formula $C_6H_{12}O_6$. Individual glucose molecules can be linked together to form glycogen (10th Martini Figure 2-13 [The Structure of the Polysaccharide Glycogen]), a storage form of carbohydrate found mostly in muscles and the liver.

Lipids: Lipids are a diverse group of molecules that share the common feature of being hydrophobic – that is, they do not mix well with water. 10th Martini Table 2-5 (Representative Lipids and Their Functions in the Body) is a nice summary of the major subgroups of lipids and their functions. Fatty acids are the main lipids that are catabolized to harvest their chemical energy, while other lipids make up cellular membranes (phospholipids, glycolipids, steroids) and/or are involved in signaling between cells (eicosanoids, steroids).

Proteins: Proteins are sometimes referred to as the machines of the cell, since they do almost all of the "work" of cellular growth and maintenance, which Martini (p. 51) encapsulates as seven major functions: support; movement; transport; buffering; metabolic regulation; coordination and control; and defense. We will talk more about these functions when we encounter individual proteins that perform them. For example, actin and myosin are proteins responsible for muscle contraction (movement); Na^+ and K^+ ion channels are proteins that let these ions pass in and out of cells (transport); and keratin is a protein that protects the skin (defense). For now, note that proteins are made out of amino acids, which are initially linked together kind of like beads on a string, but ultimately fold into complex 3D shapes, as shown in 10th Martini Figure 2-21 (Protein Structure).

Nucleic Acids: These include deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the stuff that makes up your chromosomes, which contain your genes. RNA helps convert the information in these genes into the production of proteins, as discussed in Chapter 3. DNA and RNA both are made of three interlocking components: phosphate groups, sugars (deoxyribose for DNA; ribose for RNA), and nitrogen-containing bases (A, C, G, and T for DNA; A, C, G, and U for RNA) – see 10th Martini Figures 2-23 (Nucleotides and Nitrogenous Bases) and 2-24 (The Structure of Nucleic Acids). The phosphate groups and sugars are constant from one

section of a nucleic acid to the next, but the sequence of bases varies, and it is these sequences that contain the genetic information. Chapter 3 will show how this works in more detail.

ATP: adenosine triphosphate (ATP) is a convenient molecule for storing chemical energy. When catabolic pathways release the chemical energy of food, much of this energy is recaptured in the form of newly made ATP, which itself can be broken down to release energy needed for energy-requiring processes (such as anabolic pathways). To see the structure of ATP, consult 10th Martini Figure 2-25 (The structure of ATP). The word "triphosphate" means "three phosphates," and, sure enough, ATP includes three phosphate groups linked via covalent bonds. It is mostly the third and final phosphate group that gets added and removed during energy-harvesting and energy-using processes; thus ADP (adenosine diphosphate) and ATP are interconverted constantly.

2.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 2: #12, #13, #14, #20, #24, #29, #31, #32. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 3: The Cellular Level of Organization

With this chapter we continue our march through the body's levels of organization (recall the top of 10th Martini Figure 1-1). In Chapter 2 we discussed the body at the chemical level; here in Chapter 3 we will focus on the cellular level. Chapter 4 will address the tissue level.

3.0: Outline

3.1: What are the parts of a cell, and what do they do?
- Specialized functions within cells are carried out by organelles.
- The plasma membrane is a selectively permeable barrier made up mostly up lipids and proteins. It surrounds the cytoplasm of the cell.
- Carriers and channels are proteins that allow substances to pass through the plasma membrane.
- Other important organelles include cilia (for sweeping extracellular materials), the cytoskeleton (for intracellular transport), the ER, the Golgi complex (for packaging and shipping proteins), microvilli (for absorption of nutrients), mitochondria (for making ATP), the nucleus (for storing DNA), and ribosomes (for synthesizing proteins).

3.2: How do genes get expressed?
- DNA gets transcribed into RNA, which gets translated into protein. Each set of three DNA bases in a gene codes for one amino acid of the corresponding protein.
- Transcription occurs in the nucleus, where the enzyme RNA polymerase makes an RNA strand that is complementary to the template strand of DNA.
- Translation occurs at ribosomes, where tRNA molecules bring amino acids that are joined together in an order specified by the mRNA.

3.3: How do substances get across membranes?
- The cell has both passive (non-ATP-using) and active (ATP-using) processes for getting substances across membranes. Passive processes include simple diffusion, which includes osmosis, and facilitated diffusion. Active processes include active transport, endocytosis, and exocytosis.

3.4: How do cells create new cells?
- Cells go through a life cycle that includes Interphase (which includes subphases G_0, G_1, S, and G_2) and M phase (which includes the stages of mitosis – prophase, metaphase, anaphase, and telophase – plus cytokinesis).
- Genetic mutations can cause cells to speed through their life cycle too rapidly, sometimes leading to cancerous tumors. Some cancer treatments try to block DNA synthesis (S phase of interphase) or the formation of the mitotic spindle (prophase of mitosis).

3.5: Recommended review questions

3.1: What are the parts of a cell, and what do they do?

Just as the body has specialized organs for carrying out specific functions, cells likewise have specialized sub-parts, often called organelles ("little organs"). And just as the structure of an organ is directly related to its function, so too is the structure of each organelle related to its function.

We will not cover all of the cell's organelles here, but we will start with the plasma membrane and then briefly introduce the following additional organelles: cilia, cytoskeleton, endoplasmic reticulum (ER), Golgi complex, microvilli, mitochondria, nucleus, and ribosomes.

The plasma membrane, also called the cell membrane, surrounds the cell. It has been described as "keeping the insides in and the outside out," and also as a "selectively permeable barrier." Both of these are true; the membrane needs to separate the contents of the cell from the surrounding environment, but also needs to let some substances in and out (or else the cell would die).

Remember lipids, proteins, and carbohydrates from Chapter 2? They are all components of the plasma membrane. Lipids give this membrane its overall form – hence the common description of the plasma membrane as a lipid bilayer (that is, there are two layers of lipid molecules). By definition, lipids are hydrophobic, so hydrophilic substances (sugars, amino acids, ions, etc.) cannot pass through a membrane of pure lipids. However, many of these hydrophilic substances can cross cell membranes with the help of proteins that are embedded in the lipid bilayer. Proteins that allow transport across the membrane can either be considered *carrier proteins*, which bind to specific molecules, or *channels*, which do not attach to the substance being transported but (as the name suggests) serve as a passageway for it.

Mutations in transport proteins can have severe consequences. The disease of cystic fibrosis (CF), highlighted in the Clinical Case "What is Wrong with My Baby?" in 10th Martini Chapter 2, stems from problems with a membrane protein called CFTR that serves as a channel for chloride ions (Cl^-). In CF patients, the flow of Cl^- through this channel is impaired. A nice picture of CFTR can be seen at this web page:
http://www.hopkinscf.org/what-is-cf/basic-science/cftr/structure/

Many additional membrane proteins have functions unrelated to transport; for example, as we'll see in Chapter 4, proteins called Cell Adhesion Molecules bind cells to adjacent cells in structures called desmosomes.

In contrast to lipids and proteins, carbohydrates are a relatively minor component of cell membranes. Chains of carbohydrates get attached to some of the lipids and proteins in the membrane, forming glycolipids and glycoproteins, respectively. (Recall from the appendix of CTM Chapter 1 that "glyco-" means "sugar.") Perhaps the most well-known example of glycoproteins are those responsible for the A/B/O blood types. A, B, and O refer to different carbohydrate groups attached to the same membrane protein, as pictured here (note that the different colors of hexagons represent different sugar molecules):
http://en.wikipedia.org/wiki/ABO_blood_group_system#mediaviewer/File:ABO_blood_group_diagram.svg

Overall, we can say that the plasma membrane's structure of a lipid bilayer containing embedded proteins serves its function of restricting movement into and out of the cell while still allowing some substances through. Let us now look at how other organelles' structures go hand in hand with their functions, as summarized in CTM Table 3.1 below. Be sure to look at the 10th Martini figures to get a clearer sense of each organelle's structure (what it looks like).

CTM Table 3.1: Structure and Function of Selected Organelles

Organelle	Figure in 10th Martini	Structure/Function	Example of cells where this organelle is especially important
Cilia	Figures 3-1 and 3-4c	Cilia are fairly stiff "oars" that can make sweeping power strokes.	epithelial cells lining the respiratory tract (trachea down to small bronchi), which use cilia to sweep mucus and debris up toward the throat
Cytoskeleton	Figure 3-3	The cytoskeleton includes rope-like proteins that span long distances in the cell and (in Martini's words) "serve as a kind of monorail system to move vesicles or other organelles."	nerve cells, which can be VERY long, and thus depend on intracellular transport by the cytoskeleton
Endoplasmic Reticulum (ER)	Figure 3-5a	The word "reticulum" means "network," and the ER is an intracellular network of membranes. Some of the ER, the so-called Rough ER, also includes ribosomes for protein synthesis (see below). Newly made proteins are then often shipped to the Golgi complex for further processing. Materials can travel through the cell via the network of the ER.	calcium ions must be released throughout muscle cells to trigger muscle contraction, so the ER (called the sarcoplasmic reticulum, or SR, in muscle) is well suited for storing and releasing calcium ions
Golgi complex	Figure 3-7	The structure of the Golgi includes lots of "stations" (called cisternae), as at a factory. This relates to its function of packaging and shipping proteins, often for secretion.	cells that make protein hormones, which get secreted; e.g., the cells of the pituitary gland make growth hormone
Microvilli	Figure 3-3b	Microvilli are protrusions of the cell membrane, which provide a large surface area for absorption of nutrients.	epithelial cells lining the intestine
Mitochondria	Figure 3-9a	Mitochondria are packed with enzymes for breaking down food and using the chemical energy to make ATP.	cardiac muscle cells (beating constantly, so need sustained aerobic ATP production by mitochondria)
Nucleus	Figure 3-11	The nucleus contains DNA. The main job of the nucleus is to store this DNA.	Almost all cells. (Mature red blood cells have lost their nucleus.)
Plasma membrane	Figure 3-2	The plasma membrane's lipid bilayer with embedded proteins restricts movement into and out of the cell while still allowing some nutrients and wastes through.	All cells!
Ribosomes	Figure 3-13 (focus on step 1)	The ribosome is a multi-part machine that contains binding sites for mRNA and tRNA molecules; the latter carry amino acids with them. These binding sites make sense because the ribosome's job is to hook	Rapidly dividing cells, which must make lots of new proteins quickly.

		together amino acids (carried by the tRNAs) in an order specified by the mRNA.	

Two other cellular architecture terms to know are cytosol and cytoplasm. They are sometimes used interchangeably; technically, cytosol refers to the intracellular fluid of the cell, while the cytoplasm includes the entire interior of the cell (the cytosol plus all organelles).

3.2: How do genes get expressed?

You are already aware that your genes are segments of DNA in your chromosomes. Perhaps you also know that all of your genes together are called your genome, and that (with a few exceptions) each gene contains the instructions to make one protein. But how exactly does the cell convert a gene's information into a protein?

One way to think about this is the following:

- Genes are strings of DNA bases (A, C, G, and T).
- Proteins are strings of amino acids (there are 20 naturally occurring ones).
- Each set of three DNA bases – a "triplet codon" – codes for one amino acid.

10th Martini Table 3-1 (Examples of the Genetic Code) gives some examples of this so-called genetic code. For example, in the top line, when the gene's coding strand of DNA has a base sequence of TTT, that leads to the insertion of the amino acid phenylalanine into the protein. Similarly, a base sequence of TTA in the coding strand specifies the amino acid Leucine.

(By the way, the 20 amino acids have both one-letter and three-letter abbreviations. For example, Phenylalanine can be abbreviated Phe or F, while Leucine can be abbreviated Leu or L. You do not need to memorize these abbreviations, just be aware that they exist.)

The conversion of DNA to protein happens in two steps. DNA is used to make RNA in a process called transcription, and then the RNA is used to make protein in a process called translation. This DNA-to-RNA-to-protein progression is often referred to as the "Central Dogma of Molecular Biology" (a term introduced by Francis Crick, the co-discoverer of the structure of DNA).

Transcription is portrayed in 10th Martini Figure 3-12 (mRNA Transcription). Let's note a couple of points about this process:

- The two strands of DNA must be "unzipped" before the DNA-to-RNA process can begin. The two strands are complementary: A pairs with T, and C always pairs with G. The shapes of these complementary bases fit together like puzzle pieces.
- An enzyme called RNA polymerase makes a messenger RNA (mRNA) molecule using the template strand of DNA as a guide. The new mRNA molecule is made with bases complementary to the DNA template, although mRNA includes U in place of T.

Next comes translation of the mRNA into protein. Translation is shown in great detail in 10th Martini Figure 3-13 (The Process of Translation). Again, we will limit our attention to a few key points:

- The ribosome (a complex molecular machine that includes a large subunit and a small subunit) binds both to the mRNA and Transfer RNA (tRNA) molecules. tRNA molecules carry amino acids.
- Based on the way that mRNA codons match with complementary tRNA anticodons, each mRNA codon causes a specific amino acid to be added to the growing protein. For example, in the figure, the first codon, AUG, specifies the amino acid Methionine (M); the second codon, CCG, specifies the amino acid Proline (P); and so on.
- The end of the mRNA includes a "stop codon" to indicate that the translation of that mRNA is finished. The mRNA and completed protein (sometimes called a polypeptide at this stage; the distinction is not important for our purposes) then are released from the ribosome.

3.3: How do substances get across membranes?

This question is answered comprehensively by 10th Martini Figure 3-22 (Overview of Membrane Transport). Note that the Active Processes (on the right side) require ATP, whereas the Passive Processes (on the left side) do not.

The three Passive Processes are as follows (quotes taken from 10th Martini):

- Diffusion: "the movement of molecules … down a concentration gradient." Note that this includes diffusion through ion channels in membranes.
- Osmosis: "the diffusion of water molecules across a selectively permeable membrane."
- Facilitated Diffusion: "movement [down a concentration gradient" of materials across a membrane by a carrier protein."

And here are the three active processes:

- Active Transport: "requires carrier proteins that move specific substances across a membrane against their concentration gradients."
- Endocytosis (endo = inside): "the packaging of extracellular materials into a vesicle [sac surrounded by membrane] for transport into the cell." (At this point, we will not worry about the differences between receptor-mediated endocytosis, pinocytosis, and phagocytosis.)
- Exocytosis (exo = outside): "extracellular vesicles fuse with the plasma membrane to release fluids and/or solids from the cells."

The examples mentioned in 10th Martini Figure 3-22 are good. Note that the sodium-potassium exchange pump moves two ions simultaneously – sodium (Na^+) and potassium (K^+) – each against its gradient.

An example of exocytosis not mentioned in this figure is the release of neurotransmitters by nerve cells, which we will cover in Chapter 12.

Finally, the insulin-regulated glucose transporter, GLUT4, is interesting because it ties together a few distinct aspects of this chapter. GLUT4 is a carrier protein that carries out facilitated diffusion of glucose; i.e., GLUT4 binds to glucose and helps it move down its concentration

gradient into cells. When glucose levels in the blood are high, and more glucose needs to be taken out of the blood, vesicles containing GLUT4 fuse with the plasma membrane in an exocytosis-like process, except that GLUT4 is inserted into the plasma membrane rather than dumped outside the cell. And how did GLUT4 come to be in those vesicles in the first place? Proteins packaged in this way are generally made at the Rough ER and then are packaged into vesicles by the Golgi complex.

3.4: How do cells create new cells?

We conclude this chapter with a look at how cells make more of themselves.

What is necessary for one cell to divide into two? Lots of things must get duplicated: organelles, individual proteins, the chromosomes, etc. Even the plasma membrane must be expanded so that there is enough of it to surround two cells rather than one. Then all of the cellular components must be divided (equally, in most cases) between the daughter cells.

The phases of the cell's life cycle (referred to simply as the cell cycle by most biologists) are shown in 10th Martini Figure 3-24 (Stages of a Cell's Life Cycle). The phases include the following, in order:

- Interphase, which includes the following sub-phases:
    - G_0: cells that are not actively dividing are said to be in G_0 phase, where they may stay indefinitely.
    - G_1: this phase includes duplication of organelles.
    - S: S stands for synthesis of DNA, which is the major accomplishment of this phase.
    - G_2: here the cell crams for its impending division by performing "last-minute protein synthesis."
- M phase, which includes the following sub-phases:
    - Mitosis: the separation of the chromosomes into two daughter nuclei. Mitosis itself can be subdivided into several stages (prophase, metaphase, anaphase, telophase) according to the status of the chromosomes. Interestingly, most cells' chromosomes cannot be seen under a normal microscope until they condense during mitosis.
    - Cytokinesis: the separation of the entire cytoplasm into two daughter cells.

You may be aware that the body's cells vary greatly in the speed with which they progress though the cell cycle. Mature muscle cells and neurons are essentially stuck in G_0; they do not divide. At the other extreme, surface cells exposed to environmental threats (skin cells, cells lining the gastrointestinal tract) wear out quickly and are constantly being replaced by stem cells. While a high turnover rate seems useful, there are disadvantages too. Rapid cell growth and division is energetically costly, using up lots of ATP. Moreover, each cell seems limited to a certain number of divisions because bits of its ends (telomeres) are lost during DNA replication.

Many factors can speed up or slow down the cell cycle. Various growth factors, such as Growth Hormone, bind to receptors that ultimately cause transcription and translation of genes that speed

up the cycle. On the other hand, the so-called tumor suppressor genes can put a break on such processes. When tumor suppressor genes mutate, the result may be cancer – the unregulated growth of cells. Mutations (whether or not they lead to cancer) can come from several sources, such as:

- Bacterial or viral infections
- Chemicals
- Radiation
- Spontaneous mistakes in DNA replication

Current cancer treatments are often complex and multifaceted, but a couple of classical approaches can be understood in terms of concepts from this chapter, as shown in CTM Table 3.2.

CTM Table 3.2: Old Approaches to Cancer Chemotherapy

Type of drug	Mechanism	Life cycle stage	Will affect healthy dividing cells too?
DNA nucleotide analogues	Disruption of DNA replication. Nucleotide analogues get inserted into DNA, which then cannot be extended further.	S phase (DNA synthesis)	Yes.
Anti-microtubule agents (vinca alkaloids, taxanes)	Disruption of formation of the mitotic spindle, which is made out of microtubules and orchestrates chromosome movements.	M phase (prophase of mitosis)	Yes.

3.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 3: #7, #9, #10, #17, #18, #20, #21, #22, #23, #27, and #28. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 4: The Tissue Level of Organization

With this chapter we conclude our introductory march through the body's levels of organization (recall the top of 10th Martini Figure 1-1). We discussed the chemical level in Chapter 2 and the cellular level in Chapter 3; now in Chapter 4 we look at the tissue level, before moving on to the organ systems (integumentary, skeletal, muscular, and nervous) that will comprise the rest of the course.

4.0: Outline

4.1: Introduction to tissues
- A tissue is a group of cells specialized for certain functions.
- There are four basic types of tissues: epithelial, connective, muscular, and nervous.

4.2: Epithelial tissue
- Epithelial tissues cover external and internal surfaces of the body.
- Epithelial cells attach strongly to each other and to the underlying basement membrane via gap junctions, tight junctions, spot desmosomes, and hemidesmosomes.
- Epithelial tissues can be classified according to the number of layers of cells in the tissue (simple, stratified, or pseudostratified) and the shape of those cells (squamous, cuboidal, columnar, or transitional).
- Endocrine glands (which secrete hormones) and exocrine glands (which secrete other things) are also classified as epithelial tissue.

4.3: Connective tissue
- Connective tissues are extremely diverse. Collectively, they can be thought of as "anything that isn't epithelial, muscular, or nervous tissue."
- Subtypes of connective tissue include connective tissue proper (loose and dense; provides cushioning and connections to other tissues), fluid connective tissue (blood and lymph; provides transport of materials), and supporting connective tissue (cartilage and bone; provides strength and structural support).
- Most connective tissues have relatively few cells and relatively abundant extracellular matrix, often including extracellular proteins like collagen.

4.4: Tissue membranes
- Epithelial tissue is always adjacent to connective tissue – in particular, areolar tissue.

4.5: Muscle and nervous tissue
- Muscle tissue includes skeletal and cardiac muscle, which are striated, and smooth muscle, which is not.
- Nervous tissue includes neurons, which transmit electrical information, and supporting cells called glia.

4.6: How does the inflammation process involve all four tissue types?
- Epithelial cells in the skin are damaged; connective cells release histamine (mast cells), engulf debris (macrophages), and lay down new collagen during the repair process (fibroblasts); smooth muscle in blood vessel walls controls blood flow; the nervous system includes pain receptors in the skin.

4.7: Recommended review questions

4.1: Introduction to tissues

Since tissues are a level of organization above cells, tissues must be made up of cells. But what exactly are tissues? 10th Martini defines them as "collections of specialized cells that carry out a limited number of functions." There are four basic types of tissue: epithelial, connective, muscular, and nervous. Each includes multiple subtypes with different roles, but to get started, we will describe each simplistically (CTM Table 4.1).

CTM Table 4.1: The Four Basic Types of Tissue

Tissue Type	Major role(s)
Epithelial tissue	• Covers surfaces and passages • Forms glands
Connective tissue	• Provides structural support • Fills internal spaces • Transports materials
Muscular tissue	• Contracts and moves
Nervous tissue	• Transmits information electrically

If we return to the example of the heart featured in the top of 10th Martini Figure 1-1 (Levels of Organization), we see that cardiac muscle tissue consists of cardiac muscle cells working together. At even higher levels of organization, the four different tissue types combine to make organs and organ systems. The heart, for example, is surrounded by a pericardium, which includes epithelial and connective tissue; it connects to major arteries and veins whose walls include epithelial, connective, and (smooth) muscular tissue; and it is governed by nervous tissue such as the sympathetic and parasympathetic nerves that can increase or decrease heart rate.

4.2: Epithelial tissue

10th Martini provides a helpful, simple definition of epithelial tissue: "layers of cells that cover external or internal surfaces." This position as a covering layer means that epithelial cells must execute several distinct functions, such as those listed in CTM Table 4.2. Cellular structural features that enable these functions are also listed in this table; note that the three organelles listed – microvilli, vesicles, and cilia – were introduced in Chapter 3.

CTM Table 4.2: Structural and Functional Traits of Epithelial Cells

Structural feature (10th Martini figure)	Functions (structural features that support this function or make it necessary)
Attachment: Epithelial cells attach to the basement membrane of connective tissue underneath them (Fig. 4-1, 4-2e). **Border Outside Environment** (sometimes): Your skin epithelium does this, but your mouth, anus, etc. also interface with substances from the environment. **Cell Junctions:** Epithelial cells are close together (Fig. 4-2).	• **Protect body** (A, BOE, CJ, C, I) • **Limit permeability** (CJ, P) • **Sense stimuli** (I) • **Absorb nutrients** (M, V) • **Secrete wastes and other materials** (V) • **Regenerate quickly** (BOE) Abbreviations: A = Attachment

Cilia (sometimes): This organelle cleans surfaces by sweeping (Fig. 4-1). **Innervation:** Epithelial cells are connected to nerves (Fig. 5-1). **Microvilli** (sometimes): This organelle promotes absorption of nutrients (Fig. 4-1). **Polarity:** Sides of epithelial cells are not all the same! They have apical and basolateral sides (Fig. 4-1). **Vesicles** (sometimes): This organelle allows release and uptake of materials (Fig. 4-1).	BOE = Border Outside Environment CJ = Cell Junctions C = Cilia I = Innervation M = Microvilli P = Polarity V = Vesicles

One fundamental property of epithelial cells is their polarity – the fact that they have an apical side, which faces the outside or internal environment, and a basolateral side. The permeabilities and transporters of these two sides can be very different, as demonstrated by kidney cells like those pictured in 10th Martini Figure 26-13a (Countercurrent Multiplication and Urine Concentration).

If epithelial tissue forms a true protective barrier, they must attach strongly to each other and to the underlying connective tissue. A variety of cell junctions made out of proteins, shown in 10th Martini Figure 4-2 (Cell Junctions), ensure these strong connections:

- *Gap junctions* (Fig. 4.2b): These look kind of like ion channels (Chapter 3), but are larger and span two adjacent epithelial cells. Gap junctions are also used by non-epithelial cells like cardiac muscle cells for tasks like propagating electrical signals.
- *Tight junctions* (Fig. 4.2c): Proteins from adjacent epithelial cells prevent substances from diffusing from the environment above the epithelium to the connective tissue below it (or vice versa). Unlike gap junctions, tight junctions do not help adjacent cells share materials with each other.
- *Spot desmosomes* (Fig. 4.2d): These use proteins called Cell Adhesion Molecules (CAMs) to stick adjacent epithelial cells together. Spot desmosomes are a bit like tight junctions but do not themselves cut off diffusion between the environment and connective tissue.
- *Hemidesmosomes* (Fig. 4.2e): These structures anchor epithelial cells to the basement membrane beneath them. "Hemi" means "half," so a hemidesmosome can be thought of as a half of a desmosome (only one cell is involved, rather than two).

Despite epithelial cells' strength, they are subjected to constant wear and tear – even the constant friction of a passing fluid like blood can be hard on these cells. Therefore they must be replaced frequently. Epithelial stem cells, located near the basement membrane, divide often to keep up with this demand. As you can imagine, their progression through the cell cycle (G_1, S, G_2, M) can be rather fast, taking only about a day.

Epithelial tissues can be classified according to the number of layers of cells in the tissue and the shape of those cells. Simple epithelial tissue has a single layer of cells, while stratified epithelial tissue has more than one layer. The three basic cell shapes are squamous (flat – when you see the word squamous, think "squat" or "squashed"), cuboidal (cube-like), or columnar (column-like – tall and thin). Multiplying the two possible layering options by the three possible shape options gives us a total of six possible arrangements: simple squamous, stratified squamous,

simple cuboidal, stratified cuboidal, simple columnar, and stratified columnar. Beyond these six, there are also a couple of "bonus" types:

- pseudostratified columnar epithelium: there is only a single layer of cells, but the cells' varied shapes can (misleadingly) suggest a stratified appearance
- transitional epithelium: this stratified epithelium has cells that can be pillow-like or stretched into flatter shapes

These types of epithelial tissue are shown in 10th Martini Figures 4-3 (Squamous Epithelia), 4-4 (Cuboidal and Transitional Epithelia), and 4-5 (Columnar Epithelia). We will look at these cells in lab. For now, let's just note how structural features of some of these cells relate to their functions (CTM Table 4.3).

CTM Table 4.3: Structures and Functions of Selected Epithelial Tissues

Epithelial tissue type	Features	Examples of where this epithelial tissue is found
Simple squamous epithelium	Single layer of flat cells provides minimal protection but is good for quick diffusion	• internal linings where strong protection is not needed, e.g., lining of blood vessels • air sacs of lungs
Simple columnar epithelium	Goblet cells produce mucus to lubricate the digestive tract; microvilli promote absorption	• lining of intestine
Pseudostratified columnar epithelium	Goblet cells produce mucus to trap polluting substances and cilia to sweep them up toward the throat	• lining of respiratory tract
Transitional epithelium	Pillow-shaped cells can stretch out to accommodate changes in volume (of, say, urine in the bladder)	• lining of urinary tract
Stratified squamous epithelium	Having multiple layers of cells provides good protection against the external environment	• skin, mouth, throat, esophagus, rectum, anus, vagina

For completeness, we should note that glands are also classified as epithelial tissue rather than connective, muscular, or nervous tissue. Glands do not quite fit the definition of covering external or internal surfaces, but they arise from epithelial tissue during development and thus are considered epithelial tissue as well. There are two main types of glands, which we won't dwell on but will mention in passing:

- Exocrine glands: These secrete digestive enzymes, milk, oil, sweat, etc. Substances are released into ducts. Examples include your sebaceous glands and sweat glands, which we will come to in Chapter 5.
- Endocrine glands: These secrete hormones, which are released directly into the blood rather than into ducts. Examples include the thyroid gland and parathyroid gland, whose calcium-regulating hormones (calcitonin and parathyroid hormone, respectively) are covered in Chapter 6.

Interestingly, the pancreas can be considered both an endocrine gland AND an exocrine gland, as it produces and releases both hormones (insulin, glucagon) and digestive enzymes.

4.3: Connective tissue

Connective tissue is probably the most diverse of the four tissue types. In fact, one way of defining connective tissue is as "anything that isn't epithelial, muscular, or nervous tissue," all of which tend to be more homogeneous and relatively easy to recognize. Below is a hierarchy of the many connective tissue subtypes.

1. Connective tissue proper
    a. Loose connective tissue
        i. Areolar
        ii. Adipose (i.e., fat)
        iii. Reticular
    b. Dense connective tissue
        i. Dense regular (includes tendons and ligaments)
        ii. Dense irregular
        iii. Elastic
2. Fluid connective tissue
    a. Blood
        i. Red blood cells
        ii. White blood cells
        iii. Platelets
    b. Lymph
3. Supporting connective tissue
    a. Cartilage
        i. Hyaline cartilage
        ii. Elastic cartilage
        iii. Fibrocartilage
    b. Bone

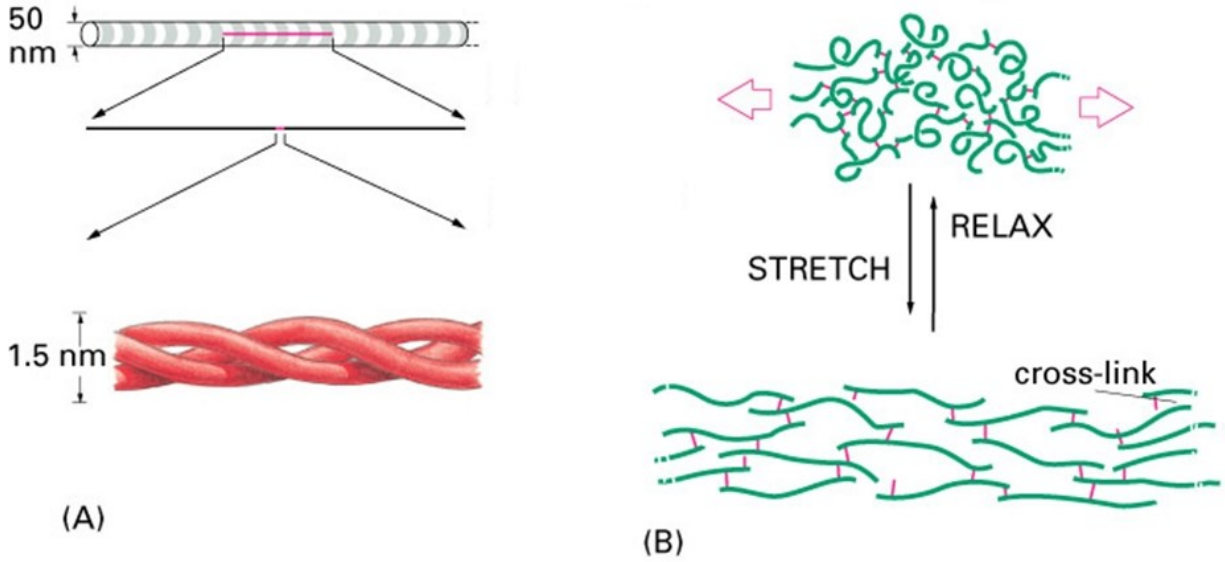
This outline is one way of portraying the diversity of connective tissues. 10th Martini Figure 4-8 (The Cells and Fibers of Connective Tissue Proper) is another way. Note all the different types of cells (adipocytes, fibroblasts, lymphocytes, macrophages, mast cells, melanocytes, mesenchymal cells … and fibrocytes [not pictured]) and proteins (collagen fibers, elastic fibers, reticular fibers) included in connective tissue proper, though they won't all be found in the same location.

This diversity is one trait that sets connective tissue apart from the other tissue types. Another difference between connective tissue and the other tissue types is that the extracellular matrix – the stuff outside the cells themselves – is uniquely important in connective tissue. In fact, a majority of the volume of connective tissue is extracellular matrix rather than cells. We can think of the extracellular matrix as having two major components: ground substance and protein fibers.

Like molasses, ground substance is a sticky, viscous fluid that contains lots of carbohydrates. In ground substance, many of these carbohydrates are attached to proteins – glycoproteins and proteoglycans are both components of ground substance, and both of these terms refer to combinations of sugar (glyc) and protein.

Protein fibers are basically proteins that are long, rather than globular. As noted above, there are three major kinds in connective tissue: collagen fibers, reticular fibers, and elastic fibers. Collagen fibers are unbranched, while reticular and elastic fibers are branched. (The word "reticular" means "network" and thus suggests branching. Recall from Chapter 3 that the endoplasmic reticulum is a network inside the cell.) CTM Figure 4.1 shows the molecular structures of collagen and elastin (the protein that makes up elastic fibers).

CTM Figure 4.1: Proteins structures suggest their functional properties. The rope-like structure of collagen (A) allows it to resist stretching, while the protein elastin (B) has numerous cross-links that allow it to curl up and stretch out. Figure taken from Essentials of Cell Biology, *2nd edition, by Bruce Alberts et al., published by Garland Science (2003).*



As with epithelial tissue, 10th Martini offers lots of details on each subtype of connective tissue. Again, we will inspect these tissues in lab; for now, let's give some examples of how their anatomical locations and structures relate to their functions. (Please note that CTM Table 4.4 is NOT comprehensive.)

CTM Table 4.4: Partial List of Connective Tissues' Structures and Functions

Connective tissue type (10th Martini figure)	**Location/structure**	**Function(s)**
Mesenchyme (Fig. 4-9)	Mostly found in embryo.	• Gives rise to all connective tissues

Areolar (Fig. 4-10)	Diverse cell types include macrophages and mast cells.	• Involved in inflammation and immune response
Adipose (Fig. 4-10)	Mostly fat cells.	• Energy storage, cushioning, warmth/insulation
Reticular (Fig. 4-10	Found in lymphoid organs (lymph nodes, bone marrow, spleen).	• Involved in development of new blood cells and disposal of old ones
Dense Regular (Fig. 4-11)	Found in ligaments and tendons.	• Connect bones to bones and bones to muscle; elastic storage of energy
Elastic (Fig. 4-11)	Elastic fibers are found in walls of large arteries.	• Stretching and relaxation of blood vessel walls
Red Blood Cells, a.k.a. Erythrocytes (Fig. 4-12)	These are essentially little bags of hemoglobin, a protein that binds oxygen.	• Oxygen transport through the blood
Bone (Fig. 4-15)	Extracellular matrix is dry, with calcium carbonate and calcium phosphate instead of polysaccharides.	• Minerals provide strength (resist compression)

Because there is so much diversity within the realm of connective tissue, it is hard to summarize in statements that are both accurate and specific. However, if we return to the three main types of connective tissue – connective tissue proper, fluid connective tissue, and supporting connective tissue, the following generalizations are roughly true:

- Connective tissue proper provides cushioning and connects epithelial tissue to other types of tissues.
- Fluid connective tissue transports materials.
- Supporting connective tissue provides strength and structural support.

4.4: Tissue membranes

10th Martini defines tissue membranes as "membranes that line or cover body surfaces." These sound a lot like epithelial tissues, but they include connective tissue too. For our purposes, the main point here is that epithelial tissues always have connective tissue next to them. This is evident in 10th Martini Figure 4-16 (Types of Membranes). For each of the figure's four panels (a through d), note that the epithelium is flanked by areolar connective tissue. Thus, whenever you see epithelial tissue, you can be sure that connective tissue is nearby.

4.5: Muscle and nervous tissue

We will have much more to say about muscular tissue in Chapter 10, and about nervous tissue in Chapter 12. For now, a few comments will suffice.

There are three main types of muscle tissue, as presented in CTM Table 4.5 and 10th Martini Figure 4-18 (Types of Muscle Tissue). Under the microscope, one can make a fundamental distinction between striated muscle, whose repeating units of sarcomeres (details in Chapter 10) give them a striped appearance, and smooth muscle, which do not appear striped. Both skeletal muscle and cardiac muscle qualify as striated.

CTM Table 4.5: Types of Muscular Tissue

Muscle tissue type	Description of cells	Locations
Skeletal	Striated, long, multi-nucleated, cylindrical.	• All muscles under voluntary control
Cardiac	Striated, short, sometimes branching, usually one nucleus.	• The heart
Smooth	NOT striated, tapered at ends, one nucleus.	• The walls of many hollow organs (blood vessels, digestive tract, etc.)

Nervous tissue includes excitable nerve cells called neurons – "excitable" meaning that their membranes' voltages change as a means of passing information from cell to cell. Neurons generally have many branches – dendrites for receiving inputs and an axon for delivering outputs – attached to a cell body, which contains the nucleus. 10th Martini Figure 4-19 (Neural Tissue) shows these branches. A neuron whose dendrites are hard to see or absent and a long, prominent axon may resemble a sperm cell with its flagellum, except that neurons are much larger than sperm. This is an example of how the scale of a microscope image may help you determine what you're looking at; the most obvious difference between a neuron and a sperm cell might be the relative sizes.

Aside from neurons, nervous tissue also includes nonexcitable supporting cells called glial cells or glia. "Glia" means "glue," and, indeed, these cells are the metaphorical glue that holds the nervous system together.

4.6: How does the inflammation process involve all four tissue types?

10th Martini Figure 4-20 (Inflammation and Regeneration) provides a nice example of how all four tissue types can be involved in a physiological process.

Inflammation can be summarized as follows: a cut or scrape that penetrates the skin activates mast cells, which release histamine and other chemicals, which lead to many aspects of inflammation (as shown in the figure): increased blood flow, increased blood vessel permeability, pain, increased local temperature, increased delivery of oxygen and nutrients, increased phagocytosis (engulfment of pathogens and debris), and removal of toxins and wastes. Then the damaged tissue is replaced with scar tissue.

So what role does each tissue type play in this process? Let's take a look.

- *Epithelial tissue*: If the injury penetrated down to connective tissue, epithelial tissue must initially have been damaged or destroyed. The increased blood vessel permeability that is part of inflammation results from fluids leaking out of epithelial cells lining the blood vessels.
- *Connective tissue:* The histamine-releasing mast cells are connective tissue, as are the blood cells themselves. Debris and pathogens are engulfed by macrophages, which are connective tissue cells. The subsequent repair process is led by collagen-producing fibroblasts, which are connective tissue cells too, and the scar tissue that replaces the damaged connective tissue is also connective tissue.
- *Muscle tissue:* Blood flow is controlled in part by smooth muscles around medium-sized blood vessels called arterioles. When these muscles relax, the vessels dilate (open wider) and more blood can flow through them.
- *Nervous tissue:* As stated by 10th Martini, "the abnormal conditions within the tissue and the chemicals released by mast cells stimulate nerve endings that produce the sensation of pain."

4.7: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 4: #1, #2, #3, #9, #11, #15, #22, #24, #26, #27, #31, #32. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 5: The Integumentary System

We are done with the introductory chapters (1 through 4) – hooray! Now we are ready to focus on our first specific organ system: the integumentary system. The level of detail provided by 10th Martini is, at times, excruciating (Figures 5-12 and 5-15 are examples of this), but here in CTM we will try to keep things reasonable.

5.0: Outline

5.1: What is the integumentary system?
- The integumentary system encompasses the skin and structures embedded in it.
- Layers of the integumentary system include the epidermis, dermis, and hypodermis.
- The integumentary system's accessory structures include hairs with arrector pili muscles, sebaceous and sweat glands, blood vessels, and sensory receptors of the nervous system.

5.2: Layers (strata) of the epidermis
- The bottom layer, the stratum basale, includes melanocytes and epithelial stem cells.
- The upper layers consist mostly of keratinocytes. In the top layer, the stratum corneum, these cells are dead vessels full of keratin.

5.3: How does melanin protect us from UV light?
- Melanin is a pigment produced by melanocytes.
- Melanin absorbs UV light that might otherwise cause genetic mutations and lead to cancer.
- Melanin's production is stimulated by cellular damage caused by UV light.
- Melanin is transferred from melanocytes to keratinocytes so that they too are protected from UV light.

5.4: Where does vitamin D_3 come from?
- Vitamin D_3 can be obtained from food or synthesized from a steroid precursor.
- Vitamin D_3 is converted into calcitriol, a hormone that promotes calcium absorption in the intestine.

5.5: Hair, sebaceous glands, and sweat glands
- Hairs, sebaceous glands, and sweat glands are all derived from the epidermis.
- Hair insulates the body and protects the skull.
- Sebaceous glands' oil inhibits bacterial growth and prevents dehydration.
- Sweat glands help unload excess heat. Blood flow to the skin does this too.

5.6: Healing the integument
- Recovery from a skin injury involves migration of epithelial cells, phagocytes, and fibroblasts, and proliferation of the collagen-secreting fibroblasts.
- Risks from integument injuries such as burns include dehydration, hypothermia, and infection.

5.7: Recommended review questions

5.1: What is the integumentary system?

While different sources use the words integument and integumentary system slightly differently, "integument" is generally equivalent to "the skin," and "integumentary system" generally means "the skin and associated structures." The integumentary system basically includes everything pictured in 10th Martini Figure 5-1 (The Components of the Integumentary System) plus the nails. (Note that the hypodermis is not always considered part of the integumentary system.) The big-picture message of 10th Martini Figure 5-1 is that when we say "skin," "integument," or "integumentary system" we are talking about the layers beneath the outside-facing surface of the body and well as the surface itself.

Now let's analyze 10th Martini Figure 5-1 in greater detail.

First notice the layer labels on the left side: epidermis, dermis, and hypodermis. The order of these should be easy to remember if you can recall (from the Appendix in Chapter 1, for example) that epi means "around" or "outer" and "hypo" means "below" or "lower."

After your studies of the four tissue types in Chapter 4, you will not be surprised to find that the epidermis consists of epithelial tissue and that the dermis and hypodermis include connective tissue (which is always found next to epithelial tissue). You may even be able to guess at the specific types of connective tissue pictured in Figure 5-1 based on their appearance. The many wavy pink lines in the reticular layer of the dermis indicate an abundance of collagen (found here in dense irregular tissue), and the yellow globs are adipocytes (fat cells). The correspondence of integumentary system layers and tissue types is summarized in CTM Table 5-1. Note that, despite the name, the reticular layer of the dermis is NOT made up of the reticular connective tissue mentioned in Chapter 4.

CTM Table 5.1: Layers of the Integumentary System

Integumentary System Layer	Tissue Type	Tissue Sub-Type
Epidermis	Epithelial tissue	Stratified squamous epithelium
Dermis		
Papillary Layer	Connective tissue	Areolar connective tissue
Reticular Layer	Connective tissue	Dense irregular connective tissue
Hypodermis	Connective tissue	Adipose connective tissue, etc.

The right side of 10th Martini Figure 5-1 lists "accessory structures" embedded in the different layers. These include (A) hairs with arrector pili muscles, (B) sebaceous (oil) and sweat glands, (C) blood vessels, and (D) sensory structures of the nervous system. (A) and (B) will be covered below in a bit more detail; for now, let us briefly consider (C) and (D).

As you know, blood vessels transport blood throughout the body, delivering nutrients and picking up waste products. 10th Martini Figure 5-1 uses the usual color-coding, which is that arterial or oxygenated blood is shown in red and venous or deoxygenated blood is shown in blue. Beyond the usual nutrient delivery and waste pick-up, blood flow to the skin also affects body temperature. Blood flow to the skin comes from the body's core, where the temperature is about 98.6 °F (37 °C). The more blood that flows to the surface of the body, the more heat is delivered

to the surface tissues and then lost to the environment via convection. Blood flow to the skin (cutaneous blood flow) is thus an effector in the negative feedback system that governs body temperature; if body temperature gets too high, cutaneous blood flow increases.

Multiple types of sensory receptors from the nervous system are also embedded in the integumentary system. These are positioned at different depths and are responsive to different types of stimuli. They include receptors for pain, temperature, light touch (tactile or Meissner's corpuscles), and deep pressure (lamellated or pacinian corpuscles). We will defer the details until Chapter 15 (if we get to it).

5.2: Layers (strata) of the epidermis

The epidermis can be subdivided into several layers – four for most skin, five for the thick skin on the palms of the hands and the soles of the feet. As pictured in 10th Martini Figure 5-3 (The Epidermis), they are (from outermost to innermost): stratum corneum, stratum lucidum (thick skin only), stratum granulosum, stratum spinosum, and stratum basale. "Stratum" means "layer," so each of the names simply indicates a different layer. I do not want you to memorize the names and details of all of these layers; we will focus mostly on a few aspects of the top and bottom layers.

The outer layer, the stratum corneum, consists of many layers of dead cells stuffed with the protein keratin. These keratin-containing cells are called keratinocytes, and the process by which these cells migrate up from the lower layers and are transformed into inert holders of keratin is called keratinization. (The name "stratum corneum" may be more memorable if you know that keratinization is also called cornification, and that a corn is a hard thickening of the skin.) The cells' organelles are lost during this process, such that, just as red blood cells are basically sacs of hemoglobin and skeletal muscle cells are made up almost entirely of actin and myosin and associated contractile proteins, keratinocytes likewise become extremely specialized. The type of keratin found in skin (and in nails) is extremely tough and thus offers good protection against the environment.

The bottom layer, the stratum basale ("basal" means "bottom"), interfaces with the connective tissue beneath it, so these epithelial cells attach to the basement membrane via hemidesmosomes, as discussed in Chapter 4. The stratum basale includes epithelial stem cells and spider-shaped cells called melanocytes. The latter produce the pigment melanin, discussed below; the former constantly divide into daughter cells that can differentiate and replace the mature keratinocytes that are constantly wearing out and sloughed off. It's advantageous that these stem cells are in the stratum basale – they are somewhat protected from the external environment and are also close to the blood supply (refer back to 10th Martini Figure 5-1) and can get the nutrients they need. This is in contrast to the dead keratinocytes in the stratum corneum, which, being dead, do not need access to the blood.

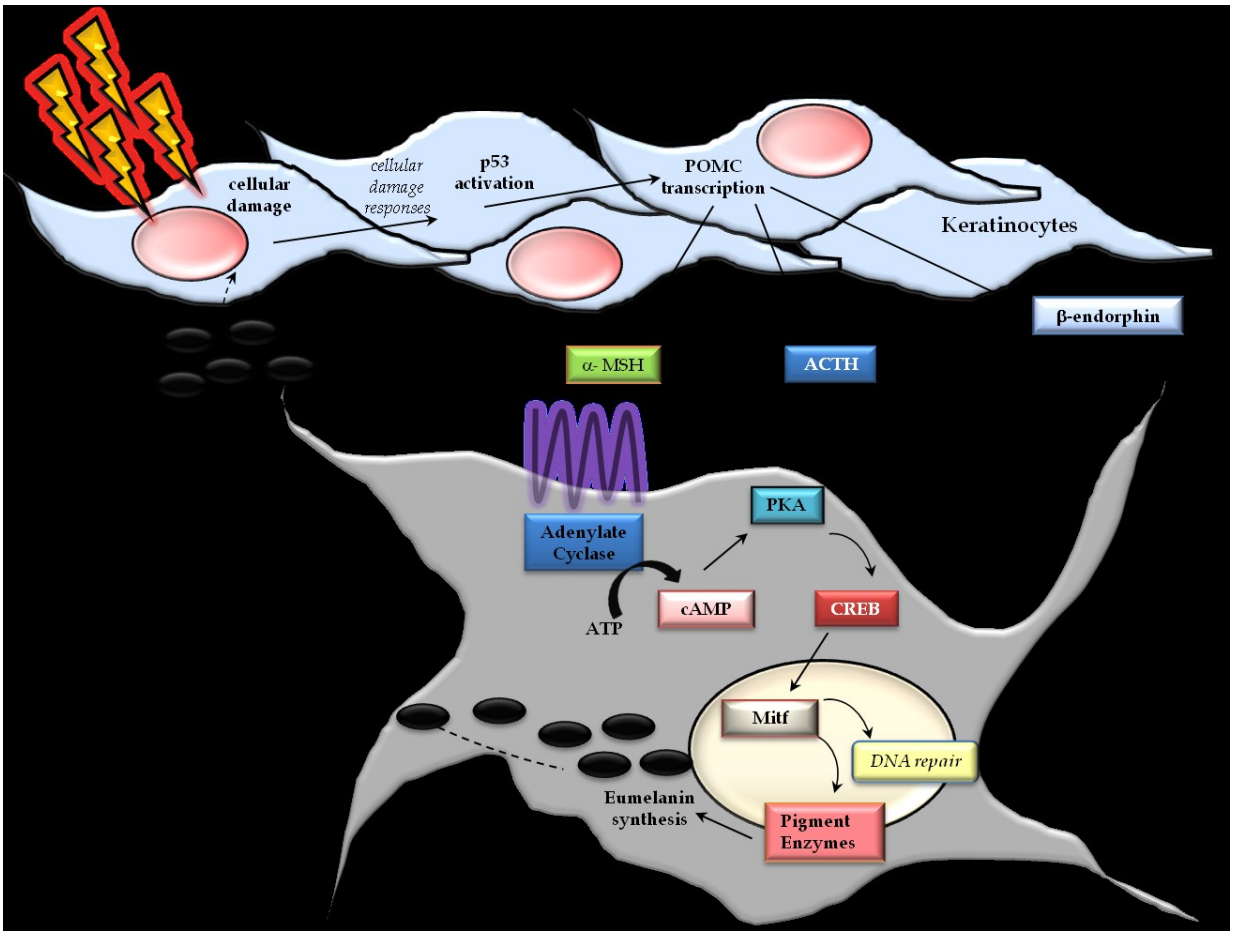
5.3: How does melanin protect us from UV light?

Melanin is a pigment – not a protein, but an organic molecule synthesized by enzymes in melanocytes. It absorbs potentially harmful ultraviolet radiation (UV light) from the sun, which could otherwise damage DNA, potentially leading to cancer.

Here is a paradox to ponder: melanin is made by melanocytes, which are in the deepest layer of the epidermis (stratum basale). Yet most cells of the epidermis, including the more superficial ones that absorb a lot of the UV light, are not melanocytes. How could production of melanin by the melanocytes protect the epidermis as a whole?

The short answer is that melanin is transferred from melanocytes to keratinocytes via exocytosis of melanin-containing organelles called melanosomes. More details can be seen in CTM Figure 5.1 and are described in the legend of this figure. Can you see how the components pictured could be considered a negative feedback system?

CTM Figure 5.1: The epidermal response to UV light. UV light causes cellular damage in the keratinocytes. This activates the tumor suppressor p53, which (through mechanisms we won't worry about) causes the pituitary gland in the brain to secrete Melanocyte-Stimulating Hormone (MSH), which causes the melanocytes to make more melanin, which is then transferred to the keratinocytes and absorbs more UV light so that it does less damage to the keratinocytes. Figure taken from "Melanoma – epidemiology, genetics and risk factors" by J.A. D'Orazio et al., which is Chapter 1 of the book Recent Advances in the Biology, Therapy and Management of Melanoma*, edited by Lester M. Davids and published by Intech (2013).*



5.4: Where does vitamin D_3 come from?

One other important physiological function of the epidermis is to contribute to the production of calcitriol, a hormone that aids in the absorption of calcium and phosphate from the small intestine. (The first two syllables of "calcitriol" should make you think of calcium.) Calcium and phosphate, identified by 10th Martini Table 2-1 (Principal Elements in the Human Body) as key elements in the body, are especially important in bones, as we will see in Chapter 6.

Calcitriol can be made via multiple routes, as summarized nicely by 10th Martini Figure 5-6 (Sources of Vitamin D_3). The compound cholecalciferol, also known as vitamin D_3 (or vitamin D for short), can be obtained from food, absorbed, and taken up by the liver, which converts the compound to a form that can then be further converted by the kidney into calcitriol. Alternatively, sunlight can stimulate epidermal cells to convert a steroid compound into vitamin D_3, which then is further processed by the liver and kidney. Because sunlight plays this role in vitamin D_3 production, vitamin D_3 is often called "the sunshine vitamin."

5.5: Hair, sebaceous glands, and sweat glands

Hair and sebaceous and sweat glands all arise from epidermal cells that, in the course of development, burrow their way down into the dermis while still remaining connected to the rest of the epidermis.

Like the stratum corneum of the "regular" epidermis, individual hairs are made up mostly of dead keratinocytes full of keratin. These hairs can be pulled erect by the erector pili muscles. Our evolutionary predecessors probably benefitted from this ability to thicken their coat of insulation and thus conserve heat.

Sebaceous and sweat glands are both exocrine glands, rather than endocrine glands. As covered in Chapter 4, endocrine glands secrete hormones, but exocrine glands secrete other things, such as oil in the case of sebaceous glands and sweat in the case of sweat glands.

If you compare the left panel of 10th Martini Figures 5-13 (The Structure of Sebaceous Glands and Sebaceous Follicles) with the middle panel of Figure 5-14 (Sweat Glands), you may notice that sebaceous and sweat glands have somewhat similar structures. For example, both of them have ducts that can empty either into hair follicles or directly out to the surface of the skin. However, sebaceous glands have a multi-lobed structure, whereas sweat glands look more like coiled tubes.

Sebaceous glands secrete an oily substance that inhibits the growth of bacteria (though many bacteria do live on our skin anyway) and keeps the skin and hair from drying out. (Water cannot escape as easily if it has to pass through a hydrophobic layer.) The sweat released by sweat glands provides another mechanism of keeping our body temperature under control; evaporation of sweat from the skin uses up heat and thus cools the body.

At this point, we can summarize the major functions of the integumentary system in the form of CTM Table 5.2.

CTM Table 5.2: Structures and Functions of the Integumentary System

Structure	Function
Epidermis	
Keratin	Protect against physical and chemical threats from the environment
Melanin	Protect against UV light
Sensory receptors of nervous system	Detect pressure, temperature, and pain
Blood vessels	Regulate body temperature (and deliver nutrients and remove wastes)
Hair	Insulate the body, protect the skull
Sebaceous glands	Inhibit bacterial growth, prevent dehydration of skin and hair
Sweat glands	Cool the surface of the body
Nails	Support and protect the tips of the digits (fingers and toes)

We have seen that the integumentary system includes not one but two mechanisms for cooling the body: increasing blood flow to the skin, and secreting sweat from sweat glands. It turns out that elderly people tend to have deficits in both of these areas: they send less blood to the skin, and they produce less sweat. In part for these reasons, the elderly are more vulnerable to heat stroke than the general population.

5.6: Healing the integument

Having examined the integumentary system in some detail, we are now ready to ponder what happens when that system gets injured.

In Chapter 4 we looked at how injuries to the skin can trigger an inflammation process that involves all four tissue types. Here we will revisit skin injuries, now focusing more on the repair process. Please refer to 10th Martini Figure 5-16 (Repair of Injury to the Integument) for visuals.

Initially, penetration of the skin causes mast cells in the dermis to secrete chemicals such as histamine, which trigger an inflammatory response that includes increased blood flow, swelling, a local increase in temperature, and redness. But how can the damage be reversed? 10th Martini divides the recovery period into a Migratory Phase (panel 2 of Figure 5-16), a Proliferation Phase (panel 3), and a Scarring Phase (panel 4).

In the Migratory Phase (hours post-injury), multiple types of cells are migrating. Cells from the stratum basale of the epithelium are migrating to create a new epithelial layer underneath the scab that has formed from clotted blood. Meanwhile, phagocytes have migrated into the region to "eat up" debris, and fibroblasts have migrated to start generating new extracellular matrix components such as collagen.

In the Proliferation Phase (days post-injury), the new epidermal layer is complete and is pushing the scab outward. Fibroblasts are proliferating and creating new connective tissue in the dermis.

In the Scarring Phase (weeks post-injury), the repair of the injury is essentially complete. Note that this area of the skin is not quite the same as it was before. The new connective tissue will generally have fewer blood vessels, glands, and sensory receptors than before, and thus cannot quite be considered "as good as new."

While the previous paragraphs emphasize beneficial aspects of the normal healing process, this process also entails clinical risks. Major risks include dehydration (fluid loss), hypothermia (heat loss), and infection.

One situation in which these risks are evident is the voluntary surgery of liposuction (Clinical Note on page 163 of 10th Martini). Since the fat to be sucked out is in the hypodermis, a penetration must be made through the epidermis and dermis. This creates the possibility of an infection and/or loss of sensation in the area of the surgery (if the sensory receptors are damaged or destroyed). Loss of heat, fluids, and/or blood are also possible, although small incisions into the body should limit these problems.

A related clinical situation is that of a burn victim (Clinical Note on page 171 of 10th Martini). Infection is again a risk, so wounds should be cleaned and treated with antibiotics. Depending on how much of the skin was burned, dehydration and hypothermia may also be likely. Dehydration may be countered by giving the patient fluids (intravenously, if necessary); heat loss can be minimized through appropriate "bundling" in clothing and blankets, and also providing nutrients to maintain the patient's metabolism and the heat production that accompanies it.

5.7: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 5: #1, #5, #10, #21, #24, #27, #29, and #30. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 6: Osseous Tissue and Bone Structure

Having dispensed with our first specific organ system, the integumentary system, in Chapter 5, we now move on to another organ system, the skeletal system, which is the primary topic of Chapters 6 through 9.

6.0: Outline

6.1: What is the skeletal system?
- The skeletal system includes the following connective tissues: bones, cartilage, ligaments, and tendons.

6.2: Bone structure: gross anatomy
- Long bones have compact bone and a hollow interior along the main shaft (diaphysis), and spongy bone at the end (epiphysis).
- Bones have features called markings that assist in the formation of joints, provide places for tendons and ligaments to attach, and accommodate nerves and blood vessels.

6.3: Bone structure: molecular and cellular details
- Compact bone is organized into osteons, which include concentric layers (lamellae) of matrix surrounding a central canal.

6.4: How do bones handle forces?
- Bones are composites of collagen, which resists expansion (tension) well, and minerals like calcium and phosphate, which resist compression well.

6.5: How do bones develop and get remodeled?
- Most bones mature via endochondral ossification, in which cartilage is laid down first and then replaced by bone. This also happens following a bone fracture.
- Bones elongate at the metaphysis (between diaphysis and epiphysis) until the end of puberty.
- Bone remodeling by osteoclasts and osteoblasts continues throughout life.
- Osteoclasts resorb existing bone and release calcium into the blood, while osteoblasts use calcium from the blood to build new bone tissue.

6.6: How is calcium homeostasis maintained?
- Calcitonin from the thyroid gland increases calcium use by osteoblasts, decreases calcium absorption in the intestine, and increases calcium excretion via the kidneys. Parathyroid hormone has the opposite effects.
- Calcitriol increases calcium absorption in the intestine.

6.7: How do diet, exercise, and age affect bone health?
- To maintain strong bones, obtain plenty of vitamin D3 and calcium, do a variety of higher-impact exercises that stress different bones, and monitor sex hormone levels.

6.8: Recommended review questions

6.1: What is the skeletal system?

When you hear or see the word "skeletal," you may think "skeleton." Indeed, the skeletal system includes the body's bones. Also included are ligaments (which connect bones to other bones), tendons (which connect bones to muscles), and cartilage. All of these are connective tissues that were introduced in Chapter 4. Here we will focus mostly on the bones themselves.

When we think of bones, we often think of the structural support they provide for the body, and this is definitely one of the skeletal system's key functions. However, 10th Martini lists four additional functions:

- Store minerals (e.g., calcium, phosphate) and lipids (in yellow marrow)
- Produce blood cells (in red marrow)
- Shield soft tissues and organs from harm
- Serve as levers for muscles to pull on, enabling movement

6.2: Bone structure: gross anatomy

Bones come in various shapes. Our most common image of a bone may be the long bones that dogs like to chew on. We can distinguish long bones from other bone shapes: short (box-like), flat, and irregular. (Your lab manual includes sutural and sesamoid bones in the irregular category, and we will do the same.) We won't worry too much about sorting bones into these shape categories, but you should be aware that differently shaped bones have different internal structures. Compare the femur (a long bone) and the parietal bone of the skull (a flat bone) in 10th Martini 6-3 (Bone Structure), for example. While both bones include both compact bone and spongy bone, the arrangement of the two is quite different. While we are on this figure, note the following long-bone terminology:

- *Epiphysis:* the end of a long bone ("epi" often means "outer")
- *Diaphysis:* the main shaft of a long bone
- *Metaphysis:* where the epiphysis and diaphysis meet ("meta" often means "middle")
- *Medullary cavity:* the hollow middle of a long bone ("medulla" also means "middle"; the medulla is an inner part of the brain, and the inner layer of the kidney is also called the medulla)

You have probably noticed that most bones are not completely smooth and symmetrical. Most have a bunch of irregularities (bumps, grooves, etc.) collectively called surface features or bone markings. 10th Martini Figure 6-2 (An Introduction to Bone Markings) lays out the many different terms used to refer to these markings. The markings may be grouped according to their functions, as done by your lab manual:

- *Projections for tendon or ligament attachment*
    - Crest (narrow ridge)
    - Epicondyle (raised area above a condyle)
    - Line (narrow ridge, smaller than a crest)
    - Process (generic term)
    - Trochanter (very large projection on femur)
    - Tubercle (small, rounded projection)
    - Tuberosity (larger, rounded projection)
- *Projections for forming joints with other bones*
    - Condyle (rounded projection at joint)
    - Facet (smooth, nearly flat projection at joint)
    - Head (enlarged end of a bone)
    - Ramus (arm-like bar; pronounced "RAY-mus")
- *Depressions/openings for blood vessels/nerves*

  - Fissure (narrow slit)
  - Foramen (rounded opening)
  - Groove (narrow valley)
  - Notch (indentation)
- *Other depressions/openings*
  - Fossa (shallow depression)
  - Meatus (canal; pronounced "mee-AY-tus")
  - Sinus (air-filled cavity)

I don't expect you to memorize these terms, but do notice their meanings and functional groupings. This list will be a helpful reference when we examine specific bones. For example, if you are looking for the foramen magnum in the skull, it is useful to know that "foramen" means "rounded opening" – especially if you are referring to a diagram whose labeling is not entirely clear.

Some bone markings are unique to particular individuals and circumstances. Anthropologists and pathologists can use bone markings to solve crimes, infer living conditions, etc. Here are a couple of examples from the Smithsonian Institute website "Written in Bone" (http://anthropology.si.edu/writteninbone/):

- A body was found in a fire, but was the fire the cause of death? Broken ribs showed wounds made by a long knife, with no signs of healing … so the building was apparently set on fire to hide a murder!
- A baby's skull from 17th-century Maryland was thin and had extra holes in it. This indicated to anthropologists that the baby was malnourished.

6.3: Bone structure: molecular and cellular details

We began learning about the microscopic structure of bone tissue in Chapter 4 (and in Exercise 6 of your lab manual). Now we will zoom in again. 10th Martini Figure 6-6 (The Structure of Compact Bone) shows details of compact bone – the kind that is found along the edges of the diaphysis of long bones (see above). Compact bone is organized into osteons, each of which consists of concentric layers (lamellae; singular: lamella) of extracellular matrix around a central canal of blood vessels. Tucked between the lamellae are small pockets called lacunae (singular: lacuna) in which mature bone cells (osteocytes) reside. The lacunae are connected by tiny passageways called canaliculi (singular: canaliculus).

The dense, solid appearance of compact bone shown in 10th Martini Figure 6-6 contrasts with the looser meshwork of spongy bone shown in 10th Martini Figure 6-7 (The Structure of Spongy Bone). While both types of bone have lamellae, spongy bone's bundles (trabeculae) of lamellae are interspersed with softer bone marrow.

6.4: How bones handle forces

Because of how the human skeleton is arranged, the weight of our trunk does not come down directly on top of our femur; rather, our body weight is directed toward the medial side of the femur. This subjects the femur to potential bending: the material in the medial side of the femur undergoes compression (is pushed together), while the material in the lateral side undergoes tension (is expanded or stretched apart), as diagrammed in 10th Martini Figure 6-8 (The Distribution of Forces on a Long Bone). Imagine the bone in Figure 6-8 getting bent slightly to the right under the weight of the body; the materials in the medial shaft will be compressed, while the materials on the opposite side will be stretched apart. This can also be visualized with a straw (another hollow cylinder), rather than a bone, being bent.

In between the side of the bone that experiences compression and the side that experiences tension, there is a so-called neutral axis where there is no net force on the bone (neither compression nor tension), which is one reason why bones like the femur are hollow – it is not advantageous to put strong material where there are no forces to resist!

Although one side of a bone might be subjected to compression more frequently, and another side might most often experience tension, the fact is that bones generally need to be able to handle both compression and tension (as well as shearing and torsion). Interestingly, few materials (biological or otherwise) are good at resisting both compression and tension. Therefore, stress-resistant materials (biological or otherwise) tend to be composites containing both compression-resistant ingredients and tension-resistant ingredients.

In bone, proteins like collagen are highly tension-resistant but not very compression-resistant. This is perhaps unsurprising if you consider collagen's rope-like structure (recall CTM Figure 4.1, which compared collagen and elastin). If you try to pull on both ends of a rope, good luck making it longer – it will be hard to do! However, you can push the ends of the rope together quite easily – that is, the rope is not very resistant to compression.

Conversely, minerals – for example, combinations of calcium and phosphate – are often very good at resisting compression, but very susceptible to tension. Thus, the extracellular matrix of bone has good all-around strength because it is a mixture of tension-resistant protein fibers (like collagen) and compression-resistant minerals (like calcium and phosphate).

Finally, note that in a long bone such as the femur, all of the osteons will be aligned along the long axis, and that the bone will be highly resistant to stresses along that axis but much more vulnerable to stresses perpendicular to that axis. For example, the femur (10th Martini Figure 6-3) is well designed for handling the body of the body coming down from above, but is more liable to break during sideways collisions.

6.5: How do bones develop and get remodeled?

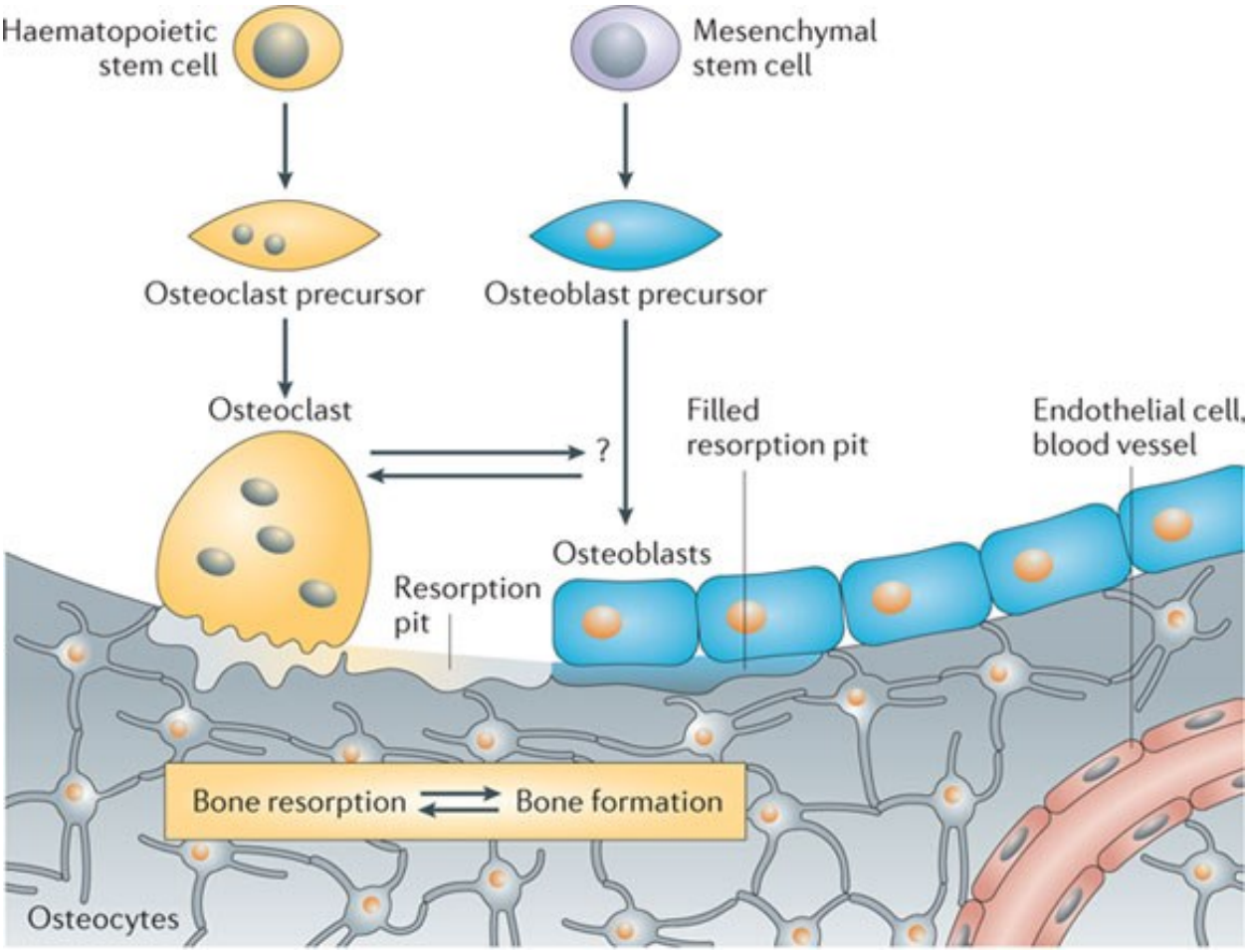
There are two fundamental types of bone development: endochondral ossification and intramembranous bone formation. The basic difference between the two is that in endochondral ossification, cartilage is laid down first and then is replaced with bone ("chondral" means "cartilage"), while intramembranous bone formation does not have a cartilage stage. Long bones

such as the femur, humerus, etc. develop by endochondral ossification. The full process is captured in the seven panels of 10th Martini Figure 6-11 (Endochondral Ossification). This figure is a good one to look over, but does not need to be memorized. Let's note the following points:

- One major difference between cartilage and bones is that cartilage has a very limited blood supply, whereas bones are highly vascularized. This is reflected in the fact that, in stage 1, the cartilaginous fetal bone does not have much of a blood supply, and that when blood vessels start "invading," the cartilage starts getting replaced by true bone.
- Steps 1 through 5 are essentially completed prenatally; after that, endochondral ossification mainly occurs at the metaphysis, the border between the diaphysis and the epiphysis. Chondrocytes (cartilage cells) continue to migrate toward the epiphysis, divide, and enlarge, while chondrocytes on the diaphysis side die and are replaced by osteocytes. In this way, long bones gradually get longer until the end of puberty, at which point distinct regions between the diaphysis and epiphysis becomes much harder to see, as shown in 10th Martini Figure 6-10 (Bone Growth at an Epiphyseal Cartilage).
- This developmental process of replacing cartilage with bone is mimicked somewhat during the repair of bone fractures, as we will see shortly.

Besides bones' growth from the embryonic stage through puberty, they are constantly being remodeled as well. This is contrary to many people's intuition; we think of bones as inert and unchanging. In fact, though, two rival populations of bone cells are continually at work: osteoclasts chew up (resorb) existing bone tissue while osteoblasts create new bone tissue. (An iconoclast is someone who attacks or "tears down" celebrities; likewise, an osteoclast is a cell that tears down bone tissue.) The dueling activities of osteoblasts and osteoclasts are depicted in CTM Figure 6.1.

CTM Figure 6.1: Osteoclasts resorb bone tissue while osteoblasts form new bone tissue. The "resorption pits" are areas where existing bone has been digested away; osteoblasts can fill in these pits. Figure taken from "Inflammatory bone loss: pathogenesis and therapeutic intervention" by Kurt Redlich & Josef S. Smolen, Nature Reviews Drug Discovery *11: 234-250, 2012.*



While this constant remodeling may seem excessive and inefficient, it has at least two advantages. First, micro-fractures in bones get repaired in this way. Second, bones' structures can be adjusted according to the demands that are placed on them. For example, bones that are regularly subjected to high stresses can become thicker, and thus better able to handle the stresses. This kind of change happens when osteoblast activity exceeds osteoclast activity. On the other hand, if osteoclasts resorb bone faster than osteoblasts make it, the bone will get thinner.

Although bone remodeling occurs throughout life, certain periods are more conducive to bone-building than others. Since osteoblast activity and bone matrix synthesis are stimulated by hormones like growth hormone and the sex hormones (androgens and estrogens), teenagers going through puberty are able to build bones especially robustly. Conversely, older folks with waning hormone levels (for example, post-menopausal women) will tend to find it harder to strengthen their bones.

The competing activities of osteoblasts and osteoclasts generally result in gradual and moderate changes to bones. When a bone is fractured, though, a more drastic type of remodeling is necessary; see the lower part of 10th Martini Figure 6-16 (Types of Fractures and Steps in Repair). This process has both similarities and differences compared to the response to integumentary injuries (Chapter 5). For both bone and integument, the first step is the formation

of a blood clot. However, while the integument is mostly repaired with collagen-rich scar tissue, the fractured bone receives new cartilage that gets replaced by bone, a partial recapitulation of endochondral ossification. The fully healed bone will usually be "as good as new" in the sense of being as strong as it was before, or even stronger. The repaired region may swell into a callus, which should not cause problems as long as there is anatomical room to accommodate it.

6.6: How is calcium homeostasis maintained?

Calcium is not only a key component of bones; it is vital to the functioning of many different types of cells. (For example, calcium triggers the contraction of muscle cells, as we'll see in Chapter 10, and it triggers neurotransmitter release in nerve cells, as we'll see in Chapter 12.) Therefore bones must share the body's calcium with other tissues. Calcium levels in body fluids such as blood are carefully regulated so that the needs of all tissues can be met, and since bone is a major reservoir of calcium, it can maintain blood calcium levels within normal limits by releasing or taking up calcium as needed. In brief, if blood calcium is too high, osteoblasts will be stimulated by the hormone calcitonin – produced by the thyroid gland – to channel some of it into the creation of new bone tissue. Conversely, if blood calcium is too low, osteoclasts will be stimulated by parathyroid hormone – produced by the parathyroid gland – to break down existing bone tissue so that the freed-up calcium can be added to the blood.

Osteoblast and osteoclast activities are not the only factors that influence blood calcium levels, however. A more complete picture is given by 10th Martini Figure 6-15 (Factors That Alter the Concentration of Calcium Ions in Blood). Parathyroid hormone (PTH) not only stimulates osteoclasts, but also increases calcium's absorption by the intestine and its retention by the kidney. In contrast, calcitonin decreases intestinal absorption and kidney retention in addition to stimulating osteoblasts. Furthermore, the kidneys can adjust their production of calcitriol – remember this vitamin D_3 derivative from Chapter 5? – which can also affect intestinal uptake of calcium. (The calcitriol arrows in Figure 6-15 may be confusing. They indicate that calcitriol is produced by the kidney and affects the intestine.)

6.7: How do diet, exercise, and age affect bone health?

The information above has important practical implications for keeping bones healthy.

First of all, it certainly makes sense to keep up one's vitamin D_3 (cholecalciferol) levels via diet and/or exposure to sunlight. The calcitriol made from vitamin D_3 promotes the absorption of dietary calcium. Of course, you can only absorb the calcium that you ingest, so calcium intake is important too. This is why milk is heavily promoted as a drink for growing children, and why most milk is fortified with extra vitamin D_3.

Regular exercise is a vital strategy for keeping bones healthy, but not all exercise is equally beneficial. Since bones get stronger in response to being stressed, the goal is to stress the bones adequately (as opposed to focusing on heart rate, for instance). Weight-bearing exercise and strength training will do this most effectively. For example, from a bone-building perspective,

running might be considered superior to walking, cycling, and swimming because running generates the highest impact forces on the bones. Any single exercise is unlikely to be a complete bone-building solution, though; for example, running stresses the vertebrae and leg bones but doesn't do much for the arms. Ideally, a variety of exercises should be used to target different areas of the body. Of course, an exercise program will only be effective if the person enjoys it enough to keep doing it, and if its difficulty is well-suited to the person's body and temperament.

As hinted at above, a person's age also affects what is going on with their bones. Teenagers undergoing a growth spurt are hormonally primed to reinforce their bones, so calcium and vitamin D_3 intake, and a healthy diet in general, are especially important for them. Anorexia, the condition of not eating enough to support the body's needs, is an especially serious problem for teenagers in part because if they do not build strong bones as teenagers, it is more difficult to build them later in life. That said, even people in their 70s and 80s can improve bone density with appropriate weight-bearing exercise. While some osteopenia (bone loss) is inevitable with aging, due in part to declining levels of sex hormones, elderly people can counter the problem somewhat with an active, bone-stressing lifestyle. Hormone replacement therapy may also help in some cases.

6.8: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 6: ##1, #6, #9, #14, #17, #20, #21, #23, #24, and #29. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 7: The Axial Skeleton

A primary focus of Chapters 7 (The Axial Skeleton) and 8 (The Appendicular Skeleton) is simply learning the names of the bones in the body, and that is best done in a hands-on laboratory setting. However, we will still use the textbook to provide some context and functional information.

7.0: Outline

7.1: Subdivisions of the 206
- The human skeleton includes the axial skeleton (the skull, vertebral column, and rib cage) and the appendicular skeleton (everything else).

7.2: The skull and associated bones
- The skull includes the bones of the cranium (for protecting the brain) and the facial bones (for feeding and facial expressions).
- Associated bones include the auditory ossicles and hyoid.

7.3: The vertebral column
- The spine includes 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, 1 sacral bone, and 1 coccygeal bone.
- The spine protects the spinal cord, which passes through the vertebral foramen of each vertebra.
- Features of the vertebrae include the spinous process, transverse processes, vertebral body, intervertebral foramen, and intervertebral disc.

7.4: The rib cage
- The rib cage includes the sternum and 12 pairs of ribs, which connect to the thoracic vertebrae.

7.5: Recommended review questions

7.1: Subdivisions of the 206

The human skeleton's 206 bones can be divided as follows.

- Skeleton (206)
  - Axial skeleton (80)
    - Skull and associated bones (29)
    - Vertebral column (26)
    - Rib cage (25)
  - Appendicular skeleton (126)
    - Pectoral girdles (4)
    - Upper limbs (60)
    - Pelvic girdle (2)
    - Lower limbs (60)

(The exact numbers of bones in each category are not important to remember.) For illustrations, see 10th Martini Figures 7-1 (The Axial Skeleton) and 8-1 (An Anterior View of the Appendicular Skeleton).

Note that the entire skeleton may be divided into two parts: the axial skeleton, so named because it forms the longitudinal axis of the body, and the appendicular skeleton, so named because it is "appended" (attached or stuck on) to the axial skeleton. This chapter is about the axial skeleton, while Chapter 8 is about the appendicular skeleton.

We can see from the outline above and from 10th Martini Figure 7-1 that the axial skeleton may be further divided into the skull and associated bones, the vertebrae, and the rib cage. We will work our way through each of these subsections.

7.2: The skull and associated bones

Let's keep subdividing, shall we? "Skull and associated bones" can be further broken down into the following categories, with the number of bones and functions indicated. The bones you will need to be able to identify in lab are listed in italics; you should find and mark these bones in multiple figures (from different perspectives, e.g., a lateral view vs. a superior view) in your textbook and lab manual.

- Cranium (8): protects the brain
    - *frontal, occipital, parietal, temporal*
- Facial bones (14): help ingest food, allow facial expressions by facial muscles, and support the eyes and nose
    - *mandible, maxilla, nasal, zygomatic*
- Auditory ossicles (6): transmit sounds to the inner ear
- Hyoid (1): supports the larynx ("voice box")

The cranium can itself be divided into the cranial vault (the top and sides) and the cranial base. The cranial base is worth pointing out because it is not obvious in a typical anterior or lateral view of the skull, yet is important for separating the brain from the rest of the head. A nice view of it is presented in 10th Martini Figure 7-4b (Sectional Anatomy of the Skull: The Floor of the Cranium).

The frontal, temporal, parietal, and occipital bones have names reflecting the lobes of the cerebral cortex of the brain: the frontal, temporal, parietal, and occipital lobes, respectively. Each lobe is just deep to the corresponding bone. We shall say more about these lobes in Chapter 14.

Two other cranial bones, the sphenoid and ethmoid bones, are also worth knowing about even though you won't need to identify them on a lab quiz. Both are mostly hidden by the other, more superficial bones. Their (limited) visibility from the outside can be seen in panel c of 10th Martini Figure 7-3 (The Adult Skull), where the sphenoid is purple (not the nasal bone) and the ethmoid bone is green. Note that the sphenoid is posterior to the ethmoid. Both articulate (form joints) with many other cranial and facial bones. Both also include openings for cranial nerves; the

sphenoid bears the optic canal for cranial nerve II (optic nerve), and the ethmoid has the olfactory foramina in the cribriform plate for cranial nerve I (olfactory nerves). (Cranial nerves are traditionally numbered from 1 to 12 with Roman numerals: I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII.)

Joints of the skull bones are quite rigid, with essentially no movement between the bones. The one exception in adults is at the temporomandibular joint (TMJ), where the mandible (lower jaw) attaches to the temporal bone. The mandible not only rotates in this joint, but also moves forward when the mouth opens wide. (This can be seen in animations such as https://www.youtube.com/watch?v=mB468Jh9aAY.) The "looseness" of this joint helps explain why it is such a common site of jaw problems.

Newborn children have a few additional slightly flexible joints between cranial bones. Their so-called fontanelles are patches of connective tissue where three or four bones come together, as shown in 10th Martini Figure 7-16 (The Skull of an Infant). The fontanelles' flexibility eases passage of the head through the birth canal and permits rapid brain growth before and after birth.

7.3: The vertebral column

The vertebral column, or spine, protects the spinal cord, which carries information to and from the brain. It also supports the weight of the upper body when we are in an upright position. From top to bottom, it can be divided into five regions: cervical, thoracic, lumbar, sacral, and coccygeal. See 10th Martini Figure 7-17 (The Vertebral Column). The cervical, thoracic, and lumbar vertebrae are numbered from C_1 to C_7, from T_1 to T_{12}, and from L_1 to L_5, respectively. A mnemonic to remember how many vertebrae are in each region is to think of eating breakfast at 7, lunch at 12, and dinner at 5. The sacral and coccygeal regions each consist of a single bone representing several fused vertebrae. These bones are called the sacrum and coccyx ("COCK-six"); the latter is also called the tailbone.

10th Martini Figure 7-17 also shows that the spine includes several curves. These can be thought of as serving two competing functions: accommodating other internal organs, for which it is best for the spine to be superficial, and supporting the upper body's weight, for which it for best for the spine to be deep (more directly over the pelvis). Animals that do not walk upright do not have so many different curves in their spines. (For example, here is the ruffed lemur: http://eskeletons.org/boneviewer/nid/12541/region/skull/bone/cranium.)

Each individual vertebra is a somewhat complicated bone with many features, as shown in 10th Martini Figure 7-18 (Vertebral Anatomy). Note especially the following:

- Spinous process: the most posterior part of the vertebra.
- Transverse processes: stick out laterally; connect to bones (ribs) and muscles.
- Vertebral body: the most anterior part of the vertebra; sort of oval-shaped.
- Vertebral foramen: space in the center of the vertebra through which the spinal cord passes.
- Intervertebral foramen: space between vertebrae where nerves pass into and out of the spinal cord.

- Intervertebral disc: pad between adjacent vertebrae; includes a soft gel-like center (nucleus pulposus) and a tough fibrocartilage coating (annulus fibrosis). This disc is what people are talking about when they refer to a herniated disc or "slipped disc."

The vertebrae look rather different as you work your way down from the cervical ones to the lumbar ones. Many differences are documented in 10th Martini Table 7-1; we will not worry about all of these details, but note that the lower vertebrae have more weight to support and thus have larger vertebral bodies.

A few individual vertebrae have "special" names. C_1 is called the atlas (think of the atlas bone holding up the head, as the giant Atlas held the world on his shoulders according to Greek mythology), C_2 is called the axis, and C_7 is called the vertebra prominens ("prominent vertebra" – its spinous process stick out much more prominently than those of C_1 through C_6).

Although the vertebrae protect the spinal cord, the spinal cord does not extend all the way down; it ends at about L_2. To avoid damaging the spinal cord, spinal anesthesia (e.g., for childbirth) is administered below L_2. Similarly, sampling of cerebrospinal fluid (e.g., to test for meningitis) is done below L_2.

7.4: The rib cage

The rib cage consists of the sternum and 12 pairs of ribs. It is pictured in 10th Martini Figure 7-23 (The Thoracic Cage). The rib cage plus the thoracic vertebrae (T_1 to T_{12}; see above) are called the thoracic cage. The function of these cages is to protect the contents of the thoracic cavity (e.g., heart and lungs) and to provide attachment points for muscles involved in breathing and other movements.

The sternum, often called the breastbone, is a medial bone at the anterior of the chest. Its three parts, from top to bottom, are the manubrium, the body, and the xiphoid process.

The pairs of ribs are numbered 1 to 12, corresponding to the thoracic vertebrae with which they articulate. They can be subdivided as follows:

- Pairs 1 through 7 are called true ribs or vertebrosternal ribs (extending from vertebrae to sternum). Each of these pairs is connected to the sternum through its own costal cartilage ("costal" means "rib").
- Pairs 8 through 12 are called false ribs because they do not connect directly to the sternum.
    - Pairs 8 through 10, the vertebrochondral ribs (recall that "chondral" means "cartilage"), have cartilage that connect to rib pair 7's cartilage, which in turn connects to the sternum.
    - Pairs 11 and 12, the vertebral ribs or floating ribs, have no associated cartilage and do not connect to the sternum at all.

7.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 7: #1, #4, #10, #20, and #25. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 8: The Appendicular Skeleton

In Chapter 8, we complete our tour of the skeleton that began in Chapter 7. As with Chapter 7, much of this material is best learned in lab, but we will outline some key points here for context and reinforcement. Chapter 9 then looks at how bones come together to form joints.

8.0: Outline

8.1: What's included in the appendicular skeleton?
- The appendicular skeleton includes the pectoral and pelvic girdles and the upper and lower limbs.

8.2: The pelvis: a fusion of confusion
- The pelvis includes the pelvic girdle plus the sacrum and coccyx.
- Each bone of the pelvic girdle is a fusion of the ilium, ischium, and pubis.

8.3: Bone markings revisited
- Recall that bone markings generally enable formation of joints, attachment of tendons and ligaments, or accommodation of nerves or blood vessels.
- Examples of prominent bone markings include the femur's head, which forms a joint with the acetabulum of the pelvis, and the femur's greater trochanter, where tendons from several muscles attach.

8.4: The effect of sex and age on bone structure
- The pelvis of females tends to be broader (for carrying a fetus) and to have a wider pelvic inlet and pelvic outlet (for delivering a fetus).
- Sex difference stem from the TDF gene on the Y chromosome, which causes gonads to develop into testes, which produce testosterone.
- Bones continue to ossify and fuse with other bones throughout childhood. Reductions in bone mass are common later in life, especially after age 60.

8.5: Recommended review questions

8.1: What's included in the appendicular skeleton?

As we saw at the start of Chapter 7, appendicular skeleton is appended (attached) to the axial skeleton. Its 126 bones can be grouped as follows.

- Pectoral girdles (4)
  - Clavicle ("collarbone") – 2
  - Scapula ("shoulder blade") – 2
- Upper limbs (60)
  - Humerus – 2
  - Ulna – 2
  - Radius – 2
  - Carpals – 16
  - Metacarpals – 10
  - Phalanges – 28
- Pelvic girdle (2)
  - Hip bone – 2
- Lower limbs (60)
  - Femur – 2
  - Patella – 2
  - Tibia ("shin bone") – 2
  - Fibula – 2
  - Tarsals – 14
    - includes *calcaneus* (heel bone) and *talus* (forms joint with tibia)
  - Metatarsals – 10
  - Phalanges – 28

A visual overview of the appendicular skeleton is given by 10th Martini Figure 8-1 (An Anterior View of the Appendicular Skeleton).

The outline above includes the so-called *pectoral girdles* and *pelvic girdle*. These terms may not be intuitive to everyone. In general, a girdle can be defined as an "encircling or ringlike structure" (rhymezone.com), often providing structural reinforcement. Here, the pectoral and pelvic girdles essentially surround and reinforce the connections between the axial skeleton and the limbs.

Note that, in the table above, the numbers of bones listed cover the left and right sides summed together. While the totals aren't especially important, it is interesting that the upper limbs and lower limbs each contain 60 bones. Furthermore, moving from proximal to distal each upper limb and each lower limb have a single long bone closest to the axial skeleton, then two long bones side by side, then 7 or 8 carpals or tarsals, 5 metacarpals or metatarsals, and 14 phalanges. Although the lower limb has fewer tarsals (7) than the upper limb has carpals (8), the lower limb also has an additional bone – the patella, or "kneecap" – so the total number of bones for the lower limb is the same as for the upper limb.

You may wonder why 10th Martini refers to "upper limb" and "lower limb" rather than, say, "arm" and "leg." To an anatomist, the first pair of terms is not equivalent to the second pair; the

arm is defined as the shoulder to the elbow, and the leg is defined as the knee to the ankle. (The region from the elbow to the wrist is the forearm, and the region from the hip to the knee is the thigh.) Thus, "upper limb" and "lower limb" are more inclusive terms that cover the entire limb, including the hand or foot.

8.2: The pelvis: a fusion of confusion

When we classify each bone as belonging to the axial skeleton or the appendicular skeleton, we must be careful when we get to the pelvis.

"What's the issue?" an attentive student may ask. "The outline above clearly indicates that the pelvic girdle is appendicular!"

Yes, but *pelvic girdle* is not quite the same as *pelvis*. 10th Martini defines the pelvis as the pelvic girdle PLUS the sacrum and coccyx, which are part of the vertebral column and therefore part of the axial skeleton (see Chapter 7). We will use this definition even though your lab manual also includes the sacrum in the pelvic girdle.

As defined by 10th Martini, and as shown in the outline above, the pelvic girdle consists of two bones. Various sources refer to these as the hip bones, pelvic bones, coxal bones (remember "coxal" from Exercise 1 in your lab manual?), or os coxae. Each of the two bones is itself a fusion of three bones: the ilium, the ischium, and the pubis. Consult 10th Martini Figure 8-7 (The Right Hip Bone), noting that the ilium is superior to the ischium and pubis and that the pubis is anterior to the ischium. You should not be obsessed with all of this terminology, but you should not let it confuse you either!

10th Martini Figure 8-7 shows a hip bone in isolation, but we should remember this bone's connections to other bones, which are much clearer in 10th Martini Figure 8-8 (The Pelvis of an Adult Male). In the posterior, the hip bone joins the sacrum; in the anterior, the pubis joins the pubis from the other side at the *pubic symphysis*, which is made out of fibrocartilage.

8.3: Bone markings revisited

In Chapter 6, we saw that bones can have many different types of features or markings: canals, condyles, crests, etc. We said that there are three main roles for many of these markings: forming joints, providing attachment points for tendons or ligaments, and (for depressions and openings) accommodating blood vessels and nerves. Now that we are looking at the skeleton in some detail, we can start to notice and appreciate examples of these features.

In the skull (Chapter 7), there were many obvious depressions and openings (fissures, foramina, etc.) for cranial nerves and arteries. The appendicular skeleton provides some especially dramatic examples of joint-forming and attachment-facilitating projections. Take the femur, for example. The head of the femur – as pictured in 10th Martini Figure 8-11 (Bone Markings on the Right Femur) – is a large expansion of the femoral neck into a dome-like structure. Note how

well this fits into the acetabulum of the pelvis (10th Martini Figure 8-7). The resulting joint is much more stable than if the femur was simply a "stick" projecting to a flat surface on the pelvis.

Another prominent feature of the femur is the greater trochanter (10th Martini Figure 8-11). It is not part of a joint, so why is it there? It turns out that several muscles originating in the pelvis attach at the greater trochanter. As shown in 10th Martini Table 11-16 (Muscles That Move the Thigh) and Figure 11-20 (Muscles That Move the Thigh), these muscles are as follows: gluteus medius, gluteus minimus, obturator internus, piriformis, gemelli. Find these muscles in Table 11-16; note that each has an origin somewhere in the pelvis and an insertion onto the greater trochanter. Because the greater trochanter expands the area of bone available for attachment, these muscles are bigger and stronger than they could be otherwise.

8.4: The effect of sex and age on bone structure

If we compare the skeletons of a typical female and a typical male, we notice many fairly subtle differences. These are summarized in 10th Martini Figure 8-10 (Sex Differences in the Human Skeleton). In general, males tend to have larger, heavier bones with more prominent bone markings. A comparison of the female and male pelves is especially interesting, as the female pelvis includes adaptations for carrying and delivering fetuses.

As seen in 10th Martini Figure 8-10, the ilia (plural of ilium) of the hip bones form a kind of bowl. This "bowl" is usually wider in females so that there is more room for a fetus to grow. Women are thus said to have wide hips – sometimes described as "child-bearing hips," which is anatomically correct but arguably offensive in its implication that having children should be a priority for women.

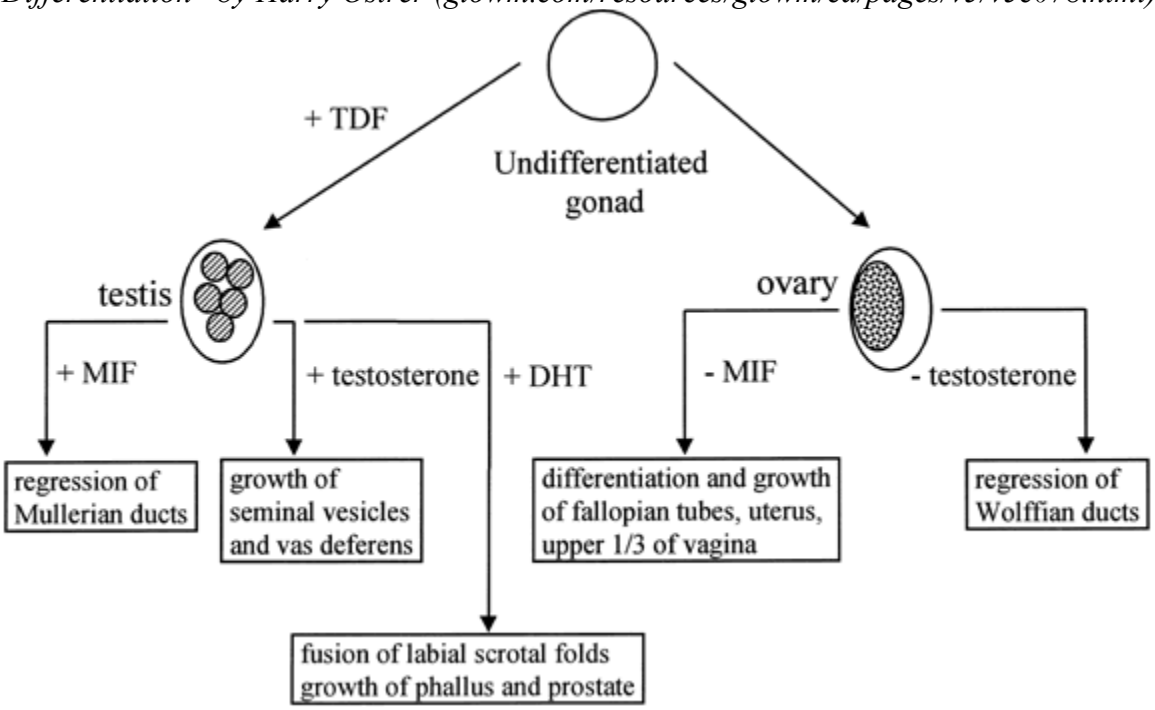
The pelvis also includes both a pelvic inlet and a pelvic outlet through which the fetus must pass during childbirth, so both inlet and outlet tend to be larger in the female. The inlet tends to be described as heart-shaped in the male and more circular in the female. The coccyx (pronounced "COCK-six") impinges on the outlet – see 10th Martini Figure 8-9a (Divisions of the Pelvis) – but less so in the female, where the coccyx points more inferiorly (downward) and less anteriorly.

As physiologists, we should not only ask HOW male and female skeletons differ, but WHY they differ. While the full story of sex-specific development is beyond the scope of this course, CTM Figure 8.1 provides a partial explanation. The Y chromosome contains a gene for a protein called the Testis Determining Factor (TDF), which binds to DNA and alters the expression (transcription and translation into protein) of various other genes are expressed. The ultimate result is that gonads lacking the TDF gene develop into ovaries, while gonads with this gene for TDF develop into testes, which produce testosterone, which, over many years, contributes greatly to sex differences such as differences in bone structure.

Chapter 8 of 10th Martini does not say much about how aging affects the skeleton, but does offer Table 8-1 (Age-Related Changes in the Skeleton), which is a nice compilation covering changes in both children and adults. Check it out. The bottom line is that ossification (bone formation)

and fusion of adjacent bones occur throughout childhood, while reductions in bone tissue are common later in life, especially after age 60.

CTM Figure 8.1: The origin of sex differences. Image taken from "Genetics of Sexual Differentiation" by Harry Ostrer (glowm.com/resources/glowm/cd/pages/v5/v5c078.html).



8.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 8: #3, #4, #6, #9, #13, #15, #17, #18, #19, #21, and #23. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 9: Joints

Chapters 6 through 8 covered bones; Chapters 10 and 11 cover muscles, which move the bones. Chapter 9 is a transitional chapter in which we focus on the joints, our usual frame of reference for understanding these movements.

9.0: Outline

9.1: What are joints?
- A joint, or articulation, is a place where two bones connect.

9.2: Two ways of classifying joints
- Joints may be classified structurally, based on the materials between the bones, as bony, cartilaginous, fibrous, or synovial.
- Joints may be classified functionally, based on how much they can move, as synarthroses, amphiarthroses, or diarthroses.

9.3: Names of individual joints
- Individual joints are usually named according to the bones that comprise them. For example, the radiocarpal joint is between the radius and the carpal bones.

9.4: Movement at synovial joints
- There are six types of synovial joints: ball-and-socket, condylar, gliding (or plane), hinge, pivot, and saddle.
- Flexion is a movement that decreases the joint angle between articulating bones; extension is a movement that increases the joint angle.

9.5: The structure of synovial joints
- Synovial joints include articular cartilage at the ends of bones and a joint capsule containing synovial fluid.
- Synovial joints may also include accessory structures such as bursae, fat pads, ligaments, menisci, and tendons.

9.6: The flexibility/stability tradeoff
- More flexible joints are less stable and vice versa.
- The flexibility and stability of a joint are affected by the way the bones fit together, the number and strength of ligaments, restriction of motion by accessory structures, and joint capsule strength.

9.7: An encapsulation of common joint problems
- Common joint problems include sprains, dislocations, arthritis, and bulging/herniated discs.

9.8: Recommended review questions

9.1: What are joints?

A joint is defined as any place where two (or more) bones connect. We usually think of joints as being highly mobile, like the shoulder joint or knee joint, but the word *joint* also applies to pairs of bones where the bones don't move relative to each other, such as the fused bones of the cranium (frontal, occipital, parietal, temporal).

The word articulation means the same thing as the word joint. Often we say things like, "the scapula articulates with the humerus"; all we mean by this is that the scapula forms a joint with

the humerus. The word *articulation* should remind you of the word *arthritis*, as they share a common root and start with "art." Arthritis refers to any inflammation of a joint, as discussed below.

To understand why having joints is useful, consider the alternative, i.e., NOT having joints. What if your skeleton was one giant bone? What problems would you have? Movement in general would be difficult, of course. It is advantageous to have the skeleton with parts that are somewhat independent of each other. Also, it might be hard to develop pre- and post-natally if you had a single giant, complicated bone that had to grow and ossify over time while meeting the body's needs at every stage.

9.2: Two ways of classifying joints

10th Martini notes that joints can be classified according to structure (what materials are between the two bones?) and according to function (how much can the joint move?). The structural categories are as follows:

- *Bony:* Nothing is between the bones; the bones interlock directly, and are often considered a single bone. Examples: the left and right mandible and left and right frontal bones of the cranium. In both cases, the left and right sides begin as separate bones and then fuse together.
- *Cartilaginous:* Cartilage is between the bones. Example: the pubic symphysis between the left and right pubic bones of the pelvis; the intervertebral discs, which are pads of fibrocartilage between vertebrae.
- *Fibrous:* Collagen-rich connective tissue that isn't cartilage (which can also contain lots of collagen) is between the bones. Example: the distal joint between the tibia and fibula, which are connected by a ligament (dense regular connective tissue).
- *Synovial:* A more complex joint capsule is between the bones – see 10th Martini Figure 9-1 (The Structure of a Synovial Joint). Examples include all joints with a wide range of motion: ankle, elbow, hip, knee, etc. More information on synovial joints is given in section 9.5 below.

When classifying joints by function, the choices are:

- The joint cannot move (*synarthrosis*).
- The joint can move a little (*amphiarthrosis*).
- The joint can move a lot (*diarthrosis*).

Note the root "arth" in all of these words, again indicating that the words are about joints. The prefix "syn" means "coming together" (think of synthesis, synergy, or synchronicity); here the bones have come together so fully that no movement is possible. "Amphi" often means "intermediate between two extremes"; an amphibian splits its time between land and water, and an amphiphilic molecule is between hydrophobic and hydrophilic. Thus an amphiarthrotic joint is between synarthrotic joints and diarthrotic joints in its extent of movement.

The structural and functional categories above can be interlaid as follows. Joints that can move a lot (diarthroses) are synovial. Joints that cannot move much or at all (synarthroses and

amphiarthroses) belong to one of the other three structural categories (bony, cartilaginous, or fibrous).

9.3: Names of individual joints

Some joints have everyday names like "ankle," "elbow," "hip," "knee," and "shoulder." These joints, and others, also have formal names derived from the specific bones that form them. Here are some straightforward examples:

- atlantoaxial joint: between the atlas (C_1 vertebra) and the axis (C_2 vertebra)
- atlantooccipital joint: between the atlas (C_1 vertebra) and the occipital bone
- carpometacarpal joint: between carpals and metacarpals
- claviculosternal joint: between the clavicle and the sternum
- femoropatellar joint: between the femur and the patella
- intercarpal joint: between carpals
- interphalangeal joint: between phalanges
- intertarsal joint: between tarsals
- intervertebral joint: between vertebrae
- metacarpophalangeal joint: between metacarpals and phalanges
- metatarsophalangeal joint: between metatarsals and phalanges
- radiocarpal joint: between the radius and carpals
- radioulnar joint: between the radius and the ulna
- sacroiliac: between the sacrum and the ilium
- tarsometarsal joint: between tarsals and metatarsals
- temporomandibular joint: between the temporal bone and the mandible
- tibiofemoral joint: between the tibia and the femur
- tibiofibular: between the tibia and the fibula

A few other joint names include parts other than bone names per se, but make sense if you know that *costal* means "ribs" and that the *glenoid cavity* and the *acromion* are parts of the scapula (remember acromial from Chapter 1?).

- acromioclavicular joint: between the scapula and the clavicle
- costovertebral: between ribs and vertebrae
- glenohumeral: between the scapula and the humerus
- sternocostal: between the sternum and ribs

I will not ask you quiz or test questions in the format of, "What is the name of the joint between the scapula and the clavicle?" However, if I refer to the acromioclavicular joint, or any of the other joint names listed above, I will expect you to know which bones I'm talking about.

9.4: Movement at synovial joints

You have probably heard of joints being described as ball-and-socket joints or hinge joints. These are two of the six types of synovial joints shown in the second page of 10th Martini Figure

9-2 (Joint Movement). Note that, while all six types are capable of significant movement, they differ in their directions and axes of movement because of the way in which the articulating bones fit together. The full list of synovial joint types, with examples, is:

- *Ball-and-socket joint:* hip, shoulder
- *Condylar joint:* radiocarpal joint; most metacarpophalangeal and metatarsophalangeal joints
- *Gliding/plane joint:* acromioclavicular, claviculosternal, intercarpal, and sacroiliac joints
- *Hinge joint:* ankle, elbow, knee, and interphalangeal joints
- *Pivot joint:* atlantoaxial and proximal radioulnar joints
- *Saddle joint:* 1st carpometacarpal joint

While we will not memorize the number of axes associated with each type of joint, we can appreciate that, for example, hinge joints (1 axis of movement) are more restricted in their movement than ball-and-socket joints (3 axes of movement).

10th Martini lists many terms referring to types of movements that can occur at synovial joints: pronation/supination, inversion/eversion, etc. Here we will focus on three pairs of terms that are especially common and important.

- *Extension/Flexion.* Flexion decreases the joint angle between articulating bones; extension increases the joint angle. When you kick a soccer ball, the kicking motion extends the knee joint. The opposite of that – "resetting" the knee joint after a kick – is flexing the knee joint.
- *Dorsiflexion/Plantar flexion.* Ankle joint terminology is confusing. The least ambiguous, most widely accepted terms are dorsiflexion for drawing your toes toward your knee and plantar flexion for pushing your toes away from your knee. When your foot pushes off the ground while running or walking, that is plantar flexion.
- *Abduction/Adduction*. Abduction means moving away from the midline of the body, whereas adduction means moving toward the midline of the body. For example, the chicken dance consists of alternately abducting your elbows (moving them up and away from your sides) and adducting your elbows (moving them down and toward your sides). This should be easy to remember if you know that the word "abduct" means "take away" (think of abducted children, alien abductions, etc.).

9.5: The structure of synovial joints

The structure of synovial joints is presented in 10th Martini Figure 9-1 (The Structural of a Synovial Joint). Note that Figure 9-1a is a "generic" synovial joint, while Figure 9-1b shows the knee in particular. Let us first notice the features common to all synovial joints, as shown in Figure 9-1a:

- The ends of the articulating bones are covered in *articular cartilage*, which is very similar to the hyaline cartilage that you learned about in Chapter 6.
- Unlike joints classified as bony, cartilaginous, or fibrous, synovial joints are bound by a *joint capsule* – a covering that extends from the periosteum of the adjacent bones. On the inside of the capsule is a synovial membrane (which we mentioned in Chapter 4 as an area in which epithelial and areolar connective tissues come together).
- Within the joint capsule is *synovial fluid*, which 10th Martini describes as a "clear, viscous solution with the consistency of egg yolk or heavy molasses." The synovial fluid provides lubrication, shock absorption, and distribution of nutrients to the articular cartilage's chondrocytes (cartilage cells). This distribution of nutrients is important because the cartilage does not have its own blood supply.

Figure 9-1b shows accessory structures that individual synovial joints may or may not have:

- *Bursa*: a fluid-filled lubricating body.
- *Fat pad*: self-explanatory.
- *Ligament*: regular connective tissue connecting bone to bone.
- *Meniscus*: C-shaped pad of fibrocartilage
- *Tendon*: regular connective tissue connecting muscle to bone.

These accessory structures are noteworthy in part because they are frequent sites of injuries. At the knee, the anterior cruciate ligament (ACL) is often overstretched and injured by athletes; torn menisci are another common sports injury.

Note that synovial joints are a category distinct from cartilaginous joints and fibrous joints even though they include both cartilage and other fibrous tissue such as ligaments.

9.6: The flexibility/stability tradeoff

There are advantages to a joint being flexible, and there are advantages to a joint being stable, but a given joint cannot be both maximally flexible and maximally stable; the more flexibility (freedom to move) is permitted, the less stability there is. This tradeoff is evident in the classifying joints on a spectrum ranging from synarthrotic (very low flexibility, very high stability) to diarthrotic (higher flexibility, lower stability). Even among the diarthrotic, synovial joints, there is much variation in flexibility and stability, which stems from variations in the components of these joints. One key factor is the way in which the bones themselves fit together. The elbow is a stable joint in large part because of the tightly interlocking structures of the humerus and ulna; likewise, the hip joint is fairly stable because the head of the femur fits nicely into the deep pocket of the acetabulum of the pelvis. In contrast to the hip joint, the shoulder joint's pocket (provided by the glenoid cavity of the scapula) is fairly shallow, making

the shoulder more flexible but less stable than the hip. Below are some additional factors that can also affect the flexibility and stability of a joint:

- The number and strength of the ligaments
- Any restriction of motion by other nearby bones, tendons, and/or fat pads
- The strength of the joint capsule

9.7: An encapsulation of common joint problems

We can summarize common joint problems in the form of the table shown below.

CTM Table 9.1: Common joint problems.

Term		Nature of problem	Common treatments
Sprain		A ligament is stretched and/or torn	Traditionally, RICE (Rest, Ice, Compression, Elevation); now often MICE (Movement instead of Rest)
Dislocation		A bone is out of place	Have a medical professional put the bone back!
Arthritis: joint inflammation	Osteoarthritis	Articular cartilage, and sometimes the bone tissue it is protecting, gets damaged and worn away	Pain medication; joint replacement surgery; moderate exercise
	Rheumatoid arthritis	Joints are attacked by the immune system (this is an autoimmune disease)	Disease-Modifying Anti-Rheumatic Drugs (DMARDs), which work via diverse mechanisms; anti-inflammatory drugs; non-inflaming exercise
	Gouty arthritis	Crystals of uric acid build up in synovial fluid	Anti-inflammatory drugs; dietary changes to lower uric acid levels
Bulging or herniated disc		Intervertebral discs impinge on spinal nerves	Education on body mechanics; physical therapy; pain medication; surgery (discectomy)

9.8: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 9: #1, #5, #6, #7, #8, #10, #15, #16, #28, #29, #30. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 10: Muscle Tissue

Having devoted a lot of attention to bones, we now look at the muscles responsible for pulling on and moving those bones. Chapter 10 looks at muscles' cellular properties, while Chapter 11 looks at how they function as whole muscles.

10.0: Outline

10.1: (Re-)Introduction to muscles
- Some basic information about cardiac, skeletal, and smooth muscles was covered in Chapter 4.
- Skeletal muscles' functions include moving bones, maintaining body position, supporting soft tissues, guarding the body's entrances and exits, storing fuel, and producing heat.

10.2: What's in a skeletal muscle?
- Muscles are made of muscle cells, also known as muscle fibers.
- Magnified muscle fibers appear striated because of the overlapping arrangement of its thick filaments, made from the protein myosin, and thin filaments, made from actin and a few other proteins.

10.3: A molecular explanation of muscle contraction
- Myosin heads bind to and pull on actin in an ATP-requiring process that shortens the sarcomeres.

10.4: Nerve to muscle: excitation-contraction coupling
- Release of acetylcholine from motor neurons causes depolarization of the muscle cell membrane, which leads to Ca^{2+} release from the SR, displacement of tropomyosin, binding of myosin heads to actin, and force production.

10.5: Factors that affect how much force is exerted
- The more of a muscle's motor units are active, the more force the muscle produces.
- For active muscle cells, the level of force corresponds to the fraction of myosin heads that have access to actin binding sites.
- Muscle contractions can be concentric, isometric, or eccentric.

10.6: Muscle cell diversity
- Fast-twitch muscle cells express a form of myosin that enables more rapid contraction. Slow-twitch muscle cells have a slower form of myosin, but have lots of mitochondria and closer proximity to capillaries for sustained O_2 delivery and aerobic ATP production.
- Skeletal muscle cells are different from cardiac and smooth muscle cells in several ways.

10.7: Recommended review questions

10.1: (Re-)Introduction to muscles

Back in Chapter 4 (The Tissue Level of Organization), we covered some basic information about muscles, such as the following:
- There are 3 basic types of muscle tissue: cardiac, skeletal, and smooth.
- Cardiac and skeletal muscles have a striated (striped) appearance under the microscope; smooth muscles do not.
- Skeletal muscle cells have multiple nuclei; cardiac and smooth muscle cells do not.
- Skeletal muscles are under voluntary control; cardiac and smooth muscles are not.

- Smooth muscles are found in most hollow organs such as arteries and the gastrointestinal tract.

Here in Chapters 10 and 11, we will focus mostly on skeletal muscles. Let's start with their functions. It is tempting to say simply that muscles' function is to move bones, and that is true, but they have several additional functions as well:

- *Maintain body position.* Even when joint angles aren't changing, muscles do the work of keeping us from collapsing to the ground.
- *Support soft tissues.* Muscles shield the more delicate structures that lie deep to them.
- *Guard entrances and exits to body.* (We can choose when to open our mouths, swallow, urinate, and defecate.)
- *Store fuel.* Muscles have a reservoir of glycogen (a storage form of glucose) and also represent a large reserve of protein that can be broken down in starvation situations.
- *Produce heat to maintain body temperature.*

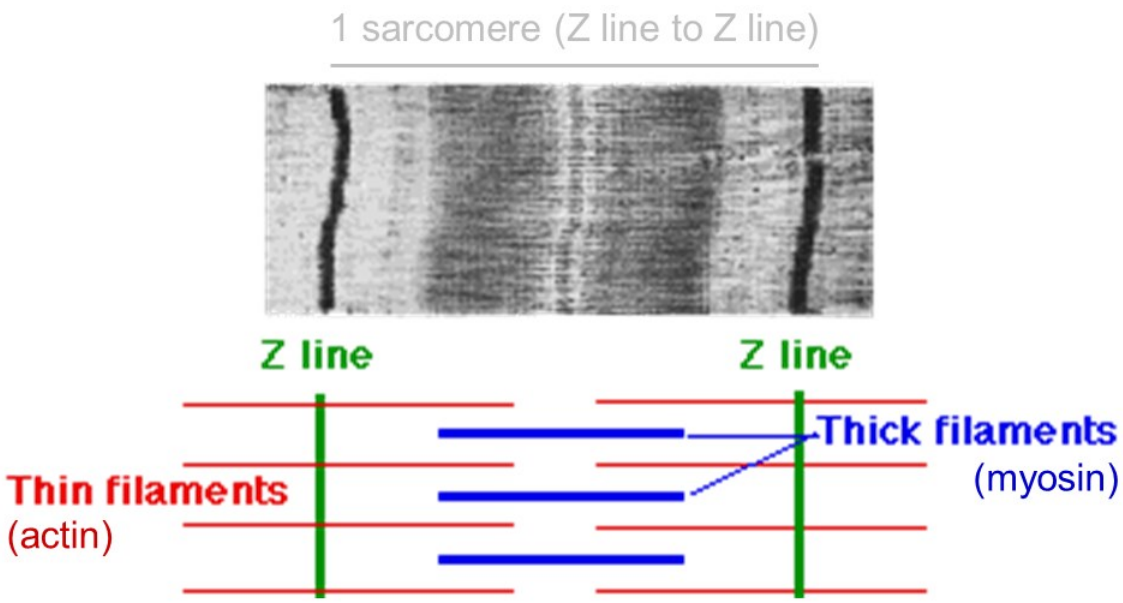
10.2: What's in a skeletal muscle?

The hierarchical structure of skeletal muscle is shown in 10th Martini Figure 10-6 (Levels of Functional Organization in a Skeletal Muscle). A whole muscle is made of muscle cells, also called muscle fibers. (The term muscle fibers may be confusing because when we talked about "fibers" in Chapter 4, we were referring to individual *proteins* secreted into the extracellular matrix: collagen, elastin, etc. Here a fiber is a complete cell, NOT an extracellular protein.) Muscle fibers, in turn, contain lots of the proteins actin and myosin, which (along with a few other associated proteins) are organized into thin and thick filaments, respectively.

The arrangement of these thin and thick filaments causes skeletal muscle cells to appear striated (striped) under the microscope. The two sets of filaments overlap somewhat, such that, if you take a cross-sectional slice though a muscle cells, you might cut across thin filaments alone, thick filaments alone, or thin and thick filaments together, as shown in 10th Martini Figure 10-5 (Sarcomere Structure, Superficial and Cross-Sectional Views). The overlapping arrangement of these filaments results in the alternating lighter and darker areas seen as striations (see CTM Figure 10.1 below).

We will gloss over much of the terminology applied to muscles and muscle cells, but one other definition is important here. A sarcomere is the basic unit of structure and function within a skeletal muscle cell. It is usually defined as the distance from one Z line (where thin filaments join together) to the next Z line. It is typically a little over 2 micrometers (microns) long in intact living muscles. Each bundle of thin and thick filaments includes many sarcomeres laid end to end to end. When each sarcomere contracts (i.e., gets shorter), the muscle as a whole contracts.

CTM Figure 10.1: The molecular basis of skeletal muscles' striations. Figure modified slightly from a version found in Wikipedia.



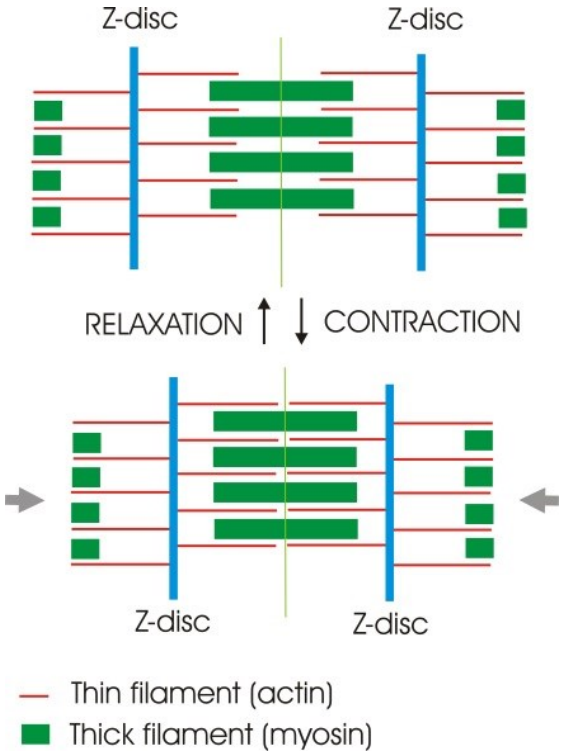
As Chapter 4 noted, skeletal muscle cells not only are unusual in their striated appearance but also contain multiple nuclei. 10th Martini Figure 10-2 (The Formation of a Multinucleate Skeletal Muscle Fiber) shows why these cells have multiple nuclei: immature cells called myoblasts fuse together to form long, multi-nucleated cells.

10.3: A molecular explanation of muscle contraction

The phrase "muscle contraction" implies that working muscles get shorter, and they do; see CTM Figure 10.2 below. Importantly, neither the thin filaments nor the thick filaments shorten contraction; rather, the overlap between the thin and thick filaments increases, so that each sarcomere becomes shorter.

Why exactly does the overlap increase during contraction? Part of each myosin molecule is a head that attaches to and pulls on the actin, causing the thin filaments to slide past the thick filaments. This process, pictured in 10th Martini Figure 10-11 (The Contraction Cycle and Cross-Bridge Formation), is known as the Sliding Filament Theory of Muscle Contraction. (The word "theory" refers to a powerful and generally accepted model, like Darwin's Theory of Evolution or Einstein's Theory of Relativity.) You can see that, from step 3 of the figure to step 4, the myosin head rotates toward the left while bound to actin. Each of these "power strokes" slightly increases the overlap between the thin and thick filaments.

CTM Figure 10.2: Sarcomere changes during muscle contraction. Z-lines are also called Z-discs, as shown here. Notice that the length of the thick filaments and the length of the thin filaments both remain constant, but the overlap between the two increases during contraction, shortening the sarcomere (distance from Z-disc to Z-disc). Figure taken from "Mechanical properties of living cells and tissues related to thermodynamics, experiments and quantitative morphology – a review" by Miroslav Holecek et al. (2011).



Do you think that myosin requires energy to tug on actin in this way? Notice that myosin binds ATP in step 5 of Figure 10-11, allowing the myosin head to detach from the actin, and that the ATP is then broken down into ADP and inorganic phosphate (P_i). This input of chemical energy "resets" the myosin head so that it can do another round of pulling on actin. An interesting fact of forensic science is that when the muscle cells of a newly dead body run out of ATP, their myosin heads can no longer detach from actin, and their "death grip" on actin renders the muscles extremely stiff.

10.4: Nerve to muscle: excitation-contraction coupling

Several steps are necessary to convert a command to contract from the nervous system into an actual contraction. Let's start with the "goal" of the process, the contraction itself, and work our way backward to the nervous system's input. To visualize the steps below, please refer to 10th Martini Figures 10-10 (Excitation-Contraction Coupling) and 10-13 (Steps Involved in Skeletal Muscle Contraction and Relaxation).

We'll note first that our muscles are not always contracting, even when we are alive and our muscle cells have plenty of ATP. Why not? One answer is that myosin simply does not have access to actin. Note this part of 10th Martini Figure 10-10: "In a resting sarcomere, the tropomyosin strands cover the active sites on the thin filaments, preventing cross-bridge formation." Tropomyosin is another protein in the thin filaments. For myosin to bind to actin, troponin (yet another thin-filament protein) must move tropomyosin out of the way.

From here, we can back up and ask, "When would troponin move tropomyosin out of myosin's way?" When troponin binds to calcium ions (Ca^{2+}), that's when! Calcium's presence causes a change in the 3D structure of troponin, which forces tropomyosin out of myosin's way, allowing myosin to bind to actin.

Where did the calcium ions come from? It was released from the sarcoplasmic reticulum (SR), which is what we call the endoplasmic reticulum (ER) in muscle cells. (The prefixes myo- and sarco- both mean "muscle.") Why did the SR release the calcium? It was a response to an electrical depolarization arriving at the SR after traveling inward into the muscle cell via invaginations of the cell membrane called t-tubules. Why did the t-tubules depolarize? Ion channels in the muscle cell membrane opened, letting sodium ions (Na^{+}) enter the cell and depolarize it. Why did these sodium channels open? They were responding to acetylcholine (ACh), which is released from motor neurons and bound to the ion channels, causing them to open. The ACh is the chemical message by which the motor neurons tell the muscle cells to contract.

In case that work-our-way-backwards approach was confusing, let's now summarize in the usual chronological order. Motor neurons – the nerve cells in the nervous system that activate muscle cells – depolarize (more on that in Chapter 12) and release acetylcholine (ACh), which binds to proteins on the muscle cell membrane that let Na^{+} into the cell. This wave of depolarization (inside of cell becoming more positively charged, relative to the outside) spreads inward via t-tubules; upon reaching the sarcoplasmic reticulum (SR), it causes the SR to open Ca^{2+} channels that let Ca^{2+} into the sarcoplasm (cytoplasm). The Ca^{2+} binds to troponin, which moves tropomyosin in such a way that myosin can now bind to actin. The myosin heads pull on actin, and the sarcomeres shorten!

At the end of a muscle contraction, the above-listed steps are reversed in a fairly straightforward manner. When the motor neurons stop releasing ACh, the muscle cell membrane repolarizes (becomes more negative on the inside again), calcium release from the SR stops, troponin lets tropomyosin get back in myosin's way, and no further contraction occurs. The one additional thing you need to know is that Ca^{2+} is pumped back into the SR, against its gradient, via active transport, thus using ATP. So even when Ca^{2+} release from the SR stops, a muscle cells continues to contract until the already-released Ca^{2+} has been pumped back into the SR.

10.5: Factors that affect how much force is exerted

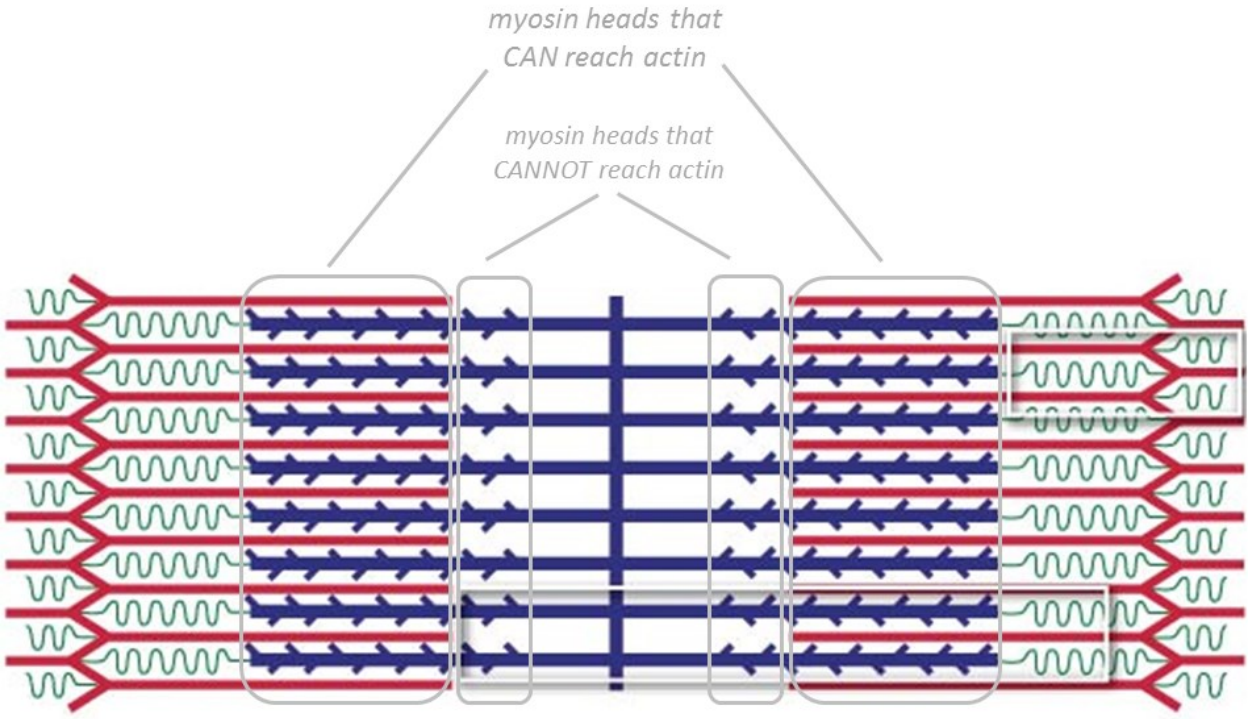
Above, we have treated muscles as being either "on" (contracting, exerting force) or "off" (relaxed). However, there are several factors that affect how *much* force is produced by a contracting muscle: motor unit recruitment, sarcomere length, muscle load, and additional factors covered in Chapter 11.

Motor unit recruitment. Motor nerves are nerves that control muscles. ("Motor" means "movement," more or less.) Motor nerves are made up of many motor neurons, each of which controls somewhere between a few and a thousand muscle cells. All of the muscle cells controlled by a single motor neuron are defined as a motor unit. The more motor units are

active, the higher the force. The muscle cells belonging to a given motor unit are dispersed throughout a muscle rather than being clumped together, as shown in 10th Martini Figure 10-17 (The Arrangement and Activity of Motor Units in a Skeletal Muscle). A state of maximum force production, known as *tetanus*, occurs when all motor units are active at the same time.

Sarcomere length. Since muscle force comes from myosin heads pulling on actin, the amount of force depends on the number of active myosin heads. In some cases, not all myosin heads are active because not all of them can reach actin, even if tropomyosin is out of the way. See CTM Figure 10.3 below.

CTM Figure 10.3: A zoomed-in version of part of 10th Martini Figure 10-7 (Thin and Thick Filaments). Some myosin heads can reach their binding sites on actin, while others can't.

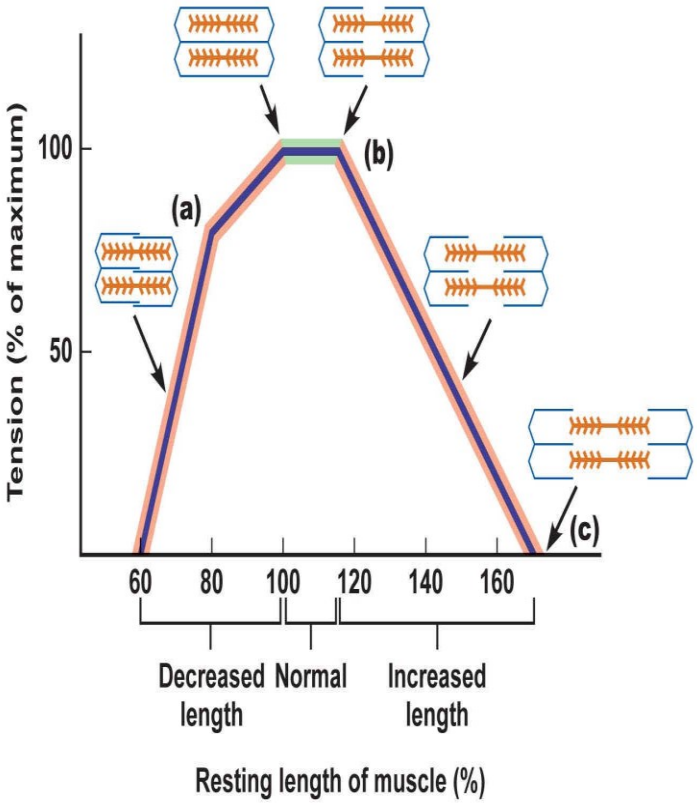


The fraction of myosin heads that can generate force thus reflects the fraction that can reach their binding sites on actin – and this depends on the amount of overlap between the thick and thin filaments, which depends on sarcomere length. Look at CTM Figure 10.4 below. In artificially extended sarcomeres (>160% of resting length), there is no overlap at all between thin and thick filaments, so NO myosin can reach actin and no active force is generated. If we move leftward on the graph toward shorter sarcomere lengths, there is more and more overlap between the filaments, so more and more force can be generated, with a plateau at about 100-120% of resting length. If the sarcomeres are shortened even further (below 100% of resting length), the smooshing together of the filaments proteins makes it harder for myosin to access actin, and force drops off.

Muscle load. So far we have assumed that muscles shorten when they are active, but this is not always the case. If the muscle is pulling against a heavy enough load, the muscle might stay at a constant length, or even get longer! Thus muscle contractions may be classified as *concentric*

(the muscle gets shorter), *isometric* (the muscle stays the same length; "iso" = "same," "metric" = "length"), or *eccentric* (the muscle gets longer). You will hear these terms frequently in muscle physiology. It turns out that isometric contractions can generate more force than concentric contractions, and eccentric contractions produce the most force of all. Because eccentric contractions involve such high forces, they are the ones that lead to most muscle damage and delayed-onset muscle soreness (DOMS – discussed in one of 10th Martini's Clinical Note boxes). A classic example of this is vigorous downhill hiking or running, which tends to damage your quadriceps muscles. As your foot lands, your quadriceps muscles are active, as if to extend the knee joint, but the angle of your knee joint actually decreases, so the quads are actually being lengthened despite their "attempt" to shorten.

CTM Figure 10.4: The length-tension relationship of a skeletal muscle. ("Tension" is a synonym for "force production.") Figure taken from Principles of Physiology *by Cindy L Stanfield (published by Pearson, 2011).*



10.6: Muscle cell diversity

"Fast-twitch" muscle cells tend to be used for short bursts of activity, while "slow-twitch" tend to be used over longer periods. The "fast" and "slow" designations refer to the specific type of myosin protein in these cells; the form of myosin expressed by fast-twitch cells can cycle through the binding and unbinding of actin more rapidly than that expressed by slow-twitch cells, so muscles dominated by these fast-twitch cells can shorten more rapidly. Several other properties tend to correlate with the specific type of myosin expressed, as shown in CTM Table 10.1. Since slow-twitch cells tend to have sustained activity, they tend to have mitochondria, which produce ATP in an aerobic, sustainable fashion. Because mitochondria require oxygen

(O_2) to produce ATP, muscles composed of slow-twitch cells also tend to have a higher density of capillaries, which deliver the O_2 for the mitochondria to use.

CTM Table 10.1: A simplified version of 10th Martini Table 10-2 (Properties of Skeletal Muscle Fiber Types)

	Fast-Twitch	**Slow-Twitch**
Overall function	• Short, fast bursts! • Poor endurance!	• Not speedy! • Good endurance!
Myosin type	Fast myosin (Type II)	Slow myosin (Type I)
Mitochondrial density	Low	High
Capillary density	Low	High
Substrates used	Mostly glucose (carbohydrates)	Carbohydrates AND lipids
Color	White/pale	Darker/redder

Finally, it should be noted that "fast-twitch" and "slow-twitch" are somewhat simplistic, extreme terms. Human muscles are mixtures of faster and slower fibers that do not conform exactly to the patterns of CTM Table 10.1. Skeletal muscles that are more extreme on the fast/slow spectrum can be found elsewhere in the animal kingdom.

Muscle cell diversity is also evident in comparisons of cardiac, skeletal, and smooth muscle cells, as shown in CTM Table 10.2 below.

CTM Table 10.2: A simplified version of 10th Martini Table 10-3 (A Comparison of Skeletal, Cardiac, and Smooth Muscle Tissues)

	Skeletal	**Cardiac**	**Smooth**
Fiber size & shape	Thick & long	Skinnier, shorter	Like cardiac
Nuclei per cell	Many	1	1
Organization of thin & thick filaments	Sarcomeres give striated appearance	Sarcomeres give striated appearance	No sarcomeres
Activation mechanism	Voluntary control; motor neurons release ACh	Pacemaker cells contract automatically; signals spread via gap junctions	Like cardiac
Calcium source	SR	SR + extracellular	Like cardiac
Calcium regulation of contraction	Calcium binds to troponin	Similar to skeletal	Different calcium-based mechanism

Contraction speed & endurance	Fast, limited endurance	Slower, super endurance!	Like cardiac
ATP production	Aerobic and anaerobic (glycolysis)	VERY aerobic (little glycolysis)	Like cardiac

10.7: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 10: #1, #3, #6, #9, #11, #12, #19, #20, #21, #24, #25, #26, #27, #28, #30. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 11: The Muscular System

Chapter 11 can be described as a whole lot of muscle anatomy … plus a few notes on muscle architecture and lever mechanics. In this summary we will focus on the conceptual information at the beginning of the chapter, leaving many of the anatomical details for the lab.

11.0: Outline

11.1: A fundamental tradeoff: contraction force vs. contraction speed
- Muscles can shorten at high speed with low force, or at low speed with high force.

11.2: Different fascicle arrangements are suited for different functions
- Muscle fascicles arranged parallel to the tendon shorten quickly, while pennate muscle fascicles exert high forces.

11.3: Bones as levers
- The force and velocity experienced by a load depend on the distance from the fulcrum to the muscle's insertion (L_i) and the distance from the fulcrum to the load (L_o).

11.4: General muscle terminology
- The origin is the more fixed end of a muscle; the insertion is the more moveable end.
- The main muscle responsible for a given action is called an agonist. It is assisted by synergists and opposed by antagonists.

11.5: How did specific muscles get their names?
- Muscles are named for their locations in the body, origins and/or insertions, fascicle organization, relative positions, structural characteristics, and actions.

11.6: The top 24 muscles
- The largest, most important, and easiest-to-spot muscles include the biceps brachii, brachioradialis, deltoid, epicranius/frontalis/occipitofrontalis, gastrocnemius, hamstrings (biceps femoris, semimembranosus, and semitendinosus), latissimus dorsi, masseter, orbicularis oculi, orbicularis oris, pectoralis major, quadriceps (rectus femoris, vastus intermedius, vastus lateralis, and vastus medialis), sartorius, temporalis, tibialis anterior, trapezius, triceps brachii, and zygomaticus.

11.7: Recommended review questions

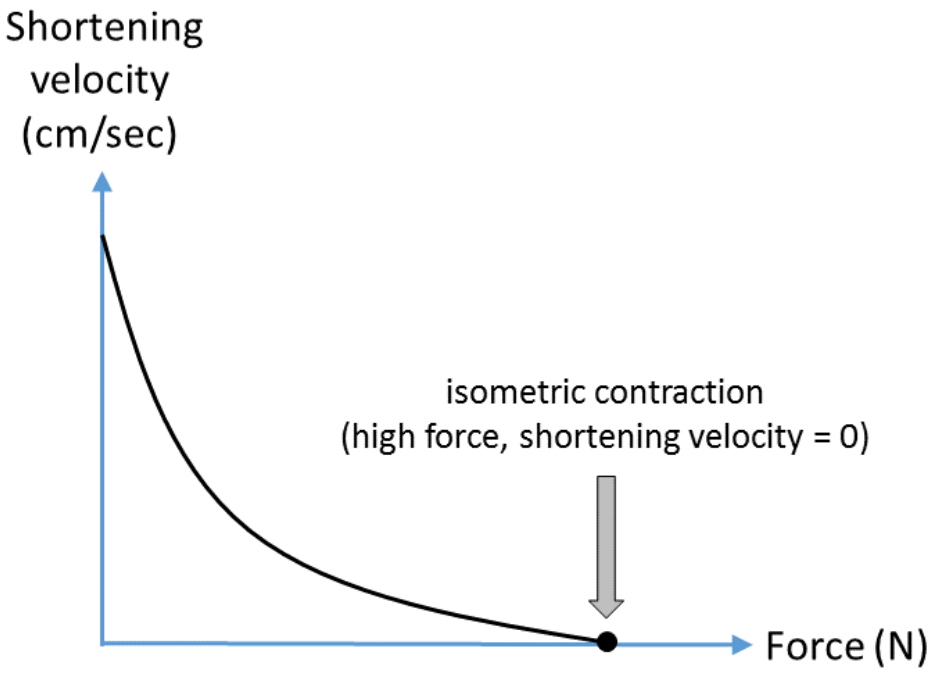
11.1: A fundamental tradeoff: force vs. speed

The basic function of muscles is to pull on what they are attached to (usually bones). At a molecular level, a muscle's force comes from myosin heads grabbing and pulling on actin. This often leads to the muscle getting shorter (literally contracting), but not always; sometimes the load that the muscle is pulling against keeps the muscle the same length (in an isometric contraction; "iso" = "same" and "metric" = "length," so **isometric** means that the length doesn't change), or even forces the muscle to get longer (in an eccentric contraction).

A comparison of concentric, isometric, and eccentric contractions reveals a tradeoff between the force that a given muscle can exert and the speed at which it shortens. At one extreme, if there is little to no load to work against, a muscle can shorten very quickly, but does not exert much force. On the other hand, if the load is large enough, the muscle cannot shorten at all, but exerts much more force in trying to hold its position.

This basic tradeoff can be portrayed graphically as a force-velocity curve (see CTM Figure 11.1 below). We will not worry about the details of this graph, but note that force goes down as shortening speed goes up and vice versa.

CTM Figure 11.1: A generic muscle's force-velocity curve, in which force goes down as shortening speed goes up and vice versa. The black dot marks the point along the curve representing an isometric contraction (when shortening velocity is 0).



We will see further examples of this force/velocity tradeoff in each of the next two sections.

11.2: Different fascicle arrangements are suited for different functions

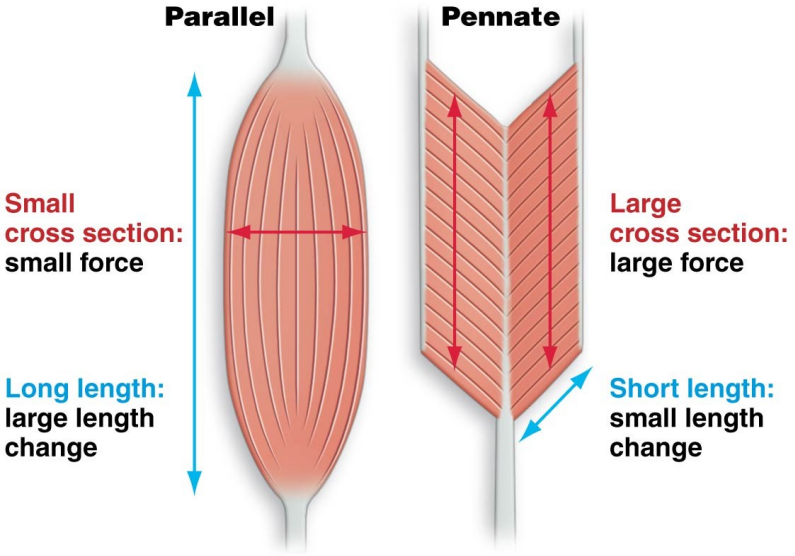
A *fascicle* is defined as a bundle of muscle cells within a muscle. The muscle cells within a fascicle are always parallel to each other, but the fascicles are not always parallel to the muscle's tendon. 10th Martini Figure 11-1 shows four basic fascicle arrangements: parallel, convergent, pennate, and circular.

Convergent muscles are interesting because different portions of them can perform different tasks. For example, note in 10th Martini Figure 11-16 (Muscles That Move the Arm) that the pectoralis major muscle connects to both the clavicle and the sternum and costal cartilage. Selective activation of the clavicular part helps raise the arm, while selective activation of the sternocostal part helps adduct and lower the arm.

Circular muscles, also known as sphincters, surround internal and external openings and regulate flow through these openings. Examples include the orbicularis oculi around the eye, the orbicularis oris around the mouth, and the esophageal and anal sphincters at the beginning and end of the digestive tract.

Pennate and parallel muscles provide another illustration of the tradeoff between muscle force and shortening velocity. In **parallel muscles**, each muscle cell is as long as possible, meaning that relatively large changes in length are possible – i.e., parallel muscles are optimal for rapid shortening. In contrast, **pennate muscles** include a larger number of shorter cells. The short cells can't shorten very much or very quickly, but the large number of cells gives the muscle a greater physiological cross-sectional area (PCSA) and thus a greater maximum force. This difference between pennate and parallel muscles is portrayed in CTM Figure 11.2 below.

CTM Figure 11.2: Parallel and pennate muscles. Parallel fascicles are best for quick, substantial changes in length, while pennate muscles are best for high-force contractions. Figure taken from Biological Science (5th edition) by Scott Freeman et al., published by Pearson.



11.3: Bones as levers

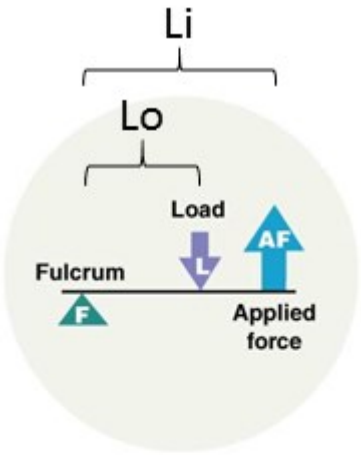
As defined by 10th Martini, "a lever is a rigid structure … that moves on a fixed point called the fulcrum." In biology, bones are levers and joints are fulcrums, so the laws of physics that govern levers can be applied to our own bodies.

A muscle's action on a load supported by a bone depends partly on the distance from the fulcrum to the muscle's insertion, often called the **in-lever** and abbreviated $\mathbf{L_i}$, and the distance from the fulcrum to the load, often called the **out-lever** and abbreviated $\mathbf{L_o}$. Examples of these distances are shown in CTM Figure 11.3.

According to the physics of levers, a muscle's force can be either amplified or diminished in being transmitted to a

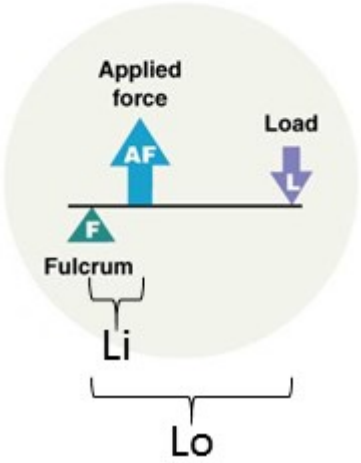
CTM Figure 11.3: In-lever (Li) and out-lever (Lo) distances. For biological systems, "Applied force" (AF) is applied where the muscle inserts onto the bone. Adapted from 10th Martini Figure 11-2 (The Three Classes of Levers).

load. If $L_i > L_o$ (as in the upper circle of CTM Figure 11.3), the mechanical advantage is greater than 1 and the force on the load is higher than the force applied by the muscle. If $L_i > L_o$ (as in the lower circle of CTM Figure 11.3), the opposite is true.



Is there any advantage to an arrangement like the lower circle of CTM Figure 11.3? If $L_i < L_o$, the load moves more than the insertion of the muscle moves, so a small change in muscle length causes a bigger change in the position of the load. Thus, while the ratio L_i/L_o should be as HIGH as possible to maximize the force on the load, L_i/L_o should be as LOW as possible to maximize the speed at which the load is moved. Again, high force comes at the expense of high speed, and vice versa.

It turns out that most levers in the body resemble the lower circle of CTM Figure 11.3. That is, L_i is less than L_o, so loads must be relatively light but can be moved quickly. This type of lever, in which the applied force is between the fulcrum and the load, is known as a third-class lever. However, evolution has acted on some joints to increase L_i and/or decreases in L_o to improve force at the expense of velocity.



11.4: General muscle terminology

In general, a muscle has two ends that attach (by tendon) to two different things (usually two different bones). We call these points of attachment the origin and insertion. But which is which? During a muscle contraction, one end is usually relatively fixed while the other end moves; the **origin** is the fixed end, and **insertion** is the movable end. Usually this means that the origin is proximal to the insertion. While there are additional rules for unusual cases, we won't worry about those. 10th Martini says, "Knowing which end is the origin and which is the insertion is ultimately less important than knowing where the two ends attach and what the muscle accomplishes when it contracts." I agree.

Recall from Chapter 9 that there are many terms for describing muscle actions, often presented as opposing pairs: extension/flexion, abduction/adduction, and so forth. These terms can be applied to the bone or region where the muscle inserts, or to the relevant joint. For example, one could say that the biceps brachii muscle flexes the forearm, or that the biceps brachii flexes the elbow joint. Either is correct.

In general, each joint can be moved by multiple muscles, which have differing contributions to different movements. For a given action, the muscle that is most important in performing that action is called the **agonist**. A muscle that helps the agonist is called a **synergist**, and a muscle that opposes an agonist (i.e., it has the opposite effect on the joint) is called an **antagonist**. For the example of elbow flexion, the biceps brachii is the agonist, the brachialis and brachioradialis are synergists, and the triceps brachii is an antagonist. Note that these assignments are specific to the particular action being discussed; for elbow *extension*, the triceps brachii would be the agonist and the biceps brachii would be an antagonist.

11.5: How did specific muscles get their names?

As you learn the names of individual muscles, it may be comforting to know that most names describe observable features of the muscles. It is less comforting to realize that this matching of names and features does not follow a systematic pattern; every muscle is different. Muscles can be names for any of the following:

- *Location in the body.* For example, the brachialis muscle is part of the brachial (arm) region of the body.
- *Origin and/or insertion.* For example, the zygomaticus muscle originates at the zygomatic bone.
- *Fascicle organization*. For example, the rectus femoris muscle has fascicles that run along the long axis of the body (*rectus* means straight).
- *Relative position.* For example, the vastus lateralis is the most lateral of the three vastus muscles.
- *Structural characteristics.*
    - Nature of origin. For example, the biceps femoris has two origins (bi = 2, ceps = heads); the triceps brachii has three origins.
    - Shape. For example, the deltoid muscle is triangular in shape (think of the Greek letter delta: Δ). The word orbicularis, like orbit, indicates a circular shape, which is true of the orbicularis oculi and orbicularis oris muscles.
    - Other striking features. For example, in the names gluteus maximus and pectoralis major, the words maximus and major indicate the large size of the muscles.
- *Action.* For example, the flexor digitorum longus flexes the fingers (digits).

Note that muscle names often combine multiple pieces of information. For example, the rectus femoris is named for both its fascicle organization (straight along the long axis) and its location in the body (along the femur).

11.6: The top 24 muscles

While 10th Martini is packed with muscular anatomy – more than you could master in a single quarter – we can focus our attention on some of the largest, most important, and easiest-to-spot muscles, as presented in CTM Table 11.1. To learn these muscles, it is not enough to read through the table. You should also look at bone models or drawings and identify the specific

markings to which these muscles attach; you should look at muscle models or drawings and find these muscles amongst the many others; and you should make sure that the muscles' listed actions make sense based on where they originate and insert.

CTM Table 11.1: The top 24 human muscles, according to Dr. C.

MUSCLE – 10th Martini Figure(s)	ORIGIN	INSERTION	ACTION
Biceps brachii – Fig. 11-4a	Coracoid process [anterior, lateral; NOT coronoid process] and glenoid cavity of scapula (2 heads)	Tuberosity of anterior proximal radius	Flexes elbow, supinates forearm [palm turns from posterior to anterior]
Biceps femoris (a hamstring muscle) – Fig. 11-4b	Tuberosity of inferior ischium; linea aspera of femur (2 heads)	Head of fibula, lateral condyle of proximal tibia	Extends thigh, flexes knee
Brachioradialis – Fig. 11-4a	Lateral ridge at distal end of humerus	Lateral styloid process of distal radius	Flexes elbow
Deltoid – Fig. 11-4a, 11-4b	Lateral clavicle, acromion [lateral, superior] and spine [posterior] of scapula	Deltoid tuberosity of humerus [halfway down, lateral]	Abducts arm (if whole muscle is activated)
Epicranius/Frontalis/ Occipitofrontalis – Fig. 11-4a	Epicranial aponeurosis	Skin of eyebrows, bridge of nose	Raises eyebrows
Gastrocnemius – Fig. 11-4b	Condyles of distal femur	Calcaneus	Plantar-flexes foot
Gluteus maximus – Fig. 11-4b	Dorsal ilium, sacrum, coccyx	Gluteal tuberosity of posterior proximal femur; iliotibial tract	Extends thigh
Latissimus dorsi – Fig. 11-4b	Spinous processes of lower thoracic and lumbar vertebrae, lower ribs, crest of ilium	Floor of intertubercular groove/sulcus of anterior proximal humerus	Extends arm; adducts and medially rotates arm
Masseter – Fig. 11-5	Zygomatic arch [temporal & zygomatic bones], maxilla	Lateral surface of ramus of mandible	Closes jaw (chewing)
Orbicularis oculi – Fig. 11-5	Medial margin of orbit	Skin around eyelids	Closes eyes
Orbicularis oris – Fig. 11-5	Maxilla and mandible	Lips	Closes lips
Pectoralis major – Fig. 11-4a	Inferior medial clavicle; sternum; cartilage of ribs 1-6	Intertubercular groove/sulcus of anterior proximal humerus	Flexes, adducts, and medially rotates arm
Rectus femoris (a quadriceps muscle) – Fig. 11-4b	Ilium: anterior inferior spine and superior rim of acetabulum	Tuberosity of proximal anterior tibia	Extends knee, flexes thigh
Sartorius – Fig. 11-4a	Anterior superior spine of ilium	Medial proximal tibia	Flexes, and laterally rotates thigh; flexes knee
Semimembranosus (a hamstring muscle) – Fig. 11-4b	Tuberosity of inferior ischium	Medial proximal tibia	Extends thigh, flexes knee
Semitendinosus (a hamstring muscle) – Fig. 11-4b	Tuberosity of inferior ischium	Medial proximal tibia	Extends thigh, flexes knee
Temporalis – Fig. 11-5	Fossa [shallow depression] of temporal bone	Coronoid process of mandible [not condylar process, which is more	Closes jaw (chewing)

		posterior; not coracoid process of scapula]	
Tibialis anterior – Fig. 11-4a	Lateral condyle and upper tibia	Inferior surface of first cuneiform and metatarsal I	Dorsiflexes foot
Trapezius – Fig. 11-4b	Occipital bone; ligamentum nuchae [connects occipital bone & C_7]; spinous processes of thoracic vertebrae	Acromion [lateral, superior] and spinous process [posterior] of scapula; lateral clavicle	Stabilizes scapula; exact action depends on state of other muscles
Triceps brachii – Fig. 11-4a	Inferior margin of glenoid cavity and posterior humerus (3 heads)	Olecranon of posterior ulna	Extends forearm
Vastus intermedius (a quadriceps muscle) – Fig. 11-21c	Anterior lateral femur, and linea aspera	Tuberosity of proximal anterior tibia	Extends knee
Vastus lateralis (a quadriceps muscle) – Fig. 11-4a	Anterior femur distal to greater trochanter, and linea aspera	Tuberosity of proximal anterior tibia	Extends knee
Vastus medialis (a quadriceps muscle) – Fig. 11-4a	Linea aspera of posterior femur	Tuberosity of proximal anterior tibia	Extends knee
Zygomaticus (major and minor) – Fig. 11-5	Zygomatic bone	Corners of mouth	Smiling!

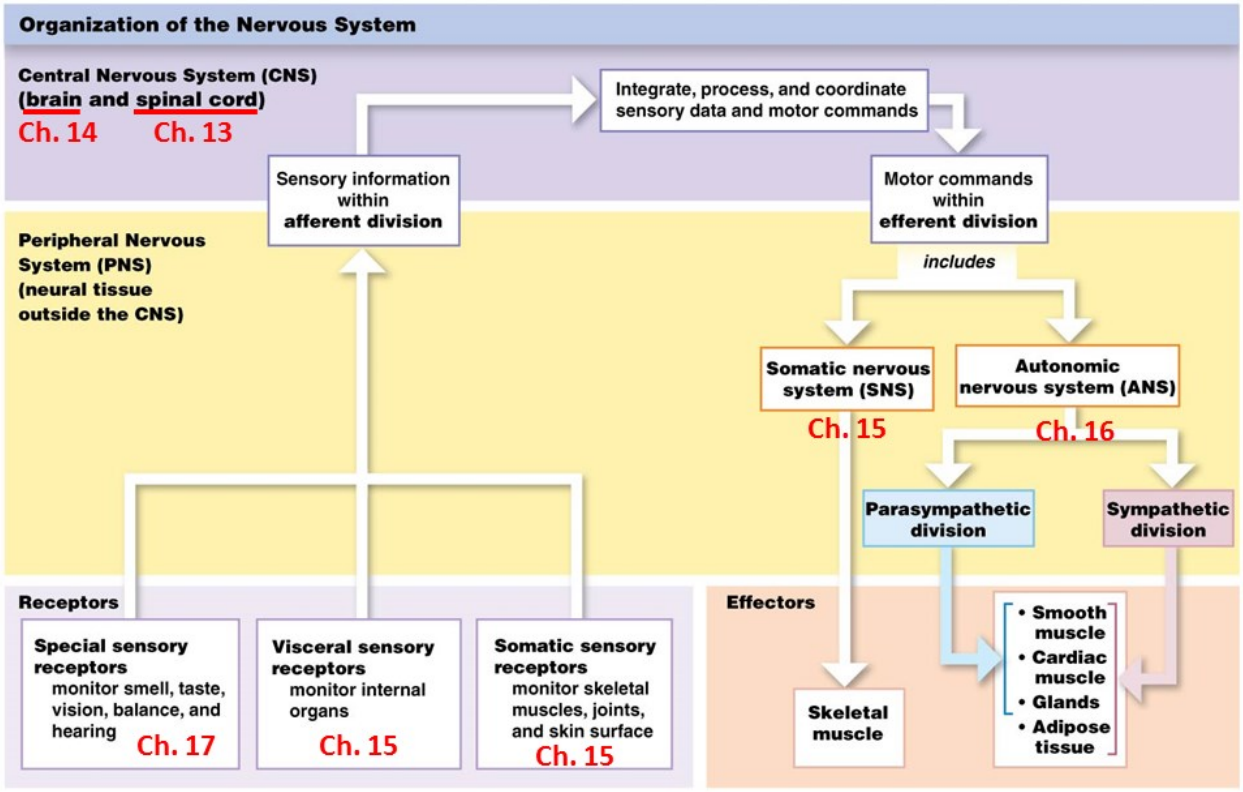
11.7: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 11: #3, #4, #5, #10, #13, #14, #27, #31. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 12: Neural Tissue

With Chapter 12, we enter the realm of the nervous system. 10th Martini covers the nervous system in six chapters – Chapters 12 through 17 – most of which can be mapped onto 10th Martini Figure 12-1 (A Functional Overview of the Nervous System), as shown in CTM Figure 12.1 below. Although Chapter 12 is not explicitly shown in this figure, it explains how neurons (nerve cells) work and thus applies to the entire nervous system. Chapter 12 could therefore be considered the most important chapter of the entire book!

CTM Figure 12.1: An Overview of the Nervous System, showing which parts are covered in which 10th Martini chapters. Based on 10th Martini Figure 12-1 (A Functional Overview of the Nervous System).



12.0: Outline

12.1: Review: anatomy of a neuron

- Neurons generally have dendrites (which receive signals from other neurons), somas, and axons (which release neurotransmitters that communicate with other neurons).

12.2: Membrane potentials compare electrical charge inside and outside the cell

- A "resting" neuron typically has a membrane potential of about -70 mV.

- When ions move into or out of a neuron, its membrane potential changes. Such changes transmit information through the nervous system.

12.3: Electrochemical gradients: which way will ions go?

- Each ion's direction of movement across the cell membrane is governed by its electrochemical potential, the net influence of electrical and chemical gradients.

12.4: Ion channels: gates through the membrane

- Ligand-gated ion channels open when ligands bind to them, while voltage-gated channels open in response to changes in membrane potential.

12.5: Action potentials: fundamental units of information transmission

- An action potential is a predictable rise in membrane potential from about -70 mV to about +30 mV, followed by a drop back to about -70 mV.
- An action potential is caused by the opening of voltage-gated Na^+ channels and Na^+ entry into the cell, followed by the opening of voltage-gated K^+ channels and K^+ exit from the cell.
- Lateral diffusion of Na^+ enables action potentials to travel down the axon.

12.6: Synapses: on to the next cell!

- At electrical synapses, ions pass through gap junctions from the pre-synaptic neuron into the post-synaptic cell.
- At chemical synapses, neurotransmitters released by a pre-synaptic neuron bind to receptors in a post-synaptic cell, directly or indirectly affecting ion channels in the post-synaptic cell.

12.7: Post-synaptic potentials: EPSPs and IPSPs

- Changes in post-synaptic ion channels lead to excitatory and inhibitory potentials (EPSPs and IPSPs).
- The sum of the EPSPs and IPSPs determines whether the axon hillock reaches threshold and begins propagation of an action potential down the axon.

12.8: Recommended review questions

12.1: Review: anatomy of a neuron

We've gotten some glimpses of the nervous system in Chapters 4 and 10. Let's review. Nervous tissue is made up of nerve cells, usually called neurons, which conduct electrical signals, as well as glial cells, which do not conduct electrical signals but provide support for the neurons. (This support includes helping neurons grow, repairing damaged neurons, insulating neurons' axons with myelin, and maintaining the composition of the interstitial fluid.) Neurons generally have many **dendrites** – thin extensions of the cytoplasm that receive signals from other neurons – and a single **soma** (cell body) and **axon**, the end of which releases chemicals called neurotransmitters, which pass messages on to other neurons (or other cells like muscle cells, as we saw in Chapter 10). A generic neuron is shown in 10th Martini Figure 12-2 (The Anatomy of a Multipolar Neuron), and some variations on this generic structure are shown in 10th Martini Figure 12-4 (Structural Classifications of Neurons). Finally, recall that connections between neurons, through which information passes, are called **synapses**.

To the above summary, we can add that all neurons fall into one of three basic categories: sensory neurons, interneurons, and motor neurons. Sensory neurons report on the external

environment; motor neurons control muscle cells; and interneurons process information from other neurons. Most of the body's neurons are interneurons.

12.2: Membrane potentials compare electrical charges inside and outside the cell

As you know, many of the body's key components carry an electrical charge. These ions can range in size from individual atoms that have gained or lost electrons, like Na^+ or Cl^-, to large macromolecules like proteins and nucleic acids. *A fascinating central fact of biology is that cells, including neurons, almost never have the same electrical charge inside and outside their cell membrane.* The inside of the cell is generally slightly negative when compared to the outside. We can visualize this using 10th Martini Figure 12-9 (Resting Membrane Potential). Notice that there are positively charged ions (cations) and negatively charged ions (anions) both inside and outside the cell; however, if you were to sum up all of the charges inside and outside, you would find that the outside is slightly positive compared to the inside, which is the same as saying that the inside is negative relative to the outside.

In physics, any difference in relative charge is known as a voltage. Here we have a voltage across a cell membrane – a **membrane potential**. It is a relatively small difference, measured in millivolts (mV). A typical value for most cells, including most neurons, is in around -70 mV, meaning that the inside of the cell is slightly negative relative to the outside. A neuron that is not actively receiving or transmitting electrical information will have a membrane potential in this range and is said to be at its **resting potential**.

How can a cell's membrane potential change? Clearly, the distribution of ions between the two sides of the membrane must change in some way. Can ions cross from one side of the membrane to the other? Some – like proteins – are much too large to switch sides quickly, but others – like Ca^{2+}, Cl^-, K^+, and Na^+ – can pass through ion channels if those ion channels are open. These movements can either drive the membrane potential toward 0 mV (**depolarization**) or farther away from 0 mV (**hyperpolarization**). The ways in which ion movements can change the membrane potential are summarized in CTM Table 12.1.

CTM Table 12.1: How movements of ions affect a cell's membrane potential.

ION MOVEMENT	EFFECT ON MEMBRANE POTENTIAL
Cations (+ charge) move into the cell	Makes membrane potential more positive / less negative
Anions (- charge) move out of the cell	Makes membrane potential more positive / less negative
Cations (+ charge) move out of the cell	Makes membrane potential less positive / more negative
Anions (- charge) move into the cell	Makes membrane potential less positive / more negative

Membrane potentials are a vital concept to understand *because information is transmitted through the nervous system via changes in neurons' membrane potentials.* Regardless of whether the message is that your hand is cold, your biceps brachii should contract, or something else, the neurons carrying the message open and close their ion channels, ions flow in and out, and the membrane potential is altered. (The details of how this process are covered in the sections below.)

12.3: Electrochemical gradients: which way will the ions go?

In principle, when an ion's channels open, the flow of ions could either be inward or outward. Which way the ion will actually go depends on two factors: the *electrical* gradient, and the ion's *chemical* gradient. The net result of these two gradients is known as the **electrochemical gradient**.

Each gradient, taken on its own, is easy to understand. The electrical gradient simply refers to the membrane potential, i.e., whether the inside of the cell is more negative than the outside or vice versa. The more negative side will attract cations like Na^+ and will repel anions like Cl^-; the more positive side will attract anions and repel cations.

Ions are also influenced by chemical gradients, also known as concentration gradients. As you know, substances are driven down their chemical gradients, i.e., from higher concentrations to lower concentrations.

To see how ion movements are governed both by electrical gradients and chemical gradients, examine 10th Martini Figure 12-10 (Electrochemical Gradients for Potassium and Sodium Ions). Let's start with part (c) of this figure. In a "resting" neuron, the inside of the cell is negative relative to the outside, so this electrical gradient favors entry of Na^+ into the cell. In addition, the Na^+ concentration outside the cell is higher than it is inside the cell (145 mM vs. 10 mM), so the chemical gradient favors Na^+ entry as well. Thus, for Na^+, the electrical and chemical gradients reinforce each other, and Na^+ will go into the cell if there are open ion channels through which it can pass.

The flow of K^+ (10th Martini Figure 12-10a) is less straightforward. As for Na^+, the electrical gradient tends to attract the positively charged K^+ ions into the cell; however, K^+ is much more concentrated inside the cell than outside (140 mM vs. 4 mM), so this chemical gradient favors K^+ movement out of the cell. It turns out that, under typical "resting neuron" conditions, the outward driving force of the chemical gradient is stronger than the inward driving force of the electrical gradient; therefore we say that the electrochemical gradient (the net influence of both gradients) drives K^+ out of the cell.

Each ion is subject to its own electrochemical gradient. Sometimes the electrical and chemical components reinforce each other (as is the case with Na^+ and Ca^{2+} in resting neurons), and sometimes the two components oppose each other (as is the case with K^+ and Cl^- in resting neurons).

12.4: Ion channels: gates through the membrane

As you know, ion channels are proteins found in membranes. Many of them restrict passage to a particular type of ion, which is why we speak of "sodium channels" or "chloride channels," for example. When an ion channel opens, the ions diffuse down their electrochemical gradient.

But *why* do ion channels open? There are two main reasons: a particular chemical (ligand) binds to the channel, or the channel responds to a change in voltage (membrane potential). The first type of ion channel is a **chemically gated (or ligand-gated) channel**; the second type is a **voltage-gated channel**. Both types are pictured in 10th Martini Figure 12-11 shows both of these types (along with a third variety that we won't worry about).

Both kinds of channels are vital in passing information within and between neurons. As we shall see below, voltage-gated channels transmit action potentials down axons; neurotransmitters released by these axons then open ligand-gated channels in the dendrites and soma of post-synaptic neurons, changing the membrane potential of these post-synaptic neurons.

12.5: Action potentials: fundamental units of information transmission

With all of the above background in mind, we can understand how signals spread through the nervous system. For clarity, we will start with the spread of a signal down the axon of a neuron. Changes in an axon's membrane potential follow a highly predictable pattern known as an action potential. The steps of an action potential at a particular section of an axon, as shown in 10th Martini Figure 12-14 (Generation of an Action Potential), are the following:

- *1. Depolarization to threshold.* A flow of sodium ions from "upstream" depolarizes the cell membrane somewhat. If this depolarization from the resting potential (say, -70 mV) reaches a threshold value (-55 to -60 mV), voltage-gated Na^+ channels will open.
- *2. Activation of sodium channels and rapid depolarization.* Na^+ ions rush inward (i.e., down their electrochemical gradient) through the open Na^+ channels. The inside of the cell becomes positive relative to the outside.
- *3. Inactivation of sodium channels and activation of potassium channels.* The sodium channels automatically close within a millisecond after having driven up the membrane potential to a peak voltage of about +30 mV. Meanwhile, voltage-gated K^+ channels open in a delayed response to the depolarization of steps 1 and 2. K^+'s electrochemical gradient drives it out of the cell; this outward flow of positive ions repolarizes the neuron back toward its resting potential of -70 mV.
- *4. Closing of potassium channels.* The voltage-gated K^+ channels close, and this part of the axon is essentially back to its initial state.

After step 4, the axon can go through another round of steps 1-4 once the Na+ channels come out of their **refractory period**, a short time (1 to 2 msec) during which they are unable to re-open.

The changes in membrane potential from -70 mV up to +30 mV and then back down to -70 mV (or slightly below) during the steps above are collectively called an action potential. Usually, when we use the word *potential*, we are referring to a single specific voltage (e.g., -45 mV), but the term *action potential* is an exception to this rule.

To understand how an action potential propagates down an axon, we only need to add a couple more details to the steps above. As shown in 10th Martini Figure 12-15 (Propagation of an Action Potential), once the voltage-gated Na^+ channels open and Na^+ enters the neuron (steps 1 and 2), the Na^+ diffuses laterally along the axon. The diffusion of this Na^+ "downstream" (toward

the right side of the figure) depolarizes the downstream section of cell membrane, which then opens the voltage-gated Na^+ channels in that section of membrane, and the cycle repeats itself. These newly entering Na^+ ions diffuse laterally and trigger the opening of voltage-gated Na^+ channels even further downstream, and so on. Note that the lateral diffusion of Na^+ also depolarizes the cell membrane just *upstream* of the open Na^+ channels; however, the upstream Na^+ channels do not open because they are still in their refractory period.

A final point about action potential propagation, also covered by 10th Martini Figure 12-15, is that most human axons are wrapped in glial cells, which insulate the axons with layers of fat. This allows the laterally diffusing Na+ ions to travel much farther down the axon before sparking another action potential. This saltatory propagation (*saltatory* means "jumping") speeds up the spread of the signal down the axon.

12.6: Synapses: on to the next cell!

Once an action potential travels all the way down a neuron's axon, the signal needs to be passed to the next neuron (or to other cells) across a synapse. How does this happen?

There are two basic types of synapses: electrical synapses and chemical synapses. Electrical synapses, which are rare in humans, are simple and fast. Ions simply pass through gap junctions (remember them from Chapter 4?) that connect the two cells; thus Na^+ from the pre-synaptic neuron can depolarize the post-synaptic neuron. (This is essentially how electrical signals spread between cardiac muscle cells, although those connections are not called synapses because cardiac muscle cells are not neurons.)

Chemical synapses are illustrated in 10th Martini Figure 12-16 (Events in the Functioning of a Cholinergic Synapse). They too can depolarize the post-synaptic neuron, but do so via a chain of steps involving voltage-gated Ca^{2+} channels, vesicles (remember them from Chapter 3?) that contain chemicals called neurotransmitters, and post-synaptic receptors. As the action potential reaches the end of the axon, it triggers the opening not of voltage-gated Na^+ channels but of voltage-gated Ca^{2+} channels (step 2 of the figure). The calcium binds to a protein (called synaptotagmin) in vesicle membranes, causing the vesicles to fuse with the cell membrane and dump the neurotransmitter molecules into the synapse (still step 2 of the figure). The neurotransmitter (acetylcholine in the figure; other well-known examples include serotonin, dopamine, glutamate, GABA, and norepinephrine) diffuses to the post-synaptic cell and binds to receptors, which either function as ligand-gated channels or stimulate ion channels to open (step 3 of the figure). In this way, changes in the pre-synaptic membrane potential lead to changes in the post-synaptic membrane potential. Note that the connections between motor neurons and skeletal muscle cells, previously described in Chapter 10, are examples of chemical synapses.

12.7: Post-synaptic potentials: EPSPs and IPSPs

A neurotransmitter's (direct or indirect) effects on post-synaptic ion channels can either depolarize or hyperpolarize the post-synaptic cell, depending on which ions are involved.

Opening post-synaptic sodium channels, as acetylcholine often does, spurs an influx of Na^+ and depolarization of the post-synaptic membrane. Because this change brings the post-synaptic cell closer to its threshold, it is known as an **excitatory post-synaptic potential (EPSP)**. Conversely, the neurotransmitter GABA generally opens Cl^- channels; if Cl^- enters the cell, it becomes hyperpolarized, a change known as an **inhibitory post-synaptic potential (IPSP)**.

The ions underlying these EPSPs and IPSPs passively diffuse through the dendrites and soma to the start of the axon, also called the **axon hillock**. Here the question is, does the membrane of the axon hillock reach its threshold (typically around -60 mV)? If enough EPSPs are summed together over time and space, threshold will be reached and an action potential will fire at the axon hillock and continue down the axon. This is shown in 10th Martini Figure 12-18 (Temporal and Spatial Summation). And so we arrive back at the axon, where we started tracing the propagation of signals in section 12.5 above.

12.8: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 12: #3, #5, #6, #7, #8, #12, #13, #17, #18, #23, #25. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 13: The Spinal Cord, Spinal Nerves, and Spinal Reflexes

As seen in 10th Martini Figure 12-1 (A Functional Overview of the Nervous System), the nervous system consists of the central nervous system (CNS – the spinal cord and brain) and the peripheral nervous system (PNS). Chapters 13 and 14 cover the two components of the CNS: the spinal cord (Chapter 13) and brain (Chapter 14). These two components are summarized in 10th Martini Figure 13-1 (An overview of Chapters 13 and 14).

The main function of the spinal cord is to transmit information between the brain and the PNS. However, as shown in 10th Martini Figure 13-1, certain reflexes can be executed by the spinal cord itself, without the brain being involved.

13.0: Outline

13.1: Basic anatomy and organization of spinal cord and spinal nerves
- The spinal cord itself consists of white matter, which passes information up and down the spinal cord, and gray matter, which processes information at that level.
- From deep to superficial, the spinal cord connects to dorsal and ventral roots, dorsal and ventral rami, and plexuses of the ventral rami.

13.2: Neural circuits: ways of connecting neurons
- To convert inputs to outputs, neural circuits can be connected in five basic patterns: divergences, convergence, serial processing, parallel processing, and reverberation.

13.3: Reflexes: rapid, automatic responses to specific stimuli
- Reflexes are a form of information processing in which sensory neurons connect to motor neurons either directly (monosynaptic reflexes) or with relatively few synapses in between (polysynaptic reflexes).
- Examples include stretch reflexes (e.g., the patellar reflex) and the crossed extensor reflex.

13.4: Clinical issues
- Since the spinal cord ends at about the L_2 vertebra, CSF can be safely accessed from the subarachnoid space inferior to L_2.
- Catastrophic disruption of the spinal cord can result in paraplegia or quadriplegia.
- Sciatica is pain or numbness in the lower back, leg, or foot caused by compression of the sciatic nerve in or near the spinal cord.

13.5: Recommended review questions

13.1: Basic anatomy and organization of spinal cord and spinal nerves

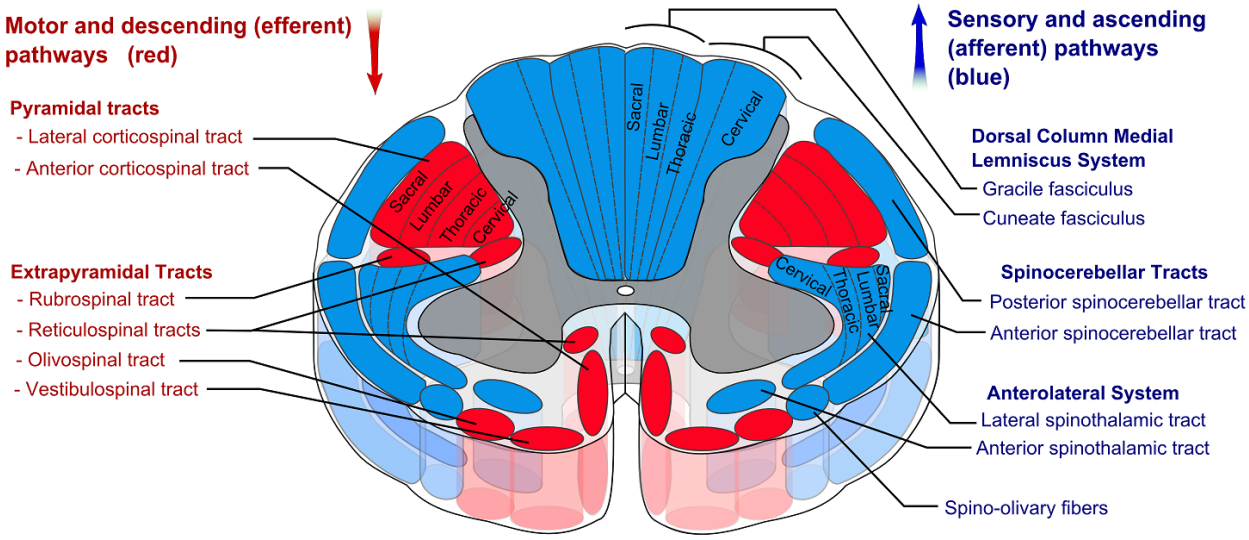
The spinal cord sits within the vertebral foramina of the vertebrae (covered in Chapter 7). As stated above, the main function of the spinal cord is to transmit information between the brain and the peripheral nervous system (PNS). To perform this function, the spinal cord obviously needs specific connections to the brain (white matter) and to the PNS (dorsal and ventral roots). We will now discuss these connections to the brain and PNS in more detail.

The connections to the brain take the form of various tracts within the **white matter** of the spinal cord (CTM Figure 13.1). The whiteness of the white matter is due to the many layers of pale-

colored myelin surrounding the axons of neurons running between the brain and spinal cord. There is no need to memorize the names or locations of these tracts, but notice that their names often hint at their origins and destinations. For example:

- Descending pathways
  - Corticospinal tract: from cortex to spine
  - Rubrospinal tract: from red nucleus to spine
  - Olivospinal tract: from olivary body (in medulla) to spine
  - Vestibulospinal tract: from vestibular nuclei of pons and medulla to spine
- Ascending pathways
  - Spinocerebellar tract: from spine to cerebellum
  - Spinothalamic tract: from spine to thalamus

CTM Figure 13.1: Ascending and descending tracts of the spinal cord's white matter. Ascending tracts (carrying sensory information toward the brain) are shown in red, and descending tracts (carrying motor information away from the brain) are shown in blue. Figure by Polarlys and Mikael Häggström via Wikipedia.



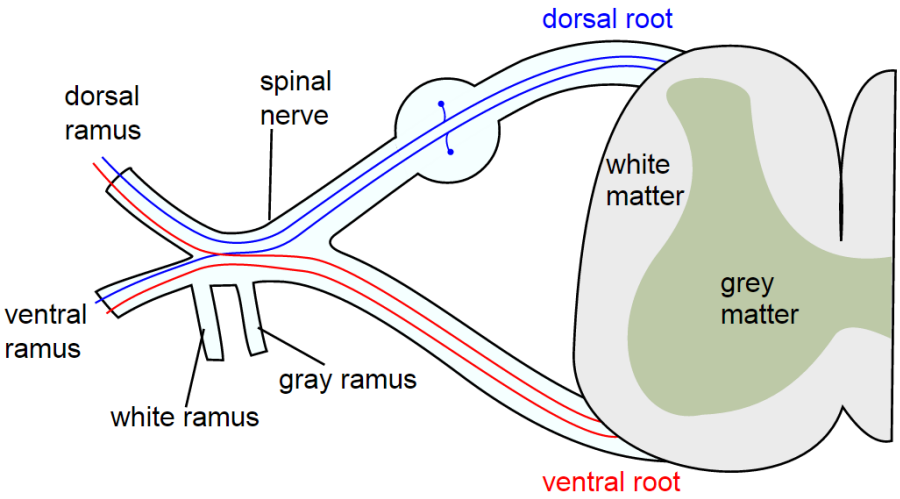
Deep to the white matter lies the butterfly-shaped **gray matter**. The gray matter integrates and analyzes information, which requires neurons to communicate with each other via synapses. Since synapses include many unmyelinated dendrites and cell bodies, the myelin is not as dominant here and the gray matter is gray, not white.

In the following paragraphs, we will gradually work our way away from the spinal cord.

Dorsal roots, carrying sensory information, and ventral roots, carrying motor information, connect to the spinal cord through the intervertebral foramina at each vertebral level: C_1, C_2, etc., all the way down to coccygeal level Co_1. Aside from their dorsal location, dorsal roots can be distinguished from the ventral roots because each dorsal root has a dorsal root ganglion: a bulge to accommodate the cell bodies of the sensory neurons. (Motor neurons' cell bodies are within the gray matter.)

As we follow a pair of dorsal and ventral roots away from the spinal cord, they join together briefly, then branch apart into a dorsal ramus and a ventral ramus (CTM Figure 13.2). These dorsal and ventral rami carry both sensory and motor information. A dorsal ramus sends sensory and motor information to and from the back (dorsal side of the body), while a ventral ramus sends sensory and motor information to and from the limbs and the ventral and lateral sides of the body.

CTM Figure 13.2: The spinal cord, roots, and rami. Figure produced by Mysid and Tristanb for Wikipedia.



Ventral rami from adjacent levels of the spinal cord join together to form plexuses, as shown in 10th Martini Figure 13-9 (Peripheral Nerves and Nerve Plexuses). Note that, while the T_3 to T_{11} rami do not fuse with other rami, the other rami do. These plexuses are summarized in CTM Table 13.1.

CTM Table 13.1: The four plexuses.

Plexus	**Ventral rami**	**Body areas covered**
Cervical	C_1 to C_5	Neck, shoulders, diaphragm
Brachial	C_5 to T_1	Shoulders, arm, forearm, hand
Lumbar	L_1 to L_4	Lower abdominopelvic region, anterior thigh
Sacral	L_4 to S_4	Butt, posterior thigh, leg, foot

From these plexuses, various nerves emerge. This is illustrated nicely by 10th Martini Figure 13-11 (The Brachial Plexus), which shows how four major nerves (musculocutaneous, radial, median, and ulnar) arise from the brachial plexus, incorporating different contributions from the lower cervical and uppermost thoracic spinal segment. These large nerves branch into smaller nerves that innervate individual muscles, specific patches of skin, etc. Thus the neural path from the spinal cord to the biceps brachii includes the dorsal and ventral roots at C_5, C_6, C_7, C_8 (yes, there are 8 cervical spinal segments even though there are only 7 cervical vertebrae), and T_1. These become ventral rami that form the brachial plexus, which in turn gives rise to the musculocutaneous nerve, which includes the biceps brachii's motor neurons.

13.2: Neural circuits: ways of connecting neurons

The above narrative applies to nerves, which are huge numbers of neurons and glial cells bundled together. To understand how the spinal cord (and the rest of the nervous system) processes information, though, we need to think at the level of synapses – connections between individual neurons. There are many ways of arranging synapses between pre-synaptic and post-synaptic neurons; some general categories are shown in 10th Martini Figure 13-13 (Neuronal Circuits: The Organization of Neuronal Pools). 10th Martini also provides good examples of situations where each type of circuit is needed (summarized in CTM Table 13.2).

CTM Table 13.2: The five main types of neural circuits.

TYPE	DEFINITION	EXAMPLE
(a) Divergence	1 input diverges to many outputs	Visual info is sent to several areas of the brain, affecting posture, balance, etc.
(b) Convergence	Many inputs converge on 1 output	Conscious and subconscious inputs converge at the motor neurons that control your breathing.
(c) Serial processing	1 input leads to 1 output	Pain information passes sequentially through multiple neuronal pools on the way to your consciousness.
(d) Parallel processing	The same info is processed via multiple pathways	A response to stepping on a sharp object may include withdrawing your foot, shifting your weight, moving your arms, feeling pain, and shouting "Ouch!"
(e) Reverberation	Postsynaptic neurons feed back on presynaptic ones	Positive feedback may help maintain cyclical processes such as breathing.

The language of neural circuits may sound reminiscent of electrical engineering or computer sciences. This is no accident. Circuits are engineered to produce desired outputs from a given set of input; your nervous system is also in the business of converting inputs (from pre-synaptic neurons) to outputs (to post-synaptic neurons). We will see some examples of this in the next section.

13.3: Reflexes: rapid, automatic responses to specific stimuli

10th Martini defines reflexes as "rapid, automatic responses to specific stimuli." This definition accommodates many different types of reflexes, as indicated in 10th Martini Figure 13-15 (The Classification of Reflexes). In particular, note that some reflexes are learned or acquired over time; 10th Martini cites the examples of a skilled driver braking in anticipation of danger ahead. Nevertheless, the rapid and automatic nature of all reflexes means that the translation of inputs into outputs is relatively straightforward, involving relatively few synapses.

A classic textbook example of a reflex is the **patellar reflex**, also known as the knee-jerk reflex. It turns out that there are sensory receptors within muscles that can sense the stretching of the muscle and initiate a stretch reflex, in which the stretched muscle responds by contracting. This is diagrammed in 10th Martini Figure 13-14 (Spinal Reflexes). **Stretch reflexes** are the simplest

possible reflexes in the sense that they only involve a single synapse between a sensory neuron (which sends a message of "My muscle is being lengthened!") and a motor neuron (which sends a message of, "Well, make it shorter again!"). The fancy word for "involving only one synapse" is **monosynaptic**. In terms of the spinal anatomy above, the sensory neuron enters the spinal cord through a dorsal root and connects to a motor neuron in the gray matter; the motor neuron then sends its signal out through a ventral root back to the muscle.

A somewhat more complicated reflex, also shown in 10th Martini Figure 13-14, is the **crossed extensor reflex**. Here the person steps on something sharp; the response is to pull the affected foot away while putting one's weight on the other foot. Thus, as shown in the figure, the sensory information triggers responses by four different muscle groups – stimulating the knee flexors ipsilateral to (on the same side as) the painful stimulus and the knee extensors contralateral to (on the opposite side as) the painful stimulus, and inhibiting the ipsilateral knee extensors and contralateral knee flexors. Since this communication goes to multiple muscles at multiple levels of the spinal cord, it is **polysynaptic**, i.e., there is more than one synapse between the sensory neurons and the motor neurons. In terms of the neural circuits described above, the crossed extensor reflex exhibits divergence and parallel processing (the same information is sent along several different paths, leading to the ipsilateral and contralateral extensors and flexors), as well as reverberation (to maintain the appropriate muscle response after the stimulus subsides).

10th Martini says that both of these reflexes, and others, conform to the following five-step process:

1. The arrival of a stimulus and activation of a receptor.
2. The activation of a sensory neuron.
3. Information processing in the CNS. (Though the two reflexes described above are handled by the spinal cord, others involve the brain.)
4. The activation of a motor neuron.
5. The response of a peripheral effector.

Personally, I'm not crazy about this five-step summary; for the stretch reflex, steps 1 and 2 are the same thing (the receptor IS the sensory neuron), and to call the activation of a motor neuron by a sensory neuron "information processing" seems a bit grandiose. Nevertheless, the overall flow of information should make sense.

13.4: Clinical issues

We conclude this chapter with a quick look at three clinical topics related to the spinal cord: anesthesia, paraplegia/quadriplegia, and sciatica.

Anesthesia is a lack of sensation – a dulling of the senses, generally to avoid feeling pain. Anesthetic drugs can be injected either next to the spinal column, or directly into it. To understand the difference, it is important to appreciate two key bits of spinal cord anatomy.

First, the spinal cord (as well as the brain) is surrounded by three **meninges** (layers of protective covering): the outer **dura mater**, the **arachnoid mater**, and the inner **pia mater**. The cerebrospinal fluid (CSF) resides in the subarachnoid space between the arachnoid mater and pia mater. Second, the spinal cord does not itself extend below vertebra L_2, although the dorsal and ventral roots attached to it extend farther down before passing through intervertebral foramina.

Because of this second fact, anesthetic drugs can be safely injected into the L_3-L_5 range of the subarachnoid space without fear of damaging the spinal cord. Sampling of CSF to test for bacterial or viral infections (which can cause meningitis, i.e., inflammation of the meninges) is done in the same range for the same reason. Injection of drugs into the CSF and withdrawal of CSF samples are both commonly called **lumbar punctures** and **spinal taps**. A drug's distribution in the CSF is affected by its density relative to that of CSF (will it sink or float?); the preferred distribution can be achieved by choosing a drug of the appropriate density and/or by tipping the patient.

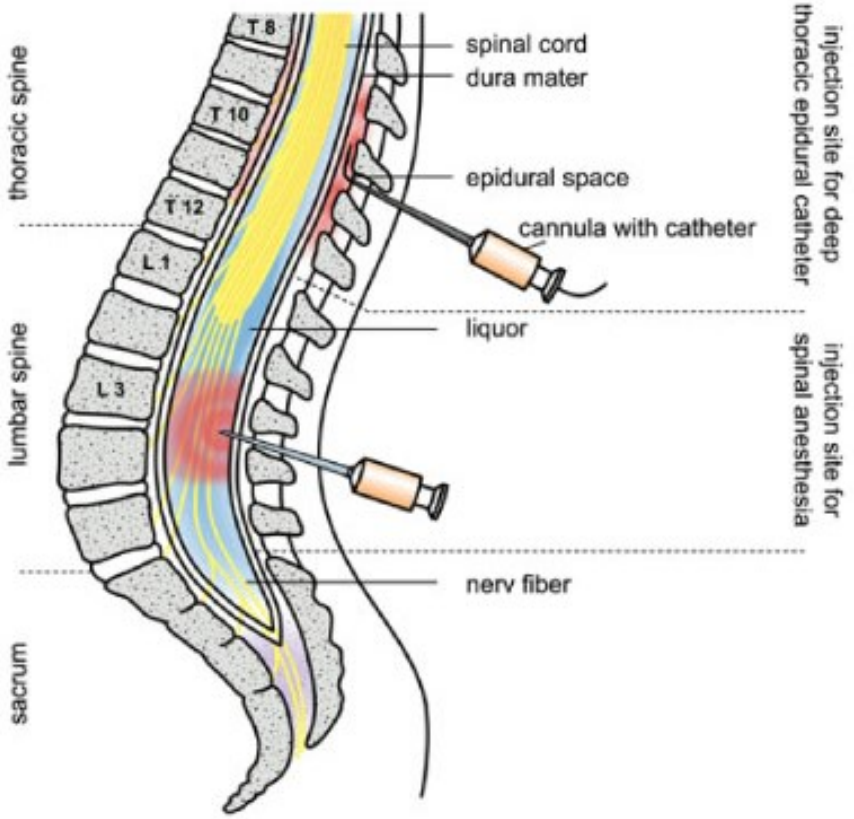
An alternative to spinal anesthesia is **epidural anesthesia**, in which the drug is injected into the epidural space next to the spinal column (CTM Figure 13.3). Because this space is filled with fat rather than fluid, the spread of epidural injections is slower and more limited than the spread of spinal injections.

Paraplegia is the loss of control of the lower limbs, while **quadriplegia** is the loss of control of both upper and lower limbs. The medical explanation for these conditions is usually straightforward: a traumatic injury to the spinal cord will cut off communication to any regions of the body whose spinal nerves are inferior to the location of the injury. Interestingly, spinal reflexes like the patellar stretch reflex may remain intact following spinal cord injury; they may even be exaggerated in cases where the brain had previously suppressed the reflex.

Unfortunately, injuries to the CNS do not heal nearly as well as injuries to the peripheral nervous system (PNS). In the PNS, glial cells secrete growth-promoting factors that help axon stumps grow back together, but in the CNS, glial cells may secrete growth-inhibiting factors and may form "glial scars" that block regrowth. Ongoing research is investigating whether CNS regrowth can be enhanced via injections of growth factors and/or stem cells to injury sites.

Less severe than paraplegia, but still potentially crippling, is the condition of **sciatica**. As the name suggests, this is a problem with the sciatic nerve, which forms from spinal segments L_4 to S_3 and innervates much of the musculature and skin in the leg and foot. Compression of the sciatic nerve can lead to pain and/or numbness in the lower back, butt, leg, and/or foot. We saw in Chapter 9 that bulging or herniated intervertebral discs can impinge on nerves entering or exiting the spine. Narrowing of the vertebral foramen (either due to disc problems or other factors) and interference by the piriformis muscle are among sciatica's other possible causes.

CTM Figure 13.3: Spinal versus epidural lumbar punctures. Figure taken from M. Friedrich-Freksa et al., International Brazilian Journal of Urology ***38****: 645-651, 2012.*



13.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 13: #1, #2, #4, #5, #6, #10, #11, #13, #18, #23, #24, #26, #30. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 14: The Brain and Cranial Nerves

With this chapter we complete our tour of the Central Nervous System (CNS) that we began in Chapter 13 (The Spinal Cord, Spinal Nerves, and Spinal Reflexes). The 10th Martini version of this chapter is VERY heavy on anatomical details, many of which we will skip.

14.0: Outline

14.1: Overview of brain anatomy
- The brain includes six major regions: the cerebrum, cerebellum, diencephalon, midbrain, pons, and medulla.

14.2: Protecting the brain
- The brain is protected physically and chemically by the cranial bones, the cranial meninges, the cerebrospinal fluid (CSF), and blood-brain barrier.

14.3: The twelve cranial nerves
- Cranial nerves connect directly with the brain rather than the spinal cord.
- The twelve cranial nerves are: olfactory (I), optic (II), oculomotor (III), trochlear (IV), trigeminal (V), abducens (VI), facial (VII), vestibulocochlear (VIII), glossopharyngeal (IX), vagus (X), accessory (XI), and hypoglossal (XII).

14.4: Example of a cranial reflex: the pupillary reflex
- In reaction to bright light, sensory information from cranial nerve II (optic) leads to motor output through cranial nerve III (oculomotor), contracting the pupillary muscles in the iris and thus reducing the size of the pupil.

14.5: Clinical issues
- Examples of brain disorders include meningitis, stroke, aphasia, seizures, Parkinson's Disease, and Alzheimer's Disease.

14.6: Recommended review questions

14.7: Appendix: the top 24 muscles … and their innervation

14.1: Overview of brain anatomy

Before plunging into anatomical details, 10th Martini offers a reasonable overview of the brain in Figure 14-1 (An Introduction to Brain Structures and Functions) and the text accompanying it. According to 10th Martini, there are six major brain regions: the cerebrum, cerebellum, diencephalon, midbrain, pons, and medulla. The outline below shows how some other important structures, many of which you've seen in lab, fit into these six regions. The outline is not comprehensive (for example, the diencephalon includes more than just the thalamus and hypothalamus).

- Cerebrum
    - Cerebral cortex (Fig. 14-16)
        - Frontal lobe (Fig. 14-16a): includes motor cortex (control of voluntary muscles) and prefrontal cortex (decision-making, problem-solving)
            - Broca's area (Fig. 14-16b): affects speech production

        - Parietal lobe (Fig. 14-16a): perceives touch/pressure, taste, pain, and temperature
        - Temporal lobe (Fig. 14-16a): perceives smells and sounds
            - Wernicke's area (Fig. 14-16b): interprets language and sensory information
        - Occipital lobe (Fig. 14-16a): perceives visual information
    - Corpus callosum (Figs. 14-12, 14-15): connects the two cerebral hemispheres
    - Hippocampus (Fig. 14-12): a center for learning and memory
    - Amygdala (Fig. 14-12): influences emotions and their connections to memories
- Cerebellum (Fig. 14-1): subconsciously adjusts posture and movement
- Diencephalon (Fig. 14-5)
    - Thalamus (Fig. 14-12): relays and processes visual and auditory information, etc.
    - Hypothalamus (Fig. 14-12): regulates body temperature, heart rate, blood pressure, fluid loss, etc. (negative feedback central!)
- Midbrain (Fig. 14-5)
    - Superior colliculus (Fig. 14-5c): relays and processes visual information
    - Inferior colliculus (Fig. 14-5c): relays and processes auditory information
    - Substantia nigra (Fig. 14-9): subconscious control of muscle
- Pons (Fig. 14-5): relays sensory and motor information
- Medulla (Fig. 14-5): controls basic functions like heart rate, blood pressure, and rate of breathing

Note that the groupings above are not the only possible way to think about the organization of the brain. For example, 10th Martini notes that the limbic system is defined as a group of structures that control emotion, motivation, and memory, which are split between the diencephalon (e.g., thalamus, hypothalamus) and the cerebrum (e.g., hippocampus, amygdala).

14.2: Protecting the brain

The brain is protected physically and chemically by the cranial bones (discussed in Chapter 7), the cranial meninges, the cerebrospinal fluid (CSF), and blood-brain barrier.

You may recall from Chapter 13 or from lab that the spinal cord is covered with three layers of meninges: the dura mater (outermost), arachnoid mater (middle), and pia mater (innermost). You may also recall that CSF resides in the subarachnoid space between the arachnoid mater and pia mater. This information also holds true for the brain. In the brain, subarachnoid spaces are expanded into four ventricles, as pictured in 10th Martini Figure 14-2 (Ventricles of the Brain). The CSF cushions and supports the brain and also transports nutrients, chemical messengers, and waste products.

The blood-brain barrier protects the brain in a different way: by strongly limiting the substances that can diffuse from the blood into the brain. Capillaries in the brain are lined by endothelial cells connected by tight junctions (remember these from Chapter 4?), so, to get into the brain, a substance must either pass through open channels in the endothelial cell membrane or be hydrophobic enough to pass directly through the membrane. As a company develops a new drug

intended to act upon the brain, part of the development process is to make sure the drug can get through the blood-brain barrier.

14.3: The twelve cranial nerves

As discussed in Chapter 13, most neural information flowing from the brain to the peripheral nervous system (PNS), or vice versa, travels through the spinal cord. The exceptions to this rule are the 12 **cranial nerves**, which connect directly to the brain, as shown in 10th Martini Figure 14-19 (Origins of the Cranial Nerves). The cranial nerves are numbered from 1 to 12 using Roman numerals. Roman numerals are easy to handle if you know three simple rules:

- I stands for 1, V stands for 5, X stands for 10, L stands for 50, etc.
- In general, add the values of all numerals to get the total.
    - For example, XXVIII = 28.
- If a smaller numeral comes before a larger numeral, subtract the smaller numeral from the larger numeral.
    - For example, IV = 4 and IX = 9.

Thus the correspondence between Roman numerals and Arabic numbers is as follows.

1	2	3	4	5	6	7	8	9	10	11	12
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII

As you can see from 10th Martini Figure 14-9, the numbering of the cranial nerves goes roughly from anterior to posterior, which cranial nerve I is most anterior, cranial nerve II is next-most anterior, etc. The exception is that cranial nerve XII is not the most posterior cranial nerve.

Each cranial nerve has not only a number but a name corresponding to its function, as shown in CTM Table 14.1. Also notice that some of these nerves carry sensory information, some carry motor information, and some carry both. The nerve names and modalities (sensory/motor/both) can be remembered via mnemonics such as "Oh Oh Oh, To Touch And Feel Very Good Velvet; Ah, Heaven!" and "Some Say Money Matters, But My Brother Says Big Brains Matter More," as shown in CTM Table 14.2.

CTM Table 14.1: Key information about the 12 cranial nerves. (Nerves marked as M for motor are almost entirely motor but not 100% motor.)

#	Name	Sensory? Motor? Both?	Function	Passage through the cranium
I	Olfactory	S	Smell	Olfactory foramina in cribriform plate of ethmoid
II	Optic	S	Vision	Optic canal of sphenoid
III	Oculomotor	M	Eye muscles	Superior orbital fissure of sphenoid
IV	Trochlear	M	Eye muscles	Superior orbital fissure of sphenoid
V	Trigeminal	B	Facial senses, chewing	Superior orbital fissure, foramen rotundum, and foramen ovale of sphenoid (3 branches)
VI	Abducens	M	Eye muscles	Superior orbital fissure of sphenoid
VII	Facial	B	Facial expressions, taste	Internal acoustic meatus of temporal bone

VIII	Vestibulocochlear	S	Balance and hearing	Internal acoustic meatus of temporal bone
IX	Glossopharyngeal	B	Salivary glands and taste	Jugular foramen (between temporal and occipital bones)
X	Vagus	B	Parasympathetic innervation of visceral organs	Jugular foramen (between temporal and occipital bones)
XI	Accessory	M	Back and neck muscles	Jugular foramen (between temporal and occipital bones)
XII	Hypoglossal	M	Moving the tongue	Hypoglossal canal of occipital bone

CTM Table 14.2: Cranial nerve mnemonics. An additional mnemonic – a song to remember the cranial nerves' functions – can be found online at http://faculty.washington.edu/crowther/Misc/Songs/cranial.shtml.

I		Oh	→	O	→	Olfactory			Some	→	S	→	Sensory
II		Oh	→	O	→	Optic			Say	→	S	→	Sensory
III		Oh,	→	O	→	Oculomotor			Money	→	M	→	Motor
IV		To	→	T	→	Trochlear			Matters	→	M	→	Motor
V		Touch	→	T	→	Trigeminal			But	→	B	→	Both
VI		And	→	A	→	Abducens			My	→	M	→	Motor
VII		Feel	→	F	→	Facial			Brother	→	B	→	Both
VIII		Very	→	V	→	Vestibulocochlear			Says	→	S	→	Sensory
IX		Good	→	G	→	Glossopharyngeal			Big	→	B	→	Both
X		Velvet;	→	V	→	Vagus			Brains	→	B	→	Both
XI		Ah,	→	A	→	Accessory			Matter	→	M	→	Motor
XII		Heaven!	→	H	→	Hypoglossal			More.	→	M	→	Motor

Additionally, note that to get into and out of the brain, the cranial nerves must pass through holes in the cranium (canals, fissures, foramina, meatuses, etc.). We saw some of these holes when studying the axial skeleton in Chapter 7; now we are in a better position to see which ones go with which nerves. These holes are listed in CTM Table 14.1. In some cases, there is more than one hole for a given nerve; the olfactory foramina include many tiny holes through the cribriform plate, while the three branches of the trigeminal nerve (ophthalmic, maxillary, and mandibular) each go through separate openings. We are thus reminded that, like other nerves, cranial nerves have branches and subdivisions. The branching of the facial nerve (10th Martini Figure 14-24) is especially spectacular.

14.4: An example of a cranial reflex: the pupillary reflex

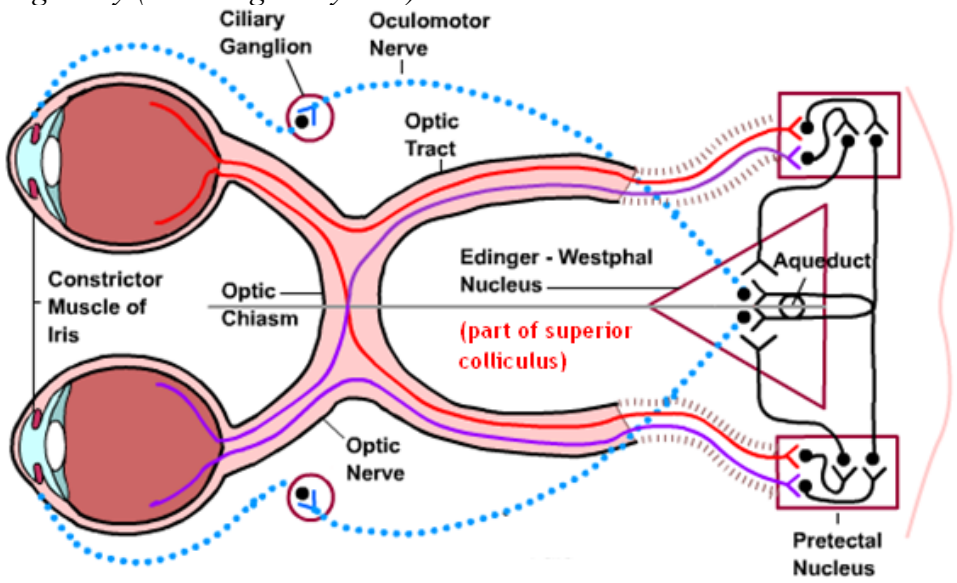
Chapter 13 discussed reflexes – defined as "rapid, automatic responses to specific stimuli" – and described spinal reflexes such as the patellar reflex and the crossed extensor reflex. Cranial reflexes are similar to spinal reflexes except that the neural information goes into and out of the brain rather than the spinal cord. Cranial reflexes are listed in 10th Martini Table 14-5; note that each translates sensory information (in cranial nerve II, V, or VIII) into motor commands (in cranial nerve III, IV, VI, VII, or X).

The pupillary reflex, also known as the direct light reflex, is a good example of the cranial reflexes. Its purpose is to limit the amount of light flowing into the retina. To understand how it

works, we need to know a bit about the anatomy of the eye. As depicted in 10th Martini Figure 17-5a (The Sectional Anatomy of the Eye), the iris is a structure just anterior to the lens, made mostly out of smooth muscles called pupillary muscles. The center of the lens, which is not covered by the iris, is called the pupil. Incoming light is stopped by the iris but can pass through the pupil to reach the retina at the back of the eye. To reduce the amount of light that reaches the retina, the size of the pupil is reduced via contraction of the pupillary muscles, as shown in 10th Martini Figure 17-6 (The Pupillary Muscles).

So how does the pupillary reflex actually work? The optic nerve (cranial nerve II) receives input from the retina that the light is very bright. This information goes to structures in the midbrain: the pretectal nucleus, which is adjacent to the superior colliculus, and then the superior colliculus itself. The signal for the pupillary muscles to contract is sent out via the oculomotor nerve (cranial nerve III). This simple circuit is diagrammed in CTM Figure 14.1.

CTM Figure 14.1: The pupillary reflex, also known as the direct light reflex. Figure taken from Dr. Ted Montgomery (tedmontgomery.com).



14.5: Clinical issues

Brain disorders are fascinating! Due to time constraints, we will only touch briefly upon a few of them.

Meningitis is literally an inflammation of the meninges – the protective layers surrounding the brain and spinal cord. This is usually due to a bacterial or viral infection. Symptoms can be diffuse but often include headache or neck stiffness. To determine whether there is an infection, CSF can be withdrawn from the spinal canal below L_2 and analyzed in a clinical laboratory.

Stroke is a general term for any interruption of blood flow to a portion of the brain. Since neurons depend on a constant supply of oxygen, they begin to die within minutes. The ultimate effects of a stroke depend greatly on which part of the brain failed to receive blood. Strokes at the lower brain stem are usually fatal because the pons and medulla control basic bodily

functions necessary for life, like breathing. Nonfatal strokes can cause problems like aphasia and seizures (see below).

Aphasia is any impairment in speaking or reading. It includes such diverse problems as Broca's aphasia (caused by damage to Broca's area in the frontal lobe) and Wernicke's aphasia (caused by damage to Wernicke's area in the temporal lobe). Patients with Broca's aphasia produce words slowly and with great difficulty, though their comprehension is often good. Patients with Wernicke's aphasia speak more freely, with a flow of words that resembles normal speech, but make little sense. A Broca's patient might say, "Book book two table," meaning, "There are two books on the table." A Wernicke's patient might spew nonsense like, "You know that smoodle pinkered and that I want to get him round and take care of him like you want before" (www.nidcd.nih.gov/health/voice/pages/aphasia.aspx).

Seizures are acute events in which neurons in the brain are excessively active and more synchronized than usual. The potential causes are numerous and remain poorly understood; however, the fact that seizures can spread widely across the brain is a reminder of just how extensively interconnected the brain's neurons really are. In the mid-20th century, a seizure-prone patient would occasionally have his or her corpus callosum cut to stop seizures from spreading from one cerebral hemisphere to the other. Advances in medication have since made that treatment obsolete.

Parkinson's Disease is caused by destruction of the substantia nigra in the midbrain. The causes are unclear. Normally, by releasing the neurotransmitter dopamine, substantia nigra neurons inhibit motor activation by cerebral structures called the basal nuclei. When the substantia nigra is (mostly) destroyed, muscles become chronically tense, leading to the symptoms of rigidity, shaking, slow movements, and difficulty walking. Administration of dopamine-like compounds can temporarily suppress this muscle activation and improve function.

Alzheimer's Disease is another brain problem whose causes are not well-understood. Alzheimer's patients have memory problems and many other cognitive difficulties. As with Parkinson's, symptoms can be linked to the death of neurons, though Alzheimer's damage may impact large areas of the cerebrum. Damaged regions exhibit deposits of proteins both intracellularly (neurofibrillary tangles) and extracellularly (plaques).

14.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 14: #1, #8, #12, #16, #18, #20, #23, #24, #27. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

14.6: Appendix: the top 24 human muscles … and their innervation

The table below is a beefed-up version of CTM Table 11.1. Now that we've learned about the spinal cord (Chapter 13) and cranial nerves (this chapter), the additional column of "Innervation" has been added.

MUSCLE – 10th Martini Figure(s)	ORIGIN	INSERTION	ACTION	INNERVATION
Biceps brachii – Fig. 11-4a	Coracoid process and glenoid cavity of scapula (2 heads)	Tuberosity of anterior proximal radius	Flexes elbow, supinates forearm [palm turns from posterior to anterior]	Musculocutaneous nerve (C_5-C_6)
Biceps femoris (a hamstring muscle) – Fig. 11-4b	Tuberosity of inferior ischium; linea aspera of femur (2 heads)	Head of fibula, lateral condyle of proximal tibia	Extends thigh, flexes knee	Tibial nerve (L_5-S_3)
Brachioradialis – Fig. 11-4a	Lateral ridge at distal end of humerus	Lateral styloid process of distal radius	Flexes elbow	Radial nerve (C_5-C_6)
Deltoid – Fig. 11-4a, 11-4b	Lateral clavicle, acromion [lateral, superior] and spine [posterior] of scapula	Deltoid tuberosity of humerus [halfway down, lateral]	Abducts arm (if whole muscle is activated)	Axillary nerve (C_5-C_6)
Epicranius/Frontalis/ Occipitofrontalis – Fig. 11-4a	Epicranial aponeurosis	Skin of eyebrows, bridge of nose	Raises eyebrows	Cranial nerve VII (facial nerve)
Gastrocnemius – Fig. 11-4b	Condyles of distal femur	Calcaneus	Plantar-flexes foot	Tibial nerve (S_1-S_2)
Gluteus maximus – Fig. 11-4b	Dorsal ilium, sacrum, coccyx	Gluteal tuberosity of posterior proximal femur; iliotibial tract	Extends thigh	Inferior gluteal nerve (L_5-S_2)
Latissimus dorsi – Fig. 11-4b	Spinous processes of lower thoracic and lumbar vertebrae, lower ribs, crest of ilium	Floor of intertubercular groove/sulcus of anterior proximal humerus	Extends arm; adducts and medially rotates arm	Thoracodorsal nerve (C_6-C_8)
Masseter – Fig. 11-5	Zygomatic arch [temporal & zygomatic bones], maxilla	Lateral surface of ramus of mandible	Closes jaw (chewing)	Cranial nerve V (trigeminal nerve)
Orbicularis oculi – Fig. 11-5	Medial margin of orbit	Skin around eyelids	Closes eyes	Cranial nerve VII (facial nerve)
Orbicularis oris – Fig. 11-5	Maxilla and mandible	Lips	Closes lips	Cranial nerve VII (facial nerve)
Pectoralis major – Fig. 11-4a	Inferior medial clavicle; sternum; cartilage of ribs 1-6	Intertubercular groove/sulcus of anterior proximal humerus	Flexes, adducts, and medially rotates arm	Pectoral nerves (C_5-T_1)
Rectus femoris (a quadriceps muscle) – Fig. 11-4b	Ilium: anterior inferior spine and superior rim of acetabulum	Tuberosity of proximal anterior tibia	Extends knee, flexes thigh	Femoral nerve (L_2-L_4)
Sartorius – Fig. 11-4a	Anterior superior spine of ilium	Medial proximal tibia	Flexes, and laterally rotates thigh; flexes knee	Femoral nerve (L_2-L_3)

Semimembranosus (a hamstring muscle) – Fig. 11-4b	Tuberosity of inferior ischium	Medial proximal tibia	Extends thigh, flexes knee	Sciatic nerve (L_5-S_2)
Semitendinosus (a hamstring muscle) – Fig. 11-4b	Tuberosity of inferior ischium	Medial proximal tibia	Extends thigh, flexes knee	Sciatic nerve (L_5-S_2)
Temporalis – Fig. 11-5	Fossa [shallow depression] of temporal bone	Coronoid process of mandible	Closes jaw (chewing)	Cranial nerve V (trigeminal nerve)
Tibialis anterior – Fig. 11-4a	Lateral condyle and upper tibia	Inferior surface of first cuneiform and metatarsal I	Dorsiflexes foot	Deep fibular nerve (L_4-S_1)
Trapezius – Fig. 11-4b	Occipital bone; ligamentum nuchae [connects occipital bone & C_7]; spinous processes of thoracic vertebrae	Acromion [lateral, superior] and spinous process [posterior] of scapula; lateral clavicle	Stabilizes scapula; exact action depends on state of other muscles	Cranial nerve XI (accessory nerve) and cervical spinal nerves (C_3-C_4)
Triceps brachii – Fig. 11-4a	Inferior margin of glenoid cavity and posterior humerus (3 heads)	Olecranon of posterior ulna	Extends forearm	Radial nerve (C_6-C_8)
Vastus intermedius (a quadriceps muscle) – Fig. 11-21c	Anterior lateral femur, and linea aspera	Tuberosity of proximal anterior tibia	Extends knee	Femoral nerve (L_2-L_4)
Vastus lateralis (a quadriceps muscle) – Fig. 11-4a	Anterior femur distal to greater trochanter, and linea aspera	Tuberosity of proximal anterior tibia	Extends knee	Femoral nerve (L_2-L_4)
Vastus medialis (a quadriceps muscle) – Fig. 11-4a	Linea aspera of posterior femur	Tuberosity of proximal anterior tibia	Extends knee	Femoral nerve (L_2-L_4)
Zygomaticus (major and minor) – Fig. 11-5	Zygomatic bone	Corners of mouth	Smiling!	Cranial nerve VII (facial nerve)

Chapter 15: Sensory Pathways and the Somatic Nervous System

Chapter 15 builds on Chapter 13, which focused on the spinal cord, and Chapter 14, which focused on the brain. Here in Chapter 15 we follow the flow of sensory information into the spinal cord and brain, and then trace the flow of motor information out of the brain and spinal cord.

15.0: Outline

15.1: Overview and definitions
- This chapter covers somatic sensory and motor information (relating to the skin and skeletal muscles) and also visceral sensory information (relating to the internal organs). It does not cover the "special senses" (balance, hearing, sight, smell, and taste).
- Sensory receptors for the general senses are the dendrites of neurons. Most sensory receptors for the special senses are specialized non-neuronal cells.
- Sensory receptors can be tonic or phasic. Phasic receptors adapt to stimuli much more quickly than tonic receptors.
- Different types of sensory information (visual, temperature, etc.) are conveyed through different anatomical channels known as labeled lines.

15.2: What kinds of general sensory receptors are there?
- Nociceptors detect pain, thermoreceptors detect temperature, chemoreceptors detect chemicals, and mechanoreceptors detect mechanical stimuli.
- Mechanoreceptors may be subdivided into tactile receptors, baroreceptors, and proprioceptors.

15.3: Where does sensory information go?
- Sensory neurons enter the spinal cord through the dorsal roots.
- Sensory information travels through the spinal cord to the brain via the spinothalamic pathway, posterior column pathway, and spinocerebellar pathway. All pathways go through the medulla oblongata. The first two pathways also go through the thalamus and terminate at the sensory cortex; the latter pathway brings proprioceptive information to the cerebellum.

15.4: The somatic nervous system controls skeletal muscles
- Skeletal muscles are under both voluntary (conscious) control (by the corticospinal pathway) and subconscious control (by the medial pathway and lateral pathway).
- Input into the corticospinal pathway comes from the primary motor cortex; input into the medial and lateral pathways comes from the vestibular nuclei, tectum, reticular formation, and red nuclei.

15.5: Recommended review questions

15.1: Overview and definitions

This chapter covers both sensory information and motor information, but it only covers some types of each. Careful definitions will help us be clear on what is and is not covered here.

The first distinction to be made is between somatic and visceral information. **Somatic information** concerns the skin and skeletal muscles, whereas **visceral information** concerns the internal organs. This distinction applies to both sensory and motor information; it is not the same as the distinction between voluntary and involuntary motor pathways. Somatic motor commands can trigger both voluntary responses (e.g., you decide to kick your leg) and

involuntary responses (e.g., your leg kicks out as a reflex responding to a tap on your patellar tendon). Visceral motor commands are strictly involuntary.

Sensory information can be either somatic or visceral but may also be classified in other ways. A distinction is often made between the *special senses* – for balance, hearing, sight, smell, and taste – and the *general senses* – for everything else (chemicals, osmolarity, pain, pressure, proprioception, temperature, and touch). The receptors for the special senses generally have more complex structures than those for the general senses.

So, what exactly is this chapter about? Chapter 15 covers all of the general senses, both somatic and visceral, but not the special senses (which are the topic of Chapter 17). Chapter 15 also covers somatic motor information, but not visceral motor information (which is in Chapter 16).

A few additional, general points about sensory information are noted below.

Sensory receptors, which first receive sensory information, are defined as "specialized cells or cell processes that monitor specific conditions in the body or the external environment." Notice the phrase "cells or cell processes," which hints at the fact that there are two distinct types of sensory receptors:

> (A) Whole cells that are not themselves considered neurons, but that connect to sensory neurons. Examples include all of the receptors for the special senses, with the exception of olfactory receptors.
> (B) The dendrites of sensory neurons. Olfactory receptors and all of the receptors for the general senses fall into this category.

Sensory receptors can also be classified as tonic or phasic. As shown in 10th Martini Figure 15-3 (Tonic and Phasic Sensory Receptors), *tonic receptors* provide a continuous readout of the current level of sensory input (tonic), while *phasic receptors* fire only when the level of sensory input changes. Tonic and phasic receptors show different degrees of **adaptation**, i.e., a diminishing response to a constant stimulus. At the extremes, a purely tonic receptor would not show any adaptation, while a purely phasic receptor exhibits very rapid and complete adaptation.

Interconnected neurons carry information from sensory receptors to the cerebral cortex along what are referred to as **labeled lines**. This term highlights the fact that all neurons operate by firing action potentials, yet the brain must have a way of knowing which information is visual, which information is about temperature, etc. The brain knows which information is which based on which neurons in which labeled lines are transmitting it, NOT because of what those neurons are doing (i.e., firing action potentials), which is essentially the same for all.

15.2: What kinds of general sensory receptors are there?

If you think there are few senses beyond the special senses of balance, hearing, sight, smell, and taste, think again. There are *nociceptors* for detecting pain, *thermoreceptors* for detecting temperature, *chemoreceptors* for detecting chemicals, and *mechanoreceptors* for detecting mechanical stimuli.

Nociceptors (*noci-* is from the same root as *noxious*) are unusual in that they are not very specific. That is, they may be activated by many diverse stimuli: temperature extremes, mechanical damage, and/or the presence of certain chemicals. The message of pain may be conveyed quickly by nociceptors with myelinated Type A axons, or more slowly by nociceptors with unmyelinated Type C axons. Type A axons typically convey "pricking" pain, while Type C axons convey "aching" pain.

Thermoreceptors include separate subtypes for detecting warmth and for detecting cold. They provide sensory input that allows the hypothalamus to regulate body temperature via negative feedback. Some of them adapt quickly, so we are most aware of temperature *changes* rather than the absolute temperature. That is, if we move from a very cold pool to a somewhat less cold pool, we perceive the new temperature as "warm" rather than "still pretty cold."

Chemoreceptors detect concentrations of specific chemicals. For example, chemoreceptors in your carotid artery, aortic arch, and medulla monitor the levels of CO_2, O_2, and protons (H^+); high levels of CO_2 and H^+ and/or low levels of O_2 are a sign that you may need to increase your rate of breathing.

Mechanoreceptors contain ion channels that open or close in response to deformations of the cell membrane. They can be subdivided into three categories: tactile receptors, which detect touch, pressure, and vibration at or near the skin; baroreceptors, which detect pressures of internal body fluids such as blood; and proprioceptors, which detect the positions of skeletal muscles and their associated tendons. Tactile receptors themselves come in many varieties: free nerve endings, root hair plexuses, tactile discs (Merkel discs), tactile corpuscles (Meissner's corpuscles), lamellated corpuscles (Pacinian corpuscles), and Ruffini corpuscles. We will not concern ourselves with the differences between these tactile receptors.

15.3: Where does sensory information go?

Recall from Chapter 13 that, aside from the cranial nerves, sensory neurons enter the spinal cord through the dorsal roots, with their cell bodies residing in the dorsal root ganglia. 10th Martini Figure 15-5 (Sensory Pathways and Ascending Tracts in the Spinal Cord) is a good reminder of this. Recall further that the white matter of the spinal cord is organized into various ascending tracts (which carry sensory information to the brain) and descending tracts (which carry motor information from the brain). 10th Martini Figure 15-5 and Table 15-1 (Principal Ascending [Sensory] Pathways) summarize and illustrate the major sensory tracts; a condensed version of the latter is shown as CTM Table 15.1 below.

A couple of points are worth making here. First, note that there are three major ascending *pathways* (spinothalamic, posterior column, and spinocerebellar), each of which includes two tracts on each side of the spinal cord (so six tracts in total). Second, note that the spinothalamic pathway, despite its name, isn't the only pathway that goes to the thalamus; the posterior column pathway goes there too! In fact, the posterior column pathway and spinothalamic pathway are pretty similar aside from the specific types of sensory information that they carry. Third, note

that all three pathways pass through the medulla oblongata, as shown in 10th Martini Figure 15-6 (Somatic Sensory Pathways). Perhaps you now have a better sense of why the medulla and thalamus were both described in Chapter 14 as "relay stations." Fourth, sensory information from one side of the body generally crosses to the opposite side either in the spinal cord or at the medulla, such that the left brain receives sensory information from the right side of the body and vice versa.

CTM Table 15.1: Principal Ascending (Sensory) Pathways

Pathway (color in Fig. 15-5)	**Tracts included in pathway**	**General sensation(s)**	**Destinations in brain**
Spinothalamic pathway (green)	anterior spinothalamic tracts, lateral spinothalamic tracts	crude touch and pressure, pain, temperature	thalamus (ventral nuclei) and primary sensory cortex
Posterior column pathway (blue)	fasciculi cuneatus, fasciculi gracilis	fine touch, pressure, proprioception, vibration	thalamus (ventral nuclei) and primary sensory cortex
Spinocerebellar pathway (yellow)	anterior spinocerebellar tracts, posterior spinocerebellar tracts	proprioception	cortex of cerebellum

The individual neurons in these sensory pathways may be referred to as first-order, second-order, and third-order. The first-order neuron is the sensory neuron itself, whose axon enters the spinal cord through the dorsal root and either forms synapses in the gray matter or joins an ascending tract. The second- and third-order neurons are interneurons downstream of (but anatomically superior to) the first-order neuron. For example, in the spinothalamic tracts, the second-order neurons have cell bodies in the gray matter of the spinal cord and axons that stretch to the ventral nuclei of the thalamus; the third-order neurons have cell bodies in the ventral nuclei of the thalamus and axons that reach the primary sensory cortex.

Both somatic and visceral sensory information comes to the brain from both the cranial nerves and the spinal cord. Visceral sensory information in the spinal cord travels via the spinothalamic pathway. This intermingling of visceral and somatic neurons helps explain the phenomenon of **referred pain**, in which pain from visceral organs seems to stem from the surface of the body. This represents a failure to keep the above-mentioned labeled lines separate; sometimes signals within a tract get crossed, and an interneuron that should be carrying pain information from the skin gets activated in response to some internal pain. This issue is illustrated nicely in 10th Martini Figure 15-7 (Referred Pain).

15.4: The somatic nervous system controls skeletal muscles

We now turn from sensory information to motor information. Here in Chapter 15 we restrict ourselves to the **somatic nervous system**, which controls skeletal muscles. Chapter 16 covers the **autonomic nervous system**, whose outputs go to cardiac muscle, smooth muscle, glands, and adipocytes.

Skeletal muscles are under voluntary (conscious) control but may also be activated subconsciously. How do the connections of the nervous system allow both conscious and subconscious control? The motor neurons that go directly to the skeletal muscles (referred to by 10th Martini as "lower motor neurons") have their cell bodies in the spinal cord or brain stem. The output of these neurons can be enhanced or suppressed by other neurons from the brain (called "upper motor neurons" by 10th Martini and interneurons by others). Neurons from the primary motor cortex of the cerebrum provide conscious control, while neurons from subcortical regions provide subconscious control.

Just as the white matter of the spinal cord has distinct tracts for different types of sensory information, it also has tracts for different types of motor information. These are covered by 10th Martini Figure 15-8 (Descending [Motor] Tracts in the Spinal Cord) and Table 15-2 (Principal [Descending] Motor Pathways), which are condensed into CTM Table 15.2 below.

CTM Table 15.2: Principal Descending (Motor) Pathways

Pathway (conscious?)	**Tracts included in pathway**	**Tracts' origin and destination**	**Responsibility**
Corticospinal pathway (conscious)	corticobulbar tracts	from the primary motor cortex to the brainstem	skeletal muscles
	anterior and lateral corticospinal tracts	from the primary motor cortex to the spinal cord	skeletal muscles
Medial pathway (subconscious)	reticulospinal tracts	from the reticular formation (a network of brainstem nuclei) to the spinal cord	regulation of reflexes
	tectospinal tracts	from the tectum (the roof of the midbrain, including the inferior and superior colliculi) to the spinal cord	responses to visual and auditory stimuli
	vestibulospinal tracts	from the vestibular nuclei (at the border of the pons and medulla) to the spinal cord	balance, muscle tone
Lateral pathway (subconscious)	rubrospinal tracts	from the red nucleus (part of the midbrain) to the spinal cord	upper limbs

To CTM Table 15.2 we can add a note and a question. Here is the note: a difference between the medial and lateral pathways is that the former is most concerned with gross (coarse) movements of the trunk and proximal limb muscles, while the latter is most responsible for smaller-scale movements of distal limb muscles. Now for the question: the basal nuclei and cerebellum are heavily involved in motor control, yet they do not appear explicitly in CTM Table 15.2. Why not? The answer is that both the basal nuclei and the cerebellum include many neurons that affect the neurons of the tracts in CTM Table 15.2. The basal nuclei has two routes of doing this: some of its axons synapse onto neurons extending from the thalamus to the premotor cortex, thus affecting the primary motor cortex; others connect to the reticular formation, thus impacting the reticulospinal tract. The cerebellum's output affects all three pathways listed in CTM Table 15.2, often serving as a brake to prevent excessive or unnecessary contractions.

15.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 15: #1, 4, 5, 8, 15, 16, 22, and 23. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 16: The Autonomic Nervous System and Higher Order Functions

Chapter 16 is kind of a companion chapter to Chapter 15. Chapter 15 looked at the control of skeletal muscles by the somatic nervous system (SNS); Chapter 16 considers the control of other effectors (cardiac muscle, smooth muscle, glands, and adipose tissue) by the autonomic nervous system (ANS).

16.0: Outline

16.1: Overview of the Autonomic Nervous System (ANS)
- The Autonomic Nervous System (ANS) handles subconscious regulation of visceral functions.
- Effectors of the ANS include smooth muscle, glands, cardiac muscle, and adipocytes.
- The two main divisions of the ANS are the sympathetic division (active in "fight or flight" situations) and the parasympathetic division (active in "rest and digest" situations).

16.2: Sympathetic and Parasympathetic Ganglia
- The sympathetic division of the ANS has three types of ganglia: chain ganglia, collateral ganglia, and the adrenal medulla.
- The parasympathetic division of the ANS has ganglia that are close to the visceral target organs.

16.3: Sympathetic and Parasympathetic Neurotransmitters
- The parasympathetic division of the ANS uses acetylcholine (ACh) as its sole neurotransmitter. ACh exerts varied effects through two types of cholinergic receptors: nicotinic receptors and muscarinic receptors.
- The sympathetic division of the ANS uses ACh and norepinephrine (NE) as its main neurotransmitters. NE acts on five different adrenergic receptors: α_1, α_2, β_1, β_2, and β_3.

16.4: Dual Innervation and Visceral Reflexes
- Organs receiving both sympathetic and parasympathetic input are said to have dual innervation. The two divisions generally have opposite effects on a given organ.
- The ANS, especially its parasympathetic division, controls numerous visceral reflexes.

16.5: Recommended review questions

16.1: Overview of the Autonomic Nervous System (ANS)

The Autonomic Nervous System (ANS) can be defined as the part of the nervous system that handles involuntary (subconscious) regulation of visceral functions – "visceral" referring to the internal organs. It can be contrasted with the Somatic Nervous System (SNS), which governs skeletal muscles, which are under voluntary (conscious) control. Both the ANS and SNS include components of both the central nervous system (CNS) and peripheral nervous system (PNS); they are not simply a part of one or the other, but overlap with both.

10th Martini compares the ANS and SNS in Figures 16-1 (The Organization of the Somatic and Autonomic Nervous Systems) and 16-10 (A Comparison of Somatic and Autonomic Function) and in Table 16-5 (A Comparison of the ANS and SNS). The best of these may be Figure 16-1, from which the following differences are evident:

- The SNS controls skeletal muscles alone, whereas the ANS controls several distinct types of effectors: smooth muscle, glands, cardiac muscle, and adipocytes.
- The "higher" brain region controlling the SNS is the primary motor cortex, whereas for the ANS it is the hypothalamus (in particular, the visceral motor nuclei there).
- In the SNS, the ultimate effector neurons are called ("lower") motor neurons and have cell bodies in the spinal cord and brainstem and axons that extend out to their target muscles. In the ANS, the ultimate effector neurons are called ganglionic neurons and have cell bodies in ganglia outside the spinal cord and brainstem.

To expand on that last point, the neurons that synapse onto the ganglionic neurons stretch from the central nervous system (CNS) to the ganglia in the peripheral nervous system (PNS) and are called preganglionic neurons. The axons of preganglionic and ganglionic neurons are also called preganglionic and postganglionic fibers, respectively.

The two main divisions of the ANS are the **sympathetic division** and the **parasympathetic division**. The sympathetic division is associated with the phrase "fight or flight," whereas the parasympathetic division is often labeled as "rest and digest." These labels provide succinct summaries of the overall functions of the two systems, as encapsulated in CTM Table 16.1.

CTM Table 16.1: Contrasting Functions of the Sympathetic and Parasympathetic Nervous Systems

Sympathetic Division	**Parasympathetic Division**
Increased metabolic rate; Activation of energy reserves	Decreased metabolic rate
Increased heart rate and blood pressure	Decreased heart rate and blood pressure
Reduced digestive function	Increased secretion by salivary/digestive glands; Increased motility/blood flow in digestive tract
Reduced urinary function	Stimulation of urination and defecation
Heightened mental alertness	--

The sympathetic and parasympathetic divisions are also known as the thoracolumbar and craniosacral divisions, respectively, because of where their preganglionic neurons exit the CNS. The sympathetic division's preganglionic fibers exit the CNS between T_1 and L_2 (i.e., the thoracic and lumbar regions of the spinal cord – hence "thoracolumbar"); the parasympathetic division's preganglionic fibers exit through cranial nerves III, VII, IX, and X and between S_2 and S_4 of the sacral spinal cord (hence "craniosacral").

Some similarities and differences between the sympathetic and parasympathetic divisions can be seen in 10th Martini Figure 16-2 (Overview of the Autonomic Nervous System). Notice that many of the same organs and tissues are innervated by both divisions; those pictured here are (from top to bottom) the eyes, salivary glands, heart, lungs, gastrointestinal organs, adrenal gland, kidney, urinary bladder, and reproductive organs. However, aside from the very different distribution of preganglionic fibers coming out of the CNS, note also that the sympathetic division has ganglia (where the preganglionic neurons synapse onto the ganglionic neurons; see above) that are relatively close to the spinal cord, whereas the parasympathetic ganglia are closer to the target organs.

Finally, note that the ANS is also considered to have a third division: the enteric nervous system, which is found in the walls of the digestive tract. It is influenced by, but somewhat independent of, the sympathetic and parasympathetic divisions.

16.2: Sympathetic and Parasympathetic Ganglia

Recall that a ganglion is a cluster of cell bodies in the peripheral nervous system (PNS). The motor neurons of the Somatic Nervous System (SNS) do not form ganglia because their cell bodies are within the gray matter of the spinal cord. However, the effector neurons of the sympathetic and parasympathetic divisions of the ANS do form ganglia – and are known as ganglionic neurons. The positions of these ganglia are quite different for the sympathetic and parasympathetic divisions.

The sympathetic division has three different types of ganglia: sympathetic chain ganglia, collateral ganglia, and the adrenal medullae. These are shown in 10th Martini Figures 16-3 (Sites of Ganglia in Sympathetic Pathways) and 16-4 (The Distribution of Sympathetic Innervation).

As seen in Figure 16-4, the **sympathetic chain ganglia** sort of resemble a string of pearls. They are symmetrically arranged outside of but close to the spinal cord on both the left and right sides. Even though sympathetic neurons exit the spinal cord only between T_1 and L_2, ganglia are found above and below those levels as well; each sympathetic chain includes 3 cervical ganglia, 10-12 thoracic ganglia, 4-5 lumbar ganglia, 4-5 sacral ganglia, and 1 coccygeal ganglion. (Adjacent ganglia sometimes fuse; hence the ranges given.)

Also as seen in Figure 16-4, the postganglionic fibers emerging from these ganglia innervate the skin, blood vessels, sweat glands, arrector pili muscles, and adipose tissue. The cervical and upper thoracic ganglia also send out fibers innervating the eyes, salivary glands, and (in the thoracic cavity) the heart and lungs.

Three **collateral ganglia**, somewhat farther from the spinal cord than the chain ganglia, can also be seen in Figure 16-4. These innervate many of the digestive, excretory, and reproductive organs of the abdominopelvic cavity, reducing their blood flow and energy use. The **medulla of the adrenal gland** is the third and final type of sympathetic ganglion. The cells there are considered neuroendocrine cells because they produce neurotransmitters – norepinephrine and epinephrine – but release them into the blood rather than forming synapses. Thus, norepinephrine and epinephrine from the adrenal medulla act more as hormones than as neurotransmitters (a distinction to be revisited in Chapter 18).

Now turn to the ganglia of the parasympathetic division, pictured in 10th Martini Figure 16-6 (The Distribution of Parasympathetic Innervation). Here the ganglia are far away from the CNS and close to the visceral target organs, and so the postganglionic fibers do not branch as much as most sympathetic postganglionic fibers do (compare with Figure 16-4); most simply go to the single closest organ. Do not confuse the parasympathetic ganglia (represented as yellow "bulges" in Figure 16-4) with the autonomic plexuses (also shown in Figure 16-6), which do not

contain cell bodies. Also note there are no parasympathetic ganglia serving the skin, blood vessels, sweat glands, arrector pili muscles, and adipose tissue; these are only innervated by the sympathetic division. You can confirm this using 10th Martini Table 16-3 (A Functional Comparison of the Sympathetic and Parasympathetic Divisions of the ANS).

16.3: Sympathetic and Parasympathetic Neurotransmitters

Neurons communicate with each other and with target tissues via neurotransmitters, as discussed in Chapter 12. Well-known neurotransmitters include acetylcholine (ACh), dopamine, gamma-amino butyric acid (GABA), glutamate, and norepinephrine (NE).

As it turns out, most neurons in the autonomic nervous system release ACh or NE. In fact, the parasympathetic division of the ANS uses ACh as its sole neurotransmitter! Things are not quite as simple as they sound, however; ACh has two different types of receptors, which can trigger different changes in the cells that possess them. These receptors – nicotinic receptors and muscarinic receptors – are named for toxins that selectively bind to one or the other. We have previously encountered nicotinic receptors in Chapter 10; they are the ACh receptors found on skeletal muscle cells. As you may recall, these receptors are ligand-gated channels through which Na^+ enters, causing excitatory post-synaptic potentials (EPSPs). Thus, ACh always causes excitation of post-synaptic cells with nicotinic receptors. The effects of ACh binding to muscarinic receptors are more variable; they depend on the specific G proteins activated by these receptors in a given cell.

The sympathetic division of the ANS employs ACh and NE as its predominant neurotransmitters. NE has five different types of receptors – α_1, α_2, β_1, β_2, and β_3 – which are expressed in different target tissues. To complicate matters further, these receptors can also bind to the neurotransmitter/hormone epinephrine (E). Here is an illustration of how the different receptors contribute to our well-being in fight-or-flight situations. NE and E stimulate the heart to contract more frequently and forcefully via its β_1 receptors. These substances also stimulate the contraction of smooth muscles lining many arterioles via the α_1 receptors, thus causing vasoconstriction. Vasoconstriction is helpful in reducing blood flow to organs that do not need it at that moment – for example, the digestive organs, whose needs are deprioritized in fight-or-flight situations. But what about the skeletal muscles, which require lots of blood flow in these situations, but whose arterioles also contain smooth muscle cells with α_1 receptors? These smooth muscle cells also have β_2 receptors, which cause muscle relaxation and thus vasodilation to counter the vasoconstriction promoted by the α_1's.

The ANS's NE/E ("adrenergic") receptors and ACh ("cholinergic") receptors are summarized in 10th Martini Table 16-1 (Adrenergic and Cholinergic Receptors of the ANS).

16.4: Dual Innervation and Visceral Reflexes

We said above that the sympathetic and parasympathetic divisions of the ANS have opposite effects on the body, and that many visceral organs receive input from both divisions. 10th

Martini Table 16-3 (A Functional Comparison of the Sympathetic and Parasympathetic Divisions of the ANS) spells out how individual organs are, in many cases, pulled in opposite directions by the two divisions. The digestive system provides especially clear examples. Sympathetic input constricts sphincters, while parasympathetic input dilates them; sympathetic input inhibits secretory glands, while parasympathetic input stimulates them; and sympathetic input stimulates glycogen breakdown in the liver, while parasympathetic input stimulates glycogen synthesis in this organ.

A final key point about the ANS is this: although we often think of reflexes as being in the domain of skeletal muscles (and thus the somatic nervous system), the body has many visceral reflexes as well. Some important ones are listed in 10th Martini Table 16-4 (Representative Visceral Reflexes). These are mostly but not entirely subconscious; for example, urination, defecation, coughing, and swallowing can be consciously modified. All visceral reflexes are polysynaptic, but some bypass the CNS, as seen in 10th Martini Figure 16-9 (Visceral Reflexes). Most involve a single organ. Since sympathetic signals often propagate through many branches to multiple organs simultaneously, they are ill-suited for controlling single-organ reflexes, most of which are thus controlled parasympathetically. (Notice the list of parasympathetic reflexes in Table 16-4 is much longer than the list of sympathetic reflexes.)

16.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 16: #3, 4, 6, 12, 13, 14, 20, 24, 26, 30, and 31. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 17: The Special Senses

Sensory pathways were introduced in Chapter 15. After reviewing some information from that chapter, we focus on the so-called "special senses," i.e., balance, hearing, smell, taste, and vision.

17.0: Outline

17.1: Sensory receptor basics
- Sensory receptors are either whole, non-neuronal cells that form synapses with sensory neurons, or the dendrites of sensory neurons.
- All sensory information is converted into action potentials by the nervous system.

17.2: Smell (Olfaction)
- Olfactory receptor cells are neurons whose dendrites contain receptor proteins for odorant molecules. Binding of these molecules causes "EPSPs" (not technically the correct term, but close enough); if enough EPSPs sum together, threshold will be reached and action potentials will occur.

17.3: Taste (Gustation)
- There are five main types of taste receptors. They sense saltiness, sourness, sweetness, bitterness and umami-ness. These receptors are not neurons, but release neurotransmitter when depolarized.

17.4: Vision
- The lens of the eye focuses images onto the retina. The ciliary muscle adjusts the thickness and focusing power of the lens.
- Photons of light are absorbed by rhodopsin within photoreceptor cells. Photon absorption leads to the closing of cGMP-controlled Na^+ channels and a decrease in neurotransmitter release from the photoreceptors.
- Color vision is made possible by red, blue, and green cones, whose collective output indicates the color being seen.

17.5: Hearing
- Sound waves pass from the auditory canal through the tympanic membrane, auditory ossicles, and oval window to hair cells whose distortions indicate what sounds are being received.
- Hair cells at different parts of the cochlea's basilar membrane respond to sounds of different pitches (frequencies).

17.6: Balance (Equilibrium)
- The vestibular system, which helps you maintain your balance, includes the semicircular ducts (which sense head movement) and the saccule and utricle (which sense head position and acceleration).

17.7: Recommended review questions

17.1: Sensory receptor basics

General information on sensory receptors and sensory pathways may be found in 10th Martini Chapter 15. Here is a quick summary.

Sensory receptors are defined as "specialized cells or cell processes that monitor specific conditions in the body or the external environment." Notice the phrase "cells or cell processes,"

which hints at a confusing piece of sensory physiology. There are two basic types of sensory receptors:

(A) Whole cells that are not themselves considered neurons, but that release neurotransmitters, causing EPSPs and IPSPs[1] (remember those from Chapter 12?) in sensory neurons. Examples include photoreceptors for detecting light, taste receptors for detecting taste (duh), and hair cells for detecting sound and balance.

(B) The dendrites of sensory neurons. Examples include the dendrites of olfactory sensory neurons, and the "free nerve endings" (dendrites) of other less specific sensory neurons.

Different sensory receptors respond to different stimuli. We have nociceptors to sense pain, thermoreceptors to sense temperature, mechanoreceptors to sense touch, and chemoreceptors to sense chemicals. These will not be discussed further here, but they are considered receptors for the "general senses," as opposed to the "special senses" covered by Chapter 17 (smell, taste, vision, hearing, balance).

For sensory information to be received by the nervous system, it must be converted into action potentials (remember them from Chapter 12?). If the receptors are sensory neuron dendrites (category B above), the stimuli simply cause changes in membrane potential that spread to the axon hillock, where the "decision" to fire action potentials is made, based on whether threshold has been reached. If the receptors are non-neuronal cells (category A above), the stimuli do not cause action potential in these receptors, but do change the receptors' membrane potential, which causes changes in their release of neurotransmitters. The neurotransmitters bind to receptors on the dendrites and cell bodies of sensory neurons, leading to EPSPs and/or IPSPs, and perhaps bringing the sensory neurons to their threshold and causing action potentials in these sensory neurons.

When sensory neurons do fire action potentials, these action potentials spread down the axon, leading to the release of neurotransmitters that cause EPSPs and/or IPSPs in interneurons in the central nervous system (CNS). At this point the neuron-to-neuron relay of information (discussed in Chapter 13) is underway. Once sensory information is processed by the interneurons of the spinal cord and brain, responses are often sent via the effector neurons that control muscles, glands, and adipose tissue. This flow of information is shown in 10th Martini Figure 15-1 (An Overview of Events Occurring Along the Sensory and Motor Pathways).

Sensory receptors exhibit **adaptation**, in which the response to a given stimulus fades over time. This helps avoid constant bombardment of your brain with unimportant, potentially distracting information, such as, "Your butt is touching the chair.… Your butt is still touching the chair…. Your butt is STILL touching the chair…."

17.2: Smell (Olfaction)

[1]It can be argued that "neurotransmitter," "EPSP," and "IPSP" are not the correct terms here because the sensory receptors are not neurons. I personally prefer to use these terms, which you already know, rather than introduce a whole new set of terms for non-neuronal cells.

The olfactory pathway is shown in panel A of 10th Martini Figure 17-1 (The Olfactory Organs). Olfactory receptors – which are neurons, as noted above – connect via cranial nerve I (the olfactory nerve!) to interneurons in the olfactory bulb of the cerebrum, which you may have seen in lab. The neurons in the olfactory bulb then project to the olfactory cortex, hypothalamus, and limbic system.

How olfactory receptors work is shown in the upper half of 10th Martini Figure 17-2 (Olfaction and Gustation). The first thing to note is that smells are not transmitted magically – there are specific airborne molecules (odorant molecules) that bind to receptor proteins on the surface of receptor cells. (Note that the word "receptor" has two common meanings in biology; it can refer to either a ligand-binding protein or a whole cell.)

We said above that, in general, stimuli change the membrane potential of sensory neurons, whose axons will transmit action potentials if threshold is reached. Changes in membrane potential must be caused by changes in ion flows in and out of the cell. For olfactory receptors, as a result of a multi-step pathway whose details we won't worry about, Na^+ channels open and Na^+ comes in, depolarizing the membrane (10th Martini Figure 17-2). If the concentration of the odorant molecules is high enough, the receptor cells will reach threshold and action potentials will occur.

17.3: Taste (Gustation)

As you might guess, the taste receptors are found in the taste buds of your tongue. Much of the information from these receptors passes through cranial nerve IX, the glossopharyngeal nerve, which covers saliva and taste, as you know from Chapter 14. Additional taste information comes through cranial nerves VII (facial nerve) and X (vagus nerve). These nerves join the medulla, which in turn pass the information to the thalamus and cerebral cortex.

The taste receptors are not neurons (i.e., they belong in category A of "Sensory receptor basics" above), so they differ from olfactory receptors in this respect. The five main types of taste receptors are named for the sensations to which they respond: salty, sour, sweet, bitter, and umami (savory). The sweet, bitter, and umami receptors resemble olfactory receptors in the sense that they contain cell-surface proteins that bind to specific molecules, and the binding of these molecules opens ion channels, depolarizing the cell, causing neurotransmitter release. The salt and sour receptors are a bit different; in these cases the ions to be sensed (Na^+ and H^+, representing saltiness and sourness, respectively) simply pass through their ion channels, depolarizing the cell directly, causing neurotransmitter release. 10th Martini Figure 17-2 shows both types of situations.

With only five different taste sensations, why do foods provide such a rich variety of flavors? Not only can the relative strengths of the five tastes be combined in many ways, but texture and smell (sensed by other receptors, NOT the taste receptors) contribute greatly to foods' flavors.

One final point about 10th Martini Figure 17-2…. On the left-hand side, it shows action potentials occurring in the presence of the stimulus, and not occurring in the absence of the

stimulus. This is correct. Be aware, though, that the intensity of a stimulus can be represented by the firing frequency of the action potentials, e.g., the saltier a food is, the more action potentials the salt-responsive sensory neurons will fire.

17.4: Vision

We started talking about the visual system in Chapter 14. We noted that cranial nerve II, the optic nerve, carries sensory information from the eyes to the brain; that cranial nerves III, IV, and VI (the oculomotor, trochlear, and abducens nerves, respectively) all control eye muscles; and that the thalamus, superior colliculus, and occipital lobe of the cerebral cortex all help process visual information. We also studied the pupillary light reflex, which adjusts the size of the pupil to regulate the amount of light received by the retina.

Now it's time to see how the eyes work in a bit more detail.

10th Martini covers an overwhelming amount of eye anatomy. The most important components are listed in CTM Table 17.1 below.

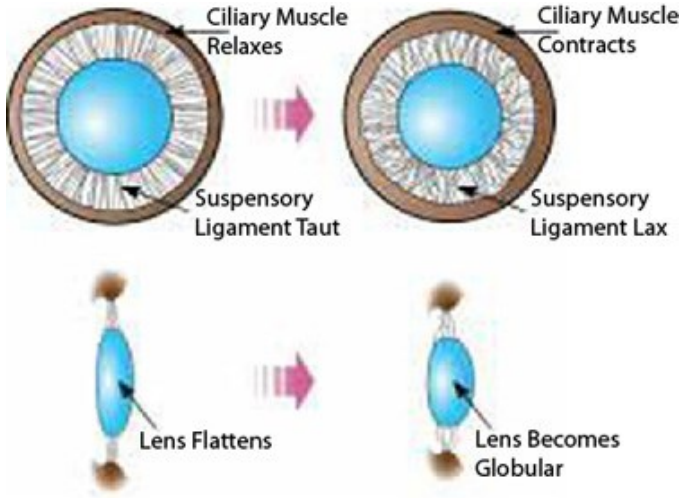
CTM Table 17.1: Important pieces of eye-natomy

Term (10th Martini figure)	**Description**
Ciliary Muscle (Fig. 17-11)	A circular muscle that surrounds the lens and controls its thickness (and thus its focusing power).
Cornea (Fig. 17-5a)	The transparent, most anterior part of the eye. It helps focus light, but is not adjustable.
Iris (Fig. 17-5)	A pigmented tissue surrounding the pupil. It stops light from entering the eye. Its size, and thus the pupil's size, is adjusted via the pupillary muscles (Fig. 17-6).
Lens (Fig. 17-5)	It focuses light on its way to the retina. Its thickness, and thus its degree of focusing, can be adjusted by the ciliary muscle.
Optic Nerve (Fig. 17-20)	Cranial nerve II, which carries visual information to the brain.
Photoreceptors (Fig. 17-14)	The receptor cells that absorb light. They reside in the retina. Photoreceptors include both rods (for black-and-white vision) and cones (for color vision).
Pupil (Figs. 17-5a & 17-6)	The black region in the center of the eye. Light comes in here because it is not blocked by the iris.
Retina (Fig. 17-5)	The inner tissue layer of the (hollow) eyeball. Photoreceptors are found here.

Let's trace the flow of light and information through these structures. Light passes through the cornea and the lens, both of which focus the light on the retina. At the retina light is absorbed by photoreceptors, which synapse with bipolar cells, which synapse with ganglion cells, whose axons form the optic nerve.

Focusing of light by the lens is shown in 10th Martini Figures 17-10 (Factors Affecting Focal Distance), 17-11 (Accommodation), and 17-13 (Refractive Problems). While we won't go too deeply into the physics of lenses, Figure 17-13 has a nice comparison between a camera and an eye. Both the camera and the eye have a fixed surface (the film or the retina, respectively) on which to project images. The camera can focus on objects at different distances by adjusting the lens's *distance* from the film; the eye can focus on objects at different distances by adjusting the lens's *thickness* (a thicker lens has more focusing power). Adjustment of lens thickness by the ciliary muscle is shown in CTM Figure 17.1; in brief, contraction of the muscle thickens the lens.

As presented in 10th Martini Figure 17-13, some people have focusing problems that can be corrected by eyeglasses – or by LASIK surgery on the cornea. "Near-sighted" people see nearby objects well but see far-away objects poorly; the opposite is true for "far-sighted" people. Far-sightedness becomes more common with age as lenses lose some of their flexibility, roundness, and focusing power.



CTM Figure 17.1: How the ciliary muscle controls the thickness of the lens. The ciliary muscle is circular, so when it contracts, the circle shrinks, and the lens attached to its ligaments becomes rounder (less flat). Image source: atlasofophthalmology.org.

Once light arrives at the retina, how is it sensed by photoreceptors? The (rather complicated) answer is presented by 10th Martini Figure 17-16. One important thing to know about photoreceptors is that, unlike most other cells, they have Na^+ channels that, in darkness, are kept open by the binding of cyclic GMP (cGMP). When it is dark, Na^+ flows in and keeps these cells relatively depolarized, with a membrane potential of about -40 millivolts. The absorption of photons of light is handled by **rhodopsin**, which consists of a small organic molecule (**retinal**) bound by a membrane protein (**opsin**). The steps of photoreception (reception of light) are as follows (step numbers below follow those in the figure):

1. Absorption of a photon flips the retinal from one form to another. The change in retinal's shape causes the opsin protein to change shape as well.
2. The activated opsin protein stimulates a G protein, which in turn stimulates an enzyme called phosphodiesterase (PDE).
3. Phosphodiesterase breaks down cGMP. The drop in cGMP leads to the closing of the Na^+ channels mentioned above.
4. Hyperpolarization of the membrane potential (from -40 mV toward -70 mV) leads to a decrease in neurotransmitter release.

Thus, the absorption of light by these cells ultimately leads to a *decrease* in neurotransmitter release.

Finally, we should say a word about color vision. Photoreceptors include rods and cones, named for their respective shapes, as shown in 10th Martini Figure 17-14 (Structure of Rods, Cones, and Rhodopsin Molecule). Color vision comes from the absorption of light of different wavelengths by blue cones, green cones, and red cones; see 10th Martini Figure 17-15 (Cone Types and Sensitivity to Color). Each type of cone can absorb light of many different wavelengths, at least to some extent; the relative amount of lights absorbed by each of the three types indicates the color to the nervous system. For example, according to 10th Martini Figure 17-15, if a light is

highly absorbed by both green and red cones, but not absorbed by the blue cones, that light is probably yellowish in color, with a wavelength between 550 and 600 nanometers).

17.5: Hearing

10th Martini covers much more ear anatomy than we have time to master. Key terms are highlighted in CTM Table 17.2.

CTM Table 17.2: Important pieces of ear-natomy

Term (10th Martini figure)	Description
Auditory ossicles (Fig. 17-30)	Three tiny bones – the malleus, incus, and stapes – in the middle ear. They transmit sound waves from the tympanic membrane to the oval window.
Basilar membrane (Fig. 17-30)	Part of the cochlea. Its vibrations cause distortion of the associated hair cells.
Cochlea (Fig. 17-27)	A snail-shaped structure containing the hair cells responsible for sensing sounds.
Hair cells (Fig. 17-24d)	Sensory receptor cells of both the auditory and vestibular systems. They contain stereocilia, projections whose distortions open or close ion channels in the hair cell membrane.
Saccule and Utricle (Fig. 17-25)	Inner-ear structures that sense position and acceleration of the head.
Semicircular Ducts (Fig. 17-24)	Inner-ear structures that sense rotation of the head.
Tympanic membrane (Fig. 17-30).	The "eardrum." It receives sound waves and transmits them to the malleus of the auditory ossicles.
Vestibulocochlear nerve (Fig. 17-21)	Cranial nerve VIII, carrying sensory information from both the vestibular and auditory systems.

Now let's trace the passage of sound waves into the body, using 10th Martini Figure 17-30 (Sound and Hearing) as a visual guide. Sound waves travel through the auditory canal to the tympanic membrane (eardrum), which vibrates (like a real drum!). Those vibrations move the malleus, incus, and stapes, the three tiny bones collectively known as the auditory ossicles. The stapes pushes on the oval window, causing pressure waves to ripple through the perilymph. These pressure waves distort the basilar membrane, distorting the hair cells connected to the basilar membrane, opening ion channels in the hair cells, depolarizing the hair cells, leading to neurotransmitter release. Sensory neurons receive the neurotransmitter and carry the messages through cranial nerve VIII (the vestibulocochlear nerve). This auditory information then travels to the superior olive of the pons, the inferior colliculus, the thalamus, and the auditory cortex of the temporal lobe. It is straightforward to remember that the temporal lobe is the one that perceives sound because this lobe is the one closest to the ears.

How do we sense the *loudness* of a sound? The louder the sound, the more strongly the basilar membrane is shaken, the more distorted and depolarized the hair cells get, and the more neurotransmitter they release.

How do we sense the *pitch* (or *frequency*) of a sound? This is covered by 10th Martini Figure 17-31 (Frequency Discrimination), in which the snail-shaped cochlea is depicted as if it were unrolled into a linear structure. It turns out that the basilar membrane's flexibility varies along its length, such that different sections respond best to sounds of different frequencies. The

sections toward the left side of the figure sense frequencies above 10,000 Hertz (10,000 vibrations per second), while the sections toward the right side sense frequencies below 1,000 Hertz.

17.6: Balance (Equilibrium)

Sensing one's position in space may seem quite different than sensing sounds, yet both are performed by hair cells. The **vestibular system**, which is responsible for your sense of balance (equilibrium), has hair cells quite similar to the hair cells of your auditory system.

Your vestibular system has two main components:

- The semicircular ducts, which sense *rotation* of the head.
- The utricle and saccule, which sense *position and acceleration* of the head.

There are three semicircular ducts (anterior, lateral, and posterior), corresponding to the three dimensions of space. Each duct includes an ampulla, an enlargement of the duct containing the hair cells. The way these hair cells work is shown in 10th Martini Figure 17-24 (The Semicircular Ducts). Basically, when the head rotates, the stereocilia sticking out of the hair cells experience inertia as they are dragged through the surrounding endolymph. The distortions of the stereocilia lead to depolarization or hyperpolarization of the hair cells, altering neurotransmitter release.

The utricle and saccule are connected to the semicircular ducts. Hair cells of the utricle and saccule, like those of the semicircular ducts, have stereocilia whose distortion affects the membrane potential. The utricle and saccule contain calcium carbonate crystals known as otoliths ("ear stones"); they function as gravity sensors. Because the otoliths are dense, they always settle as low to the ground as possible, thus indicating the direction of "down." The otoliths' position can lead to bending of the stereocilia, as shown in Figure 17-25 (The Saccule and Utricle).

Now that we have talked about both the vestibular system and the auditory system, it may be clearer why cranial nerve VIII is named the vestibulocochlear nerve. Since the structures for sensing balance and sounds are both located in the inner ear, it is unsurprising that a single cranial nerve delivers information about both senses to the brain.

17.7: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 17: #2, 3, 4, 5, 13, 17, 23, 24, 25, 26, 27, and 28. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 18: The Endocrine System

Chapters 12 through 17 were all about the nervous system. In Chapter 18, we leave the nervous system behind (sort of). The endocrine system is an alternative system for communicating messages through the body. Although it interfaces with the nervous system, its cells and messages are fairly distinct from those of the nervous system.

18.0: Outline

18.1: Types of intercellular communication
- There are 4 basic types of intercellular communication: direct, synaptic, paracrine, and endocrine.

18.2: Types of hormones and responses
- In terms of chemical structure, hormones are amino acid derivatives, peptides, or lipid derivatives.
- Hormone receptors can be on the cell surface and can cause changes in intracellular second messengers like cAMP and Ca^{2+}, or they can be intracellular and and change gene expression.

18.3: The hypothalamic-pituitary axis: multi-level negative feedback!
- The hypothalamus secretes releasing hormones that control the release of other hormones from the anterior pituitary gland. These other hormones then stimulate other endocrine tissues to release still other hormones, which limit production of the upstream hormones via negative feedback.

18.4: Overview of the body's major hormones
- The anterior pituitary gland secretes adrenocorticotropic hormone (ACTH), follicle stimulating hormone (FSH), growth hormone (GH), luteinizing hormone (LH), prolactin (PRL), and thyroid-stimulating hormone (TSH).
- The posterior pituitary gland secretes antidiuretic hormone (ADH; also called vasopressin) and oxytocin (OXT).
- The thyroid glands secrete calcitonin and thyroid hormones (T_3 and T_4).
- The parathyroid glands secrete parathyroid hormone (PTH).
- The cortex of the adrenal gland secretes aldosterone and glucocorticoids (cortisol, corticosterone). The medulla of the adrenal gland secretes epinephrine (also called adrenaline).
- The pancreas secretes insulin and glucagon.
- The kidneys secrete erythropoietin and calcitriol.
- The ovaries produce estrogens and progesterone. The testes produce androgens like testosterone.

18.5: Hormone synergy during growth, stress, and reproduction
- Growth during childhood depends critically on hormones like growth hormone (GH), insulin, and calcitonin.
- Stressful situations require adjustments in hormones like epinephrine and glucocorticoids.
- Reproduction is dependent on hormones like follicle stimulating hormone (FSH), testosterone, luteinizing hormone (LH), oxytocin (OXT), and prolactin (PRL).

18.6: Recommended review questions

18.1: Types of intercellular communication

In any multicellular animal, the cells must be able to communicate with each other. At a cellular level, "communication" refers to the passing of a chemical from one cell to another. There are four general ways in which this may occur, as summarized by 10th Martini Table 18-1 (Mechanisms of Intercellular Communication). They are:

- *Direct communication* (discussed in Chapter 4, mentioned again in Chapter 12, and to be mentioned again in Chapter 20): chemicals pass directly from one cell to the next via gap junctions (protein channels that span the membranes of both cells).

- *Synaptic communication* (discussed in Chapter 12): neurotransmitters travel across synapses.
- *Paracrine communication*: this is similar to synaptic communication – chemicals released by one cell affect other nearby cells – but involves non-neuronal cells. Examples of paracrine signals include the cytokines used by the immune system (Chapter 22).
- *Endocrine communication*: the focus of this chapter. Similar to paracrine communication, but occurs over longer distances.

Note that all of these mechanisms of communication depend on (intracellular or extracellular) protein receptors to receive the chemical messages that are released.

Both the nervous system and the endocrine system maintain the body's homeostasis, using negative feedback to keep regulated variables within certain limits. An important difference between the two is the time scale over which they operate. The nervous system is faster; messages may pass from the brain to the toes via the nervous system in a fraction of a second. In contrast, adjustments to endocrine system generally occur over seconds to days.

18.2: Types of hormones and responses

Hormones are defined by 10th Martini as the chemical messengers of endocrine communication; they "are released in one tissue and transported in the bloodstream to alter the activities of specific cells in other tissues." Hormones can thus be distinguished from paracrine messengers, which do not generally travel in the blood.

According to their chemical structures, hormones are grouped into three categories: amino acid derivatives, peptide hormones, and lipid derivatives. These categories are depicted in 10th Martini Figure 18-2 (Structural Classification of Hormones).

- *Amino acid derivatives* are created from two amino acids in particular: tyrosine, which gives rise to thyroid hormones and epinephrine, and tryptophan, from which melatonin is created.
- *Peptide hormones* are all bigger than the amino acid derivatives because they consist of multiple amino acids linked together. They range in length from 9 amino acids (antidiuretic hormone and oxytocin) to >200 amino acids (thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone).
- *Lipid derivatives* are made from lipids, as their name indicates. There are two distinct sub-categories: eicosanoids and steroids. Eicosanoids are most important as paracrine messengers, but some have endocrine functions as well. Steroids are molecules that are chemically similar to cholesterol, with its characteristic 4-ring structure, and include the female and male sex hormones (estrogens, progesterone, and androgens like testosterone).

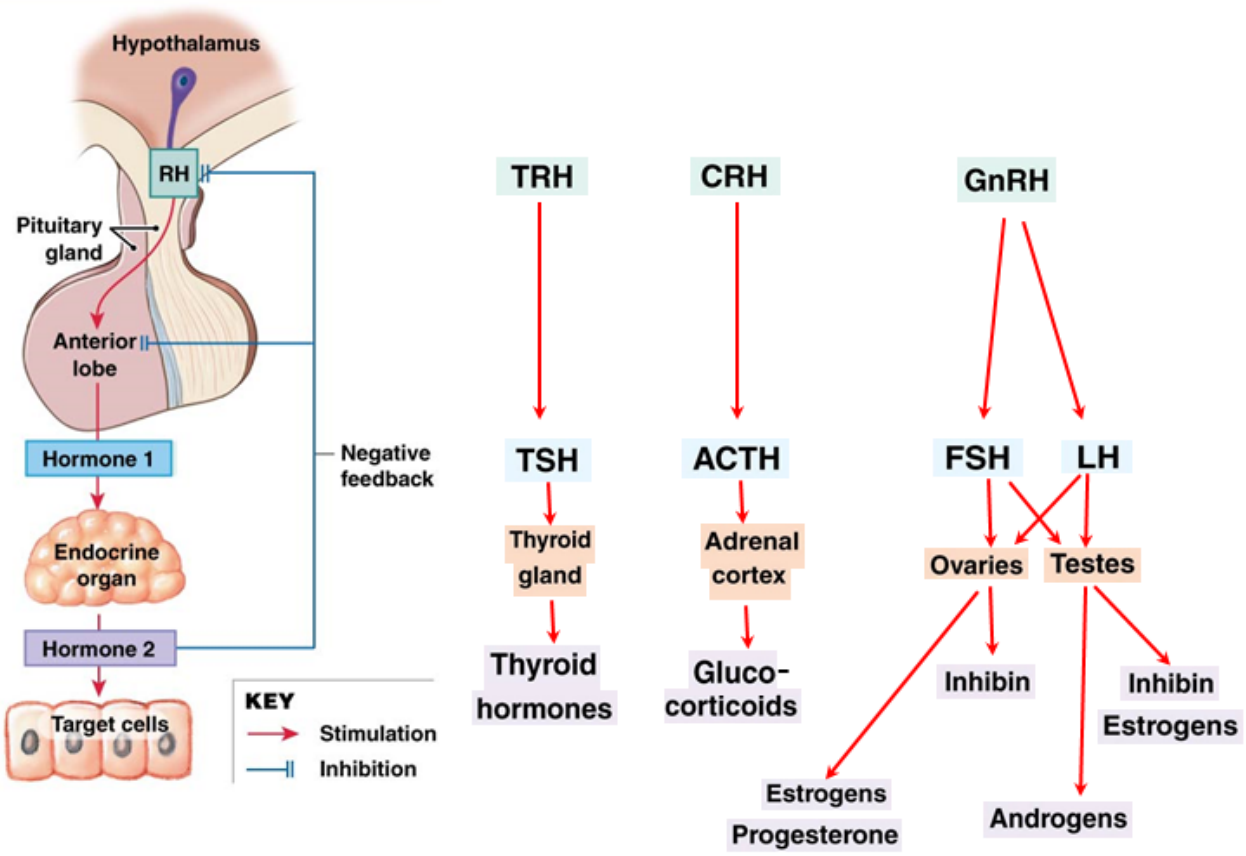
The chemical structures of these hormones influence the location of their protein receptors. Since amino acid derivatives are hydrophilic, and peptide hormones are large (and hydrophilic), they can't pass through cell membranes, so their receptors reside on the surface of the cell. Conversely, lipid derivatives CAN pass through cell membranes, so their receptors are found inside the cell.

These different locations of hormones' receptors correspond to different types of responses to each hormone. Actions triggered by the cell-surface receptors are illustrated in 10th Martini Figure 18-3 (G Proteins and Second Messengers). In short, binding of an amino acid-derived or peptide hormone causes the receptor to change shape such that a G protein connected to it is affected as well. G proteins have many effects, but most of them result in changes in intracellular levels of cyclic AMP (cAMP) or calcium (Ca^{2+}). cAMP and Ca^{2+} are known as "second messengers" because they carry the messages of the hormones (the first messengers) into the interior of the cell.

Actions triggered by intracellular hormone receptors, in contrast, are shown in 10th Martini Figure 18-4 (Effects of Intracellular Hormone Binding). Here the hormone-receptor complex travels to the DNA and alters transcription of specific genes, ultimately changing the expression of the corresponding proteins.

18.3: The hypothalamic-pituitary axis: multi-level negative feedback!

Hormones are produced by many different tissues of the body, as shown in 10th Martini Figure 18-1 (Organs and Tissues of the Endocrine System). Many of the most important hormones are part of what is often called the hypothalamic-pituitary axis (CTM Figure 18.1). This name reflects the fact that hypothalamic secretions control anterior pituitary secretions, which in turn govern other secretions. The final hormone of the pathway – "Hormone 2" in the figure – generally inhibits secretion of the Releasing Hormone and Hormone 1, which then lowers secretion of Hormone 2. In this way, hormones often limit their own secretion. An example is inhibin, a hormone produced by the testes and ovaries in response to Follicle Stimulating Hormone (FSH). Inhibin inhibits release of Gonadotropin Releasing Hormone (GnRH) and FSH. Thus, high inhibin levels lead to a lowering of inhibin levels, and vice versa.



CTM Figure 18.1: The hypothalamic-pituitary axis. This is a rearrangement of some parts of 10th Martini Figure 18-8 (Feedback Control of Endocrine Secretion). Left: The general pattern of hormonal control. The hypothalamus sends a Releasing Hormone (RH) to the anterior pituitary, which then secretes a hormone (Hormone 1) that prompts an endocrine gland to secrete another hormone (Hormone 2). Hormone 2 then negatively feeds back on the hypothalamus and anterior pituitary so that secretion of the Releasing Hormone and Hormone 1 is reduced. Right: Specific examples, colored and spaced according to the general pattern on the left. For example, Thyrotropin Releasing Hormone (TRH) made by the hypothalamus stimulates the anterior pituitary to secrete Thyroid Stimulating Hormone (TSH; Hormone 1), which then prompts the thyroid gland (endocrine organ) to secrete thyroid hormones (Hormone 2).

18.4: Overview of the body's major hormones

In its usual fashion, 10th Martini provides very detailed information about the 30 or so hormones produced by the human body. We will highlight a few points here, working our way through SOME of the producers of these hormones.

Hypothalamus

- As noted above, the hypothalamus produces several *releasing hormones* that stimulate the anterior pituitary gland to release hormones. Examples are shown in CTM Figure 18.1.

Pituitary Gland

- The pituitary, a pea-sized gland located directly under the hypothalamus, is often called the "master gland" because its hormones control so many other parts of the endocrine system. It has two distinct lobes, the *anterior pituitary* (adenohypophysis) and *posterior pituitary* (neurohypophysis). They are fairly distinct from each other histologically; the anterior pituitary is full of endocrine cells, while the posterior pituitary contains the axons of hypothalamic neurons (hence the name "neurohypophysis").
    - The *anterior pituitary* releases hormones such as the following:
        - Adrenocorticotropic hormone (ACTH): stimulates production of corticosteroids from the cortex of the adrenal gland.
        - Follicle Stimulating Hormone (FSH): stimulates secretion of estrogens from ovaries; stimulates development of ovarian follicles.
        - Growth hormone (GH): controls growth of the body.
        - Luteinizing Hormone (LH): stimulates secretion of progesterone from the ovaries and testosterone from the testes; stimulates ovulation and formation of the corpus luteum.
        - Prolactin (PRL): controls milk production in nursing mothers.
        - Thyroid-stimulating hormone (TSH): stimulates production of thyroid hormone by the thyroid gland.
    - The axon termini of the *posterior pituitary* release two major hormones:
        - Antidiuretic hormone (ADH; also called vasopressin): causes reabsorption of water so that it is not lost in the urine.
        - Oxytocin (OXT): stimulates contractions of the uterus; also involved in sexual arousal.

Thyroid Glands (2)

- In response to TSH from the anterior pituitary gland, the thyroid glands secrete two iodine-containing hormones (see 10th Martini Figure 18-1 to confirm the presence of iodine, whose chemical abbreviation is I). They are named for the number of iodine atoms they contain; triiodothyronine (or T_3) contains three, while tetraiodothyronine (or T_4) contains four. As you may be aware, table salt is "iodized," meaning that a small portion of it is NaI rather than NaCl, thus ensuring that your diet includes adequate iodine.
- Collectively, T_3 and T_4 are often referred to simply as "thyroid hormones." Their overall function is to speed up cellular metabolism.
- As we saw in Chapter 6, the thyroid glands also produce calcitonin, which promotes bone-building activity by osteoblasts.

Parathyroid Glands (4)

- As we saw in Chapter 6, the parathyroid glands secrete parathyroid hormone (PTH) in response to low levels of calcium in the blood. PTH leads to bone resorption by osteoclasts, releasing more calcium back into the blood. It also increases the kidney's retention of calcium and the kidney's production of calcitriol, thus increasing calcium absorption by the digestive tract.

- The combined actions of calcitonin and PTH were shown in 10th Martini Figure 6-15 (Factors That Alter the Concentration of Calcium Ions in Blood) and are also shown in 10th Martini Figure 18-13 (The Homeostatic Regulation of Calcium Ion Concentrations).

Adrenal glands (2)

- If you can remember that *renal* refers to the kidneys, then you should be able to remember that the adrenal glands are just above the kidneys (ad = "near").
- Like other tissues such as bones and the brain, the adrenal gland has an outer region called the cortex and an interior region called the medulla.
    - The adrenal cortex produces aldosterone, which increases Na^+ retention in the kidney, and glucocorticoids such as cortisol and corticosterone, which alter the release and usage of lipids, amino acids, and glucose by the liver, adipose tissue, and skeletal muscles.
    - The adrenal medulla produces epinephrine (also called adrenaline – a name which reminds us of its source) and the related compound norepinephrine (noradrenaline), which increase heart rate and blood pressure.

Pancreas

- As we will see in Chapter 24, most cells of the pancreas promote digestion via secretion of enzymes and bicarbonate. However, the pancreas also includes small patches of cells, called islets, which secrete hormones such as insulin and glucagon. Insulin promotes removal of excess glucose from the blood, while glucagon promotes addition of glucose to the blood. Diabetes mellitus is a condition where either inadequate insulin is produced (type I diabetes mellitus) or cells do not respond efficiently to insulin (type II diabetes mellitus).

Kidneys (2)

- Like the pancreas, the kidneys are not primarily endocrine organs. Their major functions of waste removal and water balance are covered in Chapters 26 and 27. However, the kidneys also secrete two important hormones: erythropoietin (epo for short), which stimulates red blood cell production in red bone marrow, and calcitriol, which stimulates absorption of calcium and phosphate by the digestive tract. Recall that calcitriol is produced via a complicated pathway also involving the skin and liver, as diagrammed in 10th Martini Figure 5-6 (Sources of Vitamin D_3).

Gonads (2)

- The male gonads, the testes, secrete androgens (such as testosterone – the name indicates that it is produced by the testes), which promote sperm development, protein synthesis in skeletal muscles, and the development of male sexual characteristics such as facial hair.
- The female gonads, the ovaries, secrete estrogens – which promote maturation of ovarian follicles and the development of female sexual characteristics such as breast enlargement – and progesterone – which prepares the uterus for implantation of a fertilized egg.

18.5: Hormone synergy during growth, stress, and reproduction

In reading the above descriptions of what the various hormones do, you might imagine that several of them cooperate to meet complex physiological demands … and indeed they do! Here are a few examples of scenarios requiring the action of multiple hormones.

Growth. Growing children require, among other things, growth hormone (GH) to promote development of tissues such as muscle and bone, insulin to promote uptake of glucose (which provides energy needed for growth), and calcitonin to promote calcium absorption for building bones.

Stress. In a "fight or flight" situation, epinephrine from the adrenal gland helps raise heart rate and blood pressure; it also promotes release of glucose and fatty acids into the blood so that exercising muscles are well-fueled. For longer-term stress lasting hours or days, glucocorticoids from the adrenal cortex adjust the body's metabolism to conserve and replace valuable glucose reserves, promoting synthesis of new glucose by the liver and promoting the use of lipids and proteins as energy sources, rather than glucose.

Reproduction. We will explore reproduction more fully in Chapter 28. For now, we can simply note the critical roles of several hormones listed above.

- Eggs (oocytes) are surrounded by supporting follicle cells, and the whole thing (egg + follicle cells) is known as a follicle. Follicle development is guided by follicle stimulating hormone (FSH).
- Meanwhile, sperm maturation in the testes is guided by testosterone produced by the testes.
- Luteinizing hormone (LH) triggers release of an egg from the ovary into its fallopian tube – an event called ovulation. The now-ruptured follicle, now called the corpus luteum, secretes progesterone, which builds up the lining of the uterus in anticipation of possible implantation of the egg.
- During labor and delivery, oxytocin (OXT) stimulates contractions of the uterus.
- Milk production by the mammary glands of new mothers is promoted by prolactin (PRL).

18.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 18: #1, 2, 3, 4, 5, 6, 13, 15, 18, 23, 24, 25, 27, and 28. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 19: Blood

We have mentioned the cardiovascular system – the heart ("cardio") and blood vessels ("vascular") – in several previous chapters. Most recently, in Chapter 18 (The Endocrine System), we saw that blood played the role of transporting endocrine hormones. Chapters 19 through 21 cover the cardiovascular system in detail. Chapter 19 covers blood, Chapter 20 covers the heart, and Chapter 21 covers the blood vessels and circulation.

19.0: Outline

19.1: Review/overview of the composition of blood
- Blood includes red blood cells (which transport oxygen); white blood cells (which provide immunity); platelets (which cause blood to clot); proteins like albumins, globulins, and fibrinogen; and other substances dissolved in water.

19.2: Red blood cells and oxygen transport
- The main job of red blood cells, or erythrocytes, is to transport oxygen (O_2) through the body.
- Within red blood cells, oxygen is carried by a protein named hemoglobin.
- Binding of O_2 to hemoglobin is temporary and reversible. At the lungs, where O_2 is abundant, hemoglobin gets loaded up with O_2. At other tissues of the body, where O_2 is more scarce, O_2 detaches from the hemoglobin and diffuses into the tissues.

19.3: White blood cells and antibodies
- The many functions of white blood cells include triggering the inflammatory response, phagocytosing invaders and cellular debris, and producing antibodies.
- Antibodies are proteins that bind antigens.
- The classification of blood types as A, B, AB, and O reflects the production of antibodies that bind to glycoprotein antigens on the surface of red blood cells.

19.4: Platelets and blood clotting
- Human platelets are fragments of large bone marrow cells called megakaryocytes.
- Stoppage of bleeding includes three phases: a vascular phase, in which damaged blood vessels are pinched off by their smooth muscles and become sticky; a platelet phase, in which platelets sticking to the endothelial cells release clotting factors and other materials; and a coagulation phase, in which clotting factors are sequentially activated in a cascade that creates a strong meshwork of the protein fibrin.

19.5: Recommended review questions

19.1: Review/overview of the composition of blood

In this chapter we will expand our knowledge of blood, which we started learning about in Chapter 4. Recall from that chapter that blood is a connective tissue that (along with lymph) belongs to the subcategory of fluid connective tissue, and whose primary function is transport of materials around the body.

In Chapter 4, we used 10th Martini Figure 4-12 as a brief summary of the functions of blood cells: red blood cells (erythrocytes) transport oxygen; white blood cells (leukocytes) constitute a large part of the immune system, which protects the body from foreign intruders; and platelets enable blood clotting. (Technically, platelets are only fragments of cells, so red blood cells,

white blood cells, and platelets are collectively called "formed elements" rather than cells.) To these fundamental functions of blood we can add (A) transport of many additional materials besides oxygen (hormones, nutrients, ions, etc.), (B) adjustment of the composition of interstitial fluids (which exchange substances with the blood), and (C) regulation of body temperature (via adjustment of flow to the surface of the body, where heat can be lost).

Many details about the development of red blood cells, white blood cells, and platelets are now known, and are pictured in 10th Martini Figure 19-10 (The Origins and Differentiation of Formed Elements). The big picture is that all of these arise from hematopoietic stem cells in the red bone marrow – as opposed to the yellow bone marrow, which is fat. The clinical case highlighted in Chapter 19 is a case of aplastic anemia, in which red marrow has been replaced by yellow marrow. As a result, counts of red blood cells, white blood cells, and platelets are all reduced, and all of the corresponding functions (oxygen transport, fighting infections, and blood clotting, respectively) are impaired.

Blood cells and platelets make up about 45% of blood; the remaining 55% or so is called plasma. Plasma consists of water, plasma proteins, and other solutes such as ions, nutrients, hormones, and wastes. Details are provided by 10th Martini Figure 19-1 (The Composition of Whole Blood). The most abundant plasma proteins include the following:

- *Albumins.* Because they are the most abundant plasma proteins, they contribute more to the plasma's osmotic pressure (tendency to draw water via osmosis) than any other proteins.
- *Globulins.* These include antibodies (also called immunoglobulins), which bind to foreign invaders and proteins.
- *Fibrinogen.* This protein, when activated into fibrin, forms a meshwork that enables blood to clot. (See CTM section 19.4 below.)

In the following sections, we will say a bit more about red blood cells, white blood cells, and platelets in turn.

19.2: Red blood cells and oxygen transport

The development of red blood cells is shown in 10th Martini Figure 19-10 (The Origins and Differentiation of Formed Elements) and also in Figure 19-5 (Stages of RBC Maturation). The main thing to note is that red blood cells lose their nucleus! This allows them to fill most of their cellular space with **hemoglobin**, the oxygen-binding protein. Since mature red blood cells do not have DNA or transcription/translation machinery, they have limited ability to repair themselves. Because of this, an average red blood cell only lasts 120 days before it ruptures and its components are recycled.

Hemoglobin is a protein with four polypeptide subunits (two alpha chains and two beta chains), each of which is associated with a flat heme group. Each heme group includes an iron (Fe) ion at its center, where O_2 molecules covalently bind. Since each hemoglobin molecule contains four Fe ions, and since each Fe can bind one molecule of O_2, each hemoglobin can bind up to four molecules of O_2. 10th Martini Figure 19-3 (The Structure of Hemoglobin) shows you the overall

structure of hemoglobin and zooms in on the structure of the heme, but doesn't actually show O_2! Don't lose sight of the fact that hemoglobin exists mostly to carry O_2!

A key aspect of O_2 binding to hemoglobin is that it is *reversible*. This means that a given O_2 molecule does not stay stuck on hemoglobin, but rather it hops on and off. Whether most of the hemoglobin binding sites are occupied or empty depends on the concentration of O_2. In the pulmonary capillaries of the lungs, O_2 is abundant, so hemoglobin picks up lots of O_2 and its binding sites become almost 100% occupied. In the muscles and other working tissues of the body, O_2 is constantly being used by the mitochondria as soon as it is delivered, so the O_2 concentration is lower there and the O_2 hops off the hemoglobin as it arrives. It then diffuses out of the blood into the surrounding tissues where it is used.

Because oxygen is so vital for mitochondrial ATP production, and because hemoglobin is so vital for oxygen transport, hemoglobin problems cause a variety of clinical disorders. **Anemia** is the general term for an inadequate supply of red blood cells in the blood. **Hematocrit** – the percentage of blood that is red blood cells only, excluding white blood cells, platelets and plasma – is typically around 40-45% in healthy people, but can be much lower in anemic patients.

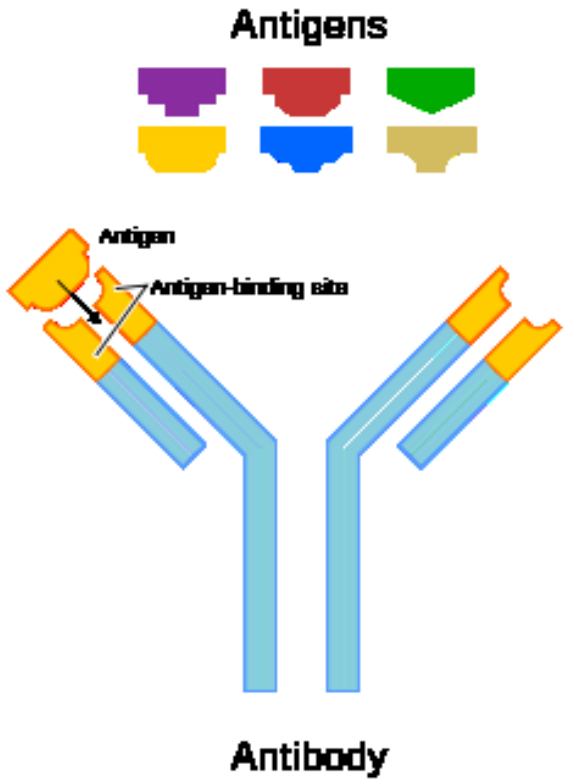
19.3: White blood cells and antibodies

When we examined inflammation in Chapter 5, we saw that some cells released chemicals like histamine to trigger the inflammatory response, while other cells engulfed invading microbes and debris, a process called phagocytosis. All of these cells are white blood cells; thus the functions of white blood cells include stimulating the response to inflammation and phagocytosis. At this point we will add one additional function (out of many) of some white blood cells, which is to secrete Y-shaped proteins called antibodies (CTM Figure 19.1).

Antibodies are produced by specific white blood cells called B lymphocytes, or B cells. They help defend the body by binding to antigens. An antigen is defined as anything to which an antibody will bind; in the context of the immune system, an antigen generally represents a piece of a foreign invader, such as a protein on the surface of a bacterium. By binding to antigens, antibodies facilitate the destruction or removal of the invader.

Each antibody binds to a very specific antigen, so each individual antibody is not much of a defense against anything. However, healthy people have a great variety of antibodies (thanks to cellular gene-splicing tricks that we won't go into here) which collectively can counter almost any antigen.

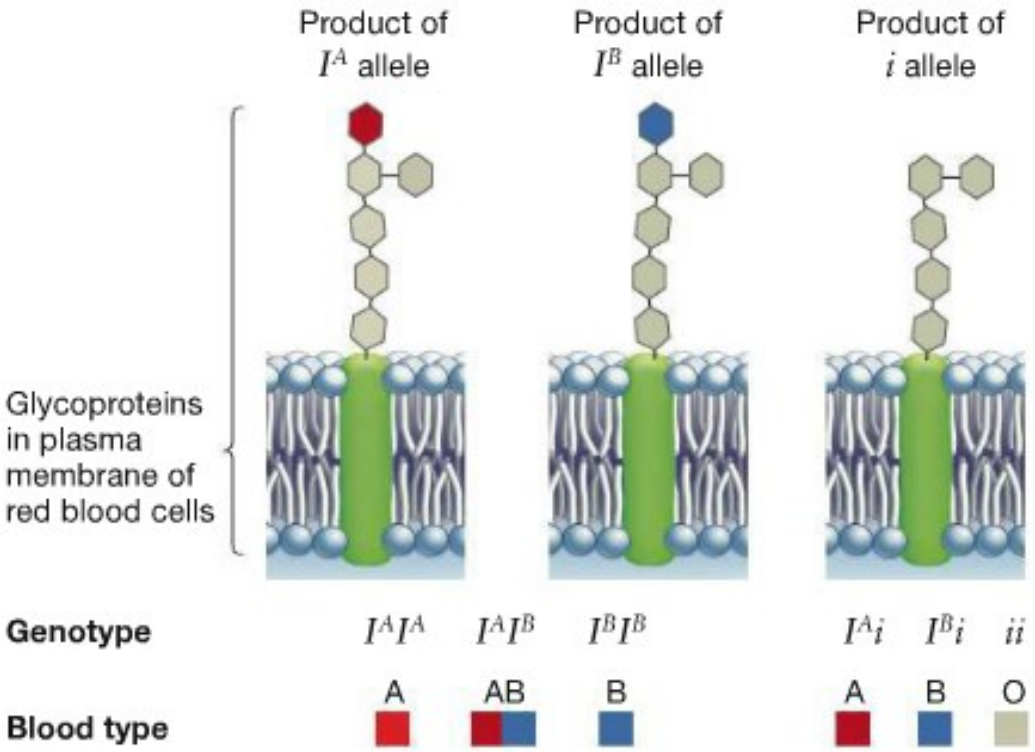
CTM Figure 19.1: The molecular structure of an antibody. The tips of the "arms" of the "Y" are the parts that bind to an antigen. Image from wikimedia.org.



As one specific example of how antibodies work, let's consider the "ABO" system of blood typing, which refers to antigens on the surface of red blood cells. In particular, these antigens are sugar groups attached to cell-surface proteins. CTM Figure 19.2 shows that everyone's blood cells have proteins with a "core" set of sugar groups, but some proteins have additional sugar groups that are recognized by antibodies as "A" antigens or "B" antigens.

Each person's immune system is "trained" to distinguish self from non-self so that it does not make antibodies against the person's own proteins. A person whose red blood cells include only the A antigen will not make antibodies to the A antigen, but will make antibodies to the B antigen, which is "foreign" to this person. Conversely, someone whose red blood cells have only the B antigen will make anti-A antibodies but not anti-B antibodies. People with blood type AB have *both* A antigens and B antigens on their red blood cells, so they won't make antibodies to either A or B. Neither A antigens nor B antigens are naturally present in people with blood type O, so these people make antibodies to both A and B antigens.

How is this relevant to human health? When these circulating antibodies encounter these cell-surface antigens, they cause the cells to clump together, as shown in 10th Martini Figure 19-6b. This is a first step toward destruction of the foreign cells. This is why blood transfusions need to be done between people with compatible blood types; if the types are NOT compatible, the recipient's immune system will simply destroy the transfused blood cells!



CTM Figure 19.2: A, B, AB, and O blood types. The different colored hexagons on the proteins represent related but distinct sugars. Figure taken from Scott Freeman et al., Biological Science (5th edition), 2014.

Since type O blood doesn't have either A antigens or B antigens, people with type O blood can donate blood to anyone without provoking the recipients' immune systems. Thus, people with type O blood are referred to as "universal donors." Conversely, type AB blood doesn't include anti-A or anti-B antibodies, so people with type AB blood can receive blood from all blood types; these people are "universal recipients."

19.4: Platelets and blood clotting

Platelets cause blood to clot, thus preventing unnecessary loss of fluids and maintaining blood pressure. As shown in 10th Martini Figure 19-10 (The Origins and Differentiation of Formed Elements), platelets form from megakaryocytes ("mega" denotes the large size of these cells). Platelets in most vertebrates are legitimate full cells called thrombocytes (blood clotting is also called thrombosis); in humans and other mammals, though, platelets are cell fragments without nuclei.

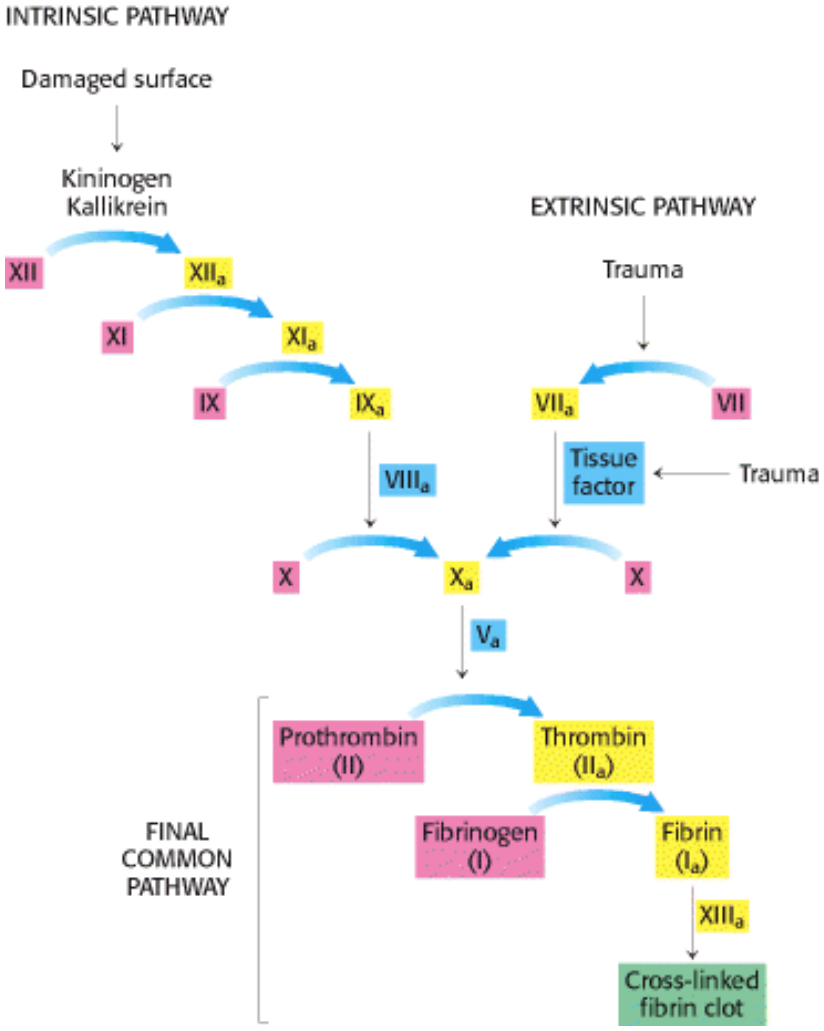
The process by which bleeding is stopped is called hemostasis ("hemo" = blood, "stasis" = constant or steady). It can be conveniently divided into the three phases shown in 10th Martini Figure 19-11 (The Vascular, Platelet, and Coagulation Phases of Hemostasis and Clot Retraction). In the **vascular phase**, the damaged blood vessel stimulates its surrounding smooth muscle to contract, thus reducing blood flow through this now-leaky vessel. The membranes of the endothelial cells also become sticky, so these cells stick to each other and to platelets. In the

platelet phase, platelets release many substances, including a bunch of proteins that ultimately cause clotting. These proteins are activated in the **coagulation phase**, diagrammed in step 3 of 10th Martini Figure 19-11 and perhaps more clearly in CTM Figure 19.3. Each protein shown is a proenzyme, an inactive form of an enzyme which can be activated by cleavage (removal of a piece of the protein by another enzyme).

In this cascade, an enzyme called kallikrein activates factor XII (remember your Roman numerals from the cranial nerves?); the activated factor XII (the subscript "a" stands for "activated") activates factor XI; the activated factor XI activates factor IX; and so on. The cascade ends with the conversion of the soluble protein fibrinogen into an insoluble form called fibrin. Fibrin is NOT an enzyme, but rather a rod-shaped protein whose units are cross-linked together by activated factor XIII. The resulting meshwork prevents the blood from spreading.

Clotting is eventually stopped via the release of several anti-clotting substances, including heparin, which is commonly used clinically to prevent collected blood samples from clotting.

CTM Figure 19.3: The blood clotting pathway. Each proenzyme, once activated, catalyzes a cleavage of the next proenzyme into its active form. Figure taken from blogs.scientificamerican.com/the-curious-wavefunction/.



19.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 19: review questions #6, 7, 11, 12, and 16, plus clinical case wrap-up questions #1 and 2. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 20: The Heart

Here in Chapter 20, The Heart, we continue our tour of the cardiovascular system that we began in Chapter 19 (Blood). Still ahead is Chapter 21 (Blood Vessels and Circulation).

20.0: Outline

20.1: What we already know about the heart
- Like skeletal muscle cells, cardiac muscle cells are striated and contract due to interactions between myosin and actin.

20.2: Basic anatomy of the heart
- The heart has four chambers: the right atrium, right ventricle, left atrium, and left ventricle.
- Great vessels connecting with the heart include the vena cava, pulmonary arteries, pulmonary veins, and aorta.
- One-way flow of blood through the heart is ensured by the heart's four valves: the tricuspid valve, the pulmonary semilunar valve, the bicuspid (mitral) valve, and the aortic semilunar valve.
- Electrical signals spread through the heart from the sinoatrial (SA) node to the atrioventricular (AV) node, the bundle of His (AV bundle), left and right bundle branches, and Purkinje fibers.

20.3: Electrical events: action potentials and cell-to-cell conduction
- The overall rhythm of the heart is set by the pacemaker cells of the SA node. These cells depolarize spontaneously thanks to Na^+ leak channels.
- The spread of depolarization throughout the heart can be easily monitored with surface electrodes, whose signals generate electrocardiograms (EKGs).
- An EKG is a repeating cycle of P waves (representing atrial depolarization), QRS complexes (representing ventricular depolarization), and T waves (representing ventricular repolarization).

20.4: The cardiac cycle and the Wiggers diagram
- The cardiac cycle includes phases of atrial contraction, ventricular contraction, and relaxation of both atria and ventricles.
- A Wiggers diagram relates EKG measurements to pressures, volumes, and heart sounds.

20.5: Cardiac output and its control
- Cardiac output is the volume of blood pumped per minute by the heart.
- Cardiac output is calculated as heart rate times stroke volume.

20.6: Recommended review questions

20.1: What we already know about the heart

We have previously mentioned the heart, rather briefly, in Chapters 4 (The Tissue Level of Organization) and 10 (Muscle Tissue). Let us review some key points.

- There are three basic types of muscle tissue: cardiac muscle, skeletal muscle, and smooth muscle. Like skeletal muscle, cardiac muscle is striated because of its precise, regular arrangement of actin, myosin, and associated proteins.
- Cardiac muscle cells have outstanding endurance supported by high densities of mitochondria for aerobic ATP production.

- The force generated by all muscle cells comes from myosin pulling on actin. In cardiac muscle (and in skeletal muscle), this process is initiated by a rush of calcium ions into the cytoplasm, causing troponin to move tropomyosin out of the way so that myosin can bind to actin.
- Substances can pass directly from one cardiac muscle cell to the next via gap junctions.

20.2: Basic anatomy of the heart

To move blood through the body, we need a pump. The heart is that pump. It pumps blood through two circuits, one circuit through the lungs and one circuit through the rest of the body, as shown in 10th Martini Figure 20-1.

In studying the anatomy of the heart, the first thing to remember is that designations of left and right are made from the perspective of the patient, not the observer. Thus, if you are looking at a diagram of an anterior view of the heart, the part of the heart that is on the left side of the page will be on the patient's *right* side.

As you may already know, human hearts have four chambers: the right atrium ("AY-tree-um"), the right ventricle, the left atrium, and the left ventricle. Both the atria and the ventricles are muscular, but the walls of the ventricles are much thicker and stronger.

Several large blood vessels – known as "great vessels" because of their size – are responsible for carrying blood into and out of the heart.

- The **vena cava**, the largest vein in the body, collects blood from all over the body and brings it to the right atrium. The vena cava has two branches. The *superior vena cava* carries blood from the head, neck, upper limbs, and chest; the *inferior vena cava* carries blood from everywhere else.
- The **pulmonary arteries** carry blood away from the right ventricle toward the lungs. Blood leaving the right ventricle passes through a single large vessel, called the *pulmonary trunk*, which branches into the left pulmonary artery and the right pulmonary artery.
- Blood heading from the lungs to the left atrium passes through the **pulmonary veins**. (There are two left pulmonary veins and two right pulmonary veins.)
- Blood leaving the left ventricle goes into the **aorta**, the largest artery feeding the body as a whole.

To keep blood flowing in the correct direction, the heart has four valves. There are two *atrioventricular (AV) valves* between the atria and ventricles, and two *semilunar valves* between the ventricles and the great vessels to which they connect.

- The *tricuspid valve* sits between the right atrium and the right ventricle.
- The *pulmonary valve* sits between the right ventricle and the pulmonary trunk.
- The *bicuspid valve*, or *mitral valve*, sits between the left atrium and the left ventricle.
- The *aortic valve* sits between the left ventricle and the aorta.

To remember which atrioventricular (AV) valve is which, 10th Martini suggests remembering the phrase "Try to be right" (try => tri => tricuspid).

Once you know the names of the above mentioned structures – which can be seen in figures like 10th Martini Figure 20-6 (The Sectional Anatomy of the Heart) – you should be able to trace the flow of blood as follows: blood flows from the vena cava into the right atrium, through the tricuspid valve into the right ventricle, through the pulmonary valve into the pulmonary trunk and pulmonary arteries, to the lungs, out of the lungs into the pulmonary veins and the left atrium, through the bicuspid valve into the left ventricle, through the aortic valve into the aorta.

A final key piece of cardiac anatomy is the heart's *conducting system* by which electrical signals are spread. Consult 10th Martini Figure 20-12 (Impulse Conduction Through the Heart). Depolarization typically begins in the **sinoatrial (SA) node** in the right atrium (near the superior vena cava) and spreads from there to the *atrioventricular (AV) node* in the floor of the right atrium, *the bundle of His* ("hiss"; also called the AV bundle), the left and right *bundle branches*, and the *Purkinje fibers*.

20.3: Electrical events: action potentials and cell-to-cell conduction

Recall that muscle cells are not neurons, yet they depolarize and repolarize similarly to neurons. Thus we can speak of cardiac action potentials, meaning all-or-none depolarization and repolarization in cardiac muscle cells.

Recall that, in general, "resting" neurons and muscle cells are fairly polarized (often at a membrane potential of -70 or -80 mV) until a stimulus from a neuron prompts them to depolarize. However, the heart contains cells that are capable of depolarizing spontaneously, i.e., without external input. The heart's most important spontaneously depolarizing cells are the **pacemaker cells** of the SA node. Since electrical signals spread from the SA node through the rest of the heart, these pacemaker cells set the pace for the entire heart.

Changes in the pacemaker cells' membrane potential are shown over time in 10th Martini Figure 20-11b (The Conducting System of the Heart). Notice the gradual upward drift of membrane potential following an action potential. This is due to Na^+ "leak" channels, which let sodium in and thereby depolarize the cells until threshold is reached. Threshold here is conceptually the same as the threshold we encountered in the axons of neurons; it's the voltage at which voltage-gated cation channels open, ensuring that an action potential will be completed. (In this case, inflows of Ca^{2+} and Na^+ both contribute to depolarization.)

Once the pacemaker cells depolarize, the depolarization spreads to adjacent cells via gap junctions, which enable cations to move directly from one cell into the next. These connections between cells are similar to the electrical synapses between neurons that we mentioned in Chapter 12. Depolarization spreads quickly through the specialized conduction structures mentioned above (AV node, bundle of His, bundle branches, and Purkinje fibers); however, it also spreads among "ordinary" cardiac muscle cells, so that all cardiac muscle cells are eventually activated directly or indirectly by the conducting system.

The depolarization of the heart can be measured clinically as an electrocardiogram, usually abbreviated EKG based on the German spelling of the word (electrokardiogramm). Surface electrodes (2 to 12 leads) are placed at various spots on the anterior of the body; waves of depolarization and repolarization are detected as differences in relative charge at two electrodes. The output is a plot of voltage (on the Y axis) versus time (on the X axis). Thus, EKGs superficially resemble graphs of membrane potential versus time, but are not the same, as membrane potential is defined as the charge difference between the inside and outside of a cell, and must be measured with invasive electrodes.

A normal EKG looks as shown in 10th Martini Figure 20-13 (An Electrocardiogram). It includes three key components:

- The P wave, corresponding to depolarization of the atria.
- The QRS complex, corresponding to depolarization of the ventricles (and repolarization of the atria, which is obscured by the ventricular depolarization).
- The T wave, corresponding to repolarization of the ventricles.

Here we should note the difference between depolarization and contraction. Depolarization is an electrical event, whereas contraction is the mechanical event spurred by the electrical event of depolarization. (Depolarization leads to calcium entry into the cytoplasm, allowing myosin to interact with actin.) Thus, atrial contraction occurs from the P wave to the QRS complex, and ventricular contraction occurs from the QRS complex to the T wave. The atria contract before the ventricles do, thanks to the conduction delay at the AV node. This is fortunate; if the atria and ventricles were to contract simultaneously, the high pressure in the ventricle would not permit any blood from the atria to enter.

Various EKG irregularities are shown in 10th Martini Figure 20-14 (Cardiac Arrhythmias). For now we will simply note that, despite their simplicity, EKGs have considerable diagnostic value. Atypical timing and/or magnitude of P, QRS, and/or T offer clues to underlying problems.

20.4: The cardiac cycle and the Wiggers diagram

The phrase *cardiac cycle* refers to the series of events that, all together, represent the full cycle of the heart contracting and relaxing. These events are shown in 10th Martini Figure 20-16 (Phases of the Cardiac Cycle). While the figure may seem complicated, it mostly combines two types of information that we have already covered: the timing of the contractions of the atria and ventricles, and the direction of blood flow through the heart. The figure uses the word *systole* ("SIS-tuh-lee") to mean contraction (of the atria or ventricle) and *diastole* ("dye-ASS-tuh-lee") to mean relaxation (of the atria or ventricle). There are many ways of dividing up the cardiac cycle, but the simplest way is to think of it in three phases: a phase where the atria contract, a phase where the ventricles contract, and a phase where neither the atria nor the ventricles contract.

One way to think about blood's movement through the heart is to think of the heart's chambers as having both "push" and "pull" actions on the blood. When a chamber contracts, pressure in the chamber increases and the blood in the chamber is pushed forward. Conversely, when a

chamber relaxes, the volume of the chamber increases, so the pressure in the chamber drops and blood is pulled into the chamber from the compartment upstream of it. Thus, for example, when the atria contract they propel blood into the ventricles; when the atria relax, they draw blood in from the vena cava (right atrium) and pulmonary veins (left atrium).

The events shown in 10th Martini Figure 20-16 are often combined into a single diagram (the Wiggers diagram) which combines measurements of EKG, pressure, volume, and heart sounds. It looks similar to 10th Martini Figure 20-17 (Pressure and Volume Relationships in the Cardiac Cycle). This diagram should be studied carefully. While you won't need to draw it, you should be able to explain why pressures and volumes change in the ways that they do. For example, when the ventricles contract between QRS and T, the volume of the ventricles decreases while the pressure inside the ventricles increases because the cardiac muscle is now pressing down on the blood contained there.

Diagrams like 10th Martini Figure 20-17 also help us understand the closing of the heart valves and the heart sounds (often written as "lub-dub" or "lub-dup") that go along with them. A valve will close when the pressure in the compartment downstream of the valve exceeds the pressure in the compartment upstream of the valve. The blood attempts to flow backward, toward the region of lower pressure, but the valve closes and prevents this. Thus, when ventricular pressure exceeds atrial pressure, the AV valves close until atrial pressure exceeds ventricular pressure. Likewise, when pressure in the great vessels exceeds pressure in the ventricles upstream of them, the semilunar valves close. The heart sounds result from the turbulence of the blood bouncing off of the now-closed valves ("lub" for AV valves, "dub"/"dup" for semilunar valves).

20.5: Cardiac output and its control

If the function of the heart is to pump blood to the rest of the body, we can quantify this function as the volume of blood pumped per unit time. This rate – the volume of blood pumped per unit time – is called the **cardiac output**. It is calculated according to a simple formula: cardiac output equals heart rate times stroke volume (CO = HR x SV). Stroke volume is defined as the amount of blood pumped in one heartbeat, or one stroke. It is also defined as the ventricle's end-diastolic volume minus the ventricle's end-systolic volume. In other words, if you start with a relaxed (end-diastolic) ventricle full of blood and then check the ventricle's volume again at the end of systole (contraction), the difference in the two volumes is the amount that was pumped in that one heartbeat.

If you calculate cardiac output by multiplying units of beats per minute by milliliters per beat, you wind up with CO expressed in units of milliliters per minute.

Since cardiac output depends on both heart rate and stroke volume, it can be changed via changes in heart rate or stroke volume or both. This is captured in 10th Martini Figure 20-20 (Factors Affecting Cardiac Output). During exercise, input of the sympathetic nervous system stimulates the pacemaker cells of the SA node, increasing heart rate. Simultaneously the sympathetic nervous system also increases calcium release within the cardiac muscle cells, enhancing contraction strength (contractility), reducing end-systolic volume, and increasing

stroke volume. Thus, the large increases in cardiac output that can occur during exercise are due to increases in both heart rate and stroke volume.

20.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 20: review questions #1, 9, 10, 14, 15, 22, 24, 29, 31. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 21: Blood Vessels and Circulation

In general, circulatory systems have three basic components: fluid to transport materials, one or more pumps to propel the fluid, and vessels to hold the fluid. Having covered the fluid in Chapter 19 (Blood) and the main pump in Chapter 20 (The Heart), we now consider the vessels, as well as the cardiovascular system as an integrated whole, in Chapter 21.

21.0: Outline

21.1: Overview of circulatory system anatomy
- Blood flowing away from the heart proceeds through arteries, arterioles, capillaries, venules, and veins. Arteries and veins are the fewest in number and are the biggest in terms of lumen size and wall thickness.

21.2: Forces affecting blood flow: pressure and resistance
- Bulk flow through a blood vessel is directly proportional to the pressure difference between the start of the vessel and the end of the vessel. Flow is inversely proportional to the resistance, which in turn depends on vessel length, vessel radius and fluid viscosity. These influences in blood flow are encapsulated in Poiseuille's Law of Laminar Flow.

21.3: Filtration, reabsorption, and exchange at the capillaries
- Fluid movement out of and into capillaries depends on hydrostatic pressure (higher in the capillaries, driving fluid out) and osmotic pressure (higher outside the capillaries, driving fluid into the capillaries).
- Capillaries exchange nutrients and wastes with tissues via diffusion, which is governed by Fick's Law.

21.4: Regulation of blood pressure
- Blood pressure must be maintained at or above a setpoint to ensure adequate flow to the body's tissues, especially the brain.
- Baroreceptors located in the carotid arteries and aorta sense changes in blood pressure.
- The sympathetic nervous system responds immediately to falling blood pressure by increasing the pumping of the heart and constricting the arterioles.
- Longer-term hormonal responses to low blood pressure include the release of antidiuretic hormone (ADH) by the posterior pituitary, erythropoietin by the kidney, and aldosterone by the adrenal cortex.

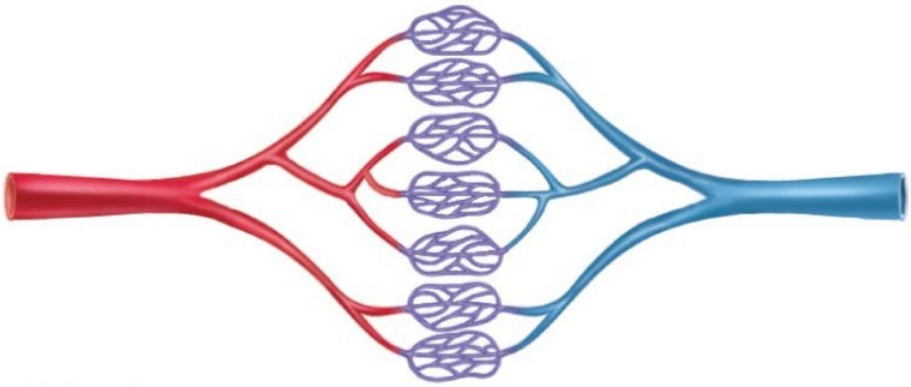
21.5: Recommended review questions

21.1: Overview of circulatory system anatomy

The word "cardiovascular" literally means the heart (cardio) plus blood vessels (vascular). Having looked in detail at the heart in Chapter 20, we will now focus on the vessels to which it is directly or indirectly connected.

The general arrangement of cardiovascular circuits is shown in 10th Martini Figure 21-17 (A Schematic Overview of the Pattern of Circulation). Note that the pulmonary circuit, which carries blood to the lungs, is separate from the systemic circuit, which carries blood everywhere else. Also note that the systemic circuit includes several parallel branches: to the brain, upper limbs, kidneys, gastrointestinal organs, gonads, and lower limbs.

As an overview figure, 10th Martini Figure 21-17 simplifies both the number of "branches" of the circulatory system and the branching pattern within each branch. If you consult 10th Martini Figure 21-23 (Major Arteries of the Trunk), you will see that there are more than 15 major arteries off of the aorta. (We shall see a bit later that blood flow can be selectively directed toward the specific systemic branches that need it most.) In addition, within a given "branch," the main artery divides into smaller arteries, which in turn form arterioles, capillaries, venules, and veins, as shown in CTM Figure 21.1.



CTM Figure 21.1: The branching of the circulatory system. A major artery branches into several smaller arteries and arterioles, which branch into capillary beds, which merge into venules and then veins. Figure taken from Scott Freeman et al., Biological Science *(5th edition).*

As you might expect, the structure of the large arteries and veins is quite different from that of the tiny capillaries. While all blood vessels are lined with endothelial cells, the walls of arteries and veins also include considerable amounts of connective tissue (including elastic fibers) and smooth muscle. Capillaries have only a thin coat of connective tissue surrounding the endothelial cells; arterioles and venules have walls only slightly thicker than those of capillaries. Detailed cross-sectional views of the vessels are shown in 10th Martini Figure 21-2 (Histological Structure of Blood Vessels).

21.2: Forces affecting blood flow: pressure and resistance

If you have taken physics, you may remember Ohm's law, which states that the flow of current through a conductor (such as a wire) equals the voltage divided by the resistance: $I = V/R$. A very similar relationship governs blood flow; blood flow through a vessel (often abbreviated Q) equals the pressure difference between the beginning and the end of the vessel divided by the resistance: $Q = \Delta P/R$.

Perhaps the idea of a pressure difference is fairly straightforward: blood flows from an area of higher pressure to an area of lower pressure. But what does resistance mean in the context of blood flow? Resistance encompasses factors that slow down the flow of blood, including the viscosity of the blood, friction between the blood and the surrounding walls, and turbulence

(disruptions to uniform flow caused by high flow speeds and irregularities in vessels). If we ignore the turbulence issue for now, we can write out an equation for resistance as follows: Resistance = **(**(8/π)*(viscosity)*(length)**)**/(radius)^4. This is commonly abbreviated as: R = **(**(8/π)*viscosity*L**)**/r^4. Note that the dominator is radius to the 4th power! That is, if the radius of the vessel doubles, the resistance goes down to 1/16 of what it was before! Therefore even small changes in vessel radius can cause significant changes in resistance, and thus blood flow.

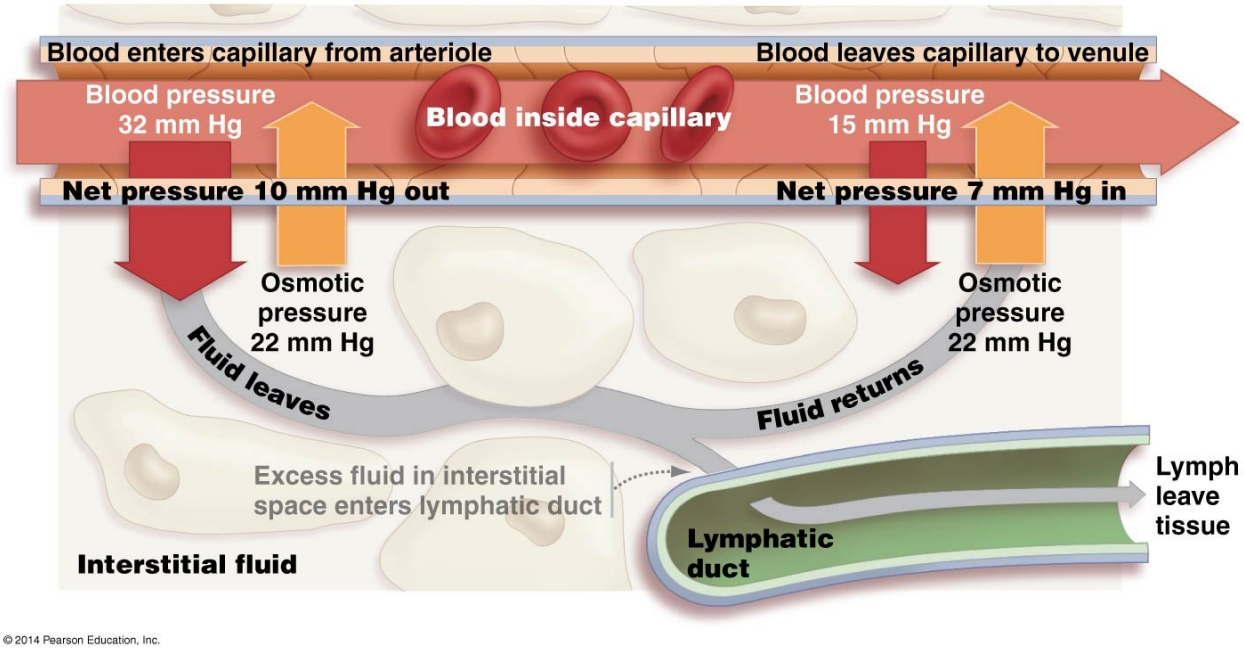
If we substitute the formula for R into our previous equation of Q = ΔP/R, we get what is known as Poiseuille's Law of Laminar Flow, named after the French physician who formulated it: Q = (ΔP* r^4)/**(**(8/π)*viscosity*L**)**. In this version of the relationship, it becomes more obvious that flow is directly proportional to vessel radius to the 4th power. Using the same example as before, if the radius doubles, the flow increases by a factor of 16 (assuming everything else stays constant).

Though 10th Martini is generally equation-phobic and does not formally present Poiseuille's Law, Figure 21-7 (Factors Affecting Friction and Vascular Resistance) illustrates some of the contributing variables.

21.3: Filtration, reabsorption, and exchange at the capillaries

As blood flows through the arteries and arterioles, it eventually gets to the numerous thin-walled capillaries. Blood flow through the capillaries more or less follows Poiseuille's Law; however, movement of materials also occurs through the capillary walls. Movement of fluids – and any solutes they contain that are small enough to get out – is known as *filtration* if the net movement is out of the capillaries and *reabsorption* if the net movement is into the capillaries. As shown in CTM Figure 21.2, filtration generally occurs at the upstream end of capillaries and reabsorption takes place at the downstream end.

The key to CTM Figure 21.2 is that movement of water is a balance of two forces: hydrostatic pressure (what we normally think of as blood pressure) and osmotic pressure (the attraction of water toward the region with the highest concentration of solutes). At the upstream end of the capillary, the blood is under relatively high pressure and forces some of the fluid out of the capillary. However, by the downstream end of the capillary, the blood has lost much of its remaining hydrostatic pressure (due to continuing resistance along the length of the capillary), and the higher concentration of solutes inside the capillary draws some water back into it. These filtration and absorption processes are especially important in the kidney, which has the task of getting rid of wastes while reabsorbing valuable nutrients such as glucose and amino acids.



CTM Figure 21.2: Filtration out of and reabsorption into capillaries is driven by hydrostatic and osmotic pressures. Figure taken from Scott Freeman et al., Biological Science *(5th edition).*

As shown in CTM Figure 21.2, a bit more fluid is typically filtered out of the capillaries than reabsorbed into them; the excess is taken up by the lymphatic system and ultimately returned to the veins. However, if there is an imbalance between filtration, reabsorption, and lymphatic uptake, fluid may accumulate in the interstitial fluid surrounding the capillaries – a condition known as **edema**. Edema may result from changes in hydrostatic pressure or osmotic pressure or both. For example, in people with very high blood pressure, or hypertension, higher-than-normal amounts of fluid may be driven into the interstitium. Starvation is a very different situation with a somewhat similar outcome: there is a decline in the levels of plasma proteins (which are too big to leave the capillaries, and thus provide osmotic pressure drawing water into the capillaries), so the blood has less osmotic "pull" on the water and more accumulates in the interstitium. Edema is discussed as a Clinical Note on p. 741 of 10th Martini.

Amidst all of this movement of fluids and solutes in and out of the capillaries, surrounding cells absorb nutrients (O_2, glucose, amino acids, etc.) and release waste products (CO_2, lactic acid, etc.) This exchange of nutrients and wastes between the capillaries and surrounding cells is the circulatory system's main purpose, so it's probably wrong for me to bury it here in this unremarkable paragraph. Anyway, such exchange occurs by diffusion, and is thus driven by concentration gradients (NOT the pressure gradients mentioned above for Poiseuille). To help us understand diffusion better, we have another equation (not explicitly presented by 10th Martini): Fick's Law of Diffusion. This law says that diffusion rate equals the concentration gradient times the surface area over which diffusion occurs times a diffusion constant, all divided by the thickness of the diffusion barrier. More succinctly, diffusion rate = $((C_1 - C_2)*A*k)/D$. If we are considering the diffusion of a gas, the concentration gradient ($C_1 - C_2$) will generally be reported as a partial pressure gradient ($P_1 - P_2$), but do not confuse this partial pressure gradient with the (hydrostatic) pressure gradient in Poiseuille's law; these are two very different kinds of

pressure. Also, for completeness, note that the "constant" k is only constant for a given substance diffusing through a given medium.

Fick's Law helps us understand the factors that can increase or decrease diffusion rate. For example, since diffusion rate is proportional to surface area, it makes sense that capillaries are so heavily branched, providing lots of area across which substances can diffuse. Keeping D small is also important, and thus helps explain why the capillaries' walls are so thin. In cases of edema, mentioned above, accumulation of fluid between the capillaries and nearby cells increases D and thus slows diffusion rate. This can be a real problem, for example, in the case of pulmonary edema, when fluid in the lungs impairs the diffusion of oxygen into the blood.

21.4: Regulation of blood pressure

In clinical settings, *blood pressure* usually refers to blood pressure in the main arteries, which varies during the cardiac cycle, as shown in 10th Martini Figure 21-9 (Pressures within the Systemic Circuit). The *systolic blood pressure* is the peak of arterial pressure generated during ventricular contraction (systole); the *diastolic blood pressure* is the lowest arterial pressure that occurs while the heart is relaxing (diastole). However, blood pressure can be measured all along the entire circuit, as shown in 10th Martini Figure 21-9. It can be seen that as the blood gets farther and farther away from the heart, it loses pressure as it encounters resistance. By the time the blood gets back to the heart, its pressure is close to 0 mm Hg!

Although blood flow outside the heart gets a boost from such actions as deep inhalations that create negative pressure in the thorax (the so-called "respiratory pump") and the pumping of active skeletal muscles, the fact remains that the heart is the main driver of blood flow, so blood in the arteries must have adequate momentum to traverse the rest of the circulatory system quickly. Arterial pressure is especially important for maintaining blood flow to the brain, which usually occurs against gravity. Therefore, keeping arterial blood pressure at or above a minimum setpoint is a top priority for the body.

Arterial pressure is sensed by **baroreceptors** in the aorta and carotid arteries. These receptors are similar to the mechanoreceptors that sense touch and pressure in your skin; the higher the pressure, the more distorted these receptors become, and the more dramatic the changes in their membrane potential and neurotransmitter release. If baroreceptors report to the hypothalamus – negative feedback central – that blood pressure is low, the hypothalamus makes adjustments to bring blood pressure back up. These adjustments can be divided into immediate responses governed by the nervous system and longer-term responses governed by hormones.

In the short term, the hypothalamus directs the medulla's cardiac center (controlling the heart) and vasomotor center (controlling smooth muscle tone in the blood vessel walls) to increase the pumping of the heart and constrict the arterioles. These pathways are part of the sympathetic nervous system; their effects on cardiac muscle and smooth muscle cells are caused by the neurotransmitter norepinephrine (often abbreviated NE).

Thus, the short-term solution to low blood pressure is to make the heart pump harder and to decrease the size of the containers holding the blood. A longer-term solution is to increase the amount of blood in the system. This can be achieved through actions of hormones like these:

- Erythropoietin from the kidney stimulates production of new red blood cells in the red bone marrow.
- Antidiuretic hormone (ADH, or vasopressin) from the posterior pituitary stimulates retention of water in the kidney, so that it is not lost in the urine.
- Aldosterone from the adrenal cortex promotes salt retention in the kidney, which osmotically helps the body hang onto its water.

Such regulatory mechanisms come into play in situations such as hemorrhage, where a loss of blood may lead to dangerous drops in blood pressure. If the sympathetic nervous system does not maintain blood pressure at the setpoint, the bleeding victim may faint. This seemingly inconvenient response is actually a useful mechanism for maintaining blood flow to the brain, since the heart of a passed-out person no longer has to fight gravity in pumping blood to the brain.

10th Martini covers blood pressure regulation in figures such as Figure 21-12 (Short-Term and Long-Term Cardiovascular Responses), Figure 21-13 (Baroreceptor Reflexes of the Carotid and Aortic Sinuses), and Figure 21-16 (Cardiovascular Responses to Blood Loss). On the whole, though, I find these figures unnecessarily complicated.

21.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 21: review questions #2, 4, 5, 11, 17, 20, 23, and 30. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 22: The Lymphatic System and Immunity

After three chapters about the cardiovascular system, it's time to move on. Chapter 22 can be considered a transitional chapter in that many of the key players of the immune system are found in the bloodstream, but many are also found outside the blood (e.g., in the lymphatic system).

22.0: Outline

22.1: Components of the lymphatic system
- The lymphatic system includes lymph; lymphatic vessels; lymphoid tissues and organs, like the red bone marrow, thymus, spleen, and lymph nodes; and lymphocytes and other cells like phagocytes.
- Lymphocytes include T cells, B cells, and natural killer (NK) cells. Types of T cells include cytotoxic T cells, helper T cells, memory T cells, and suppressor T cells.

22.2: Innate (nonspecific) immunity
- The immune system can be divided into innate (nonspecific) immunity and adaptive (specific) immunity.
- Innate immunity includes physical barriers, phagocytes, immune surveillance by NK cells, interferons, complement, inflammation, and fever. Phagocytes engulf pathogens, while NK cells destroy pathogens and other abnormal cells.

22.3: Adaptive immunity: cell-mediated and antibody-mediated
- Adaptive immunity can be divided into cell-mediated immunity, in which cytotoxic T cells destroy infected cells, and antibody-mediated immunity, in which B cells produce antibodies that bind to foreign antigens.

22.4: Clinical issues
- Immunodeficiency – any deficit in the functioning of the immune system – is exemplified by the HIV virus, which destroys helper T cells and thus causes AIDS.
- In autoimmune diseases, the body mistakenly attacks its own antigens. Examples include type I diabetes mellitus, Graves' disease, and myasthenia gravis.
- Vaccines introduce a pathogen's antigens into the body to elicit an immune response, so that the body is ready to attack the pathogen in the future.

22.5: Recommended review questions

22.1: Components of the lymphatic system

The main purpose of the lymphatic system is to defend the body against pathogens (disease-causing organisms or viruses). We will see how it does this below, but first we will introduce the parts of this system. You have already been introduced to some of the components in earlier chapters. Chapter 19 surveyed the contents of blood, which includes white blood cells (also called leukocytes) – many of which are lymphocytes – and antibodies (also called immunoglobulins), which are produced by B lymphocytes. Chapter 21 noted that some of the

fluid that is filtered out of capillaries is absorbed not back into the capillaries but into lymphatic ducts.

With those previous glimpses in mind, we now define the lymphatic system as including four components:

- Lymph fluid itself, which "resembles plasma but contains a much lower concentration of suspended proteins," according to 10th Martini.
- Lymphatic vessels or ducts, which slowly transport lymph fluids from peripheral tissues to central veins.
- Lymphoid tissues and organs, such as red bone marrow, lymph nodes, and the thymus and spleen.
- Lymphocytes – the main cells found in lymph – along with some other cells such as phagocytes.

The lymphatic vessels can be seen in 10th Martini Figures 22-2 (Lymphatic Capillaries), 22-3 (Lymphatic Vessels and Valves), and 22-4 (The Relationship between the Lymphatic Ducts and the Venous System). The details of the anatomy are not important for our purposes; we will simply note that the lymphatic ducts are highly branched throughout the body, and that the main ducts (the thoracic duct and right lymphatic duct) ultimately empty into the left and right subclavian veins, which feed into the brachiocephalic veins, which in turn feed into the superior vena cava.

As noted above, lymphocytes are a subgroup of white blood cells (leukocytes). The full diversity of white blood cells can be seen back in 10th Martini Table 19-3 (Formed Elements of the Blood) and Figure 19-10 (The Origins and Differentiation of Formed Elements). If we focus specifically on lymphocytes, we can see in 10th Martini Figure 22-5 (Classes of Lymphocytes) that lymphocytes include B cells, natural killer (NK) cells, and various types of T cells (cytotoxic T cells, helper T cells, suppressor T cells, and memory T cells). Some of these cells' roles are briefly described below.

Lymphoid tissues and organs include the following (plus others not described here):

- Red bone marrow. All blood cells (including non-lymphocytes such as red blood cells) arise from the hematopoietic ("blood-forming") stem cells that reside here. NK cells and B cells develop within the bone marrow; the B in the name B cells refers to bone marrow.
- Thymus (just superior to the heart). T cells are called T cells because they develop in the thymus after their precursors migrate out of the bone marrow. 10th Martini Figure 22-6 (The Origin and Distribution of Lymphocytes) shows this path along with the bone marrow-based development of NK and B cells.
- Lymph nodes. At these structures, antigens are removed from lymph before entering the venous circulation. Much phagocytosis and antigen presentation (described in section 22.3 below) occurs here.
- Spleen (toward the left of the abdomen). 10th Martini notes, "The spleen performs the same functions for blood that lymph nodes perform for lymph." Here, phagocytosis and antigen presentation lead to removal of abnormal blood cells such as those perturbed by malaria or sickle-cell anemia.

22.2: Innate (nonspecific) immunity

Your immune system uses players like those mentioned above to protect the body from innumerable threats. Within the immune system, a basic distinction can be made between innate (or nonspecific) immunity and adaptive (or specific) immunity. Specific immunity includes responses that are tailored to individual pathogens; an example would be the production of antibodies to a particular antigen that is part of a pathogenic virus or bacterium. Innate immunity includes "generic" protections such as physical barriers that keep pathogens out of the body.

Physical barriers are one of seven components of innate immunity listed by 10th Martini Figure 22-11 (Innate Defenses):

- Physical barriers such as the skin.
- Phagocytosis of pathogens and debris by macrophages and microphages.
- Immune surveillance by NK cells, which kill abnormal cells.
- Interferons, chemical signals that interfere with replication of viruses.
- Complement, a protein cascade (somewhat reminiscent of the clotting cascade discussed in Chapter 19) that punches holes in target cells.
- Inflammation, which reduces the spread of injury and infections.
- Fever, which inhibits growth of some pathogens, and speeds up our responses to them.

22.3: Adaptive immunity: cell-mediated and antibody-mediated

Moving on from innate immunity to adaptive immunity, adaptive immunity includes both "cell-mediated" and "antibody-mediated" components, as shown in 10th Martini Figure 22-17 (An Overview of the Immune Response). In cell-mediated immunity, cytotoxic T cells destroy infected cells; in antibody-mediated immunity, antibodies are produced against specific foreign antigens.

Both cell-mediated and antibody-mediated immunity are represented in 10th Martini Figure 22-18 (Antigens and MHC Proteins). The two panels of the figure show two distinct situations summarized in CTM Table 22.1. Both involve *antigen presentation* – the display of antigens bound to cell-surface proteins called Major Histocompatibility Complex (MHC) proteins, or Human Leukocyte Antigens (HLAs). Cells that are specialized for presenting antigens bound to Class II MHC proteins are known as antigen-presenting cells (APCs).

We saw in Chapter 19 how antibodies can bind to cell-surface antigens of red blood cells, leading to clumping and destruction of red blood cells from incompatible donors. The binding of antibodies to many other antigens has similar effects.

Having now covered both innate and adaptive immunity, it is worth examining 10th Martini Figure 22-25 (The Course of the Body's Response to a Bacterial Infection) to see which types of immunity are most active at what times. As you might expect, the earliest rises among immune cells are in neutrophils, NK cells, and macrophages, all of which are considered part of innate immunity. As days go by and the system starts to recognize and respond to more specific features of the pathogen, components of adaptive immunity – cytotoxic T cells and plasma cells

(mature B cells specialized for secreting antibodies) – start to dominate the immune response. The length of infection-caused illnesses depends partly on the extent to which innate immunity can eliminate the pathogens; longer-lasting illnesses may not recede until adaptive immunity has peaked, one to two weeks after infection.

CTM Table 22.1: Two Types of Antigen Presentation

	Infected cell	**Antigen-presenting cell (APC)**
Summary	Infected cells display pathogen antigens bound to Class I MHC proteins, triggering $CD8^+$ T cells to stimulate cytotoxic T (T_C) cells, which destroy the infected cells.	Phagocytes display pathogen antigens bound to Class II MHC proteins, activating $CD4^+$ helper T (T_H) cells to secrete cytokines that stimulate antibody production by B cells, etc.
Antigen-displaying cells	Any infected, nucleated cell	Phagocytic cells
Responding cells	T cells with cluster of differentiation marker CD8	Helper T (T_H) cells with cluster of differentiation marker CD4
Ultimate effect of response	Destruction of infected cells by T_C cells	Cytokines released by T_H cells promote antibody production by B cells, maturation and activity of T_C cells, and nonspecific phagocytosis
Message conveyed by antigen-MHC complex, according to 10th Martini	"Hey, I'm an abnormal cell – kill me!"	"Hey, this antigen is dangerous – get rid of it!"

22.4: Clinical issues

Let us briefly consider three clinical aspects of the immune system: immune deficiency, autoimmunity, and vaccines.

The term immune deficiency covers any unusual limitation in the function of the immune system. They can be caused by poor development of lymphoid tissues/organs, viral infections, and/or immunity-suppressing (immunosuppressive) drugs. The human immunodeficiency virus (HIV) causes immune deficiency by destroying helper T cells. While this is not fatal in and of itself, reductions in T_H cells leave the body vulnerable to other infections.

If immune deficiency refers to an inadequate defense of the body, autoimmunity is sort of the opposite: an overzealous defense system that even attacks the body's own antigens. Here are a few examples.

- In type I diabetes mellitus, the insulin-producing beta cells of the pancreas are destroyed during childhood. Plasma glucose levels are unhealthily high in these patients; chronic glucose elevations can damage the retina, nerves, kidneys, etc.
- In Graves' disease, antibodies are produced against the thyroid glands' TSH receptors. Stimulation of these receptors by the antibodies leads to hyperthyroidism and its symptoms of increased cellular metabolism, increased heart rate, goiter, nervousness, irritability, bulging eyes, etc.
- In myasthenia gravis, antibodies are made against acetylcholine receptors at the neuromuscular junction. These antibodies interfere with the binding of acetylcholine (ACh) and thus limit activation of skeletal muscle cells by motor neurons.

To close on a happier note, vaccines take advantage of the immune system's ability to "remember" past antigens. Vaccines generally consist of a killed or weakened pathogen, or one or more of its antigens. The immune system mounts a response to the antigens provided in the vaccine; if the full-fledged pathogen subsequently tries to invade, memory T_C and memory T_H cells orchestrate a swift and powerful response.

22.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 22: review questions #5, 6, 11, 15, 16, 17, 18, 28; Clinical Case Wrap-Up questions #1 and 2. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 23: The Respiratory System

Like Chapter 22, Chapter 23 can be considered a transition away from the cardiovascular system. The respiratory system, in cooperation with the cardiovascular system, allows us to exchange gases with the environment. Like the cardiovascular system, it consists of a fluid (air), tubes through which the fluid moves (conducting airways and bronchial tree), and pumps to propel this movement (respiratory muscles).

23.0: Outline

23.1: Overview of functions and anatomy
- The most important functions of the respiratory system are to move air into and out of the body and to facilitate gas exchange between the blood and the environment.
- From the nose or mouth, air passes through the pharynx (throat), larynx, trachea, bronchi, bronchioles, and alveoli.

23.2: Ventilation: moving air in and out
- During inspiration, muscles like the diaphragm and external intercostals expand the pleural cavities that contain the lungs. The decrease in intrapleural pressure forces the lungs to inflate. When the muscles relax, the intrapleural pressure increases and the lungs deflate.

23.3: Gas exchange and transport in the blood
- Fick's Law of Diffusion indicates that diffusion rate is maximized by a high surface area and a thin diffusion barrier, both of which are achieved by the anatomical arrangement of the alveoli and the pulmonary capillaries.
- In the blood, oxygen is transported by hemoglobin. Carbon dioxide is mostly transported as bicarbonate ($HCO3^-$), though some CO_2 is bound to hemoglobin and some is dissolved in plasma.

23.4: Feedback control of ventilation
- Chemoreceptors in the brainstem, carotid artery, and aorta monitor levels of O_2, CO_2, and pH, and trigger adjustments in respiration rate as needed.

23.5: Pulmonary edema
- A buildup of interstitial fluid in the lungs may decrease available surface area and increase diffusion barrier thickness, and thus may decrease rates of gas exchange.

23.6: Recommended review questions

23.1: Overview of functions and anatomy

According to 10th Martini, the respiratory system has five main functions. The first two of these are the most important: facilitating gas exchange between the blood and the environment, and moving air into and out of the body. Additional functions include communicating (via speaking, singing, etc.), assisting with odor detection, and defending the body against pathogens.

As we have seen, gas exchange is governed by Fick's law of diffusion: diffusion rate = **(**(C_1 – C_2)*A*k**)**/D, where (C_1 – C_2) is the concentration gradient, A is the surface area, k is a constant, and D is the width of the diffusion barrier. To maximize diffusion rates, the capillaries and alveoli of the lungs constitute very large surface areas over which exchange of O_2 and CO_2 occurs. Likewise, the diffusion barrier between the interior of the alveoli and the capillaries is kept very small.

The alveoli constitute the very terminal branches of the respiratory passageways. They are somewhat analogous to the capillaries of the circulatory system, although, unlike the capillaries, they are dead ends (or cul-de-sacs). Air gets to the alveoli by passing through the nose or mouth down the pharynx (throat) through the larynx (which includes the "voice box"), trachea, bronchi, and bronchioles. The trachea divides into two primary bronchi that feed the left and right lungs, respectively. An anatomical overview is provided by 10th Martini Figure 23-1 (The Structures of the Respiratory System); details of the alveoli are shown in Figure 23-10 (Alveolar Organization). Note that to pass from an alveolus to the bloodstream or vice versa, a gas molecule must only cross alveolar and capillary endothelial cells and a fused basement membrane between the two cells – a total distance D of about 0.5 μm.

23.2: Ventilation: moving air in and out

To understand movement of air into and out of the lungs, we must understand the relationship between a gas's pressure and the volume of its container. The two are inversely related: for a constant number of molecules in a sealed container, increasing the volume decreases the pressure and vice versa. See 10th Martini Figure 23-12 (The Relationship between Gas Pressure and Volume). We have already encountered this relationship in thinking about blood pressure and the volume of blood's containers; although air is much more compressible than blood, the same concepts apply.

An additional bit of relevant background is the fact that each lung is covered with the visceral pleura, and that immediately outside the visceral pleura is the parietal pleura, which covers the inside of the thoracic cavity. The (very very tiny) space in between these two pleural layers is the pleural cavity.

At any given moment, the level to which the lungs are inflated depends on two opposing forces. Much like inflated balloons, lungs have elastic recoil that drives them towards deflation. However, as they start to deflate, the visceral pleura starts to pull away from the parietal pleura, and because the volume of the pleural cavity is expanding, the pressure in the pleural cavity decreases, making it hard for the lungs to deflate further. Thus the volume of the lungs represents a balance between their elastic nature driving them to deflate, and the low (sub-atmospheric) intrapleural pressure driving them to inflate. By the way, the lungs would be driven even more strongly to deflate were it not for *surfactant*, a lipid secretion that coats the lungs and reduces the surface tension of the fluid surrounding them.

During inhalation, the diaphragm (which divides the thoracic and abdominal cavities) contracts and flattens downward, thus expanding the thoracic cavity. Meanwhile, the external intercostal

muscles (between the ribs) raise the rib cage upward and outward, also expanding the thoracic cavity. This expansion of the thoracic cavity expands the pleural cavity, making the pressure in the pleural cavity even lower than before, and the lungs are drawn outward by this negative pressure to fill with air from the environment. When these respiratory muscles relax, the thoracic cavity shrinks, the pleural cavity shrinks and adopts a less negative pressure, and the lungs partially deflate. The actions of the muscles are shown in 10th Martini Figure 23-15 (Respiratory Muscles and Pulmonary Ventilation), while the changes in lung volume are shown most clearly in 10th Martini Figure 23-13 (Mechanisms of Pulmonary Ventilation).

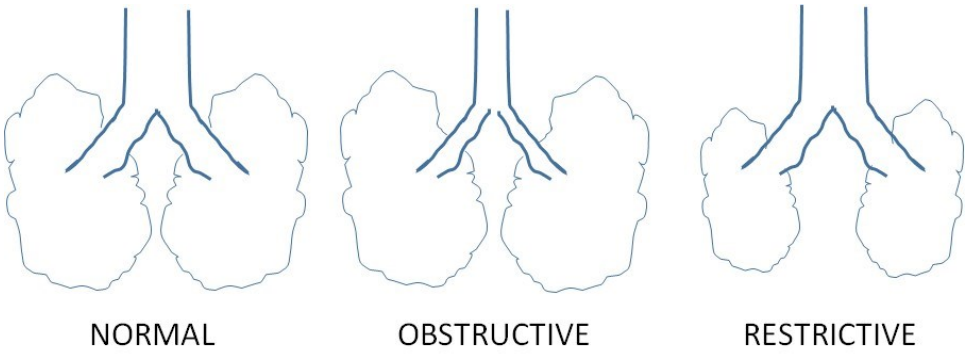
Because the intrapleural pressure is less than atmospheric pressure – about 750 to 758 mm Hg, as opposed to the typical sea-level atmospheric pressure of 760 mm Hg – this type of ventilation system is known as *negative-pressure ventilation*. If a wound (from, say, a bullet or knife) enters the thoracic cavity, the intrapleural pressure becomes equal to the atmospheric pressure and the lung on that side collapses, a condition called *pneumothorax*. Note that this happens whether or not the lung itself is actually pierced.

Various aspects of ventilation can be quantified with fairly simple equipment. 10th Martini Figure 23-16 (Pulmonary Volumes and Capacities) is a diagram of some of the many measurements that can be made. Among the most important quantities are the following:

- Residual Volume (RV), the amount of air remaining in the pulmonary system (lungs plus conducting airways) after maximal exhalation.
- Tidal Volume (TV or V_T), the volume of a single breath (whether small or large).
- Total Lung Capacity (TLC), the maximum amount of air that can be held by the pulmonary system (lungs plus conducting airways).
- Forced Expiratory Volume in 1 second (FEV1). Though not shown in Figure 23-16, this is the maximal amount of air that can be expelled from the lungs in 1 second.

Measurements of quantities like these can help diagnose lung disorders such as those shown in CTM Figure 23.1. In obstructive pulmonary disease, airways may be narrowed by factors such as inflammation, and FEV1 is usually less than normal. (Poiseuille's Law is not typically applied to respiration, but you may be reminded of its principle that the radius of a tube can greatly affect flow rates.) In restrictive disease, the lungs have lost some of their elasticity and cannot inflate as well as usual, so TLC and related volumes (IRV, VC) are usually below normal.

The rate of pulmonary ventilation per unit time is often quantified with the following equation: Pulmonary Ventilation = Tidal Volume x Respiration Rate, or PV = V_T x RR for short. (Respiration Rate is the number of breaths per minute.) Notice that this is analogous to the formula for cardiac output (CO = SV x HR), which also multiplies a volume per event by an event frequency. Just as humans can increase their cardiac output several-fold by increasing both stroke volume and heart rate, they can increase their pulmonary ventilation several-fold by increasing both tidal volume and respiration rate.



CTM Figure 23.1: A quick visual comparison of pulmonary systems that are normal, obstructive (narrowed airways), and restrictive (unable to inflate fully). Crudely drawn by Dr. C.

23.3: Gas exchange and transport in the blood

To understand gas exchange at the lungs, we turn once again to Fick's law of diffusion. Here it is one more time: diffusion rate = **(**$(C_1 - C_2)$*A*k**)**/D, where $(C_1 - C_2)$ is the concentration gradient, A is the surface area, k is a constant, and D is the width of the diffusion barrier. As noted above, the architecture of the lungs is such that A is very large and D is very small, thus enabling rapid diffusion.

Since diffusion is driven by concentration gradients, oxygen and carbon dioxide will each diffuse from regions of higher concentration to regions of lower concentration. Thus, O_2 diffuses from the lungs into the pulmonary capillaries, while CO_2 diffuses in the opposite direction.

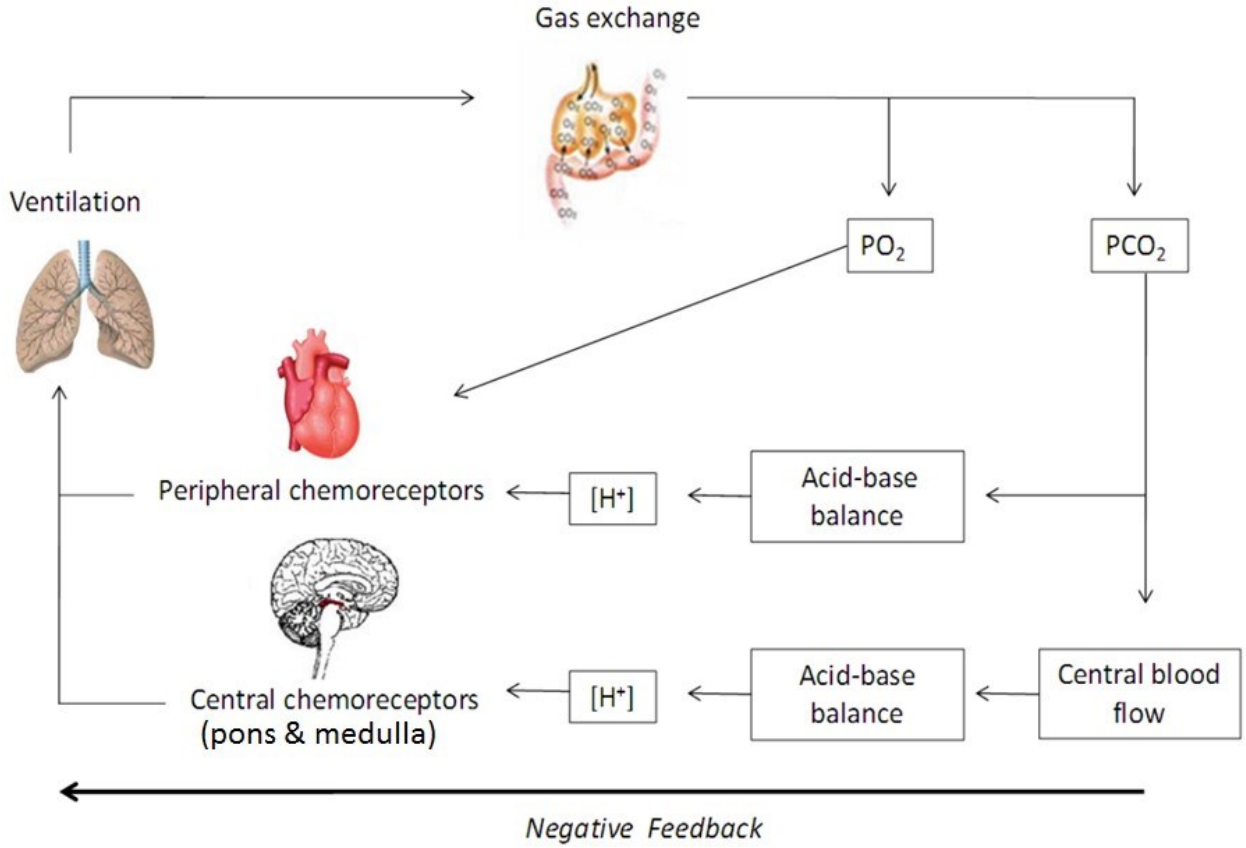
How are O_2 and CO_2 transported once they are in the blood? As discussed in Chapter 19, O_2 binds to the iron (Fe) atom of the heme groups of hemoglobin. (Oxygen transport by hemoglobin is disrupted by carbon monoxide poisoning because CO competes with O_2 for the Fe binding site, and binds to it much more tightly than O_2 does.) The story is more complicated for CO_2, though 10th Martini Figure 23-22 (Carbon Dioxide Transport in Blood) isn't a bad summary. CO_2 is more water-soluble than O_2, so about 7% of the total dissolves in plasma. Another 23% or so binds to hemoglobin (at different spots than O_2 binds, i.e., at free amino groups). The remainder is converted into bicarbonate (HCO_3^-), a highly water-soluble ion, via the action of the enzyme carbonic anhydrase: $H_2O + CO_2 \Rightarrow H_2CO_3 \Rightarrow H^+ + HCO_3^-$. Via this reaction, CO_2 makes the blood more acidic; notice the release of hydrogen ions (H^+) on the right side. Hydrogen ions are one of the signals monitored by chemoreceptors, as discussed below.

23.4: Feedback control of ventilation

At the lungs, the body unloads its CO_2 waste and picks up fresh O_2. But what if this process is not happening fast enough to keep up with CO_2 production and O_2 demand by the rest of the

body? As with so many other things, there is a negative feedback system in place to move CO_2 and O_2 levels back toward their setpoints.

The sensory receptors of this negative feedback system are known as *chemoreceptors* because they sense the concentrations of chemicals – specifically CO_2, H^+, and O_2. There are "central chemoreceptors" that monitor these concentrations in the cerebrospinal fluid in the central nervous system – specifically in the medulla and pons – and "peripheral chemoreceptors" that monitor them in the aorta and carotid artery. If CO_2 and H^+ levels get too high, and/or if O_2 levels get too low, the medulla's respiratory pacemaker cells are stimulated to increase the respiration rate, which should decrease [CO_2] and [H^+] and increase [O_2]. This feedback loop is depicted in CTM Figure 23.2 below.



CTM Figure 23.2: Negative feedback control of ventilation. Start with PO_2 and PCO_2 (partial pressures of O2 and CO2, respectively) and follow the arrows to see how the system responds to perturbations in these variables. Figure from Guilherme Veiga Guimaraes et al., Arquivos Brasileiros de Cardiologia *2011.*

23.5: Pulmonary edema

As a final integrative example, consider the case of a patient with a failing heart. If the left ventricle is weak, its ejection fraction may be low; in other words, the left heart may be struggling to pump all the blood that it is receiving. If this is the case, blood may gradually get backed up in the pulmonary capillaries. An accumulation of blood there will increase the blood

pressure and will tip the hydrostatic/osmotic pressure balance in favor of more fluid being filtered out of the capillaries. If the fluid accumulates in the interstitium, it may collapse some of the alveoli and represent an added diffusion barrier between the lungs and capillaries, thus decreasing A and increasing D in Fick's Law and decreasing the rate of diffusion.

23.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 23: review questions #1, 3, 5, 15, 17, 29. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 24: The Digestive System

In Chapter 24, we return to some concepts introduced much earlier in the book. The word "digestion" refers specifically to the chemical breakdown of substances, usually by enzymes, which were introduced way back in Chapter 2. Digestion is accompanied by absorption across cell membranes, which can occur by simple diffusion, facilitated diffusion, or active transport, as discussed in Chapter 3. The cells lining most of the digestive tract are simple columnar epithelial cells, an epithelial cell type covered in Chapter 4.

24.0: Outline

24.1: Overview of structures and functions
- Ingested substances pass through the mouth, pharynx (throat), esophagus, stomach, small intestine, and large intestine.
- Digestion in and absorption from the digestive tract is aided by accessory organs: the teeth, tongue, salivary glands, liver, gallbladder, and pancreas.
- Food provides both building blocks for building needed molecules and chemical energy to power the synthesis of such molecules.
- The digestive system has six functions: ingestion, mechanical processing, digestion, secretion, absorption, and excretion.

24.2: Ingestion and mechanical processing
- Mechanical processing occurs both in the mouth (by the teeth and tongue) and farther along the digestive tract (where smooth muscle contractions in different orientations churn the contents).

24.3: Digestion
- Carbohydrates are digested by amylase in the mouth and in the lumen of the small intestine, and by brush border enzymes of the small intestine.
- Triglycerides (the main dietary form of lipids) are digested by lipase in the mouth, stomach, and small intestine.
- Proteins are digested by acid and pepsin in the stomach and by numerous proteases in the small intestine.

24.4: Absorption
- Monosaccharides and amino acids move across epithelial cell membranes into the blood via facilitated diffusion and cotransport (secondary active transport).
- Lipids move via simple diffusion into epithelial cells, where they are packaged into chylomicrons and released into the lymphatic system.

24.5: Accessory organs
- The pancreas produces and secretes many carbohydrate-, lipid, and protein-digesting enzymes into the duodenum, as well as bicarbonate to neutralize stomach acid.
- The liver produces bile, which is stored in the gallbladder and released into the duodenum to emulsify lipids.
- The liver also detoxifies many substances before they go into general circulation.

24.6: Recommended review questions

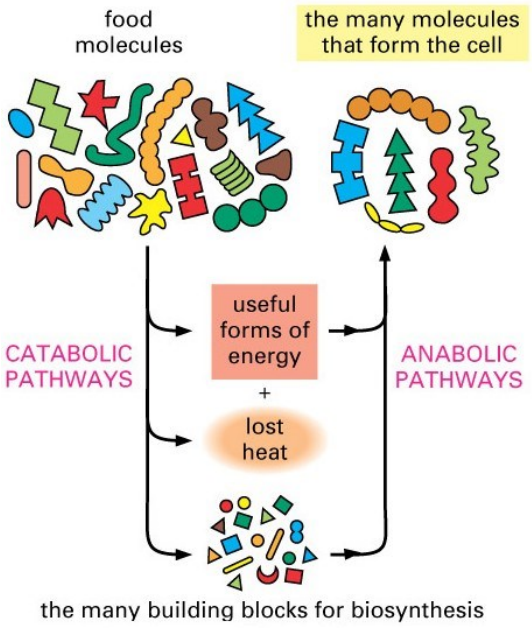
24.1: Overview of structures and functions

The main structures of the digestive system are given in 10th Martini Figure 24-1 (The Components of the Digestive System). The organs through which ingested substances pass are

collectively known by various names such as the digestive tract, GI (for gastrointestinal) tract, and the alimentary canal. The components include the mouth, pharynx (throat), esophagus, stomach, small intestine, and large intestine (colon). The small intestine is subdivided into the duodenum (most proximal), jejunum, and ileum (most distal); the large intestine is subdivided into the ascending colon (most proximal), transverse colon, and descending colon (most distal). In addition, the digestive system includes several accessory organs that assist with the digestive process; these include the teeth, tongue, salivary glands, liver, gallbladder, and pancreas.

At a very general level, the purpose of the digestive system is to extract three things from what is ingested: water, molecular building blocks, and chemical energy. The last two are shown in CTM Figure 24.1. At a somewhat more detailed level, 10th Martini lists six functions of the digestive system: ingestion, mechanical processing, digestion, secretion, absorption, and excretion. These terms basically mean what you think they mean; note the distinction between food's physical breakdown (mechanical processing) and its chemical breakdown (digestion). Also note that absorption must generally be preceded by digestion because molecules that are too large to pass through cell membranes cannot be absorbed. We will say more about these six functions below.

CTM Figure 24.1: Why do we need food? The molecules obtained in food are broken into building blocks that are used to make cellular components. Chemical energy obtained from the breakdown of food can be used to power anabolic (biosynthetic) reactions and other energy-requiring processes. Figure taken from B. Alberts et al., Essential Cell Biology, 2nd edition (2004).

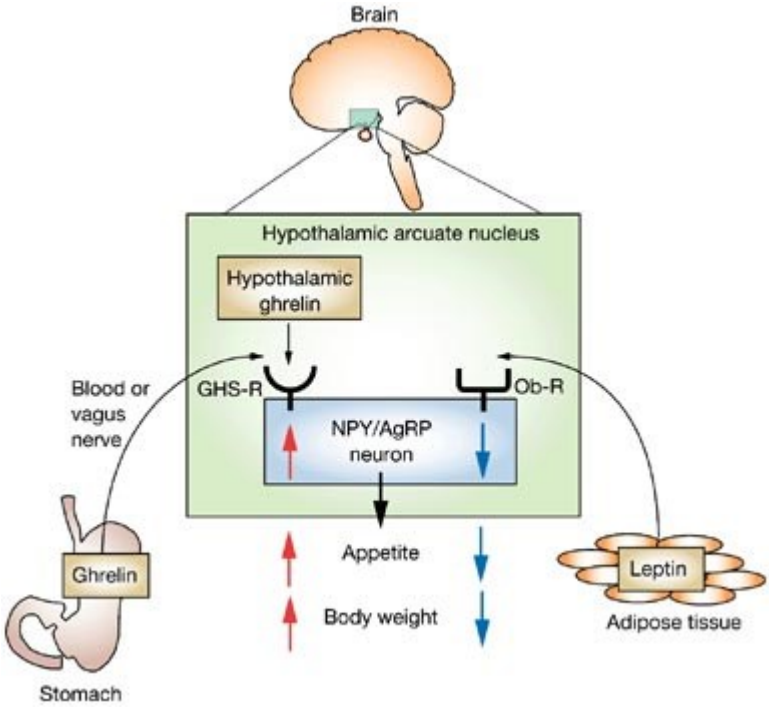


24.2: Ingestion and mechanical processing

Food must be obtained before it can be digested, of course. If access to food is adequate, what we eat when depends upon how hungry we feel, i.e., our appetite. Hunger is a fascinating intersection of physiology and psychology; for our purposes, we will simply note a couple of the major players, which are shown in CTM Figure 24.2. In this simplified scheme, our level of appetite reflects a balance between ghrelin (the "hunger hormone") and leptin (the "satiety hormone"). Ghrelin is released by cells lining the stomach when the stomach is empty. Conversely, leptin is produced by adipocytes (fat cells), so the more adipose tissue you have, the

more leptin you secrete. Ghrelin and leptin, along with other signals, provide information about how well-fed the body is to the arcuate nucleus of the hypothalamus, which you should continue to think of as "negative feedback central."

CTM Figure 24.2: What makes us hungry? Ghrelin and leptin have opposite effects on neuropeptide Y- and agouti-related protein-expressing neurons in the arcuate nucleus of the hypothalamus. Ghrelin stimulates these neurons, while leptin inhibits them. Figure from M. Kojima and K. Kangawa, Nature Clinical Practice Endocrinology & Metabolism *2: 80-88, 2006.*



Mechanical processing – the physical breakup of food into smaller pieces – begins in the mouth, thanks to the tongue and teeth. The teeth of carnivores (meat eaters) tend to be very pointy to facilitate capturing, subduing, and tearing into prey; the canines (cuspids) are often quite prominent and sharp. The teeth of herbivores often lack canines and bicuspids (premolars) and have flattened molars for grinding up plant matter. As humans are omnivores, our teeth are somewhere in between these two extremes; see 10th Martini Figure 24-8b (Teeth).

An additional evolutionary note about the oral cavity, or mouth, is that it is separated from the nasal cavity by a palate (which can be subdivided into an anterior hard palate and a posterior soft palate). While this may seem unremarkable, it allows mammals to breathe and chew at the same time, thus enabling them to chew their food thoroughly and get as much out of it as possible to support their high metabolic rates.

Mechanical processing continues beyond the mouth, mostly in the form of "churning" movements caused by contractions of smooth muscles in the walls of the digestive tract. These are distinct from the alternating contractions of circular and longitudinal muscles that push food through the digestive tract, which are called peristalsis. Other, less regular movements break up boluses of food into smaller chunks. The stomach is especially good at this because it has oblique muscles that contract at an angle to the circular and longitudinal muscles, as shown in 10th Martini Figure 24-12b (The Stomach).

24.3: Digestion

A wealth of information on the digestion of carbohydrates, lipids, and proteins is provided by 10th Martini Figure 24-27 (Chemical Events of Digestion). The figure covers most of the digestive tract, from the mouth to the intestines. The "big picture" is that digestion of carbohydrates, lipids, and proteins occurs in various locations, from the mouth to the small intestine, but that most absorption occurs in the small intestine. If we look at this figure a bit more closely, we notice that there are several parallels between the digestion of carbohydrates and the digestion of proteins. Both convert polymers (polysaccharides and proteins, respectively) to monomers (monosaccharides and amino acids, respectively) in multiple stages, with the final steps occurring at the brush border of the small intestine. Lipids are a bit different in that they do not begin as polymers, but mostly as triglycerides, which essentially are three-carbon glycerol molecules with a fatty acid tail attached to each carbon. Lipases are enzymes that cut the triglycerides into components that can more easily diffuse through cell membranes, as shown in CTM Figure 24.3.

There is also a parallel between lipid digestion and protein digestion. Lipids, being hydrophobic, tend to clump together and thus are in danger of passing through the digestive tract without being digested and absorbed. Bile salts break up these lipid clumps into smaller clumps, a process known as emulsification, thus exposing more of the lipids to the enzymes in the surrounding aqueous environment. Bile salts thus give lipases better access to their substrates. A somewhat similar role is played in protein digestion by the acidity of the stomach; this acid does not necessarily break bonds between amino acids, but DOES denature most proteins. Denatured proteins are more susceptible to proteases, which then chop up the proteins into peptide fragments.

24.4: Absorption

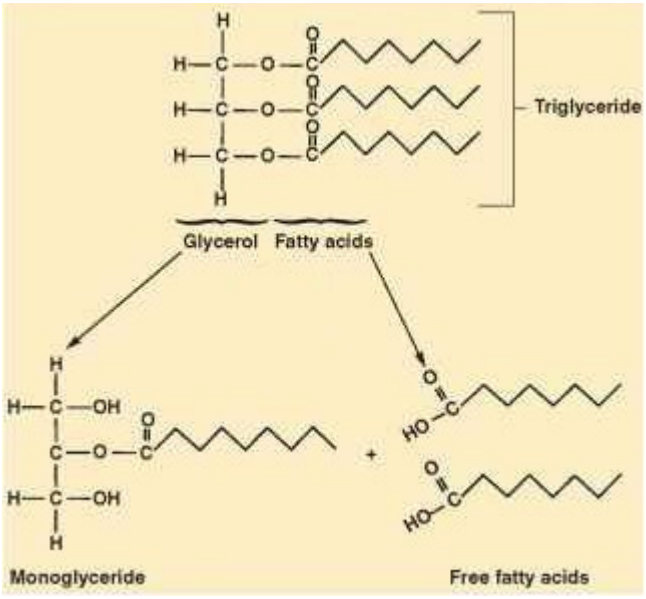
As discussed way back in Chapter 3, there are several ways to cross cell membranes:

- Simple diffusion: down a concentration gradient, with no need for protein carriers. Example: diffusion of small lipids through membranes.
- Facilitated diffusion: down a concentration gradient via a protein carrier. Example: glucose transporters shown in 10th Martini Figure 3-18.
- Channel-mediated diffusion. Distinct from facilitated diffusion in that the membrane proteins don't actually bind to the molecules that diffuse. Examples: movements of ions and water molecules through their channels.
- Active transport: against a concentration gradient, using ATP. Example: the Na^+/K^+ pump.

Active transport can be subdivided into primary active transport, which directly uses ATP in the movement of the substance across the membrane, and secondary active transport (also called cotransport) in which a protein transports two molecular species: one down its gradient and another against its gradient. For example, intestinal epithelial cells have transporters that simultaneously bring an amino acid and a sodium ion into the cells. Since ATP was used in

establishing the sodium gradient, this type of transport uses ATP indirectly and is called secondary active transport.

CTM Figure 24.3: Lipases cut triglycerides into monoglycerides and free fatty acids. Figure from 78stepshealth.us; original source unknown.



CTM Table 24.1 summarizes how different types of molecules are absorbed from the digestive tract into the blood and lymph. This combines information on carbohydrates, lipids, and proteins from 10th Martini Figure 24-27 with additional information on water and vitamins. The take-home message of this table is that lipids and fat-soluble vitamins are processed in a different way than other nutrients; they are packaged into lipoprotein carriers called chylomicrons, which pass through the lymphatic vessels before entering the circulatory system at the subclavian veins (recall 10th Martini Figure 22-4).

In general, the vast majority of nutrient absorption occurs in the small intestine, which has a very large surface area for absorption thanks to the villi (invaginations of the intestinal wall) and microvilli. For example, according to 10th Martini Figure 24-28 (Digestive Secretion and Water Reabsorption), about 85% of water reabsorption occurs in the small intestine, with the remaining 15% occurring in the large intestine. Three interesting exceptions to this general trend are three vitamins synthesized by the bacteria living in our large intestine (which therefore must also do most of the absorption of these vitamins): vitamin K, used in blood clotting reactions; vitamin B_7 (biotin), used in glucose metabolism; and vitamin B_5 (pantothenic acid), used in the synthesis of steroids and neurotransmitters.

24.5: Accessory organs

As noted above, accessory organs of the digestive system include the teeth, tongue, salivary glands, liver, gallbladder, and pancreas. We will now say a bit more about the last three of these.

CTM Table 24.1: A Summary of Nutrient Absorption

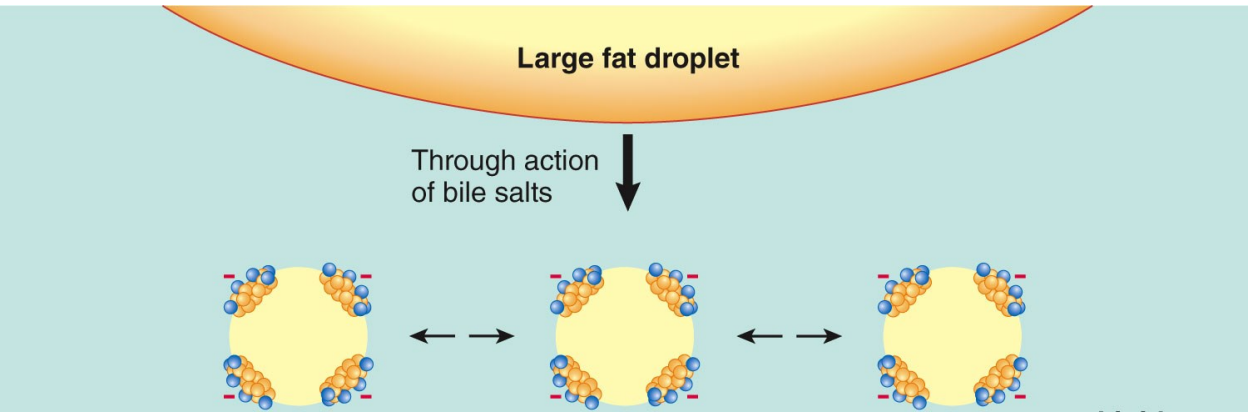
Molecule	Mechanism	Route to blood
Carbohydrates	Cotransport and facilitated diffusion into intestinal epithelial cells; facilitated diffusion into capillaries	Intestine => blood
Lipids	Simple diffusion into intestinal epithelial cells; then packaged into chylomicrons and released into lymphatic ducts via exocytosis.	Intestine => lymph => blood
Proteins	Cotransport and facilitated diffusion into intestinal epithelial cells and capillaries	Intestine => blood
Water	Osmosis, through aquaporin channels	Intestine => blood
Ions	Varied (details are given in 10th Martini Table 24-2)	Intestine => blood
Water-soluble vitamins (B series, C)	Channel-mediated diffusion	Intestine => blood
Fat-soluble vitamins (A, D, E, K)	Simple diffusion into intestinal epithelial cells; then packaged into chylomicrons and released into lymphatic ducts via exocytosis.	Intestine => lymph => blood

The pancreas is an interesting organ in that it affects digestion and absorption of nutrients through both endocrine and exocrine processes. 10th Martini Figure 24-18 (The Pancreas) shows the intermingling of the pancreas's endocrine and exocrine cells. The endocrine functions of the pancreatic hormones insulin and glucagon were discussed in Chapter 18. Here we note that a majority of the digestive enzymes listed in 10th Martini Figure 24-27 are produced by the pancreas and released into the duodenum (exocrine function) via the pancreatic duct. Note that many of the proteases (protein-digesting enzymes) are released as inactive "proenzymes" that must be activated by another protease (or, in the case of pepsin, hydrochloric acid). This activation process ensures that the proteases don't destroy proteins within the cells of the pancreas. The pancreas also secretes large amounts of bicarbonate, a base that neutralizes stomach acid as the contents of the stomach move into the small intestine. Pancreatic secretions are controlled by the duodenal hormones cholecystokinin (CCK) and secretin and by the vagus nerve.

The liver has two functions of great interest to us: it (1) produces bile and (2) detoxifies a wide range of foreign chemicals.

Bile is a mixture of water, ions, the heme breakdown product bilirubin, and bile salts (also called bile acids; the difference in the two terms is not critical). Bile salts are soap-like lipids with structures that are partly hydrophilic and partly hydrophobic. Although fat never truly "dissolves" in water to any great extent, the bile salts surround small bits of the fat, thus suspending them in the surrounding watery mixture. This dispersal of the fat into smaller bits makes it much more accessible to the lipases that digest it (see CTM Figure 24.4 below).

How does bile get from the liver to the duodenum? It is stored in the gallbladder, then is delivered to the duodenum via the bile duct. Bile secretions, like pancreatic secretions, are governed by the duodenal hormones CCK and secretin.



CTM Figure 24.4: Emulsion of lipids by bile salts. Figure taken from L. Sherwood et al., Animal Physiology: From Genes to Organisms*, 2nd edition (2013).*

Due to its unique position in the circulatory system, the liver is well-positioned to protect the rest of the body from potentially toxic chemicals that have been ingested. As shown in 10th Martini Figure 21-31 (The Hepatic Portal System), veins from the various digestive organs merge into the hepatic portal vein. By this route, blood containing newly absorbed nutrients and toxins goes to the liver before rejoining the general circulation. In the liver, enzymes such as the P450 cytochromes convert many potentially toxic substances into less harmful substances. For example, ethanol is converted in the liver to acetaldehyde and then acetic acid, the relatively safe "active ingredient" of vinegar. While the liver is quite good at detoxification, it is possible to overwhelm it with toxins, such as when years of alcoholism lead to cirrhosis of the liver.

24.7: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 24: review questions #1, 5, 7, 10, 11, 13, 18, 26, 31, 32. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 25: Metabolism and Energetics

Chapter 24 covered digestion. Now, in Chapter 25, we consider the question, "what do cells do with all of those newly ingested nutrients?"

25.0: Outline

25.1: Overview of metabolism
- Metabolism is the sum of all chemical reactions in the body.
- Chemical reactions can be grouped into metabolic pathways, which can be catabolic (breaking complex molecules into simpler ones) or anabolic (building simple molecules into more complex ones).

25.2: Carbohydrate and lipid metabolism
- Monosaccharides like glucose travel through the blood as dissolved solutes, whereas lipids travel in the form of lipoprotein complexes.
- Glucose and fatty acids are chopped into two-carbon units (carried as acetyl CoA) by the processes of glycolysis and β-oxidation, respectively. Acetyl CoA proceeds through the citric acid cycle, which generates NADH that is used to produce ATP via the electron transport chain and oxidative phosphorylation. Oxidative phosphorylation requires oxygen.

25.3: Protein metabolism
- Amino acids can get rid of their amino ($-NH_2$) groups via deamination or transamination.
- Ammonium ions (NH_4^+) produced by deamination are made into urea and excreted.

25.4: An integrated view of metabolism
- Neural tissues depend almost exclusively on chemical energy obtained from glucose in the blood.
- In the post-absorptive state, the liver maintains blood glucose levels via gluconeogenesis and by releasing glucose from its glycogen reserves. Other tissues preferentially use lipids so that glucose can be saved for neural tissues.

25.5: Basic nutrition
- Our bodies cannot synthesize eight of the 20 amino acids we need. These essential amino acids must be obtained from the diet.
- Cholesterol is carried through the blood by lipoproteins. High-density lipoproteins (HDLs) are "good cholesterol," whereas low-density lipoproteins (LDLs) are "bad cholesterol."
- Minerals are small ions such as Na^+, K^+, Ca^{2+}, etc.
- Vitamins are small organic molecules that serve as coenzymes in chemical reactions. Some vitamins (B series, C) are water-soluble while others (A, D, E, K) are fat-soluble.

25.6: Recommended review questions

25.1: Overview of metabolism

The title of this chapter is "Metabolism and Energetics." These two terms are interrelated. **Metabolism** refers collectively to all of the chemical reactions in the body – that is, all of the activities of all of the enzymes put together. **Energetics** refers to all of the ways in which energy is converted, stored, and used by cells. Much of this energy flow involves chemical reactions, all of which involve chemical energy in some way.

At the most basic level, we can think of metabolism as being subdivided into metabolic pathways with defined functions – or, from another perspective, individual chemical reactions can be grouped into metabolic pathways. A familiar example of a metabolic pathway is glycolysis, which breaks one molecule of glucose (a six-carbon molecule: $C_6H_{12}O_6$) into two molecules of pyruvate (a three-carbon molecule). Glycolysis is, more specifically, an example of a **catabolic**

pathway, which breaks complex molecules into simpler pieces, releasing chemical energy which is often recaptured in the form of molecules like ATP and NADH. The opposite of a catabolic pathway is an **anabolic pathway**, in which complex molecules are built from simpler ones, generally requiring the input of ATP and NADPH. You may remember the terms catabolism and anabolism from Chapter 2.

10th Martini Figure 25-1 (An Introduction to Cellular Metabolism) summarizes the above information (and more). Perhaps the two most important points made by the figure are these. First, most actual ATP production occurs in the mitochondria, starting with molecules generated outside the mitochondria. Second, the ATP produced there is used partly to power anabolic pathways (see above) but partly to power many other energy-requiring cellular processes (movement, contraction, intracellular transport, cytokinesis, endocytosis, and exocytosis).

25.2: Carbohydrate and lipid metabolism

Carbohydrate metabolism is a topic that is traditionally explored in great detail in introductory biology and biochemistry classes. We will not dwell on it (or lipid or protein metabolism) in such detail here, but will try to extract a few "take-home" points from the mazes of reactions that are typically shown.

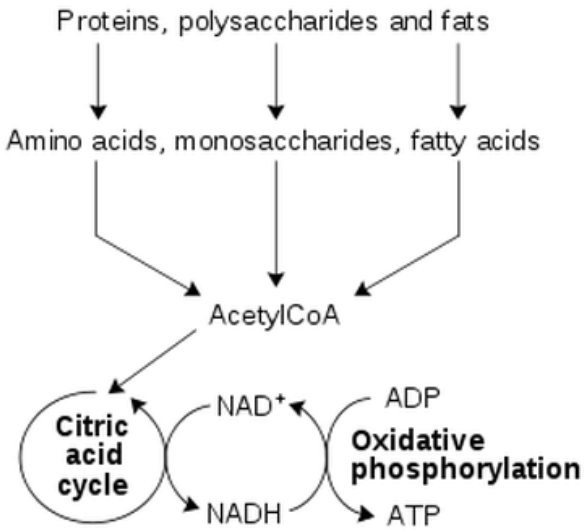
Our first point is that carbohydrates and lipids travel through the blood rather differently, as noted in Chapter 24. Monosaccharides like glucose travel as dissolved solutes; they cannot diffuse through cell membranes unassisted, but can enter cells (for storage or breakdown) via facilitated diffusion or cotransport. Lipids, after initially diffusing into intestinal epithelial cells, get packaged into lipid-protein hybrids called chylomicrons, which pass through the lymphatic system and eventually are dumped into the blood. The enzyme lipoprotein lipase, situated in the capillary endothelium, releases free fatty acids and monoglycerides from the chylomicrons, which can then diffuse into target/systemic cells (for storage or breakdown).

Our next point is that, although carbohydrate metabolism and lipid metabolism are typically presented separately, the intracellular breakdown (catabolism) of monosaccharides has a lot in common with the intracellular breakdown of free fatty acids. For starters, both breakdown processes can be considered to have the ultimate purpose of generating ATP. Now, how is that ATP made? CTM Figure 25.1 conveys the basic idea. The pathway of glycolysis (plus one additional step) chops up monosaccharides like glucose (a 6-carbon molecule) into 2-carbon acetyl groups, which are carried by Coenzyme A (CoA for short). Fatty acids, usually between 18 and 24 carbon atoms in length, are chopped up by the analogous process of beta-oxidation, again generating 2-carbon units in the form of acetyl CoA.

Both glycolysis and beta-oxidation take place in the cytoplasm, but the acetyl CoA molecules they generate then enter the mitochondria, where they join the citric acid cycle, also called the tricarboxylic acid (TCA) cycle and Krebs cycle. This cycle's products include CO_2 (which gets whisked away by the blood and exhaled at the lungs) and NADH and $FADH_2$, high-energy compounds which donate their electron pairs to the electron transport chain. The electron transport chain causes protons to be pumped out of the interior of the mitochondria, against their

gradient, and their diffusion back down their gradient is used to power an enzyme that joins ADP with inorganic phosphate (P_i) to form ATP. Note that all of the steps from acetyl CoA onward are the same for carbohydrates and lipids!

CTM Figure 25.1: Catabolism, simplified. Note that acetyl CoA can be generated from proteins, carbohydrates, and fats, and that this acetyl CoA will general ATP via the same processes, regardless of its original source. Image from Tim Vickers via Wikipedia.



More details of the metabolic pathways summarized in CTM Figure 25.1 are shown in several 10th Martini figures: 25-3 (Glycolysis), 25-4 (The Citric Acid Cycle), 25-5 (Oxidative Phosphorylation), and 25-8 (Beta-Oxidation). If you study those figures carefully (which I don't recommend), you will notice that CTM Figure 25.1 omits complications such as the fact that NADH is not only generated during the citric acid cycle, but also during glycolysis and beta-oxidation. Let us zoom out to a couple of broader points. Though not explicitly shown in CTM Figure 25.1, oxygen (O_2) is used by the mitochondria in the process of oxidative phosphorylation, and thus is needed for mitochondrial ATP production (whether starting from carbohydrates or fats or a combination). So that is why O_2 delivery by the cardiovascular system is so important: the O_2 is used by the mitochondria to make ATP.

A favorite exercise of biochemists is to calculate exactly how much ATP is generated from a single glucose or fatty acid molecule. 10th Martini presents the standard numbers of 36 ATP per glucose and 144 ATP per 18-carbon fatty acid, meaning that, pound for pound (or carbon for carbon), fats give us more ATP than carbohydrates. The difference is actually much greater than implied by this calculation because glycogen (the body's main storage form of carbohydrate) is stored with a lot of associated water, whereas fat is not – so it is <u>much</u> more efficient space-wise and weight-wise to store energy as fat than as carbohydrate-plus-water. For that reason, our bodies have very limited supplies of glycogen (mostly in our liver and skeletal muscles) but comparatively vast stores of fat, even among slender people.

25.3: Protein metabolism

As shown in CTM Figure 25.1, ATP can be generated from amino acids as well as from monosaccharides and fatty acids. For this to happen, the amino acids must get rid of their amino ($-NH_2$) group, either via **deamination** (clipping off the $-NH_2$ group) or **transamination**

(transferring the $-NH_2$ group to a different molecule: a keto acid that, upon gaining an $-NH_2$ group, becomes an amino acid). These reactions are shown in 10th Martini Figure 25-10 (Amino Acid Catabolism and Synthesis). When amino groups are removed in deamination reactions, they are released as free ammonium (NH_4^+), a toxic ion that is converted into urea, a more benign compound, via a series of reactions called the urea cycle. Urea excretion is the main route by which excess nitrogen is removed from the body.

A final point about amino acid metabolism is that some amino acids can be used to create new glucose molecules in a pathway called gluconeogenesis. This pathway, which is kind of the opposite of glycolysis, happens mostly in the liver. Amino acids are distinct from lipids, which can NOT be used to create glucose.

25.4: An integrated view of metabolism

Despite discussing carbohydrate, lipid, and protein metabolism separately, we should bear in mind that the body's uses of these different nutrients are interrelated. Perhaps this is clearest in the example of maintaining blood glucose levels within an appropriate range.

Lipids and carbohydrates, rather than proteins, are the body's main sources of chemical energy, and most tissues of the body can use either lipids or carbohydrates with no problems. However, neural tissue does not metabolize fat well, nor does it store carbohydrates as glycogen, so it is almost completely dependent on glucose obtained from the blood. Thus, a lot of your body's metabolism is controlled to ensure adequate energy for the neurons in your brain (and elsewhere). Many details are provided in 10th Martini Figure 25-11 (Absorptive and Postabsorptive States). Two important definitions are provided in this figure:

- "The **absorptive state** is the time following a meal, when nutrient absorption is underway."
- "The **postabsorptive state** is the time when nutrients are not being absorbed and your body must rely on internal energy reserves to meet its energy demands."

In the absorptive state, the overall goal is to pack nutrients away for later use. Thus, for example, glucose is taken up by the liver and stored as glycogen, and fatty acids are taken up by adipocytes and stored as triglycerides. These uptake and storage processes are stimulated by insulin, with some help from other hormones (growth hormone, androgens, estrogens).

In the postabsorptive state, a major goal is to keep blood glucose levels in the normal range even though glucose is continually being removed and used by neurons. This goal is achieved through several mechanisms. (1) Most tissues (other than neural tissue) shift to getting most of their energy from fat, thus saving most glucose for the neurons. (2) The liver breaks down its glycogen into glucose, which it releases into the blood. (3) The liver also uses gluconeogenesis to synthesize three-carbon precursors (such as those produced from amino acids) into new glucose molecules, which also get released into the blood. The hormones glucagon, epinephrine, glucocorticoids, and growth hormone all contribute to these processes.

25.5: Basic nutrition

While this is not a book about nutrition, Chapter 25 does include interesting practical information on diet and health. A few highlights are as follows.

Protein can be obtained from many sources in the diet, but not all protein is created equal. Some sources (such as meat, fish, eggs, and dairy products) contain protein with good levels of all 20 amino acids, including the eight *essential amino acids* that our bodies cannot synthesize. Vegetarians and vegans who wish to maintain optimal health strive to eat multiple proteins that collectively provide plenty of all essential amino acids. A classic example of this is eating rice and beans (not necessarily at the same time). Rice is low in the amino acid lysine but higher in the amino acid methionine, whereas beans are low in methionine but higher in lysine, so the two complement each other.

Cholesterol is a lipid in terms of its chemical structure, but is not used for energy the way triglycerides are; instead it is a structural component of cell membranes, an ingredient in bile, and a precursor of various steroid hormones. Cholesterol is a focus of much medical attention these days because it can lead to clogged arteries and associated problems such as strokes and heart attacks, as described in 10th Martini's Clinical Note on page 728. Cholesterol is carried through the blood by lipoproteins such as high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and very low-density lipoproteins (VLDLs). It turns out that high LDL levels tend to promote fatty deposits in the arteries, whereas high HDL levels tend to keep the arteries clean; hence frequent references to LDLs as "bad cholesterol" and HDLs as "good cholesterol."

As you know, carbohydrates, lipids, and proteins aren't the only important nutrients we get in our diet; there are also vitamins and minerals, for example. What's the difference? Carbohydrates, lipids, and proteins are macromolecules (large molecules) that are the body's main sources of chemical energy; vitamins and minerals are consumed in much smaller quantities and do not themselves provide significant chemical energy. Minerals are small ions; the most important of these are sodium, potassium, chloride, calcium, phosphorus, magnesium, iron, and zinc. Vitamins are small organic molecules that serve as coenzymes, i.e., they are not themselves enzymes but help enzymes perform chemical reactions.

You may be aware that some vitamins (the vitamin B series and vitamin C) are water-soluble, while others (vitamins A, D, E, and K) are fat-soluble. The body does not store water-soluble vitamins to any great extent, so a steady supply of these is important for optimal health. Fat-soluble vitamins, in contrast, get stockpiled in adipose tissue, which helps prevent the body from running out of these vitamins, but can also lead to toxic accumulations from "mega-dosing." More is not always better!

25.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 25: review questions #1, 3, 4, 6, 7, 13, 15, 16, 17. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 26: The Urinary System

Chapter 24, on the digestive system, included the excretion of feces. Here we continue our excretion extravaganza with a detailed look at how urine is produced. The most relevant material from previous chapters is probably the concept of filtration – a balance of hydrostatic and osmotic pressures – which we discussed in Chapter 21. Chapter 24 also points out kidney-specific targets of the hormones aldosterone, antidiuretic hormone (ADH), calcitonin, and parathyroid hormone (PTH), which we have mentioned in Chapters 6, 18, and 24.

26.0: Outline

26.1: Overview: structures and processes
- Urine is formed in the kidneys and then passes through the ureters, urinary bladder, and urethra.
- The main job of the kidneys is to sort through all of the small molecules in the blood, retaining what is valuable (e.g., glucose) and getting rid of what is useless or potentially dangerous (e.g., urea).
- This sorting of molecules is accomplished via the processes of filtration, secretion, and reabsorption.
- The functional unit of the kidney is the nephron, which consists of a capsule adjacent to a glomerulus, proximal convoluted tubule (PCT), loop of Henle, distal convoluted tubule (DCT), and collecting duct.

26.2: Glomerular filtration
- Glomerular filtration is the first step of urine production.
- Glomerular Filtration Rate (GFR) depends on hydrostatic pressure (which drives fluid out of the capillaries) and osmotic pressure (which drives fluid into the capillaries).
- GFR is tightly controlled via autoregulation and endocrine and neural regulation. Autoregulation adjusts the degree of dilation of the afferent and efferent arterioles, which enter and exit the glomeruli, respectively.

26.3: Journey through a nephron
- At the proximal convoluted tubule (PCT) the bloodstream reabsorbs water and many valuable nutrients such as glucose and amino acids, and also secretes many drugs and toxins.
- At the loop of Henle, the bloodstream reabsorbs water (descending limb) and salt (ascending limb) and maintains an osmolarity gradient in the interstitium surrounding the nephron.
- In the distal convoluted tubule (DCT), reabsorption of calcium and sodium is regulated by the hormones calcitonin/PTH and aldosterone, respectively.
- In the collecting duct, reabsorption of water depends on aquaporin channels, which are regulated by antidiuretic hormone (ADH). Concentrated urine is produced only when high ADH levels ensure that aquaporins are present in the epithelial cell membrane.

26.4: Recommended review questions

26.1: Overview: structures and processes

At a macroscopic level, the structures of the urinary system are shown in 10th Martini Figure 26-1 (An Introduction to the Urinary System). In order of urine's formation and path out of the body, these are the kidney, ureter, urinary bladder, and urethra. At a more microscopic level, each kidney contains about a million nephrons, the nephron being the functional unit of the kidney. The structure of a typical nephron is shown in 10th Martini Figure 26-9 (An Overview of Urine Formation).

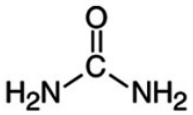
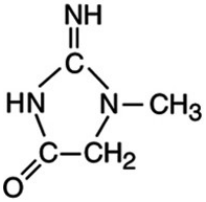
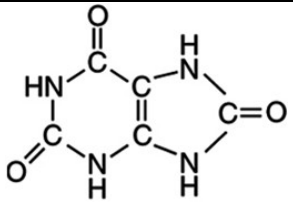
Fluid from the glomerulus – a ball of capillaries – passes into the glomerular capsule, then continues through the proximal convoluted tubule (PCT), loop of Henle, distal convoluted tubule (DCT), and collecting duct. Intermediate between the views of Figure 26-1 and 26-9 is the one offered by 10th Martini Figure 26-4 (The Structure of the Kidney). Here we see that the collecting ducts of the many nephrons empty into calyces (singular: calyx), and the calyces merge to form a renal pelvis that dumps urine into the ureter.

The plumbing itself – lots of windy little pipes feeding into bigger pipes – does not necessarily convey much about the functions of the urinary system. 10th Martini lists many functions of this system, including the following:

- Removal of wastes generated by the body's cells. (The three main waste products disposed of by the kidney are urea, creatinine, and uric acid, shown in CTM Table 26.1.)
- Regulating blood volume.
- Regulating plasma concentrations of sodium, potassium, chloride, and other ions.
- Helping to stabilize blood pH.
- Conserving valuable nutrients.

All of these functions can arguably be collapsed into the statement that the urinary system simply retains substances that are needed while letting go of substances that are not needed. (A couple of additional kidney functions – regulating blood pressure and assisting the liver with detoxification – do not fit neatly into that summary statement.)

CTM Table 26.1: Prominent waste products excreted via the urinary system. Note that nitrogen is a major component of each compound. Nitrogen is absolutely necessary for life (as a component of all amino acids and nucleic acids, for example), but can also be toxic in many forms.

Name	Urea	Creatinine	Uric acid
Chemical structure			
Molecular weight	60	113	168
Number of N atoms	2	3	4
Excretion rate	~20 grams per day	~2 grams per day	~0.5 grams per day

This selective retention of substances is accomplished via three fundamental processes: filtration, secretion, and reabsorption. In Chapter 21, we defined filtration as the bulk movement of fluid and relatively small solutes (anything smaller than a protein, basically) from the capillaries into the interstitium, and reabsorption as the movement of fluid and solutes from the interstitium into the capillaries. Here we will use these terms to refer specifically to movement between the capillaries and the lumen (interior) of the nephron tubule. While filtration is dictated simply by the hydrostatic and osmotic pressures of the two compartments and the size of the openings connecting them, reabsorption can occur either via simple diffusion or via carrier proteins in the

cell membrane that transport specific substances. Secretion is like carrier-mediated reabsorption, but in the opposite direction: from the blood into the tubule.

A summary of filtration, secretion, and reabsorption is provided in CTM Table 26.2. The distinction between simple diffusion and protein carriers is important because diffusion can never "max out," but carrier-mediated transport can. That is, the density of protein carriers in the cell membrane limits the rate at which a substance can be transported by its carriers. The maximum rate of transport for a given substance is called the transport maximum or tubular maximum, abbreviated T_m.

CTM Table 26.2: Three general processes in the kidneys contribute to urine formation.

Process	Direction	Transport mechanism
Filtration	Capillaries to tubule	Simple diffusion
Secretion	Capillaries to tubule	Protein carriers
Reabsorption	Tubule to capillaries	Simple diffusion + protein carriers

These three processes may be easiest to understand in the context of the journey along the nephron. Filtration happens only between the glomerular capillaries and the glomerular capsule (Bowman's capsule). What enters the Bowman's capsule can be thought of as "pre-urine" or "pre-pee." It resembles blood, minus the blood cells and plasma proteins (which are too large to get into the capsule). But as this fluid flows through the rest of the nephron, secretion and reabsorption greatly alter the composition of the pre-urine so that it ultimately becomes quite different from blood.

For any substance, the following equation applies: filtration rate plus secretion rate minus reabsorption rate equals excretion rate. Some of these rates are 0 for some substances. For example, glucose is filtered into the nephron tubule, but all of this glucose is normally reabsorbed; no glucose is secreted, so the rate of glucose excretion is 0.

26.2: Glomerular filtration

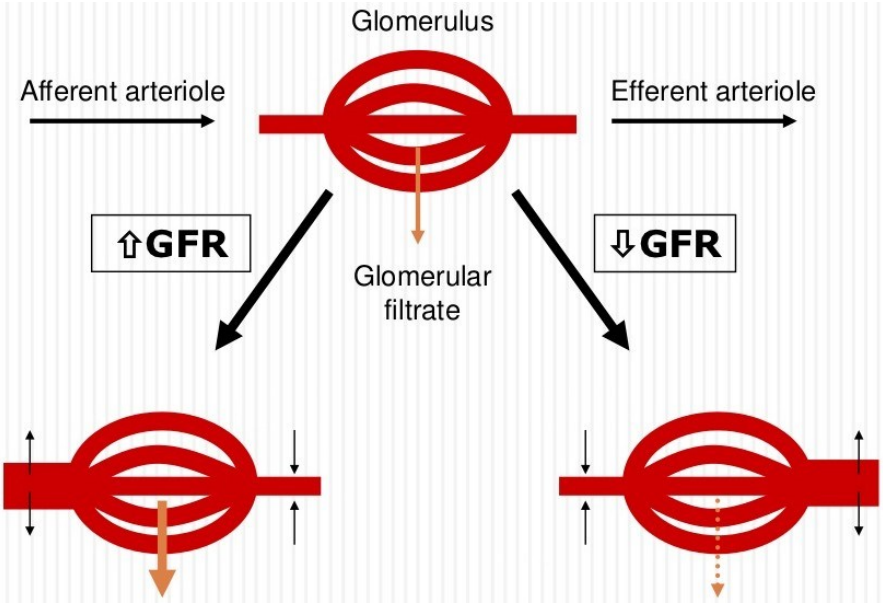
As mentioned above, filtration from the glomerulus into the glomerular capsule (Bowman's capsule) is the first step in the formation of urine. (Taken together, the glomerulus and its capsule are sometimes called the renal corpuscle.)

To leave the glomerular capillaries, fluid and solutes must pass through three layers: the endothelial cells lining the capillaries, the podocytes ("foot cells") surrounding them, and the dense layer of basement membrane in between. Together, these three layers are known as the filtration membrane. Passage into the glomerular capsule is limited mostly by the filtration slits between the "feet" of the podocytes, which proteins generally cannot get through. This is portrayed in 10th Martini Figures 26-8 (The Renal Corpuscle) and 26-10 (Glomerular Filtration).

As discussed before, the extent to which fluid leaves the capillaries depends on hydrostatic and osmotic pressures. Blood flowing through the capillaries still has some of the hydrostatic pressure that it started with upon exiting the heart, so that tends to drive fluid out. On the other hand, since plasma proteins cannot usually leave the capillaries, the osmolarity (combined

concentration of all solutes) is higher inside the capillaries than outside of them, so the osmotic pressure favors movement of fluid *into* the capillaries. This balance of forces is shown in 10th Martini Figure 26-10b (Glomerular Filtration). According to the numbers in this figure, the hydrostatic pressure is so much higher in the glomerulus than the capsule (50 vs. 15 mm Hg) that even with an osmotic pressure of 25 mm Hg attracting fluid into the capillaries, the net movement of fluid is still out of the capillaries.

The net amount of fluid filtered out of the blood per minute is known as the Glomerular Filtration Rate, or GFR. It turns out that GFR is tightly regulated, which ensures a very steady removal of wastes and toxins from the blood. Three types of regulation keep GFR steady: autoregulation of local blood flow, and endocrine and neural regulation. The basic idea of autoregulation is straightforward. If GFR becomes too low, the afferent arterioles leading into the glomerulus get more dilated and the efferent arterioles leading away from it get more constricted, so that more fluid is drawn into the glomerular capillaries and then takes the lower-resistance exit (out of the capillaries rather than through the efferent arterioles). If GFR becomes too high, the opposite changes occur. A visualization of this is given in CTM Figure 26.1.



CTM Figure 26.1: Autoregulation of GFR. Figure taken from slideshare.net/MohammedGawad/renal-physiology-ii-glomerular-structure-filtration.

Endocrine and neural regulation of GFR is more complicated, as can be seen in 10th Martini Figure 26-11 (The Response to a Reduction in the GFR). The main points are that the sympathetic nervous system and the hormones angiotensin II, aldosterone, and antidiuretic hormone increase systemic blood pressure and GFR by increasing blood volume and/or constricting the efferent arterioles. Angiotensin II and aldosterone result from the so-called renin-angiotensin-aldosterone system (RAAS). Renin is an enzyme released by the juxtaglomerular ("near the glomerulus") cells; it converts angiotensinogen, a plasma protein made by the liver, into angiotensin I. Angiotensin Converting Enzyme (ACE) in the pulmonary capillaries then converts angiotensin I into angiotensin II, and angiotensin II acts as a hormone to

stimulate the secretion of aldosterone (by the adrenal cortex) and antidiuretic hormone (by the posterior pituitary).

26. 3: Journey through a nephron

What happens to the contents of the glomerular capsule after filtration? These contents pass through the rest of the nephron – the proximal convoluted tubule (PCT), loop of Henle, distal convoluted tubule (DCT), and collecting duct – before being collected in the ureter and being sent out of the body. The refinement of this "pre-urine" by reabsorption and secretion in the rest of the nephron is summarized by 10th Martini Figure 26-9 (An Overview of Urine Formation). Water is reabsorbed into the blood at the PCT, the descending limb of the loop of Henle, and sometimes the collecting duct (see below). Solutes are reabsorbed at the PCT, ascending limb of the loop of Henle, and sometimes the DCT. Most secretion occurs at the PCT. Thus, the PCT is an especially busy exchange point.

Some of the many transport processes conducted by the PCT are shown in 10th Martini Figure 21-12b (Transport Activities at the PCT). The familiar sodium/potassium pump is present in the basolateral (lower, facing the capillaries) membrane of the tubular epithelial cells, though ATP use is not explicitly shown. The low $[Na^+]$ inside these cells, and thus the Na^+ concentration gradient from outside to inside, is used to pull glucose and amino acids into the cells via cotransport with Na^+. Meanwhile, acidic H^+ ions are secreted into the tubule lumen while bicarbonate (HCO_3^-) is reabsorbed, thus affecting the pH. Water osmotically follows the overall movement of solutes out of the tubule, and is thus reabsorbed into the blood.

The PCT is the nephron's main site for reabsorbing valuable nutrients such as glucose and amino acids. The above-mentioned concept of the transport maximum (T_m) is highly relevant here. There are only so many glucose carriers in the PCT, so only so much glucose can be reabsorbed. In cases of uncontrolled diabetes mellitus, more glucose is dumped into the tubule than can be reabsorbed, so some of the glucose stays in the pre-urine and it ultimately excreted in the purine. In other words, all filtered glucose is normally reabsorbed so that none is excreted, but when the rate of glucose reabsorption is less than the rate of glucose filtration, the difference is excreted.

After the PCT, the pre-urine enters the loop of Henle. The loop can be divided into descending and ascending limbs, and each limb can be subdivided into thick and thin segments. These different segments have different properties, but for our purposes we will simply note that most of the descending limb is permeable to water but impermeable to solutes, and that the opposite is true of most of the ascending limb. NaCl is removed from the ascending limb via cotransport (secondary active transport), as shown in 10th Martini Figure 26-13a (Countercurrent Multiplication and Urine Concentration), while water diffuses out of the descending limb via aquaporin channels in the cell membranes.

All of this transport in the loop of Henle has two major consequences:

- Much additional water and salt is recaptured from the pre-urine so that it is not lost in the urine.

- There is an osmolarity gradient between the "bottom" and the "top" of the interstitial fluid adjacent to the loop (in the medulla and cortex of the kidney, respectively). This osmolarity gradient is critical to the function of the collecting duct, as we will see below.

The distal convoluted tubule (DCT) performs some additional reabsorption and secretion. For example, the DCT is the site where calcium reabsorption is adjusted by the hormones calcitonin and parathyroid hormone (PTH). The DCT is also where aldosterone exerts its sodium-saving effects. As shown in 10th Martini Figure 26-14b (Tubular Secretion and Solute Reabsorption by the DCT), aldosterone stimulates the movement of Na^+ out of the tubule while dumping K^+ into it. Thus, Na^+ retention is associated with K^+ loss. Excessive K^+ removal may lead to hypokalemia (low potassium levels in the blood).

The final section of the nephron is the collecting duct. The collecting duct passes from the low-osmolarity cortex of the kidney into the high-osmolarity medulla. As always, water is driven to move into area of higher osmolarity, so as the pre-urine flows through regions of greater and greater osmolarity in the interstitium, more and more water is reabsorbed – but only if aquaporins are present in the membranes of the cells lining the collecting duct. The synthesis of these aquaporins and their insertion into the membrane is regulated by antidiuretic hormone (ADH), also known as vasopressin. For example, if blood pressure is low and we need to bring it back up, the posterior pituitary will secrete lots of ADH, lots of additional water will be reabsorbed, and relatively little water will be lost in the urine, which will have high solute concentrations and will be relatively dark in color. Alternatively, if we drink lots of water when it is not needed, ADH levels will be low, water will NOT be reabsorbed at the collecting duct, and abundant pale urine will be excreted. The contrasting situations in the absence and presence of ADH are shown in panels A and B of 10th Martini Figure 26-15 (The Effects of ADH on the DCT and Collecting Duct).

26.4: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 26: review questions #2, 3, 10, 16, 18, 19, 21, 26, 27, 30; clinical case wrap-up question #2. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 27: Fluid, Electrolyte, and Acid-Base Balance

As 10th Martini goes, Chapter 27 is an unusual chapter in its extent of reviewing material from earlier chapters – particularly Chapters 21 (Blood Vessels and Circulation), 23 (The Respiratory System), and 26 (The Urinary System). This is a good thing!

27.0: Outline

27.1: Key principles and hormones
- Fluid levels, electrolyte concentrations, and pH are all kept within certain ranges.
- Homeostatic mechanisms that monitor and adjust the composition of body fluids respond to changes in the extracellular fluid (ECF), not the intracellular fluid (ICF).
- Low ECF pressure and volume cause the release of antidiuretic hormone and aldosterone, while high ECF pressure and volume cause the release of the natriuretic peptides ANP and BNP.

27.2: Fluid balance
- Changes in the ECF are partly compensated by "fluid shifts" between the ICF and ECF.
- Changes in ECF volume and osmolarity are sensed by baroreceptors and osmoreceptors and lead to the appropriate hormonal responses.

27.3: Electrolyte balance
- Electrolytes are small inorganic ions such as Na^+, K^+, Ca^{2+}, Mg^{2+}, PO_4^{3-}, and Cl^-.
- Electrolyte imbalances usually have dietary or hormonal causes.

27.4: pH balance
- Buffers reduce the magnitude of changes in pH.
- In respiratory compensation, the rate of CO_2 excretion at the lungs is adjusted to bring ECF back toward normal.
- In renal compensation, the rates of H^+ and HCO_3^- secretion and reabsorption in the kidneys are adjusted to bring ECF pH back toward normal.

27.5: Recommended review questions

27.1: Key principles and hormones

Let's begin by reminding ourselves of the central physiological concept of homeostasis. As you know, homeostasis means "maintaining a similar state" and is generally achieved with negative feedback control. This chapter focuses on homeostasis with respect to three key variables: fluid levels, electrolyte concentrations, and pH. You already know what these variables are; now it's time to see how they are kept within acceptable ranges.

To understand the regulation of fluids, electrolytes, and pH, it's necessary to make a distinction between **extracellular fluid**, or **ECF**, and **intracellular fluid**, or **ICF**. Just as the names indicate, these are the fluids outside and inside the body's cells, respectively. We have previously discussed interstitial fluid and the plasma of blood; these are the two main components of the ECF. A comparison of ECF and ICF is given in 10th Martini Figure 27-1 (The Composition of the Human Body). The ECF/ICF distinction is important for the first of the four principles listed in the next paragraph.

10th Martini states that four main principles are important for understanding fluid balance and electrolyte balance:

- *All the homeostatic mechanisms that monitor and adjust the composition of body fluids respond to changes in the ECF, not the ICF.* As 10th Martini explains, "This arrangement makes functional sense, because a change in one ECF component will spread rapidly throughout the extracellular compartment and affect all the body's cells."
- *Receptors can monitor some things but not others.* For example, your body has no way of measuring how much water it contains altogether, but it can monitor plasma volume via baroreceptors and osmolarity via osmoreceptors.
- *Cells cannot move water molecules by active transport.* Since water is osmotically attracted to areas where the total solute concentration (osmolarity) is highest, the way to move water around is to move solutes around (by active transport, if necessary); the water will follow.
- *The body's content of water or electrolytes will increase if dietary gains exceed losses to the environment, and will decrease if losses exceed gains.* This one may seem obvious, but let's remember that hormones not only influence what we do with the nutrients and fluids that have entered our body, but what we ingest in the first place.

Sticking with the theme of fluid and electrolyte balance for now, three hormones are especially important: antidiuretic hormone (ADH/vasopressin), secreted by the posterior pituitary; aldosterone, secreted by the adrenal cortex; and the natriuretic peptides ANP and BNP, secreted by cardiac muscle cells. At the most basic level, note that ADH and aldosterone go together – they are secreted in response to low ECF volume and pressure, whereas the natriuretic peptides are secreted in response to high ECF volume and pressure. Panel A of 10th Martini Figure 21-15 (The Hormonal Regulation of Blood Pressure and Blood Volume) covers the first situation, while panel B covers the second one. Some of these hormones' names are easy to link to their functions. Since a diuretic causes you to pee, an antidiuretic obviously does the opposite, i.e., it helps you retain water. The word natriuretic is a related word, with "natri" coming from the Latin word for sodium – so the natriuretic peptides promote excretion of sodium in the urine.

27.2: Fluid balance

You are constantly gaining and losing water, as illustrated in 10th Martini Figure 27-3 (Fluid Gains and Losses), which does not even include the special situation of a hemorrhage. Drinking too much or not enough water can move blood pressure and volume out of their normal ranges and provoke hormonal responses. But let's back up to the point where a change in the ECF first occurs. Let's say that you sweat a lot on a hot day. This fluid – water with a few solutes – is removed from the ECF, decreasing the volume of the remaining ECF and increasing its osmolarity. Some fluid in the ICF is then drawn into the ECF so that the osmolarities of the ECF and ICF become equal again; yet, as shown in 10th Martini Figure 27-4 (Fluid Shifts between the ICF and ECF), the ECF still has a lower volume and a higher osmolarity than it did before the sweating started. These changes will be noticed by osmoreceptors in the hypothalamus and

baroreceptors in the arteries, leading to ADH and aldosterone secretion and the usual increases in water and salt retention by the nephrons of the kidney.

Of course the opposite situation can occur as well. Drinking a large volume of pure water will increase the volume and decrease the osmolarity of the ECF. ADH secretion will be shut down, but ANP and BNP secretion will increase, and loss of water and salt into the urine will increase.

In most cases the body effectively handles these challenges to fluid homeostasis. However, if the body's responses do not keep pace with the perturbations, the concentrations of individual ions may drift out of their healthy ranges. Ultraendurance athletes who drink more fluids than necessary sometimes wind up with hyponatremia (remember that "natr" means sodium), a potentially dangerous reduction in ECF sodium concentration. Which brings us to the next section…

27.3: Electrolyte balance

What are electrolytes, again? Electrolytes are small inorganic ions such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), phosphate (PO_4^{3-}), and chloride (Cl^-). The concentrations of these ions need to be kept in normal ranges, though the exact reasons why deviations cause problems are not always straightforward. In any event, the main causes of electrolyte disorders, as summarized in 10th Martini Table 27-2 (Electrolyte Balance for Average Adult), are dietary and hormonal. In short, it is possible to ingest too much or too little of most electrolytes, or too have too much or too little of a hormone that regulates the balance of that electrolyte. Take calcium as an example. One can overdose on calcium supplements or not consume enough dairy products, or one can have an overactive or underactive parathyroid gland.

Electrolyte balance is perhaps most interesting for specific ions whose distributions are interdependent. For instance, parathyroid hormone (PTH) stimulates calcium uptake from the intestine while inhibiting phosphate uptake, so hyperparathyroidism could lead simultaneously to hypercalcemia (high calcium) and hypophosphatemia (low phosphate). Here is another example: the transporter regulated by aldosterone exchanges sodium for potassium, as shown in 10th Martini Figure 26- 14b (Tubular Secretion and Solute Reabsorption by the DCT), so more sodium reabsorption means more potassium excretion. (This trade-off is explored further in Chapter 27's Clinical Case.)

27.4: pH balance

Recall from Chapter 2 that pH indicates the concentration of H^+ ions in a solution. Specifically, if the molar H^+ concentration is expressed as a power of ten, the pH is the negative exponent. For example, if the $[H^+]$ is 10^{-7} M, the pH is 7. As $[H^+]$ goes up, pH goes down, and vice versa.

Normal pH in ECF such as blood ranges from 7.35 to 7.45. What might push the pH out of this range, and what mechanisms does the body have to keep the pH in this optimal range?

The body produces a variety of acids as part of its normal metabolism. These include sulfuric and phosphoric acids (formed from sulfate and phosphate groups, respectively), lactic acid (from glycolysis; remember this from Chapter 25?), ketone bodies (from lipid metabolism; remember this from Chapter 25?), and carbonic acid (from CO_2; remember this from Chapter 23?). Thus, acidosis (in which the pH is too low) is a more common problem than alkalosis (in which the pH is too high).

pH can be controlled in three basic ways: buffers, respiratory compensation, and renal compensation. We will discuss each one in turn.

Recall from Chapter 2 that **buffers** are compounds that minimize changes in pH. They reduce these changes by absorbing H^+ ions (if the solution is getting more acidic) or releasing H^+ ions (if the solution is getting more basic). The way this works can be illustrated with a "generic" buffer Y, which sometimes has a H^+ bound to it: $HY \rightleftharpoons H^+ + Y^-$. There are two key points about this chemical reaction. First, the reaction can go in both directions – from left to right and from right to left. Second, the reaction has an equilibrium – a state where the concentrations of HY, H^+, and Y^- are such that the leftward and rightward reactions proceed at equal rates, so the concentrations don't change.

If production of acids increases, and new H^+'s are added to the pool, the concentrations of HY, H^+, and Y^- will no longer be at equilibrium, so the leftward reaction will increase to move them back toward equilibrium. This is how buffers work; they counter changes in $[H^+]$ by moving the system back toward equilibrium. Buffers alone cannot turn an acidic change into a basic one (or vice versa); they can only reduce the <u>magnitude</u> of the change.

Your body has several buffers, as shown in 10th Martini Figure 27-10 (Buffer Systems in Body Fluids). Phosphate buffers stabilize ICF pH, the carbonic acid/bicarbonate system stabilizes ECF pH, and proteins stabilize both because they are prevalent both inside and outside cells.

In respiratory compensation, the body adjusts its breathing rate, and thus its rate of removing CO_2 from the blood, to move the pH of the ECF back toward normal. The relevant chemical reaction is this: $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$. How does changing the CO_2 level change the pH? When the $[CO_2]$ changes, the concentrations of CO_2, H_2O, H_2CO_3, H^+, and HCO_3^- are no longer in equilibrium, so the leftward and rightward reaction rates adjust to move the system back toward equilibrium. For example, if CO_2 is aggressively removed from the blood at the lungs due to a high ventilation rate, the fall in CO_2 level will "pull" the above reactions to the left, thus decreasing the level of H^+ and raising the pH.

In renal compensation, the kidney adjusts its rates of H^+ and HCO_3^- secretion and reabsorption, again for the purpose of stabilizing pH. The H^+ and HCO_3^- transport processes in the distal convoluted tubules (DCTs), proximal convoluted tubules (PCTs), and collecting ducts of nephrons are shown in 10th Martini Figure 27-13 (Kidney tubules and pH Regulation). Note in panel A that H^+ can be dumped into the pre-urine via Na^+/H^+ exchangers and via H^+/Cl^- cotransporters, while HCO_3^- can be moved into the blood via Cl^-/HCO_3^- exchangers and Na^+/HCO_3^- cotransporters. Since HCO_3^- on its own is a base – a compound that removes free H^+ – retaining more HCO_3^- helps raise the pH. The transport of H^+ and HCO_3^- can be adjusted to

get ECF pH back to normal. For example, in panel C of Figure 27-13, we see that some H^+ can be reabsorbed and some HCO_3^- can be secreted – the opposite of what is shown in panel A – if the ECF pH gets too high ("alkalosis").

27.5: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 27: review questions #1, 6, 7, 11, 20, 21, 24, 27, 28; clinical case wrap-up question #1. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 28: The Reproductive System

As you will recall, Chapter 18 covered the endocrine system, in which hormones are released into the blood. Here in Chapter 28, The Reproductive System, we start to see just how complicated hormonal regulation of physiological processes can be! In particular, the ovarian and uterine cycles of the female reflect an intricate interplay between FSH, LH, estrogen, and progesterone. (Don't worry, we'll cover the male reproductive system too!)

28.0: Outline

28.1: Overview of reproduction
- New humans result from the fertilization of a female gamete (oocyte) by a male gamete (spermatozoon or sperm).
- Gametes are produced by the gonads.
- Each human gamete contains 23 chromosomes, whereas other human cells contain 46.

28.2: Male parts
- Sperm is produced in the seminiferous tubules and then travels through the epididymis, ductus deferens, ejaculatory duct, and urethra.
- Sperm are highly specialized for transporting genetic material. They contain little more than a nucleus, flagellum, and mitochondria.
- Semen consists of sperm and seminal fluid, which is generated mostly by the seminal glands and prostate gland.
- Testosterone from the testes promotes the creation and development of sperm.

28.3: Female parts
- In an ovarian cycle, one oocyte is typically released by a follicle in a process called ovulation. The oocyte travels along the uterine tube, where fertilization may occur. If fertilization does occur, the pre-embryo will implant in the uterus.
- A uterine cycle generally occurs in sync with the ovarian cycle. The follicular phase of the ovarian cycle includes menses and the proliferative phase of the uterine cycle. The luteal phase of the ovarian cycle corresponds to the secretory phase of the uterine cycle.
- Ovulation is triggered by an LH surge, which is under the influence of GnRH and estrogen.
- The buildup of the endometrium of the uterus during the secretory phase is governed by progesterone secreted by the corpus luteum (the follicle that has lost its oocyte).

28.4: Recommended review questions

28.1: Overview of reproduction

Reproduction is the creation of new individuals by combining male and female **gametes**. The male gametes are known as spermatozoa (plural of spermatozoon), or sperm. The female gametes are called oocytes prior to fertilization and ova (plural of ovum) immediately afterward. While they are often referred to as eggs, an egg is technically the container within which the ovum resides.

Gametes are produced in the **gonads:** the testes (singular: testis) for males and the ovaries for females. They arise through a cell division process called meiosis. Meiosis is somewhat similar to mitosis but produces cells with half the chromosomes of normal body cells. Most cells have

23 pairs of chromosomes, for a total of 46. **Diploid** (di = 2, as in having 2 copies) is the adjective that applies to these 46-chromosome cells.

If male and female gametes were diploid as well, fertilization would produce tetraploid individuals with 92 chromosomes per cell. That would be bad. To maintain a constant number of chromosomes from generation to generation, the gametes are **haploid** (containing only one copy of each chromosome), so that the product of fertilization has the usual 46 chromosomes per cell.

A final note on chromosomes: the 23 pairs include 22 pairs of "autosomes" (same for males and females) and one pair of sex chromosomes. Females have two copies of the X chromosome as their sex chromosomes; males have an X and a Y. The development of an individual as male depends on a specific gene called the testis-determining factor (TDF) that is present on the Y chromosome. Since females' diploid cells are XX, each of their gametes contains a single X chromosome. Since males' diploid cells are XY, each of their gametes contains either an X chromosome or a Y chromosome. Thus, when fertilization occurs, the sperm determines the sex of the offspring.

28.2: Male parts

Reproductive anatomy for males is shown in 10th Martini Figure 28-1 (The Male Reproductive System).

We can trace the path of sperm through many of these structures as follows. Immature sperm are generated within the testes – to be specific, in the seminiferous tubules, shown in 10th Martini Figure 28-9 (The Epididymus). From the seminiferous tubules, sperm travel through the straight tubules, rete testis, and efferent ductules to the head of the epididymis. These maturing but still-immobile sperm continue on through the body and tail of the epididymis into the ductus deferens, also called the vas deferens. The ductus deferens passes through the inguinal canal into the abdominal cavity, then empties into the ejaculatory duct, which empties into the urethra – specifically, the prostatic urethra, the section of the urethra that passes through the prostate gland. The remainder of the urethra is called the membranous urethra (just beyond the prostate) and then the spongy urethra (passing through the corpus spongiosum, which, as the name suggests, is spongy).

As stated by 10th Martini, "a sperm is essentially a mobile carrier for chromosomes." As such, as it develops it loses many things that would weigh it down and slow it down, such as an endoplasmic reticulum, Golgi apparatus, many other organelles, and glycogen (storage form of carbohydrate). However, it does retain mitochondria, which generate ATP from the fructose it absorbs from seminal fluid. ATP is needed to power the movements of the sperm's flagellum, for example. Seminal fluid – contributed mostly by the seminal glands (seminal vesicles) and prostate gland – plus sperm is collectively called **semen**.

For fertilization to occur, sperm must be transferred from a male into a female. The ejection of semen from the urethra is called **ejaculation**. Prior to ejaculation, sperm are stored in the

epididymis and ductus deferens. Smooth muscles surrounding these tubes propel the sperm forward during ejaculation.

The sperm will not have a chance at fertilization unless ejected into the female's vagina. Erection of the penis permits its penetration into the vagina and the release of sperm there. Erections occur via a nifty bit of vascular plumbing. Dilation of the arteries in the penis fills the penis with fluid, and the veins are compressed so that this fluid cannot escape and remains in the penis. It turns out that one of the molecular signals causing arterial vasodilation is an intracellular buildup of cyclic GMP (cGMP). The drug Viagra (sildenafil) treats erectile dysfunction by inhibiting the phosphodiesterase that breaks down cGMP, thus enhancing vasodilation.

Control of male reproductive function is largely under the control of the hormone testosterone. Testosterone secretion by the interstitial cells of the testes is stimulated by Luteinizing Hormone (LH) from the anterior pituitary, whose secretion is stimulated by Gonadotropin Releasing Hormone (GnRH) from the hypothalamus. Testosterone stimulates Sertoli or "nurse" cells in the testes to promote the creation and development of sperm; it also is responsible for libido (sexual drive), bone and muscle growth, male-pattern hair growth, etc.

28.3: Female parts

The ovaries produce the female gametes. Oocytes released by the ovaries travel along the uterine tubes (also called fallopian tubes and oviducts), where fertilization usually occurs (if it occurs at all). If fertilization is successful, the pre-embryo implants in the wall of the uterus and develops there for about nine months (three trimesters, about 40 weeks), becoming an embryo and then a fetus. (To find out what happens after that, turn to Chapter 29 … or ask your mom.)

Oocytes are much larger gametes than sperm, and have correspondingly more support. Each primary oocyte is surrounded by one or more layers of supporting cells; the whole thing is called a **follicle**. The ovaries have hundreds of thousands of primordial follicles, many of which develop into primary follicles. In general, only one primary follicle develops further into a secondary follicle during a single ovarian cycle. This follicle has essentially been chosen to release its oocyte into the uterine tube. In a typical cycle of 28 days, the secondary follicle becomes a tertiary follicle between days 10 and 14, and **ovulation** – the release of the oocyte from the follicle and the ovary – occurs on day 14. Finger-like fimbriae guide the oocyte into the uterine tube, where fertilization will usually occur within a day or so if it's going to happen at all. (Note that, to make it to this location, sperm must have passed out of the male's urethra through the female's vagina and uterus – a journey with a high attrition rate.) Meanwhile the ruptured follicle becomes a corpus luteum ("yellow body") that secretes progesterone and (to a lesser extent) estrogen until it starts degenerating about 12 days later. Changes in a "chosen" follicle are shown in 10th Martini Figure 28-16 (The Ovarian Cycle).

The **ovarian cycle** described above can be divided into two phases: a follicular phase up until ovulation (roughly days 1 to 14) and a luteal phase from ovulation onward (roughly days 14 to 28). These changes in the ovaries occur in sync with changes happening in the uterus, which constitute the **uterine cycle** or menstrual cycle. The wall of the uterus has three layers: the

endometrium, the myometrium, and the perimetrium, from innermost to outermost, as shown in 10th Martini Figure 28-19 (The Uterine Wall). It is in the innermost part of the inner layer – the "functional zone" of the endometrium – where most of the cyclical uterine changes occur.

During the 14 or so days of the follicular phase of the ovarian cycle, the uterine cycle is in menses (days 1-7) and then the proliferative phase (days 7-14). In menses, the functional zone that was built up during the previous cycle is destroyed. Vasoconstriction reduces blood flow to this zone, causing deterioration of the tissue, rupture of the blood vessels, and shedding of this part of the endometrium (menstruation). Then it's time to rebuild the functional zone in the proliferative phase. This phase is "proliferative" because cells are dividing, forming new endometrial tissue, including new blood vessels.

The luteal phase of the ovarian cycle (days 14-28 or so) corresponds to the secretory phase of the uterine cycle. Here the small secretory glands scattered throughout the endometrium continue to grow and secrete glycogen-rich mucus, which seems important for the survival of a newly fertilized oocyte (called an ovum or pre-embryo once fertilization has occurred).

The ovarian and uterine cycles described above are both summarized in 10th Martini Figure 28-24 (Regulation of Female Reproduction). What this figure indicates, aside from the changes in the follicle and uterus themselves, is that these changes are under the control of sex hormones. Let's try to explain how sex hormones cause some of the changes.

First consider ovulation on or around day 14. What's up with that? LH levels are up – way up. (See the top panel of the right side of Figure 28-24.) This "LH surge" stimulates the rupture of the wall of the follicle (thus bringing the follicle closer to becoming a corpus luteum – so the name "luteinizing hormone" makes sense) and the release of the oocyte. LH surges at this time in response to increasingly frequent pulses of GnRH from the hypothalamus. Also, interestingly, while estrogen normally acts via negative feedback to inhibit LH release, this effect is reduced at the really high estrogen levels achieved during days 10-14, so estrogen also contributes to ovulation in this way.

The **corpus luteum** – the follicle that has lost its oocyte – becomes a major producer of progesterone. As 10th Martini points out, progesterone is a well-named hormone; it is a "pro-gestation" hormone, gestation referring to pregnancy, with the "one" suffix indicating that it is a steroid. Thus progesterone promotes the continuing growth of the endometrial layer of the uterus and the secretion of mucus from this layer. Once the corpus luteum degenerates, it stops producing progesterone, and in the absence of this hormonal stimulation, the endometrial lining deteriorates and is sloughed off (days 1-7 of the next cycle) if a pre-embryo has not implanted in the uterus.

28.4: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 28: review questions #4, 5, 8, 14, 15, 16, 18, 19, 24, 26, 27. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)

Chapter 29: Development and Inheritance

In Chapter 28, The Reproductive System, we discussed oocytes ("eggs") and spermatozoa ("sperm") separately. Here in Chapter 29, we focus on what happens after they meet!

29.0: Outline

29.1: Overview of development
- Development is the changes in anatomy and physiology from conception to physical maturity.
- An individual's phenotype is the result of interactions between his/her genotype (genes) and the environment.

29.2: Fertilization
- Fertilization – the fusion of an oocyte with a sperm – generally occurs in the uterine tubes within a day of ovulation.
- Sperm carry enzymes in the tips of their heads (acrosomes) that enable penetration of the corona radiata and zona pellucida and thus formation of a zygote.

29.3: Prenatal development
- The early days and months of pregnancy include cleavage of the zygote into multiple smaller cells, implantation into the wall of the uterus, formation of the placenta (placentation), and development of the embryo's body (embryogenesis).
- To support the growing child, the mother's respiration rate, tidal volume, nutrient intake, glomerular filtration rate (GFR), and blood volume all increase.

29.4: Labor and delivery
- Childbirth, or labor, consists of the dilation, expulsion, and placental stages.
- Contraction of the smooth muscle of the uterus is driven by mechanical distortion and by the influences of estrogens, oxytocin, and prostaglandins.

29.5: Postnatal development
- Infant suckling behavior stimulates oxytocin release, which causes milk ejection from the mammary glands.
- During puberty, rising levels of GnRH from the hypothalamus stimulate FSH and LH release from the anterior pituitary, stimulating estrogen or testosterone secretion from the gonads, leading to many physiological changes.

29.6: Recommended review questions

29.1: Overview of development

This chapter covers the topic of development. **Development** is a very general term referring to changes in an individual's anatomy and physiology from conception to physical maturity. It can refer to whole tissues or organs, or to individual cells. A related term, usually applied to the cellular level, is **differentiation**, which is the process by which cells become specialized for particular functions. The transformation of stem cells into mature keratinocytes (or muscle cells, or neurons, or …) is an example of differentiation.

How an individual develops over time is determined by both the individual's genes – collectively, his/her **genotype**[2] – and numerous "environmental" factors starting with the

[2] "GEE-no-type"

prenatal environment. The individual's actual anatomy and physiology, reflecting both genes and the environment, is called his/her **phenotype**[3]. As 10th Martini states, "In architectural terms, the genotype is a set of plans, and the phenotype is the finished building."

Since this course is not a genetics course, we will not discuss genes in any great detail. Let us simply keep in mind a few basic facts:

- In general, a gene is a segment of DNA, found along a chromosome, that codes for a protein, which is made from the gene by transcription and translation.
- Mutations in genes – that is, changes in the sequence of As, Cs, Gs, and Ts – sometimes affect the structures and functions of the proteins for which they code. Examples covered elsewhere in this book include mutations in the CFTR chloride ion channel, which lead to cystic fibrosis; mutations in clotting factors such as factor VIII, which lead to hemophilia, and mutations in hemoglobin, which lead to sickle-cell anemia.
- Many patterns of inheritance are possible, as shown in 10th Martini Figure 29-15 (Major Patterns of Inheritance). Note that patterns are different for the sex chromosomes versus the other chromosomes (autosomal chromosomes), and for single-gene traits (e.g., sickle-cell anemia or cystic fibrosis) versus multi-gene traits (e.g., skin color or height).

29.2: Fertilization

Chapter 28 discussed the development of the oocytes and sperm, and briefly acknowledged that sometimes these two gametes are combined. How exactly does that happen?

First, recall that in ovulation, an oocyte is released from its follicle and ovary and begins traveling down the uterine tube. Meanwhile, sperm may be traveling up the uterine tube as a result of intercourse or intrauterine insemination (IUI). Fusion of the oocyte and sperm is called fertilization. If it is to happen, it will take place within a day or so of ovulation, before the oocyte has traveled more than a few centimeters from the ovaries.

Fertilization is depicted in 10th Martini Figure 29-1 (Fertilization). The first thing to note in panel B is that the oocyte itself is surrounded by a thick glycoprotein layer called the *zona pellucida*[4] and, outside of that, a ring of follicle cells called the *corona radiata*[5]. Somehow a sperm must penetrate these layers. The tip of the sperm head, known as the *acrosome*, contains the enzyme hyaluronidase, which digests hyaluronic acid linking adjacent corona radiata cells. Once there are gaps in the corona radiata, a sperm can use its acrosomal enzymes to burrow through the zona pellucida (step 1). The successful entry of a sperm into the oocyte triggers oocyte activation, whose consequences include hardening of the zona pellucida so that no additional sperm can enter. Once the sperm and oocyte pronuclei fuse, thus combining their 23 chromosomes apiece into the usual supply of 46, the cell is considered a zygote.

[3] "Fee-no-type"
[4] "ZOH-nuh puh-LOO-sih-duh"
[5] "co-ROH-nuh ray-dee-AH-tuh"

Males with "only" 20 million sperm per milliliter of ejaculate are considered infertile. This seemingly huge number is actually insufficient for two reasons. First, only a tiny fraction of these sperm actually get all the way into the uterine tubes, and second, breakdown of the corona radiata is a team effort, requiring the participation of many sperm.

29.3: Prenatal development

10th Martini breaks prenatal events into discussions of (A) changes in the new offspring during the first trimester (0 to 3 months of the pregnancy) and (B) changes in the mother during the second and third trimesters (3 to 9 months). Not being a reproductive expert, I will simply follow suit. By the way, the offspring is called a zygote at the one-cell stage, then a pre-embryo and an embryo. After 8 weeks of growth – 10 weeks since the mother's last menstrual period – the embryo is reclassified as a fetus, a term that applies to the rest of the pregnancy until delivery.

During the first trimester, four general processes are especially important: **cleavage**, the division of the new zygote into numerous smaller cells; **implantation**, the attachment of the pre-embryo to the uterus; **placentation**, the formation of the placenta; and **embryogenesis**, the development of the embryo itself. Below is a bit more about each of these four processes.

In most contexts, the word "cleavage" refers to a single event of splitting, such as the cleavage of a protein by a protease. In early development, though, **cleavage** refers to a series of multiple divisions in which the single zygote cell is divided numerous times, as shown in 10th Martini Figure 29-2 (Cleavage and Blastocyst Formation). By 5 or 6 days after fertilization, the organism is a hollow sphere of 200 to 300 cells – a blastocyst.

Shortly after the blastocyst stage is reached, **implantation** begins. This is shown in 10th Martini Figure 29-3 (Stages in Implantation). Interestingly, after the initial connection is made to the wall of the uterus, hyaluronidase – a key enzyme used by sperm to get to oocytes – is used to burrow into the endometrium of the uterus. By about the 10th day after fertilization, the embryo is contained entirely within the wall of the uterus, where it continues to develop until delivery, though it and its extraembryonic membranes will gradually bulge more and more into the uterine cavity, as shown in steps 4 and 5 of 10th Martini Figure 29-5 (Extraembryonic Membranes and Placenta Formation).

Placentation is the formation of the placenta, an organ that forms in the uterine wall when an embryo is present so that the mother's and child's circulatory systems can exchange nutrients and wastes. Around post-fertilization day 12, a cell migration process called gastrulation results in the embryo having three distinct germ layers: ectoderm on the outside, endoderm on the inside (facing the yolk sac), and mesoderm in between. The ultimate formation of all of the body's different tissues can be traced back to their origins in these three layers, as detailed in 10th Martini Table 29-1 (The Fates of the Germ Layers). More immediately, these germ layers create four extraembryonic membranes – the yolk sac, amnion, allantois, and chorion – shown in excruciating detail in 10th Martini Figure 29-5 (Extraembryonic Membranes and Placenta Formation). For our purposes, it is enough to know that the chorion is the outermost of these

membranes, and that it sprouts chorionic villi that will maximize exchange between the maternal and embryonic/fetal circulatory systems. These chorionic villi plus the adjacent maternal uterine tissue (decidua basalis) are together known as the placenta. The placenta is connected to the rest of the fetus via the umbilical cord, which contains two umbilical arteries and one umbilical vein. Panel 5 of Figure 29-5 has a good picture of this. Note that the umbilical arteries carry deoxygenated blood and are color-coded blue in figures like 29-6 (Views of Placental Structures), whereas the umbilical vein carries oxygenated blood and is color-coded red.

Embryogenesis, the development of the embryo itself, proceeds from the development of a head fold and tail fold in weeks 3 and 4 to the formation of organs over the first seven months of pregnancy. 10th Martini Table 29-2 (An Overview of Prenatal Development) has the gory details.

To accommodate the growing child, the uterus also increases its size and weight substantially. Much of this change is due to the enlargement of existing smooth muscle cells in the myometrium. The increasing space taken up by the uterus squeezes other abdominopelvic organs such as the urinary bladder – see 10th Martini Figure 29-9d (Growth of the Uterus and Fetus). Several other changes in the mother are attributable to the fact that she now is breathing, eating, and excreting for two. Her respiratory rate, tidal volume, appetite, nutrient intake, and glomerular filtration rate (GFR) all increase, along with her volume of blood. The mammary glands also get bigger in preparation for postnatal breast-feeding.

29.4: Labor and delivery

Childbirth, also called labor, is traditionally divided into three stages: dilation of the cervix to about 10 centimeters (4 inches), expulsion of the fetus, and ejection of the placenta. These are illustrated in 10th Martini Figure 29-11 (The Stages of Labor).

The driver of the entire process, of course, is the contractions of the smooth muscle of the uterus' myometrium. The factors causing these contractions are shown in 10th Martini Figure 29-10 (Factors Involved in the Initiation of Labor and Delivery). Mechanical distortion of the myometrium by the now-large fetus primes the smooth muscle to be more ready to contract, and spontaneous contractions do occur in the months and days before true labor occurs. In addition to this mechanical issue, chemical changes involving estrogen, oxytocin, and prostaglandins cause true labor to occur. High maternal estrogen levels promote the release of oxytocin from the posterior pituitary of both the mother and the fetus, and the estrogen and oxytocin stimulate release of prostaglandins from the placenta. Oxytocin and prostaglandins both stimulate smooth muscle contractions, leading to additional mechanical distortion and hormone release in a positive feedback loop.

While true labor normally occurs after about nine months (three trimesters) of pregnancy, it sometimes occurs much earlier. As shown in 10th Martini Table 29-2 (An Overview of Prenatal Development), most of the fetus's organs have formed by the end of the second trimester; consequently, a fetus delivered after this time can often survive if intensive, expert medical care is provided. In general, low fetal birth weights correspond to decreased readiness to survive and

thrive in the outside world. Because twins must share space in the uterus, they tend to be delivered early, with lower-than-normal birth weights and increased risks of complications.

Other variations upon the typical delivery can also make things more challenging for the mother and fetus:

- About 3-4% of the time, the fetus's legs or butt enters the vaginal canal first. This *breech birth* position can cause constriction of the umbilical cord and compromise oxygen delivery to the fetus. To avoid a breech birth, the fetus can often be manually manipulated through the mother's abdomen into a typical head-first position.
- Sometimes the fetus's head simply does not fit through the cervix. In these cases, the uterus is cut open and the fetus is removed from it. This is called a caesarean section, or "C-section."

29.5: Postnatal development

Postnatal (post-birth) development can be divided into the neonatal period (until 1 month of age), infancy (until 1 year of age), childhood (until puberty, which typically starts around 11 or 12), adolescence (puberty), maturity, and senescence (aging).

One of the most immediate postnatal changes is the baby's source of nutrients. Contractions of smooth muscle cells lining the lactiferous (milk-forming) ducts and sinuses cause milk ejection, or milk let-down. These contractions are stimulated by oxytocin from the posterior pituitary, which is released in response to the suckling of the infant.

Skipping ahead to adolescence, this period is often described as being one of "raging hormones." Sure enough, the hypothalamus increases its secretion of gonadotropin-releasing hormone (GnRH), which stimulates secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which stimulate secretion of estrogen by the ovaries and testosterone by the testes. These sex hormones promote growth of long bones and many other physiological changes associated with puberty, such as the development of mammary glands in girls and the thickening and lengthening of the vocal cords in boys.

Eventually, time takes its toll and people get old. Most 10th Martini chapters conclude with a short section on how that chapter's physiological system is affected by the aging process (senescence). I have not emphasized these sections in my Crowther's Tenth Martini summaries, but a quick overview is given in 10th Martini Table 29-3 (Effects of Aging on Organ Systems). Among many potential problems faced by older people, degeneration of the brain is becoming an increasing focus of geriatric care as medical science gets better and better at keeping people alive despite their physical limitations.

29.6: Recommended review questions

If your understanding of this chapter is good, you should be able to answer the following 10th Martini questions at the end of Chapter 29: review questions #3, 4, 7, 8, 11, 16, 18, 21, and 26. (Note that these are NOT the Checkpoint questions sprinkled throughout the chapter.)