Medical Embryology

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ABOUT THE AUTHOR

Donikë Demelezi is a dedicated medical doctor with a diverse background in pathology, general practice, and research. Currently serving as a Resident of Pathology and Cytodiagnostics at the University Clinical Center of Kosovo in Pristina, she meticulously analyzes bodily fluids and tissue specimens, compiles pathology reports, and engages in research. Previously, Donikë honed her clinical skills as a General Practitioner, where she assessed and treated patients during COVID-19 pandemic. Donikë's academic journey includes earning her MD degree from the University "Hasan Prishtina", Faculty of Medicine in Pristina. She furthered her knowledge through research summer school at the University of Angers in France. Committed to continuous learning, Donikë actively participates in extracurricular activities. Alongside her professional endeavors, she dedicates her time to volunteering with organizations like the Red Cross of Kosovo. Donikë's passion for medicine, coupled with her diverse experiences, shapes her into a compassionate and skilled healthcare professional.

Word Roots, Prefixes, and Suffixes by Chapter

Chapter 1 Introduction to Embryology

Acous/o-: Hearing
Aden/o-: Gland
Adip/o-: Fat
Adren/o-: Gland
Angi/o-: Blood vessel
Arteri/o-: Artery

Chapter 2 Ovulation to Implantation

Arthr/o-: Joint
Bucc/o-: Cheek
Bronch/i-: Bronchus
Burs/o-: Bursa
Carcin/o-: Cancer
Cardi/o-: Heart

Chapter 3 Bilaminar and Trilaminar Germ Disc

Cephal/o-: Head
Chol-: Bile
Chondri-: Cartilage
Coron-: Heart
Cost-: Rib
Crani/o-: Brain
Cutane-: Skin

Chapter 4 Gastrulation and Formation of the Germ Layers

Cyst/o-, Cysti-: Bladder or sac
Derm-, Dermat/o-: Skin
Duoden/o-: Duodenum
Gastr-: Stomach
Gloss-: Tongue
Hem-, Hema-, Hemat-, Hemo-, Hemat/o-: Blood

Chapter 5 Development of the Nervous System

Hepat/o-, Hepatico-: Liver
Hist/o-, Histio-: Tissue
Hyster/o-: Uterus
Ileo-: Ileum
Ischi/o-: Ischium
Kerat/o-: Cornea (eye or skin)
Lacrim/o-: Tear (from your eyes)

Chapter 6 Development of the Cardiovascular System

Lact/o-, Lacti-: Milk
Laryng/o-: Larynx
Lingu/o-: Tongue
Lip/o-: Fat
Lymph/o-: Lymph
Mamm-, Mast/o-: Breast

Chapter 7 Development of the Respiratory System

Mening/o-: Meninges
Muscul/o-: Muscle
My/o-: Muscle
Myel/o-: Spinal cord or bone marrow
Nephr/o-: Kidney
Neur/i-, Neur/o-: Nerve

Chapter 8 Development of the Gastrointestinal System

Oculo-: Eye
Onco-: Tumor; Bulk; Volume
Onych/o-: Fingernail; Toenail
Oo-: Egg; Ovary
Oophor/o-: Ovary
Op-, Opt-: Vision
Ophthalm/o-: Eye

Chapter 9 Development of the Urinary System

Orchid/o-, Orchio-: Testis
Orth/o-: Straight; Normal; Correct
Osseo-: Bony
Ossi-: Bone
Ost-, Oste/o-: Bone
Ot/o-: Ear
Ovar/i-, Ovario-, Ovi-, Ovo-: Ovary

Chapter 10 Skeletal System

Phalang-: Phalanx
Pharyng/o-: Pharynx; Throat
Phleb/o-: Vein
Phren/i-, Phreno-, Phrenico-: Diaphragm
Pleur-, Pleur/a-, Pleur/o-: Rib, pleura
Pneum/a- Pneumat/o-: Air; Lung
Proct/o-: Anus; Rectum

Chapter 11 Muscular System

Prostat-: Prostate
Pseudo-: False
Psych/o-, Psyche-: Mind
Radio-: Radiation; Radius
Ren/o-: Kidney
Retin-: Retina (of the eye)
Rhin/o-: Nose

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PREFACE

Clinical embryology is an advanced field that intersects the study of embryology with assisted reproductive technologies (ART). This discipline primarily focuses on the intricacies of human development from conception to the early stages of pregnancy, specifically within the context of fertility treatments. The scope of clinical embryology encompasses a broad range of techniques and processes designed to assist in the conception and ensure the healthiest possible start for human embryos. At the core of clinical embryology are sperm preparation and analysis procedures. These are critical steps in assessing the viability and quality of sperm for use in assisted reproductive techniques such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). These procedures are fundamental in selecting the best possible sperm for fertilization, aiming to increase the chances of successful pregnancy. Another crucial aspect of clinical embryology is the insemination process used in IVF and ICSI treatments. This involves carefully introducing sperm to the oocyte (egg) to facilitate fertilization. Following fertilization, embryologists undertake the evaluation of the embryos. This evaluation can be performed using traditional morphological assessment techniques or with the aid of more advanced processes. Among these, time-lapse imaging stands out as a technique that allows continuous monitoring of embryo development, providing invaluable data on the embryo's growth patterns and viability. Metabolomics, the study of chemical processes involving metabolites, and the measurement of microRNAs (miRNAs) using computational methods, offer deep insights into the health and development potential of embryos, beyond what can be discerned through visual assessment alone.

The field also involves the vitrification (fast freezing) and thawing of gametes (sperm and eggs) and embryos. This process is essential for preserving these cells for future use, without compromising their viability. The techniques and protocols for freezing and thawing are continuously refined to ensure the highest possible survival rates and maintain the integrity of the gametes and embryos. Quality control and assurance within embryology laboratories are paramount. These protocols ensure that all procedures are conducted under optimal conditions to maximize the chances of success. This includes maintaining sterile environments, ensuring equipment is functioning correctly, and adhering to strict protocols for handling gametes and embryos.

In recent years, there has been a significant emphasis on the need to assess the quality of embryos before transfer. This is crucial for improving the success rates of ART procedures. Additionally, the stimulation protocols used to induce the production of oocytes have been finely tuned to match the specific needs of each patient. This personalized approach to fertility treatment has significantly improved the quality of oocytes and subsequent embryos, tailoring the process to the individual's physiological response to stimulate medications.

Beyond the technical and procedural aspects, clinical embryology and reproductive medicine also navigate complex bioethical issues. Since the field involves the manipulation of gametes and pre-implantation stage embryos, there are profound ethical considerations to be addressed. These include the moral implications of embryo selection, the disposal of unused embryos, and the potential for genetic modifications. The field constantly grapples with these issues, striving to balance the incredible potential of assisted reproductive technologies with ethical principles and societal values.

This book provides an in-depth exploration of human development from conception through to birth, focusing on the fundamental concepts and latest advancements in the field of embryology. It is designed to bridge the gap between basic embryological knowledge and its clinical applications, thereby enhancing the understanding of human developmental processes and congenital anomalies. The text details the stages of human development, the cellular and molecular mechanisms involved, and the embryological basis of various medical conditions, aiming to equip medical students, healthcare professionals, and researchers with a comprehensive understanding of the subject.

The book will serve medical students, residents in pediatrics, obstetrics, and gynecology, as well as professionals in reproductive medicine and developmental biology as both an educational resource and a reference guide. Through clear illustrations, up-to-date text, and clinical correlates, it endeavors to enrich the reader's knowledge, aiding in diagnostic and therapeutic applications related to embryology. This book is particularly valuable for those seeking to grasp the complexities of human development, understand the origins of congenital anomalies, and apply embryological knowledge in clinical practice to improve patient care.

Chapter

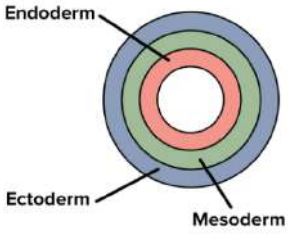
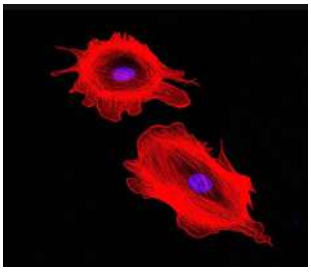
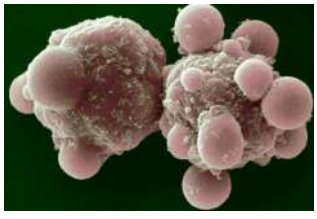
1 INTRODUCTION TO EMBRYOLOGY

Contents

Unit Introduction

The study of an embryo's growth from the point of ovum fertilization to the fetal stage is known as embryology. After fertilization, the ball of dividing cells is called an "embryo" for the first eight weeks, and then a "fetus" for the remaining duration of the pregnancy. The complex process by which a fertilized egg becomes an embryo in humans is called embryogenesis. During the first eight weeks of life, the concept develops from a single-celled zygote into a multilayered, multidimensional fetus with rudimentary organ function. Throughout the first eight weeks of development, cell signaling, proliferation, and differentiation are crucial for continued growth and increased intra-embryonic complexity. The development of the human embryo is broken down into developmental events by week because of the complexity involved. The stage of development known as the germinal stage lasts from fertilization to uterine implantation. Gamete approximation, gamete contact and fusion, fertilization, mitotic cleavage of the blastomere, morula formation, blastocyst formation, and blastocyst implantation are significant events that take place during the first week of human embryonic development.

Orientation and Directional Terms:

Terms	Definition	Illustration
Human embryo	Human embryonic development or human embryogenesis is the development and formation of the human embryo.	
Cell biology	Cell biology is the study of cell structure and function, and it revolves around the concept that the cell is the fundamental unit of life.	
Mesoderm	Mesoderm is the middle developmental layer between the ectoderm and endoderm, which gives rise to the skeleton, muscle, heart and bones.	
Cell migration	Cell migration is the directed movement of a single cell or a group of cells in response to chemical and/or mechanical signals.	
Apoptosis	Apoptosis is a form of programmed cell death that occurs in multicellular organisms and in some eukaryotic, single-celled microorganisms such as yeast.	

1.1. Basic Concept of Embryology

The area of biology known as embryology studies the growth of embryos in both plants and animals, from ovum fertilization to fetus birth or hatching. It is a broad field that includes many scientific specialties, such as anatomy, genetics, developmental biology, and cell biology. The goal of embryology is to comprehend the complex processes that transform a single fertilized egg into a sophisticated multicellular organism.

The process of fertilization, which is the union of the egg and sperm cell to form a zygote, is the first step in the development of the embryo. This first action sets off a sequence of painstakingly planned events that result in cell division, differentiation, and morphogenesis. The zygote divides quickly during mitosis shortly after fertilization, creating a hollow ball of cells known as a blastula. The ectoderm, mesoderm, and endoderm are the three main germ layers that form during the complex rearrangements that the blastula goes through during this stage, which signals the start of gastrulation.

Structures like the nervous system, epidermis, and sensory organs are produced by the ectoderm. The urogenital system, blood vessels, muscles, and bones are all developed in part by the mesoderm. The endoderm creates the lining of the respiratory and digestive systems, as well as related organs like the thyroid, pancreas, and liver. The complex organ systems that will form during the embryo's development are supported by these germ layers.

Through a process known as morphogenesis, cells continue to differentiate and arrange themselves into specialized tissues and organs as embryonic development advances. Intricate signaling pathways that control gene expression and cell behavior are involved in this process, along with cell migration, proliferation, and apoptosis (programmed cell death). Growth factors, hormones, and transcription factors are examples of signaling molecules that are essential for coordinating these developmental processes.

Genetic elements that are encoded in the DNA of the organism also affect embryonic development. Different cell types and structures form according to the timing and location of specific gene expressions. Birth defects or abnormalities in development can result from mutations or changes in these genes. Researchers study the genetic basis of embryonic development and gain insights into human development and disease by using model organisms such as frogs, fruit flies, mice, and zebrafish. Environmental factors can also affect the development of an embryo in addition to genetic factors. Developmental abnormalities can be caused by external factors that impact fetal growth, including nutrition, exposure to toxins, and maternal health. To encourage healthy development and prevent birth defects, it is essential to comprehend how these environmental factors interact with genetic processes.

Practical uses for embryology can be found in a variety of industries, such as biotechnology, agriculture, and medicine. Understanding human reproduction, identifying and treating developmental disorders, and developing assisted reproductive technologies all depend on a medical understanding of embryonic development. Embryology is essential to animal breeding programs and raising livestock productivity in agriculture. Biotechnology techniques like tissue engineering, stem cell research, and regenerative medicine leverage insights from embryology. The complex mechanisms guiding an organism's development from conception to birth or hatching are explored in the fascinating field of embryology. Through the clarification of

the molecular, cellular, and genetic processes that underlie embryonic development, scientists can acquire a deeper understanding of basic biological processes and utilize this information for a range of useful purposes. The field of embryology is still dynamic and ever evolving, with significant implications for science, medicine, and society at large.

1.1.1. Comparative Embryology

1.1.1.1. Preformationism and Epigenesis

Preformation, the theory that semen contains an embryo—a preformed, miniature infant, or homunculus—that just gets bigger during development—was the dominant conception in Western human embryology as late as the 18th century. Aristotle first put forth the alternative theory of embryonic development, known as epigenesis, 2,000 years ago. The Italian anatomists Aldrovandi, Aranzio, Leonardo da Vinci, Marcello Malpighi, Gabriele Falloppio, Girolamo Cardano, Emilio Parisano, Fortunio Liceti, Stefano Lorenzini, Spallanzani, Enrico Sertoli, and Mauro Ruscóni are largely responsible for much of the early work in embryology. Epigenesis proposes that an animal's form develops gradually from a relatively formless egg. With the advancement of microscopy during the 19th century, biologists were able to observe that embryos developed in a series of sequential steps, leading to the replacement of preformation by epigenesis as the preferred explanation among embryologists.

1. **Cleavage:** This is the initial stage of an embryo's development. The numerous mitotic divisions that follow the sperm's fertilization of the egg are referred to as cleavage. Certain animal species have unique cell division processes, which can take many different forms.
2. **Holoblastic:** A holoblastic cleavage is a complete cell division. Holoblastic cleavage can be rotational (rotational cleavage), bilateral (bilateral cleavage), spiral (spiral cleavage), or radial (radial cleavage). In holoblastic cleavage, the entire egg divides and becomes the embryo, whereas in meroblastic cleavage, some cells become the embryo and others the yolk sac.
3. **Meroblastic:** The incomplete division of cells is known as meroblastic cleavage. Since those cells obstruct the formation of membranes, the division furrow does not extend into the yolky region, resulting in incomplete cell separation. Meroblastic cleavage can occur in three different ways: bilaterally, discoidally, or centrolecithally.
4. Germ Layers:
   - The innermost layer, or endoderm, gives rise to the digestive organs, the gills, lungs or swim bladder (if present), and kidneys or nephrites.
   - The middle layer, or mesoderm, gives rise to the muscles, skeleton (if any), and blood system.
   - The outer layer of cells, or ectoderm, gives rise to the nervous system, including the brain, skin carapace hair, bristles, or scales.
5. **Drosophila Melanogaster (Fruit Fly):** Drosophila has been used as a developmental model for many years. The studies that have been

conducted have discovered many useful aspects of development that not only apply to fruit flies but to other species as well.

Outlined below is the process that leads to cell and tissue differentiation:

1. Maternal-effect genes help to define the anterior-posterior axis using Bicoid and Nanos gene.
2. Gap genes establish 3 broad segments of the embryo.
3. Pair-rule genes define seven segments of the embryo within the confines of the second broad segment that was defined by the gap genes.
4. Segment-polarity genes define another seven segments by dividing each of the pre-existing seven segments into anterior and posterior halves using a gradient of Hedgehog and Wnt.
5. Homeotic (Hox) genes use the fourteen segments as pinpoints for specific types of cell differentiation and the histological developments that correspond to each cell type.

1.1.1.2. Humans

Human embryogenesis is a complicated process by which a fertilized egg develops into an embryo. During the first eight weeks of development, the conceptus shifts from a single-celled zygote into a multi-layered, multi-dimensional fetus with primitively functioning organs. Humans are bilateral animals that have holoblastic rotational cleavage. Humans are also deuterostomes. Concerning humans, the term embryo refers to the ball of dividing cells from the moment the zygote implants itself in the uterus wall until the end of the eighth week after conception. Beyond the eighth week after conception (the tenth week of pregnancy), the developing human is then called a fetus.

1.1.2. Evolutionary Embryology

The application of Charles Darwin's theories to comparative embryology, known as evolutionary embryology, explores the evolutionary relationships among species. Darwin contended that the relationship between groups can be ascertained based on common embryonic and larval structures, in line with Karl Ernst von Baer's theories, which explained why many species frequently appear similar to one another in early developmental stages.

1.1.2.1. Von Baer's Principles:

1. General features appear earlier in development than specialized features.
2. More specialized characters develop from more general ones.
3. The embryo of a given species never resembles the adult form of a lower species.
4. The embryo of a given species does resemble the embryonic form of a lower species.

Using Darwin's theory, evolutionary embryologists have distinguished between homologous and analogous structures among different species. Homologous structures, such as the human arm and bat wings, are those whose similarities can be traced back to a common ancestor. Similar-looking structures that do not share a common ancestor are called analogous structures.

1.1.3. Origins of Modern Embryology

Although later discussions in this article demonstrate that some cultures had a fairly

refined understanding of some of the principles, there was no clear scientific understanding of embryology before Karl Ernst von Baer observed the mammalian ovum in 1827, which gave rise to modern embryology. The true developmental chronology of the human fetus was not available until the late 1950s, when ultrasonography was first used for uterine scanning. The germ layer theory of development, which was put forth by Karl Ernst von Baer and Heinz Christian Pander, assisted in explaining how the embryo developed in successive stages. This explanation included an examination of von Bauer's four principles to explain why embryos from different species frequently resemble one another in their early developmental stages.

1.1.3.1. Modern Embryology Research

Embryology is central to evolutionary developmental biology ("evo-devo"), which studies the genetic control of the development process (e.g., morphogens), its link to cell signaling, its roles in certain diseases and mutations, and its links to stem cell research. Embryology is the key to gestational surrogacy, which is when the sperm of the intended father and the egg of the intended mother are fused in a lab, forming an embryo. This embryo is then implanted into the surrogate, who carries the child to term.

1.1.4. Medical Embryology

The area of embryology that focuses on the formation of human embryos, fetuses and prenatal development is known as medical embryology. It is essential to comprehend the underlying causes of genetic disorders, congenital malformations, and developmental anomalies seen in clinical practice. Medical embryology sheds light on the genesis and pathophysiology of numerous medical disorders by providing insights into the complex processes of embryogenesis, organogenesis, and fetal development. A common application of medical embryology is the early detection of anomalies. Medical embryology studies the various forms and stages in which the 2–5% of babies born with observable abnormalities manifest. Malformations are abnormalities resulting from genetics factors. When several malformations are present, this is referred to as a syndrome. Disruptions occur when anomalies arise due to external factors. Teratogens are external factors that cause disruptions. Ionizing radiation, alcohol, retinoic acid, and hyperthermic stress are examples of common teratogens.

A single-celled zygote becomes a complex multicellular organism through a series of cellular divisions and morphogenetic events that start with fertilization, the union of sperm and egg cells. The study of medical embryology focuses on the cellular and molecular mechanisms that control various developmental processes, such as organ formation, tissue patterning, and cell differentiation. Important phases of development, including limb formation, neurulation, and gastrulation, are examined in depth to comprehend the creation of organ systems and the body plan.

Medical embryology focuses on organogenesis, the process by which organs form from the embryonic germ layers (ectoderm, mesoderm, and endoderm). Under the direction of complex signaling pathways and genetic programs, precursor cells undergo sequential development and differentiation into specialized tissues and organs. The major organ systems, such as the nervous, cardiovascular, respiratory, gastrointestinal, and urogenital systems, are formed through morphogenetic processes that are explained by medical embryology.

The study of medical embryology also focuses on the pathophysiology and etiology of birth defects and congenital anomalies, which result from abnormalities in normal embryonic development. Teratogenic substances,

environmental variables, genetic mutations, and multifactorial causes can all contribute to these abnormalities. Medical embryology improves prenatal care and maternal-fetal medicine by providing insights into the developmental causes of these conditions and informing methods for congenital disorder diagnosis, prevention, and treatment. In clinical practice, medical professionals such as physicians, surgeons, genetic counselors, and developmental biologists need to be knowledgeable about medical embryology. It offers a basis for comprehending the development of the embryo and how it relates to human health and illness, directing medical judgment, patient counseling, and research projects meant to enhance prenatal diagnosis and treatment interventions. In general, medical embryology bridges the gap between basic science and clinical medicine in the field of human development and reproduction, making it a pillar of medical education and practice.

1.1.5. Vertebrate and Invertebrate Embryology

Both vertebrates and invertebrates are subject to many of the same embryological principles. As such, research on invertebrate embryology has contributed to the advancement of vertebrate embryology research. However, there are also many distinctions. For instance, many species of invertebrates release their larvae before they reach adulthood. At the conclusion of this stage, the animal begins to resemble its parent or parents as an adult for the first time. There are countless variations in invertebrate embryology, even though different invertebrate animals share some similarities. For example, many insects go through at least one larval stage of development, whereas spiders develop directly from the egg to the adult form. For many years, several so-called normal staging tables were created, primarily emphasizing external developmental characteristics, for the embryology of specific species. Because species differ in their developmental stages, it is challenging to compare them phylogenetically.

1.1.6. Human Embryonic Development

The growth and formation of the human embryo is known as human embryonic development or human embryogenesis. The early stages of development are characterized by the processes of cell division and cellular differentiation of the embryo. The biological process of human body development involves the transformation from a single-celled zygote to an adult human. When a sperm cell enters and successfully fuses with an egg cell (ovum), fertilization takes place. The germinal stage of development then starts when the genetic material from the sperm and egg combines to form the single-cell zygote. In humans, the first eight weeks of development are referred to as embryonic development; at the start of the ninth week, the embryo is called a fetus. There are 23 phases in eight weeks. The study of development in the first eight weeks following fertilization is known as human embryology. The typical gestational period, or 40 weeks of pregnancy, is approximately nine months. The period from fertilization through the early embryo's development and the completion of implantation in the uterus is known as the germinal stage. It takes roughly ten days for the germinal stage. The zygote starts to split during this phase, a process known as cleavage. After that, a blastocyst develops and is implanted in the uterus. The processes of neurulation and organogenesis come after the next stage of embryogenesis, known as gastrulation, during which the three germ layers of the embryo form through a process known as histogenesis. The fetus has a more complete set of developing organs and more distinguishable external features compared to the embryo. Throughout the entire process of embryogenesis, changes in cell growth, differentiation, and gene expression occur in a coordinated spatial and temporal manner. Other species go through a nearly

similar process, particularly chordates. The process by which a single fertilized egg becomes a complex organism made up of trillions of cells is known as human embryonic development. It is an amazing process. The process starts with fertilization, which is the union of an egg and sperm cell that creates a zygote. This historic occurrence ushers in a journey spanning multiple developmental stages, each distinguished by unique morphological and molecular alterations. The process of cleavage, which occurs shortly after fertilization, causes the zygote to divide rapidly, creating a hollow ball of cells known as a blastocyst. The trophoblast, or outer layer of cells, and the inner cell mass make up the blastocyst. The inner cell mass will eventually develop into the embryo proper, while the trophoblast will ultimately give rise to the placenta.

The blastocyst implants into the uterine lining six to seven days after fertilization, a process that is essential to establishing pregnancy. The inner cell mass continues to differentiate after implantation, resulting in the emergence of the ectoderm, mesoderm, and endoderm germ layers. The foundation for the development of all major tissues and organs in the human body is laid by this process called gastrulation. Structures like the nervous system, skin, hair, and nails are produced by the ectoderm. The mesoderm plays a role in the development of the heart, kidneys, blood vessels, muscles, and bones. The lining of the respiratory and digestive systems, as well as organs like the thyroid, pancreas, and liver, are formed by the endoderm. The complex three-dimensional structures of the developing embryo are formed by extensive proliferative, differentiating, and migrating processes of these germ layers. Basic organs and organ systems start to form in the embryo during a process known as organogenesis, which occurs as the embryo develops. Complex molecular signaling pathways that control organ specification, tissue patterning, and cell fate determination define this phase. For instance, signaling molecules like Sonic Hedgehog and bone morphogenetic proteins direct the process of neurulation, which results in the formation of the neural tube, a precursor to the central nervous system, from the ectoderm.

Concurrently, the mesoderm cells differentiate into blood vessels, the heart tube, and blood cells, forming the rudimentary cardiovascular system. Recognizable anatomical structures emerge from the embryo's further shaping by morphogenetic movements and tissue interactions. During the eight weeks following conception to the end of the embryonic period, the major organ systems have started to develop, albeit they are still in an immature state. The placenta is an organ that develops from the trophoblast and maternal tissues to nourish and support the developing embryo. The placenta acts as a conduit for the exchange of gases, nutrients, and waste products between the fetal and maternal circulations to ensure the growth and development of the embryo.

The intricate interaction of genetic, molecular, and environmental factors precisely orchestrates the highly dynamic and regulated process of embryonic development. Understanding the processes underlying human embryogenesis is crucial because disruptions or abnormalities during this critical time can result in congenital malformations or developmental disorders. A fertilized egg develops into a developing embryo with primitive organs and organ systems through a series of sequential events that make up the complex and intricate process of human embryonic development. Through the process of dissecting the cellular and molecular mechanisms that control embryogenesis, scientists can learn more about human development, disease processes, and

possible treatments. The study of embryology is still a dynamic area with significant effects on human health and welfare.

1.2. Historical Perspective and Significance of Embryology in Medicine

Embryology has been fundamental in shaping our knowledge of human development and has significantly contributed to medical progress over time. The history of embryology in medicine dates back to ancient civilizations, where studies of embryonic development were noted and incorporated into medical knowledge. However, it wasn't until the rise of modern science and technology that embryology became a distinct area of study with important implications for medicine.

Ancient Egyptian hieroglyphs representing the stages of fetal development in utero are among the first known observations of embryonic development. Similarly, the anatomical research and philosophical investigations of ancient Greek and Roman scholars such as Aristotle and Galen led to important advancements in the field of embryology. Galen's theory of preformation, which postulated that the embryo existed inside the sperm or egg in miniature form, shaped our understanding of embryology for centuries until it was disproved during the Renaissance. Through painstaking dissections and anatomical illustrations, early Renaissance anatomists like Leonardo da Vinci and Andreas Vesalius made revolutionary discoveries. Their observations established the basis for our knowledge of human anatomy and embryonic development. However, it wasn't until the 19th century, with the development of microscopy and experimental embryology, that embryology started to take shape as a separate scientific field.

The invention of the microscope allowed scientists to view cellular and subcellular structures in unprecedented detail, completely changing the field of embryological research. Through their studies of animal embryos, scientists like Karl Ernst von Baer and Wilhelm Roux made important advances in embryology during the 19th Century. The basic ideas of embryonic development are now understood thanks to von Baer's discovery of the germ layers and Roux's tissue grafting experiments. Research on embryos was further revolutionized in the late 19th and early 20th centuries by the development of genetics and developmental biology. The genetic basis of development was clarified by the rediscovery of Gregor Mendel's work on inheritance, and researchers were able to examine gene function and embryonic patterning in model organisms thanks to developments in experimental techniques like embryonic manipulation and transplantation. The fundamental role that embryology plays in comprehending human development and the causes of congenital diseases and birth defects account for much of its importance in medicine. By clarifying the molecular and cellular mechanisms underlying embryogenesis, researchers can identify genetic and environmental factors that contribute to developmental abnormalities and design targeted interventions to prevent or treat these conditions. Furthermore, the study of embryology is vital to assisted reproductive technologies like in vitro fertilization (IVF), as it helps to maximize success rates and guarantee the health of the resulting embryos.

Moreover, by shedding light on stem cell biology and developmental processes, embryology advances tissue engineering and regenerative medicine. Developing functional tissues in vitro for transplantation and regenerative therapies can be aided by knowledge of how tissues and organs develop during embryogenesis. The historical

perspective on embryology highlights its continuing importance in science and medicine. Embryology has greatly advanced medicine and influenced our understanding of human development, from prehistoric observations to contemporary molecular techniques. By deciphering the secrets of embryonic development, researchers are advancing novel treatments and interventions to enhance human health and well-being.

1.2.1. History

1.2.1.1. Ancient Egypt

The placenta was thought to be the seat of the soul in ancient Egypt, where knowledge of it dates at least that far. An Egyptian official held the title "Opener of the King's Placenta." An Akhenaten-era Egyptian text claimed that a human's ancestry begins with the egg that develops in a woman.

1.2.1.2. Ancient India

A variety of conceptions of embryology appeared in ancient Asia. Descriptions of the amniotic sac appear in the *Bhagavad Gita, Bhagavata Purana*, and the *Sushruta Samhita*. One of the Upanishads, known as the *Garbhopanisa,* states that the embryo is "like water in the first night; in seven nights it is like a bubble; at the end of half a month it becomes a ball. At the end of a month, it is hardened; in two months the head is formed." The Indian medical tradition in the Ayurveda also has conceptions of embryology from antiquity.

The development of the human embryo is mentioned in the ancient Buddhist text of Garbhāvakrāntisūtra (1st-4th century CE). It mentions the human gestation period of 38 days. The text describes embryonic development in the first three weeks as a liquid part of yogurt, and the differentiation of body parts such as arms, legs, feet, and head in the third month.

1.2.1.3. Ancient Greece

1.2.1.3.1. Pre-Socratic Philosophers

Numerous pre-Socratic philosophers are known to have held views on various facets of embryology, though later writers like Aristotle tend to present their opinions somewhat biasedly. Empedocles, who lived in the fifth century BC and whose opinions are recounted by Plutarch in the first century AD, claimed that the embryo receives its blood from four different vessels in total—two arteries and two veins. Additionally, he believed that sinews originated from equal parts earth and air.

He went on to say that men form within the first month and are fully developed in 50 days. Asclepiades concurred that men form in 50 days, but he thought women take two months to fully develop. One observation, variously credited to Alcmaeon of Croton or Anaxagoras of Clazomenae, states that the white of a chicken egg is comparable to the milk produced by mammals. According to Diogenes of Apollonia, bone and nerve development develop after a mass of flesh first forms. Diogenes understood that the placenta provided nourishment for the developing fetus. Additionally, he mentioned that the development of males took four months, while that of females took five months. He did not believe the embryo to be living. Alcmaeon is the first person known to have practiced dissection, and he also made some contributions. One theory, put forth by Parmenides, was that the male and female embryos were connected to one another, as well as to the right and left sides of the body, respectively. Both Epicurus and Democritus assert that the fetus receives its nourishment from the mother's mouth, and that the fetus receives similar nourishment from the mother's body through similar teats. A discussion of different perspectives on the length of time it takes for particular embryonic components to form can be found in

an anonymous document called the Nutriment. Did the male and female each have a seed that contributed to the developing embryo, or did only the male have a seed that developed into the embryo inside the female womb?

This was a topic of discussion among the ancient Greeks. One-seed theorists faced a challenge in trying to explain the offspring's maternal resemblance. Two-seed theorists had to deal with the question of why the female seed was necessary if the male already had a seed. Making the claim that the female seed was either inferior or inactive was a common solution to this issue. The seed's origin was another mystery. According to the encephalomyelogenic theory, the seed came from the bone marrow, brain, or both. Later, pangenesis was proposed to explain the general resemblance in the offspring's body by claiming that the seed was taken from the entire body.

The hematogenous theory, which claimed that the seed was extracted from the blood, later came into being. How or what form the progeny existed in the seed before developing into an embryo and a fetus was the subject of a third query. Preformationists assert that the seed already contained the progeny's body in an underdeveloped but preexisting form. Homoiomerous preformationism, anhomoiomerous preformationism, and homuncular preformationism were the three types of preformationism. The first states that the homoiomerous body parts (e.g., humerus bone) are pre-formed and already present in the seed.

According to the second, the anhomoiomerous portions were the ones that were performed. Finally, the third view held that the whole was already a unified organic thing. Preformationism was not the only view. According to epigenesists, parts of the embryo successively form after conception takes place.

1.2.1.4. Hippocrates

Hippocrates and the Hippocratic Corpus are credited with some of the most well-known early theories of embryology. Discussions about the embryo are typically included in discussions of obstetrics, or pregnancy and childbirth. The Hippocratic texts On Semen, On Acute Diseases, and the Development of the Child are among the most pertinent ones when it comes to embryology. Hippocrates asserted that fire initiates the development of the embryo and that food and breath given to the mother provide nourishment. The embryo's outer layer hardens and the fire inside consumes humidity, allowing bone and nerve to develop. To route nourishment to the belly, air channels are developed from the fire in the innermost part. Additionally, the enclosed fire promotes circulation and vein formation. Rather than describing what develops, Hippocrates attempts to describe the causes of development in this description. Hippocrates advances ideas akin to preformationism, asserting that the embryo's constituent parts develop at the same time. Hippocrates also held the view that the embryo is fed by the mother's blood. This blood flows and congeals to aid in the development of the fetus's flesh. Hippocrates deduced this theory from the observation that menstrual blood stops during pregnancy, suggesting that the blood is being directed toward fetal development. Hippocrates further asserted that the flesh differentiates into various body organs, drawing comparisons between this process and an experiment in which a mixture of substances submerged in water results in the formation of distinct layers. Hippocrates also made a comparison between the stalk and the umbilical cord, comparing the seed to the embryo.

1.2.1.5. Aristotle

According to Aristotle, the female provides the material for the development of the embryo, which is formed from menstrual blood, while

the male's semen shapes that material. Contrary to some previous theories, Aristotle believed that both the male and female contributed to the actual fetus. Aeschylus and some Egyptian traditions hold that the female womb only serves to nourish the developing fetus, which only receives nourishment from the male. The Melanesians, on the other hand, believed that the fetus is only a result of the female contribution. According to Aristotle, there are no outside factors that can affect how an embryo develops. Aristotle disagreed with Hippocrates in that he thought new body parts formed gradually over time as opposed to all developing at once. He also thought about whether a new part develops independently of any previously formed part or whether it derives from a previously formed part. He chose to support the latter theory on the grounds that different body parts are not similar to one another. He also discussed the mechanical and automatic processes involved in the development of fetal parts. He describes the embryo's development as starting in a liquid state when the female's secreted material combines with the male's semen, and then the surface starts to solidify as it interacts with heating and cooling processes. The heart, which Aristotle and many of his contemporaries thought to be the seat of reason and thought, is the first bodily part to differ. According to Aristotle, vessels connect to the uterus to provide food for the growing fetus. Some of the fetus's most solid parts cool and develop into nails, horns, hooves, beaks, and other features as they lose moisture due to heat. Internal heat removes moisture, forms bones and sinews, and dries out the flesh, resulting in skin. Aristotle also goes into great detail about how birds develop in their eggs. He went on to discuss the development of dolphin embryos, some shark embryos, and many other animal embryos. More than any other pre-modern author, Aristotle wrote extensively on the subject of embryology. His contributions to the field over several centuries included the introduction of classification schemes, a method of comparison between different animals, a discussion of the development of sexual characteristics, a comparison between the development of the embryo and mechanistic processes, and more.

1.2.1.6. Later Greek Embryology

Reportedly, some Stoics claimed that most parts of the body formed at once during embryological development. Some Epicureans claimed that the fetus is nourished by either the amniotic fluid or the blood and that both males and females supply material to the development of the fetus. According to the writings of Tertullian, Herophilus in the 4th century BC described the ovaries and fallopian tubes (but not past what was already described by Aristotle) and also dissected some embryos. One advance Herophilus made, against the conceptions of other individuals such as Aristotle, was that the brain was the center of intellect rather than the heart. Though not a part of Greek tradition, in Function 10, the formation of the embryo is likened to the curdling of milk into cheese, as described by Aristotle. Whereas Needham sees this statement in Function as part of the Aristotelian tradition, others see it as evidence that the milk analogy predates the Aristotelian Greek tradition and originates in Jewish circles. In addition, the Wisdom of Solomon (7:2) also has the embryo formed from menstrual blood. Soranus of Ephesus also wrote texts on embryology which went into use for a long time. Some rabbinic texts discuss the embryology of a female Greek writer named Cleopatra, a contemporary of Galen and Soranus, who was said to have claimed that the male fetus is complete in 41 days whereas the female fetus is complete in 81 days. Various other texts of less importance also appear and describe various aspects of embryology, though without making much progress from Aristotle. Plutarch has a chapter in one of his works titled "Whether was before, the hen or egg?" Discussion on embryological tradition also appears in many Neoplatonic traditions.

Next to Aristotle, the most impactful and important Greek writer on biology was Galen of Pergamum, and his works were transmitted throughout the Middle Ages. Galen discusses his understanding of embryology in two of his texts, those being his *On the Natural Faculties* and his *On the Formation of the Foetus*. There is an additional text spuriously attributed to Galen known as *On the Question of Whether the Embryo is an Animal*. Galen described embryological development in four stages. In the first stage, the semen predominates. In the second stage, the embryo is filled with blood. In the third stage, the main outlines of the organs have developed but various other parts remain undeveloped. In the fourth stage, formation is complete and has reached a stage where we can call it a child. Galen described processes that played a role in furthering the development of the embryo such as warming, drying, cooling, and combinations thereof. As this development plays out, the form of life of the embryo also moves from that of a plant to that of an animal (where the analogy between the root and umbilical cord is made). Galen claimed that the embryo forms from menstrual blood, by which his experimental analogy was that when you cut the vein of an animal and allow blood to flow out and into some mildly heated water, a sort of coagulation can be observed. He gave detailed descriptions of the position of the umbilical cord relative to other veins.

1.2.1.7. Patristics

The question of embryology is discussed among a number of early Christian writers, largely in terms of theological questions such as whether the fetus has value and/or when it begins to have value. Several Christian authors continued the classical discussions on the description of the development of the embryo, such as Jacob of Serugh. Passing reference to the embryo also appears in the eighth hymn of Ephrem the Syrian's *Paradise Hymns*. Many patristic treatments of embryology continued in the stream of Greek tradition. The earlier Greek and Roman view that it was not was reversed and all pre-natal infanticide was condemned. Tertullian held that the soul was present from the moment of conception. The Quinisext Council concluded that "we pay no attention to the subtle division as to whether the fetus is formed or unformed." At this time, then, the Roman practice of child exposure came to an end, where unwanted yet birthed children, usually females, were discarded by their parents to die. Other more liberal traditions followed Augustine, who instead viewed that the animation of life began on the 40th day in males and the 80th day in females but not prior. Before the 40th day for men and the 80th day for women, the embryo was referred to as the *embryo information*, and after this period was reached, it was referred to as the *embryo formatus*. The notion originating from the Greeks that the male embryo developed faster remained in various authors until it was experimentally disproven by Andreas Ottomar Goelicke in 1723.

Various patristic literature from different theological backgrounds, including Nestorian, Monophysite, and Chalcedonian, explore and debate three different perspectives on the relationship between the soul and the embryo. One perspective suggests that the soul exists prior to conception and enters the embryo at that moment (prohyparxis). Another perspective argues that the soul comes into being at the moment of conception (synhyparxis). A third perspective posits that the soul enters the body after it has been formed (methyparxis). The idea of pre-existing souls, proposed by Origen, fell out of favor after the fourth century. Both the other two perspectives gained acceptance, with the second position emerging as a reaction to Origen's beliefs. However, by the sixth century, this position was also rejected as being aligned with Origenism. Origen's writings

were condemned during the Second Origenist Controversy in 553. Supporters of prohyparxis often drew on Plato's concept of the eternal movement of the soul. Those in favor of the second position also referenced Plato but disagreed with the idea of the soul's eternal nature. Supporters of the third position appealed to both Aristotle and scripture, noting Aristotle's view on the progression of soul development from a plant-like state to a sensitive state in animals, culminating in a rational soul unique to humans. Furthermore, some scriptural texts were seen as implying the formation of the soul temporally after the formation of the body (namely Genesis 2:7; Exodus 21:22-23; Zachariah 12:1). In the Gregory of Nyssa*'s De hominis opificio* of, Aristotle's triparitate notion of the soul was accepted. Gregory also held that the rational soul was present at conception. Theodoret argued, based on Genesis 2:7 and Exodus 21:22, that the embryo is only ensouled after the body is fully formed. Based on Exodus 21:22 and Zachariah 12:1, the Monophysite Philoxenus of Mabbug claimed that the soul was created in the body 40 days after conception. In his *De opificio mundi*, the Christian philosopher John Philoponus claimed that the soul is formed after the body. Later still, the author Leontius held that the body and soul were created simultaneously, though it is also possible he held that the soul pre-existed the body.

Some Monophysites and Chalcedonians seemed to have been compelled into accepting *synhyparxis* in the case of Jesus because of their view that the incarnation of Christ resulted in both one hypostasis and one nature, whereas some Nestorians claimed that Christ, like us, must have had his soul formed after the formation of his body because, per Hebrews 4:15, Christ was like us in all ways but sin. (On the other hand, Leontinus dismissed the relevance of Hebrews 4:15 on the basis that Christ differed from us not only in sinfulness but also in conception without semen, making *synhyparxis* another of Christ's supernatural feats.) They felt comfortable holding this view, under their belief that the human nature of Jesus was separate from the divine hypostasis. Some Nestorians still wondered, however, if the body united with the soul at the moment the soul was created or whether it came with it only later. The Syriac author Babai argued for the former on the basis that the latter was hardly better than adoptionism. Maximus the Confessor ridiculed the Aristotelian notion of the development of the soul on the basis that it would make humans parents of both plants and animals. He held on to *synhyparxis* and regarded the other two positions both as incorrect extremes. After the 7th century, Chalcedonian discussion on embryology is slight, and the few works that touch on the topic support *synhyparxis*. But debate among other groups remains lively, still divided on similar sectarian grounds. The patriarch Timothy I argued that the Word first united with the body, and only later with the soul. He cited John 1:1, claiming on its basis that the Word became flesh first, not a human being first. Then, Jacob of Edessa rejected *prohyparxis* because Origen had defended it and *methyparxis* because he believed that it made the soul ontologically inferior and was only being made for the body. Then, Moses Bar Kepha claimed, for Christological reasons as a Monophysite, that only *synhyparxis* was acceptable. He claimed that Genesis 2:7 has no temporal sequence and that Exodus 21:22 regards the formation of the body and not the soul and so is not relevant. To argue against *methyparxis*, he reasoned that body and soul are both present at death and, because what is at the end must correspond to what is also at the beginning, conception must also have body and soul together.

1.2.1.8. Embryology in Jewish Tradition

Many Jewish authors also discussed notions of embryology, especially as they appear in the Talmud. Much of the embryological data in the Talmud is part of discussions related to the impurity of the mother after childbirth. The embryo was described as the *peri habbetten* (fruit of the body) and it developed through various stages: (1) *golem* (formless and rolled-up) (2) *shefir meruqqam* (embroidered fetus) (3) *ubbar* (something carried) (4) *walad* (child) (5) *walad shel qayama* (viable child) (6) *ben she-kallu khadashaw* (child whose months have been completed). Some mystical notions regarding embryology appear in the Sefer Yetzirah. The text in the Book of Function relating to the fetus forming by analogy to the curdling of milk into cheese was cited in the Babylonian Talmud and even greater detail in the Midrash: "When the womb of the woman is full of retained blood which then comes forth to the area of her menstruation, by the will of the Lord comes a drop of white-matter which falls into it: at once the embryo is created. [This can be] compared to milk being put in a vessel: if you add to it some lab-ferment [drug or herb], it coagulates and stands still; if not, the milk remains liquid." The Talmud sages held that there were two seeds that participated in the formation of the embryo, one from the male and one from the female and that their relative proportions determine whether that develops into a male or a female. In the Tractate Nidda, the mother was said to provide a "red seed" which allows for the development of skin, flesh, hair, and the black part of the eye (pupil), whereas the father provides the "white seed" which forms the bones, nerves, brain, and the white part of the eye. And finally, God himself was thought to provide the spirit and soul, facial expressions, capacity for hearing and vision, movement, comprehension, and intelligence. Not all strands of Jewish tradition accepted that both the male and female contributed parts to the formation of the fetus. The 13th-century medieval commentator Nachmanides, for example, rejected the female contribution. In Tractate Hullin in the Talmud, whether the organs of the child resemble more closely those of the mother or father is said to depend on which one contributes more matter to the embryo depending on the child. Rabbi Ishmael and other sages are said to have disagreed on one matter: they agreed that the male embryo developed on the 41st day, but disagreed on whether this was the case for the female embryo. Some believed that the female embryo was completed later, whereas others held that they were finished at the same time. The only ancient Jewish authors who associated abortion with homicide were Josephus and Philo of Alexandria in the 1st century. Some Talmudic texts discuss magical influences on the development of the embryo, such as one text that claims that if one sleeps on a bed that is pointed north-south will have a male child. According to Nachmanides, a child born of a cold drop of semen will be foolish, one born from a warm drop of semen will be passionate and irascible, and one born from a semen drop of medium temperature will be clever and level-headed. Some Talmudic discussions follow from Hippocratic claims that a child born in the eighth month could not survive, whereas others follow Aristotle in claiming that they sometimes could survive. One text even says that survival is possible in the seventh month, but not the eighth. Talmudic embryology, in various aspects, follows Greek discourses, especially from Hippocrates and Aristotle, but in other areas, makes novel statements on the subject.

1.2.1.9. Embryology in the Islamic Tradition

Passing reference to embryological notions also appears in the Qur'an (22:5), where the development of the embryo proceeds in four stages from drop to a blood clot, to a partially developed stage, to a fully developed child.

The notion of clay turning into flesh is seen by some as analogous to a text by Theodoret that describes the same process. The four stages of development in the Qur'an are similar to the four stages of embryological development as described by Galen. In the early 6th century, Sergius of Reshaina devoted himself to the translation of Greek medical texts into Syriac and became the most important figure in this process. Included in his translations were the relevant embryological texts of Galen. Anurshirvan founded a medical school in the southern Mesopotamian city of Gundeshapur, known as the Academy of Gondishapur, which also acted as a medium for the transmission, reception, and development of notions from Greek medicine. These factors helped the transmission of Greek notions on embryology, such as found in Galen, to enter the Arabian milieu. Very similar embryonic descriptions also appear in the Syriac Jacob of Serugh's letter to the Archdeacon Mar Julian.

1.2.2. Terminology in Embryology

The field of embryology uses specialized terminology to explain the complex structures and processes that go into the formation of organisms from fertilization to birth or hatching. The field of developmental biology, specifically embryology, uses specialized terminology to explain the complex structures and processes involved in the formation of organisms from fertilization to birth or hatching. Basic terms in the field of embryology include 'fetus,' which refers to the later stages of prenatal development, and 'embryo,' which refers to the early developmental stage after fertilization. The terms "ectoderm," "mesoderm," and "endoderm," which give rise to different tissues and organs through processes like gastrulation and neurulation, are fundamental to the language of embryology. While neurulation results in the formation of the neural tube, the precursor to the central nervous system, gastrulation involves the transformation of the blastula into a structure with three distinct layers. Furthermore, organs such as the placenta, chorion, amnion, yolk sac, and allantois are essential for promoting the growth of the embryo and enabling the exchange of nutrients between the developing embryo and its mother's surroundings. Another crucial concept in embryology is organogenesis, the process by which cells organize and differentiate into specialized structures. Furthermore, knowledge of concepts like somites, teratogens, and stem cells is essential to comprehend the variables that affect embryonic development and the risk of birth defects. Overall, to appropriately characterize, evaluate, and comprehend the intricate processes underpinning the development of organisms, researchers, clinicians, and educators must be conversant with the terminology used in embryology. Like any scientific discipline, embryology has its specialized vocabulary for describing the various structures, functions, and developmental stages.

Some key terms commonly encountered in embryology:

1. **Embryo:** The early stage of development of a multicellular organism, following fertilization and preceding the fetal stage.
2. **Fetus:** The later stage of prenatal development in mammals, following the embryo stage and continuing until birth.
3. **Germ Layers:** Three primary layers of cells formed during gastrulation in the developing embryo: ectoderm, mesoderm, and endoderm. These layers give rise to different tissues and organs in the body.
4. **Gastrulation:** The process by which the blastula undergoes morphological changes to form the three germ layers.
5. **Blastula:** An early stage

of embryonic development characterized by a hollow sphere of cells, formed after several rounds of cell division following fertilization.

6. **Implantation:** The process by which the blastocyst attaches to and embeds itself in the lining of the uterus, allowing for pregnancy to be established.
7. **Neurulation:** The process of forming the neural tube from the ectoderm, which gives rise to the central nervous system.
8. **Somite:** Paired blocks of mesoderm cells that form along the sides of the neural tube during early development. Somites give rise to structures such as vertebrae, ribs, and skeletal muscles.
9. **Placenta:** An organ formed during pregnancy that connects the developing fetus to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's bloodstream.
10. **Chorion:** The outermost fetal membrane that contributes to the formation of the placenta.
11. **Amnion:** The innermost fetal membrane that encloses the amniotic fluid, providing protection and cushioning for the developing embryo/fetus.
12. **Yolk Sac:** A membranous sac attached to the embryo's gut, initially providing nutrients for the developing embryo before the placenta forms.
13. **Allantois:** A sac-like structure involved in waste storage and gas exchange in avian and reptilian embryos. In mammals, it contributes to the formation of the umbilical cord and urinary bladder.
14. **Organogenesis:** The process of organ formation during embryonic development, involving the differentiation, growth, and organization of cells into specialized structures.
15. **Teratogen:** Any substance, organism, or physical agent that can disrupt normal embryonic development and cause birth defects.
16. **Stem Cells:** Undifferentiated cells with the potential to develop into various cell types. They play a crucial role in embryonic development and tissue regeneration.

These terms represent only a fraction of the extensive vocabulary used in embryology. Understanding and applying this terminology is essential for accurately describing and comprehending the intricate processes of embryonic development.

1.3. Molecular Regulation and Signaling

Molecular biology has enabled new ways to investigate embryology and improve our comprehension of both normal and aberrant development. Advances in embryology are attributed to the sequencing of the human genome and the development of methods to study gene regulation at various levels of complexity. Thus, the history of embryology has developed with each chapter, adding to our understanding at the anatomical, biochemical, and molecular levels. The human genome contains about 23,000 genes, which is only about one-fifth of the predicted total before the Human Genome

Project was completed. However, the number of proteins derived from these genes aligns more closely with the originally predicted number of genes due to different levels of regulation. The theory of one gene per protein has been refuted. Thus, multiple proteins can arise from a single gene through various mechanisms.

Gene expression can be regulated at several levels: (1) different genes may be transcribed, (2) nuclear deoxyribonucleic acid (DNA) transcribed from a gene may be selectively processed to regulate which RNAs reach the cytoplasm to become messenger RNAs (mRNAs), (3) mRNAs may be selectively translated, and (4) proteins made from the mRNAs may be differentially modified.

1.3.1. Gene Transcription

Genes are contained in a complex of DNA and proteins (mostly histones) called chromatin, and its basic unit of structure is the nucleosome (Figure 1.1). Each nucleosome is composed of an octamer of histone proteins and approximately 140 base pairs of DNA. Nucleosomes are joined into clusters by binding of DNA between nucleosomes (linker DNA) with other histone proteins (H1 histones; Figure 1.1). Nucleosomes keep the DNA tightly coiled, preventing transcription. In this inactive state, chromatin appears as beads of nucleosomes on a string of DNA and is referred to as heterochromatin. For transcription to occur, this DNA must be uncoiled from the nucleosomes. In this uncoiled state, chromatin is referred to as euchromatin.

DNA strands contain genes, which are composed of sections known as exons that can be translated into proteins and introns that are inserted between exons but do not translate into proteins (Figure 1.2). A typical gene contains exons and introns as well as a promoter region that binds RNA polymerase to start transcription, a transcription initiation site, a translation initiation site that identifies the first amino acid in the protein, a translation termination codon, and a 3′ untranslated region that contains a sequence known as the poly A addition site that helps stabilize mRNA, allows it to leave the nucleus, and allows it to be translated into protein (Figure 1.2).

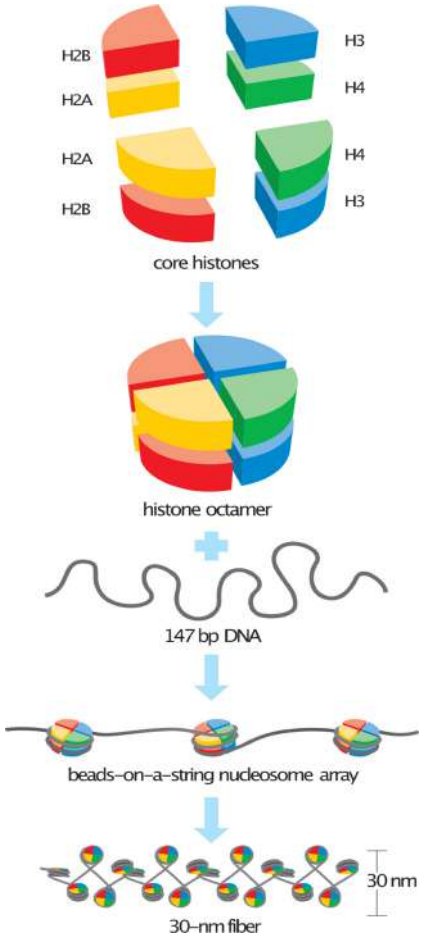


Figure 1.1. *Drawing showing nucleosomes that form the basic unit of chromatin. Each nucleosome consists of an octamer of histone proteins and approximately 140 base pairs of DNA. Nucleosomes are joined into clusters by linker DNA and other histone proteins.*

Source: By David O Morgan – The Cell Cycle. Principles of Control., Attribution, https://commons.wikimedia.org/w/index.php?curid=89674546.

Conventionally, a gene's 5' and 3' regions are described in terms of the RNA that the gene transcribes. The promoter region is located upstream from the transcription initiation site, and transcription proceeds from the 5' to the 3' end of DNA (Figure 1.2). The sequence TATA is typically present in the promoter region, which is where RNA polymerase binds. This region is referred to as the TATA box (Figure 1.2). However, the polymerase needs other proteins known as transcription factors to bind to this site (Figure 1.3). In addition, transcription factors contain a transactivating domain that either stimulates or inhibits the transcription of the gene whose promoter or enhancer they have bound. Transcription factors work in concert with other proteins to trigger the unwinding of the DNA nucleosome complex, the release of polymerase to initiate transcription of the DNA template, and the inhibition of the formation of new nucleosomes.

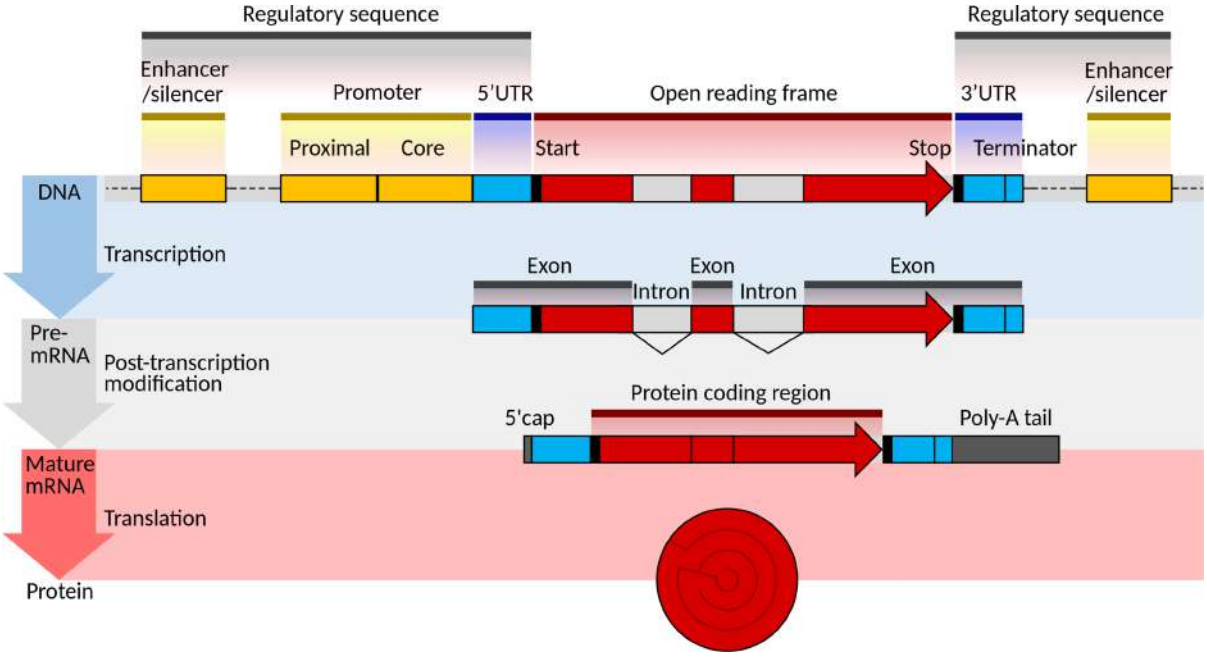


Figure 1.2. *Drawing of a "typical" gene showing the promoter region containing the TATA box; exons that contain DNA sequences that are translated into proteins; introns; the transcription initiation site; the translation initiation site that designates the code for the first amino acid in a protein; and the 3′ untranslated region that includes the poly A addition site that participates in stabilizing the mRNA, allows it to exit the nucleus and permits its translation into a protein.*

Source: https://en.wikipedia.org/wiki/File:Gene_structure_eukaryote_2_annotated.svg.

Enhancers are DNA regulatory elements that cause promoters to be used to regulate the rate and efficiency of transcription from the promoter. Enhancers are not required to be located near a promoter; they can be found anywhere along the DNA strand. Enhancers, like promoters, bind transcription factors via the transactivating domain of the transcription factor and control the expression timing and cell-specific location of a gene.

For instance, distinct enhancers within a gene can be utilized to control the expression of the same gene in various tissues. Three distinct enhancers are found in the PAX6 transcription

factor, which controls the expression of the gene in the relevant tissue and is involved in the development of the pancreas, the eye, and the neural tube. Enhancers function by either facilitating RNA polymerase binding or by changing chromatin to reveal the promoter. Sometimes known as silencers, enhancers can prevent transcription.

Because of this phenomenon, transcription factors that bind to distinct enhancers can activate one gene while silencing another. Therefore, transcription factors themselves consist of a transactivating domain that attaches to a promoter or enhancer and either activates or inhibits the gene that these elements regulate, in addition to a DNA binding domain that is specific to a particular region of DNA.

1.3.1.1. DNA Methylation Represses Transcription

Gene transcription is repressed when cytosine bases in the promoter regions of genes are methylated. Thus, this mechanism silences certain genes. For instance, this methylation process causes one of the X chromosomes to become inactive (X chromosome inactivation) in every female cell.

Similarly, methylation suppresses the expression of genes in various cell types. For example, muscle cells produce muscle proteins because the majority of their promoter DNA is unmethylated, but they do not produce blood proteins because their DNA is heavily methylated. Each cell can preserve its distinctively differentiated state in this manner. Genomic imprinting, in which only a gene inherited from the mother or father is expressed while the other gene is silenced, is also caused by DNA methylation. Human spermatogenesis and oogenesis result in the imprinting of 40 to 60 genes and the establishment of their methylation patterns. By preventing transcription factors from binding to DNA or by changing histone binding, methylation silences DNA and causes nucleosomes to stabilize and tightly coil untranscribed DNA.

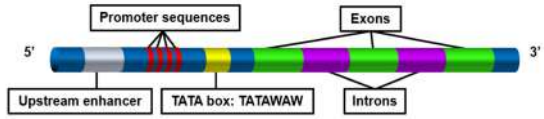


Figure 1.3. *Drawing showing binding of RNA polymerase II to the TATA box site of the promoter region of a gene. This binding requires a complex of proteins plus an additional protein called a transcription factor. Transcription factors have their specific DNA-binding domain and function to regulate gene expression.*

Source: By Luttysar – Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=63663344.

1.3.2. Other Regulators of Gene Expression

Nuclear RNA (nRNA) or occasionally pre-messenger RNA, is a gene's first transcript. Because introns are spliced out when nRNA travels from the nucleus to the cytoplasm, nRNA is longer than mRNA. Cells can produce various proteins from a single gene by using this splicing process. For instance, a process known as alternative splicing allows exons to be "spliced" in various patterns by deleting distinct introns (Figure 1.4).

Spliceosomes, which are complexes of small nuclear RNAs (snRNAs) and proteins that identify particular splice sites at the 5′ or 3′ ends of the nRNA, carry out the process. Splicing isoforms, also known as splice variants or alternative splice forms, are proteins that are produced from the same gene, allowing different cell types to use the same gene to make proteins unique to them. For instance, the functions of the WT1 gene's isoforms differs in gonadal versus kidney development.

A protein's function may be impacted by post-translational changes that occur after it is made (translated). For instance, some proteins require phosphorylation or cleavage to become active. Others must target particular cell regions, be released from sequestered sites, or combine with other proteins. There are numerous regulatory levels involved in the synthesis and activation of proteins, meaning that even though there are only 23,000 genes in the human genome, the total number of proteins that could potentially be synthesized is likely closer to five times the number of genes.

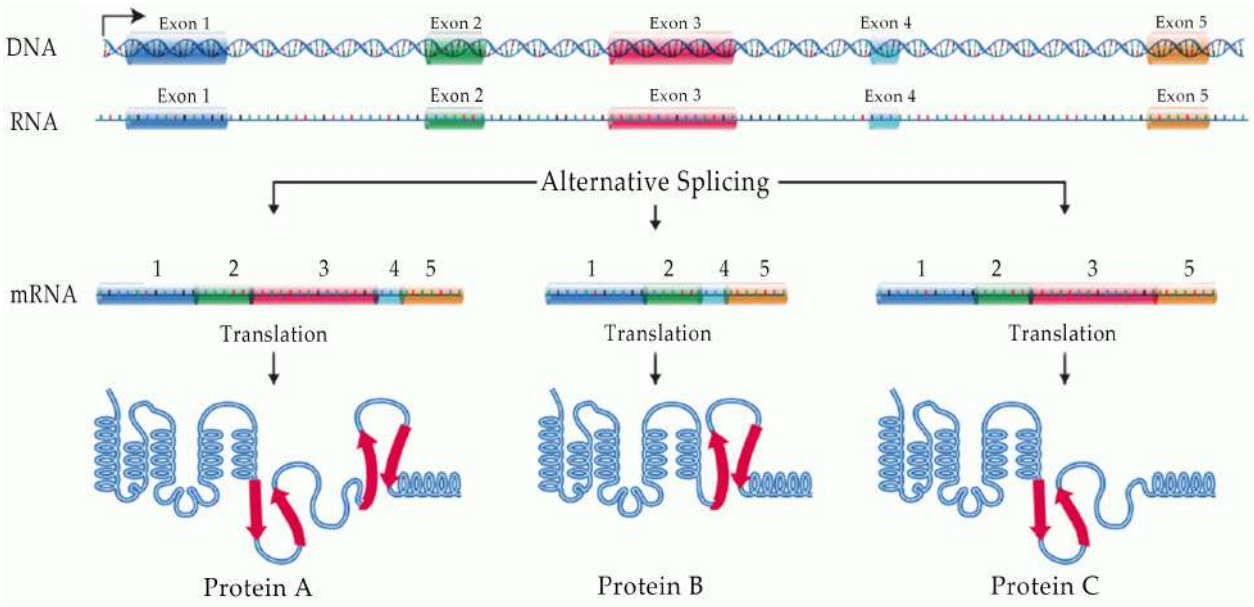


Figure 1.4. *Drawing of a hypothetical gene illustrating the process of alternative splicing to form different proteins from the same gene. Spliceosomes recognize specific sites on the initial transcript of nRNA from a gene. Based on these sites, different introns are "spliced out" to create more than one protein from a single gene. Proteins derived from the same gene are called splicing isoforms.*

Source: By National Human Genome Research Institute – http://www.genome.gov/Images/EdKit/bio2j_large.gif, Public Domain, https://commons.wikimedia.org/w/index.php?curid=2132737.

1.3.3. Induction and Organ Formation

Interactions between tissues and cells lead to the formation of organs. Most frequently, a process known as induction occurs when one set of cells or tissues influences another set of cells or tissues to alter their fate. One type of cell or tissue acts as the inducer in each of these interactions, producing a signal, while another acts as the responder to that signal. Competence is the ability to react to such a signal; to be competent, the responding tissue must be activated by a competence factor. The term "epithelial-mesenchymal interactions" refers to various inductive interactions that take place between mesenchymal and epithelial cells (Figure 1.5). While mesenchymal cells have a fibroblastic appearance and are distributed throughout extracellular matrices, epithelial cells are connected in tubes or sheets (Figure 1.5). Examples of epithelial-mesenchymal interactions include: the endoderm of the ureteric bud and the mesenchyme from the metanephric blastema to produce nephrons in the kidney; the limb mesenchyme with the overlying ectoderm (epithelium) to

produce limb outgrowth and differentiation; and the gut endoderm and surrounding mesenchyme to produce gut-derived organs, such as the liver and pancreas. Two epithelial tissues can also interact inductively, as in the case of the lens being induced by the optic cup's epithelium. Crosstalk between the two tissues or cell types is necessary for differentiation to continue, even though the inductive event is initiated by an initial signal from the inducer to the responder.

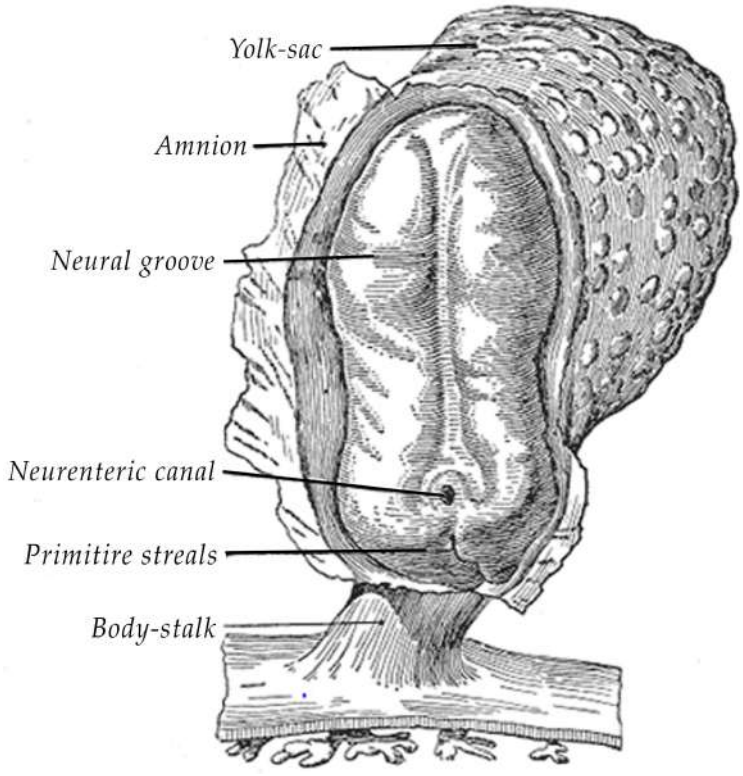


Figure 1.5. *Drawing illustrating an epithelial-mesenchymal interaction. Following an initial signal from one tissue, a second tissue is induced to differentiate into a specific structure. The first tissue constitutes the inducer, and the second is the responder. Once the induction process is initiated, signals (arrows) are transmitted in both directions to complete the differentiation process.*

Source: By Henry Vandyke Carter – Henry Gray (1918) Anatomy of the Human Body (see book section below) Bartleby.com: Gray's Anatomy, Plate 17, Public Domain, https://commons.wikimedia.org/w/index.php?curid=792208.

1.3.4. Cell Signaling

For induction, conference of competency to respond, and crosstalk between inducing and responding cells, cell-to-cell signaling is necessary. These channels of communication are created by either juxtacrine interactions, which do not involve diffusible proteins, or paracrine interactions, in which proteins synthesized by one cell diffuse over short distances to interact with other cells. Growth and differentiation factors (GDFs), also known as paracrine factors, are the diffusible proteins that mediate paracrine signaling.

1.3.4.1. Signal Transduction Pathways

1.3.4.1.1. Paracrine Signaling

Paracrine factors must first activate a signal transduction pathway directly or obstruct the activity of a pathway inhibitor (inhibiting an inhibitor, as is the case with hedgehog signaling). A signaling molecule called a ligand and a receptor are components of signal transduction pathways. With an extracellular domain (the ligand-binding region), a transmembrane domain, and a cytoplasmic domain, the receptor spans the cell membrane. A ligand that attaches to its receptor causes the receptor to change conformation, activating the cytoplasmic domain. This activation typically results in the receptor gaining enzymatic activity, most commonly in the form of a kinase that can phosphorylate other proteins by using ATP as a substrate. Phosphorylation then causes these proteins to phosphorylate other proteins, starting a chain reaction of protein interactions that eventually triggers a transcription factor. Gene expression is then either stimulated or inhibited by the transcription factor. The pathways are multiple and intricate, sometimes involving one protein inhibiting another, which then triggers another protein (similar to hedgehog signaling).

1.3.4.1.2. Juxtacrine Signaling

Diffusable factors are not involved in juxtacrine signaling, but it is mediated through signal transduction pathways nonetheless. Rather, juxtacrine signaling takes place in three ways: (1) A protein on one cell surface engages in a paracrine-like process with a receptor on a neighboring cell. One instance of this kind of signaling is the Notch pathway. When cells have Delta, Serrate, or Jagged proteins in their cell membranes, the Notch receptor protein stretches across the membrane and attaches itself to those cells. A portion of the Notch protein on the cytoplasmic side of the membrane is cleaved when one of these proteins binds to it and changes its conformation. To start the expression of a gene, the cleaved section binds to a transcription factor. Particularly crucial for somite segmentation, blood vessel specification, and neuronal differentiation is notch signaling. (2) Ligands released by one cell into the extracellular matrix interact with receptors on nearby cells. The environment that cells live in is called the extracellular matrix. Large molecules secreted by cells make up this environment, such as hyaluronic acid, collagen, and proteoglycans (chondroitin sulfates), as well as glycoproteins like laminin and fibronectin. These molecules offer cells a surface upon which they can adhere or move. For instance, fibronectin molecules form scaffolds for cell migration, and laminin and type IV collagen are elements of the basal lamina for epithelial cell attachment. Integrins are receptors that bind extracellular substances like laminin and fibronectin to cells. The cytoskeletal apparatus of a cell is "integrated" by these receptors with matrix molecules (e.g., actin microfilaments), which enables the use of contractile proteins like actin to migrate along matrix scaffolding. Additionally, integrins can control differentiation and induce the expression of genes, as in the case of chondrocytes, which need to be connected to the matrix to form cartilage. 3) Gap junctions allow signals to be directly transmitted from one cell to another. These junctions function as channels that allow ions and tiny molecules to move between cells. Because it enables coordinated action amongst closely connected cells, such as the gut and neural tube's epithelia, communication of this kind is crucial. The connexin proteins that make up the junctions themselves create a channel that is "connected" between neighboring cells.

It's crucial to remember that the signal transduction process has a lot of redundancy built in. For instance, paracrine signaling molecules frequently have a large family tree, meaning that the loss of one gene in the family may be made up for by the presence of other

genes. Therefore, aberrant development or death is not always the outcome of a gene mutation that results in the loss of function of a signaling protein. Furthermore, there is communication among pathways, making them closely linked. There are many more locations to control signaling thanks to these connections.

1.3.4.2. Paracrine Signaling Factors

Also known as GDFs, paracrine signaling factors (also known as ligands) are widely distributed. The majority belong to four families, and it is common practice to use members of these families to control the differentiation and development of different organ systems. Furthermore, the same GDFs regulate organ development throughout the animal kingdom from Drosophila to humans. The four groups of GDFs include the fibroblast growth factor (FGF), WNT, hedgehog, and transforming growth factor-β (TGF-β) families. Each family of GDFs interacts with its own family of receptors, and these receptors are as important as the signal molecules themselves in determining the outcome of a signal.

1.3.4.2.1. Fibroblast Growth Factors

Originally named for their ability to promote the growth of fibroblasts in culture, FGF genes have since been identified; by modifying their initiation codons or RNA splicing, they can produce hundreds of different protein isoforms. Currently, about two dozen genes are known to exist. These genes produce FGF proteins, which in turn stimulate a group of tyrosine receptor kinases known as fibroblast growth factor receptors (FGFRs). These receptors then cause a number of signaling pathways to become active. FGFs play a special role in mesoderm differentiation, angiogenesis, and axon growth. While there is redundancy within the family, meaning that FGFs can occasionally take the place of one another, particular developmental events may be attributed to individual FGFs. FGF8, for instance, is necessary for the development of certain brain regions and limbs.

1.3.4.2.2. Hedgehog Proteins

The hedgehog gene was given its name because it produced a pattern of bristles on Drosophila legs that resembled a hedgehog. Three hedgehog genes exist in mammals: the desert, Indian, and sonic hedgehog genes. Numerous developmental processes, such as limb patterning, neural tube induction and patterning, somite differentiation, gut regionalization, and others, are influenced by the sonic hedgehog. The hedgehog family's patched receptor attaches to a protein known as Smoothened. The hedgehog signal is transduced by the Smoothened protein, but Patched blocks it until the hedgehog protein attaches to this receptor. Therefore, rather than directly activating the transducer, the paracrine factor hedgehog's function in this example is to attach to its receptor and remove the inhibition of a transducer that would ordinarily be active.

1.3.4.2.3. WNT Proteins

There are at least 15 different WNT genes that are related to the segment polarity gene, wingless in Drosophila. Their receptors are members of the frizzled family of proteins. WNT proteins are involved in regulating limb patterning, midbrain development, and some aspects of somite and urogenital differentiation among other actions.

1.3.4.3. The TGF-β Superfamily

The TGF-β ss-superfamily has more than 30 members and includes the TGF-βs, the bone morphogenetic proteins, the activin family, the Müllerian inhibiting factor (MIF, anti-Müllerian hormone), and others. The first member of the family, TGF-β1, was isolated from virally transformed cells. TGF-β members are important for extracellular matrix formation and epithelial

branching that occurs in lung, kidney, and salivary gland development. The BMP family induces bone formation and is involved in regulating cell division, cell death (apoptosis), and cell migration among other functions.

1.3.4.4. Other Paracrine Signaling Molecules

Neurotransmitters, such as norepinephrine and serotonin, are another class of paracrine signaling molecules that are significant during development. They bind to receptors like proteins do and function as ligands. These molecules serve as crucial signals for embryonic development in addition to acting as transmitters for neurons. For instance, a wide variety of receptors, the majority of which are G protein-coupled receptors, bind to serotonin (5HT). Through its action on these receptors, 5HT controls a range of cellular processes, such as the division and migration of cells, as well as the establishment of laterality, gastrulation, heart development, and other early stages of differentiation. In addition to acting through receptors, norepinephrine also seems to be involved in the apoptosis of other cell types and interdigital spaces.

1.4. Gametogenesis: Conversion of Germ Cells into Male and Female Gametes

Gametogenesis is the process by which germ cells differentiate into mature male and female gametes (sperm and egg). A tightly controlled series of cellular and molecular processes guarantee the creation of viable gametes that can be fertilized, resulting in this amazing metamorphosis. Spermatogenesis, which occurs in the seminiferous tubules of the testes, is the first step in the gametogenesis process in males. The precursor cells, called spermatogonia, divide during mitosis to create primary spermatocytes, which subsequently go through meiosis I to become secondary spermatocytes. After going through meiosis II, these secondary spermatocytes produce haploid spermatids.

Lastly, spermatids go through structural and morphological changes to become mature spermatozoa during the process of spermiogenesis. These spermatozoa are highly specialized cells that have a flagellum for motility, a midpiece full of mitochondria for energy production, and a head that houses the genetic material. In females, oogenesis—which happens inside the ovaries—is the process by which gametogenesis happens. In contrast to spermatogenesis, oogenesis starts during the development of the embryo and stops during prophase I of meiosis until puberty. A tiny percentage of primary oocytes begin monthly development again during puberty due to hormonal influences. One or more primary oocytes go through meiosis I to create a secondary oocyte and a polar body during each menstrual cycle. Only at fertilization, when the secondary oocyte divides to produce a mature ovum and another polar body, is Meiosis II finished. The developed ovum has organelles like mitochondria that produce energy as well as the genetic material required for fertilization.

Gametogenesis in both males and females is regulated by several important factors. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are two important hormones that stimulate and regulate the process. While estrogen and progesterone produced by the ovaries in females regulate oogenesis and prime the reproductive tract for fertilization and implantation, testosterone produced by Leydig cells in the testes in males stimulates spermatogenesis. For most organisms, gametogenesis is a highly efficient process that is necessary for sexual reproduction. Nonetheless, irregularities or disturbances in the development of gametes may result in

infertility or reproductive diseases. Numerous factors can affect gametogenesis and fertility, including genetic mutations, environmental factors, and hormonal imbalances.

To sum up, the process of gametogenesis is intricate and strictly controlled, transforming germ cells into fully developed male and female gametes. Male and female spermatogenesis and oogenesis, respectively, are successive phases of cell division and differentiation that result in the production of specialized cells that can fertilize. Addressing infertility, enhancing assisted reproductive technologies, and expanding our understanding of reproductive biology all depend on our ability to comprehend the mechanisms underlying gametogenesis.

1.4.1. Primordial Germ Cells

The process by which the female gamete, the oocyte, and the male gamete, the sperm, combine to form a zygote, is known as fertilization, and it marks the beginning of development.

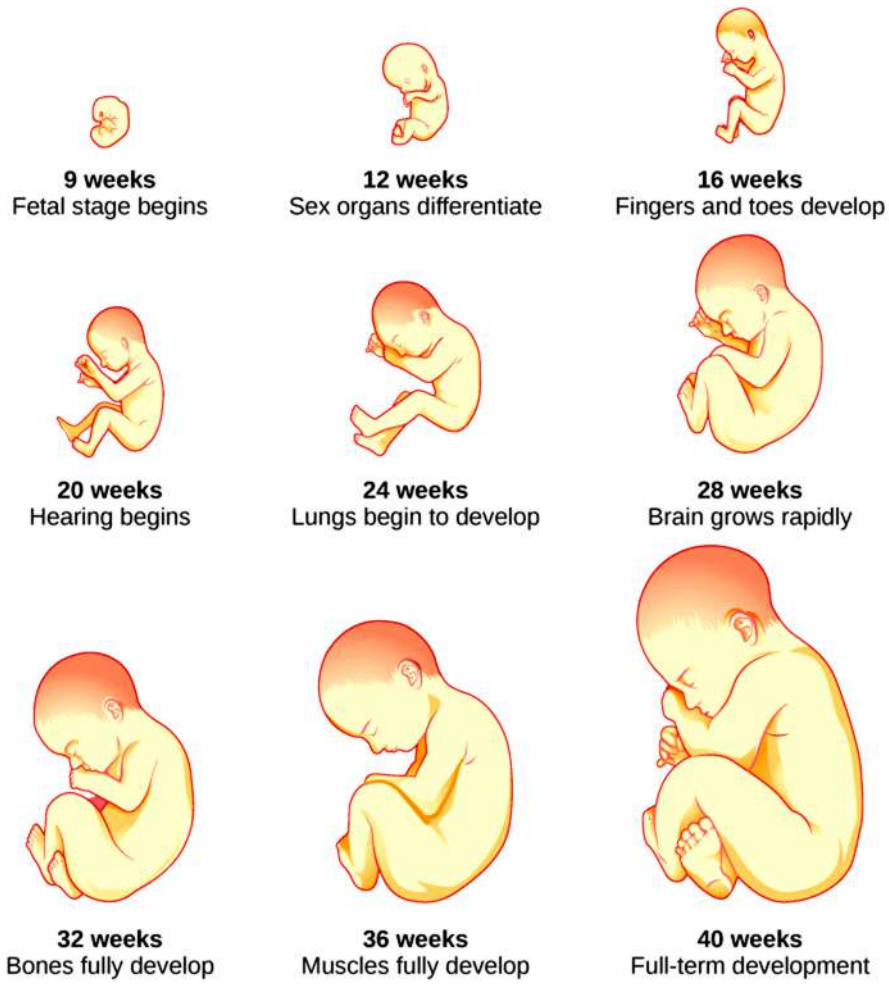


Figure 1.6. *The development of a human embryo.*

Source: https://courses.lumenlearning.com/wm-lifespandevelopment/chapter/prenatal-development/.

Primordial germ cells (PGCs), which form in the epiblast during the second week and migrate to the yolk sac wall, are the source of gametes (Figure 1.6). These cells start to move from the yolk sac into the developing gonads during the fourth week, and arrive by the end of the fifth week. Both during their migration and upon entering the gonad, mitotic divisions proliferate. Germ cells go through gametogenesis, which includes cytodifferentiation to finish their maturation and meiosis to reduce the number of chromosomes, to get ready for fertilization.

1.4.2. The Chromosome Theory of Inheritance

Certain genes on chromosomes inherited from the mother and father define an individual's traits. About 23,000 genes are located on 46 chromosomes in humans. Since they are typically inherited together, genes on the same chromosome are referred to as linked genes. Chromosomes arise as 23 homologous pairs in somatic cells, forming the diploid number 46. The autosomes, one pair of sex chromosomes, and 22 pairs of matching chromosomes are all present. The person is genetically male if the sex pair is XY, and genetically female if the pair is XX. Each pair's chromosomes come from the paternal gamete, the sperm, and the maternal gamete, the oocyte. As a result, each gamete has a haploid number of 23 chromosomes, and the diploid number of 46 is restored when the gametes unite during fertilization.

1.4.2.1. Mitosis

Mitosis is the process by which one cell divides into two daughter cells that are genetically identical to the parent cell. Each daughter cell receives a total of 46 chromosomes. Each chromosome replicates its deoxyribonucleic acid (DNA) before a cell goes through mitosis. During this replication phase, chromosomes are incredibly long, dispersed throughout the nucleus, and invisible under a light microscope. At the start of mitosis, the chromosomes coil, contract, and condense; these processes signal the beginning of prophase. At this stage, each chromosome is made up of two parallel subunits called chromatids, which are connected in a small region known as the centromere. The chromosomes continue to shorten, thicken, and condense during prophase (Figure 1.7(A)), but the chromatids are not distinguishable until prometaphase (Figure 1.7(B)). During metaphase, the chromosomes align in the equatorial plane, making their doubled structure clearly visible. (Figure 1.7(C)). Microtubules that run from the centromere to the centriole connect, forming the mitotic spindle. Each chromosome's centromere soon divides, signaling the start of anaphase and the migration of chromatids to the opposite poles of the spindle. Ultimately, during telophase, chromosomes lengthen and uncoil, the nuclear envelope reforms, and the cytoplasm divides (Figure 1.7(D)–(F)). To maintain the same number of chromosomes as the mother cell, each daughter cell receives half of the doubled chromosome material.

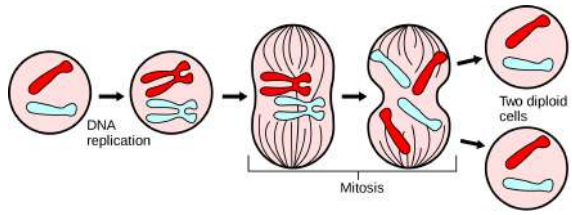


Figure 1.7. *Various stages of mitosis. In prophase, chromosomes are visible as slender threads. Doubled chromatids become visible as individual units during metaphase. At no time during division do members of a chromosome pair unite. Blue, paternal chromosomes; red, maternal chromosomes.*

Source: By Mysid – Vectorized in CorelDraw by Mysid from https://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html., Public Domain, https://commons.wikimedia.org/w/index.php?curid=1414818.

1.4.2.2. Meiosis

Meiosis is the process by which germ cells divide to produce male and female gametes, or sperm and egg cells, respectively. Meiosis reduces the number of chromosomes to the haploid number of 23 throrugh two cell divisions, known as meiosis I and meiosis II (Figure 1.8). Similar to mitosis, meiosis I begins with DNA replication in male and female germ cells (spermatocytes and primary oocytes), resulting in the sister chromatids of each of the 46 chromosomes. However, after a process known as synapsis, homologous chromosomes align themselves in pairs, unlike during mitosis. With the exception of the XY combination, the pairing is precise and point-for-point. Subsequently, homologous pairs split into two daughter cells, changing the number of chromosomes from diploid to haploid. Sister chromatids then split apart during meiosis II. As a result, each gamete contains 23 chromosomes.

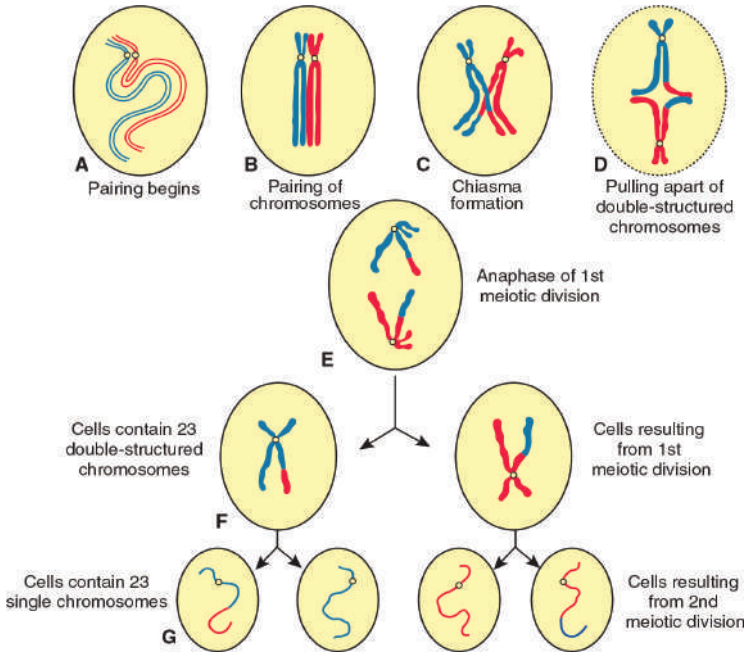


Figure 1.8. *First and second meiotic divisions. (A) Homologous chromosomes approach each other. (B) Homologous chromosomes pair, and each member of the pair consists of two chromatids. (C) Intimately paired homologous chromosomes interchange chromatid fragments (crossover). Note the chiasma. (D) Double-structured chromosomes pull apart. (E) Anaphase of the first meiotic division. (F) and (G) During the second meiotic division, the double-structured chromosomes split at the centromere. At completion of division, chromosomes in each of the four daughter cells are different from each other.*

Source: By Rdbickel – Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=49599354.

1.4.2.3. Crossover

Crossover: Crucial to meiosis I, crossovers involve the exchange of chromatid segments between paired homologous chromosomes. As homologous chromosomes split apart, chromatid segments break and exchange. Points of interchange temporarily unite as separation takes place, forming

an X-shaped structure known as a chiasma. Genes that are distantly located on a chromosome are most likely to undergo one or two of the roughly 30 to 40 crossovers per chromosome that occur during each meiotic I division.

As a result of meiotic divisions, genetic variability is enhanced through crossover, which redistributes genetic material, and random distribution of homologous chromosomes to the daughter cells. Each germ cell contains a haploid number of chromosomes so that at fertilization the diploid number of 46 is restored.

1.4.2.4. Polar Bodies

During meiosis, one primary oocyte gives rise to four daughter cells, each with 22 plus 1 X chromosomes. However, only one of these develops into a mature gamete, the oocyte; the other three, the polar bodies, receive little cytoplasm and degenerate during subsequent development. Similarly, one primary spermatocyte gives rise to four daughter cells, two with 22 plus 1 X chromosomes and two with 22 plus 1 Y chromosomes. However, in contrast to oocyte formation, all four develop into mature gametes (Figure 1.9).

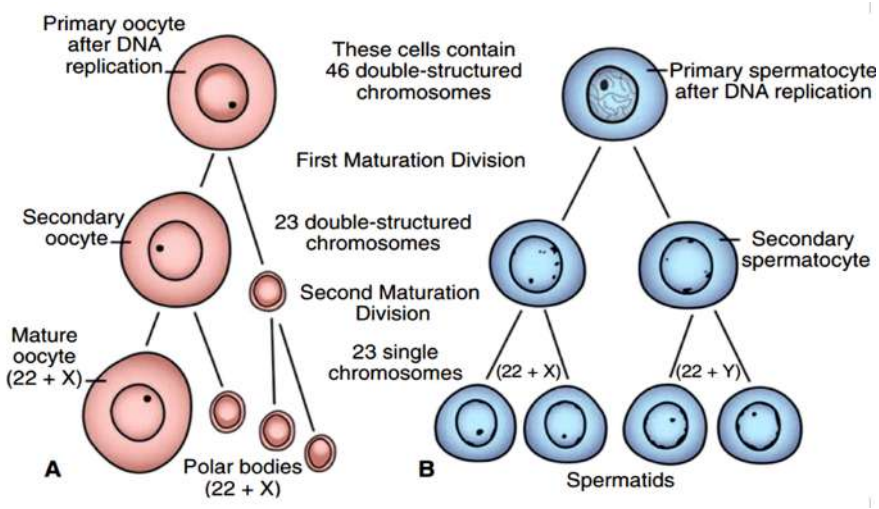


Figure 1.9. *Events occurring during the first and second maturation divisions. (A) The primitive female germ cell (primary oocyte) produces only one mature gamete, the mature oocyte. (B) The primitive male germ cell (primary spermatocyte) produces four spermatids, all of which develop into spermatozoa.*

Source: By Fred the Oyster – Own work, Public Domain, https://commons.wikimedia.org/w/index.php?curid=35184498.

A Closer Look

Yolk Sac

The yolk sac is part of the gestational sac, the protective covering that surrounds a developing baby and contains the amniotic fluid. It appears about a week or two after the embryo has implanted in the uterus (during week 4), and it disappears near the end of the first trimester.

During that time, the yolk sac provides all the nutrients a little embryo needs. It also produces red blood cells until the placenta fully forms and takes over this function.

The yolk sac should be visible during the first ultrasound, typically between weeks 6 and 9 of pregnancy.

The gestational sac is technically visible before that, around the fourth or fifth week. It looks like a round structure in the uterus that's 2 to 3 millimeters in diameter, and it increases by about a millimeter each day early in the pregnancy.

About a week later, the yolk sac has grown enough to appear on an ultrasound as well. It'll look like a round, dark mass with a bright rim measuring only a few millimeters in diameter. Like the gestational sac, it will get bigger over the next few weeks. By the 10-week mark, a yolk sac will typically measure a (still tiny!) 6 millimeters.

Sometimes, however, the technician can see a yolk sac, but it doesn't look right. This can indicate a problem with the pregnancy and portend a miscarriage. Signs include:

- An irregular shape (wrinkled with indented walls);
- Calcifications in the yolk sac that make it harder to see through;
- A yolk sac that's smaller than 2 millimeters or greater than 5 millimeters;
- A yolk sac that appears to be moving within the gestational sac.

If the gestational sac is still empty at a follow-up appointment, then it's what's known as a blighted ovum, or anembryonic pregnancy. This type of miscarriage occurs when an embryo never develops or stops developing. The most common reason this happens is because of a chromosomal abnormality.

Summary

- The study of an embryo's growth from the point of ovum fertilization to the fetal stage is known as embryology.
- The area of biology known as embryology studies the growth of embryos in both plants and animals, from ovum fertilization to fetus birth or hatching.
- Human embryogenesis is a complicated process by which a fertilized egg develops into an embryo. During the first eight weeks of development, the conceptus shifts from a single-celled zygote into a multi-layered, multi-dimensional fetus with primitively functioning organs.
- Embryology is central to evolutionary developmental biology ("evo-devo"), which studies the genetic control of the development process (e.g., morphogens), its link to cell signaling, its roles in certain diseases and mutations, and its links to stem cell research.
- The field of embryology uses specialized terminology to explain the complex structures and processes that go into the formation of organisms from fertilization to birth or hatching.
- Molecular biology has enabled new ways to investigate embryology and improve our comprehension of both normal and aberrant development.

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Chapter

OVULATION TO IMPLANTATION

2

Contents

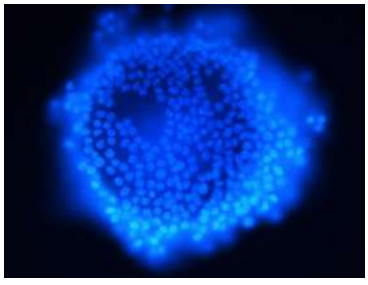
Unit Introduction

An important stage of the female menstrual cycle is called ovulation, which is the release of an oocyte—a mature egg—from the ovary into the fallopian tube, where it is ready for sperm fertilization. A spike in the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland causes ovulation, which usually happens in the middle of the menstrual cycle. Ovulation, the process by which the mature ovarian follicle bursts and releases the egg into the fallopian tube, is triggered by this surge. The cilia lining the inner walls of the fallopian tube sweep the released egg into the tube after ovulation. This is a crucial window for conception because the egg is viable for fertilization for about 12 to 24 hours following ovulation. In the meantime, sperm cells follow chemical cues and muscle contractions as they pass through the female reproductive tract during fertilization to reach the fallopian tube and come into contact with the egg.

Usually, sperm cells pierce the egg's protective layers and fuse with its plasma membrane in the ampulla of the fallopian tube, where fertilization takes place. Embryonic development begins with the union of the nuclei of the sperm and the egg to form a diploid zygote. The zygote divides rapidly to form a structure called a blastocyst, which is made up of an inner cell mass and an outer layer of cells called trophoblasts. The blastocyst is propelled by ciliary action and muscular contractions as it passes through the fallopian tube and into the uterus. The blastocyst enters the uterus six to seven days after fertilization and undergoes implantation, an essential stage in the establishment of pregnancy. Through interactions between molecules on the trophoblast and receptors on the endometrial cells, the blastocyst attaches itself to the endometrium, the lining of the uterus, during the implanting process.

After implantation, the trophoblast develops into the placenta, an essential organ that helps the fetal and maternal circulations exchange gases and nutrients. In the meantime, the inner cell mass gives rise to the embryo, which continues to grow and differentiate throughout the gestational period. In human reproduction, the process from ovulation to implantation is crucial because it results in the establishment of pregnancy and the start of embryonic development. The process entails complex physiological and molecular interactions between the reproductive systems of the male and female, culminating in the development of a new life inside the mother's uterus.

Orientation and Directional Terms

Terms	Definition	Illustration
Fallopian tube	Fallopian tube, either of a pair of long narrow ducts located in the human female abdominal cavity that transport male sperm cells to the egg, provide a suitable environment for fertilization, and transport the egg from the ovary, where it is produced, to the central channel (lumen) of the uterus.	
Sperm	Sperm is the male reproductive cell, or gamete, in anisogamous forms of sexual reproduction.	
Pregnancy	Pregnancy is the term used to describe the period in which a fetus develops inside a woman's womb or uterus.	
Uterus	The uterus is a hollow muscular organ located in the female pelvis between the bladder and rectum.	
Granulosa cells	Granulosa cells are inside your ovaries. These cells produce estrogen, progesterone and other hormones.	

2.1. Overview of Ovulation to Implantation

Ovulation is the time during the menstrual cycle when the ovary releases an egg. Many of us have been taught that cycle day 1 is the first day of the period, and that ovulation happens on cycle day 14. However, this may not always be the case. Ovulation typically occurs approximately halfway through the cycle. As you may have learned in sex education classes, ovulation should happen approximately on cycle day 14 for those with precise 28-day cycles. On the other hand, research indicates that typical cycles can span between 21 and 35 days. The ovulation takes place before or after cycle day 14, which is completely normal, depending on whether the cycle is slightly longer or shorter than 28 days.

The final stage in the process of becoming pregnant is implantation. After the egg and sperm meet earlier in the cycle, the newly formed embryo travels down to the uterus to find the place it will call home for the next nine months. A successful pregnancy depends upon successful implantation. The ovaries, the pituitary gland in the brain, and the uterus interact intricately to provide the ideal conditions for ovulation, the release of an egg, the meeting of sperm and egg, and the implantation of the fertilized egg in the uterus.

A step-by-step guide to ovulation:

- Every month the pituitary gland, which is in your brain, releases a hormone. This hormone signals the ovaries to produce a number of fluid-filled cysts called follicles. As the follicles grow, they secrete the hormone estrogen. Estrogen works to thicken the wall of the uterus in preparation for pregnancy.
- On day seven of the cycle, the follicles stop growing except for one. This follicle continues to grow and nourish a maturing egg (oocyte).
- On day 12, the maturing follicle releases a burst of estrogen into the bloodstream. The estrogen travels through your blood. When the estrogen reaches the pituitary gland in the brain, the pituitary gland responds by releasing the luteinizing hormone. This hormone gives the follicle a sudden growth spurt.
- Right before ovulation, the egg inside the follicle detaches itself. The follicle starts to release chemicals that encourage the nearby fallopian tube to move closer and surround the follicle.
- The follicle swells until it bursts open, ejecting the egg and fluid into the abdominal cavity.
- Small finger-like protrusions at the end of the fallopian tube, called fimbriae, sweep across the burst follicle and pick up the egg.
- The egg is transported to the entrance of the fallopian tube. Once inside the fallopian tube, muscle contractions push the egg gently towards the uterus.
- The egg will either meet sperm on its journey through the fallopian tube, resulting in fertilization, or it will arrive in the uterus unfertilized and be absorbed back into the body.

2.1.1. Ovarian Cycle

The female starts having regular monthly cycles at puberty, regulated by hypothalamus. The hypothalamus releases gonadotropin-releasing hormone (GnRH), stimulating the anterior pituitary gland to release gonadotropins. These gonadotropins are Follicle-stimulating hormone

(FSH) and luteinizing hormone (LH), hormones that regulate and stimulate the ovary's cyclical changes.

FSH stimulates the growth of 15 to 20 primary (preantral) stage follicles at the onset of each ovarian cycle. The hormone is not required to encourage primordial follicle development to the primary follicle stage; however, in its absence, these primary follicles undergo atrophy and die. Consequently, FSH recruits 15–20 of these cells from a constantly forming a pool of primary follicles (Figure 2.1). Only one of these follicles matures to full capacity and releases an ovum under normal circumstances; the remaining follicles atrophy and degenerate. Another set of primary follicles is recruited in the subsequent cycle, and once more, only one follicle matures. Because of this, the majority of follicles degenerate without ever maturing fully. A corpus atreticum is created when a follicle becomes atretic, degenerating the oocyte and surrounding follicular cells, and is replaced by connective tissue. Additionally, FSH promotes the follicular (granulosa) cells that surround the oocyte to mature. Growth differentiation factor-9 (GDF-9), a member of the transforming growth factor-β (TGF-β) family, mediates the proliferation of granulosa cells. Granulosa cells work together to produce estrogens, which have three combined effects: (a) inducing the uterine endometrium to enter the follicular or proliferative phase; (b) thinning the cervical mucus to facilitate sperm passage; and (c) stimulating the pituitary gland to release LH. An LH surge occurs mid-cycle, which causes follicular rupture and ovulation. It (a) increases maturation-promoting factor concentrations, causing oocytes to complete meiosis I and begin meiosis II, (b) stimulates progesterone production by follicular stromal cells (luteinization), and (c) causes follicular rupture.

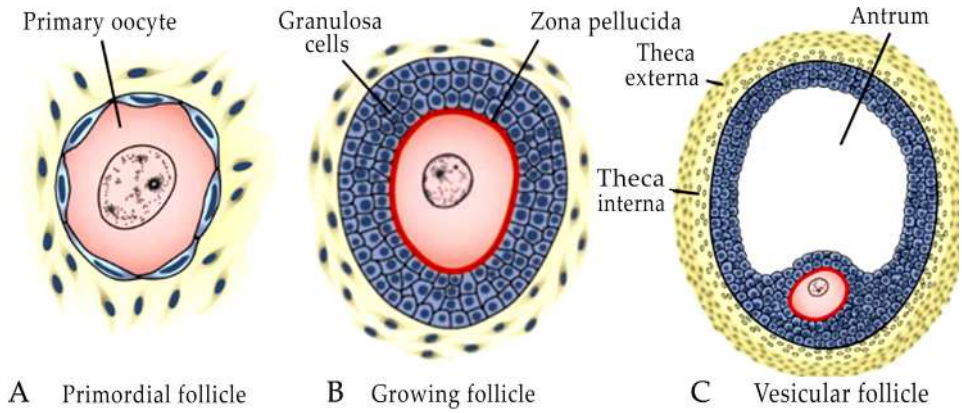


Figure 2.1. *From the pool of primordial follicles, every day some begin to grow and develop into secondary (preantral) follicles, and this growth is independent of FSH. Then, as the cycle progresses, FSH secretion recruits primary follicles to begin development into secondary (antral, Graafian) follicles. During the last few days of maturation of secondary follicles, estrogens, produced by follicular and thecal cells, stimulate increased production of LH by the pituitary, and this hormone causes the follicle to enter the preovulatory stage, to complete meiosis I, and enter meiosis II where it arrests in metaphase approximately 3 hours before ovulation.*

Source: By Acedatrey2 – Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=90764380.

2.1.2. Ovulation

Under the influence of FSH and LH, the secondary follicle grows quickly to a diameter of 25 mm in the days just before ovulation. The primary oocyte completes meiosis I, and the follicle enters the preovulatory stage as the secondary follicle reaches its final stage of development due to an abrupt increase in LH. Meiosis II also starts, but about three hours before ovulation, the oocyte is arrested in metaphase. Meanwhile, the ovary's surface starts to enlarge locally, and the stigma—an avascular area—appears at the apex. Collagenase activity is elevated by high LH concentrations, leading to the breakdown of collagen fibers surrounding follicles. In response to the LH surge, prostaglandin levels rise, resulting in localized muscular contractions in the ovarian wall. Those contractions extrude the oocyte, which, together with its surrounding granulosa cells from the region of the cumulus oophorus, breaks free (ovulation) and floats out of the ovary (Figures 2.2 and 2.3). Some of the cumulus oophorus cells rearrange themselves around the zona pellucida to form the corona radiata.

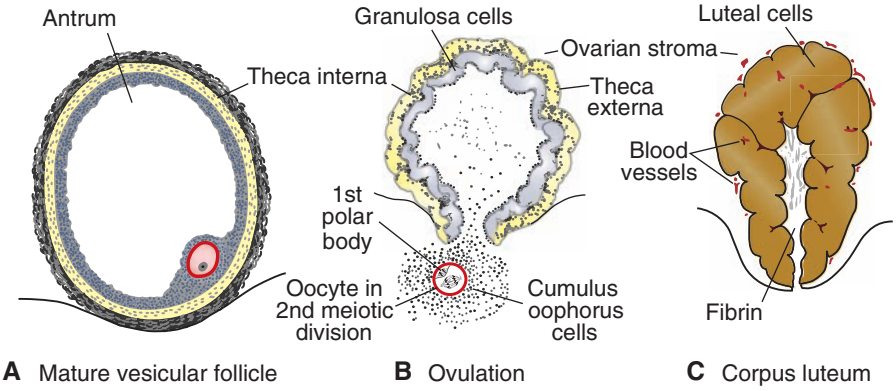


Figure 2.2. *(A) Preovulatory follicle bulging at the ovarian surface. (B) Ovulation. The oocyte, in metaphase of meiosis II, is discharged from the ovary together with a large number of cumulus oophorus cells. Follicular cells remaining inside the collapsed follicle differentiate into lutein cells. (C) Corpus luteum. Note the large size of the corpus luteum, caused by hypertrophy and accumulation of lipids in granulosa and theca interna cells. The remaining cavity of the follicle is filled with fibrin.*

Source: By Ljaffe – Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=79215239.

2.1.3. Corpus Luteum

Following ovulation, the surrounding vessels vascularize the granulosa cells that are still inside the ruptured follicle wall, as well as the cells from the theca interna. These cells become yellowish and transform into lutein cells when exposed to LH. These cells then form the corpus luteum and secrete progesterone (Figure 2.2(C)). The uterine mucosa enters the progestational or secretory stage in advance of the embryo's implantation, when progesterone and estrogenic hormones work together.

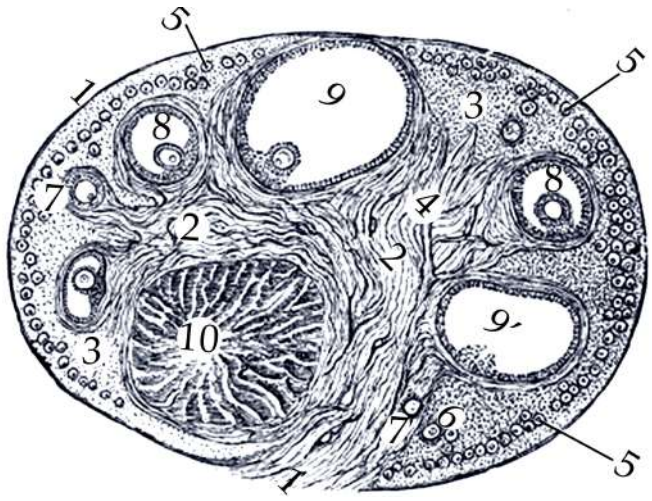


Figure 2.3. *The stages from the preovulatory follicle to the formation of the corpus luteum.*

1)Cuboidal epithelium, 2) Tunica albuginea, 3) Peripheral stroma 4) Bloodvessels. 5) Vesicular follicles in their earliest stage, 6), 7), 8) More advanced follicles, 9) An almost mature follicle. 9') Follicle from which the ovum has escaped. 10) Corpus luteum.

Source: By Henry Vandyke Carter – Henry Gray (1918) Anatomy of the Human Body (see book section below) Bartleby.com: Gray's Anatomy, Plate 1163, Public Domain, https://commons.wikimedia.org/w/index.php?curid=567136.

2.1.4. Oocyte Transport

Shortly before ovulation, fimbriae of the oviduct begin to sweep over the surface of the ovary, and the tube itself begins to contract rhythmically. It is thought that the oocyte, surrounded by some granulosa cells (Figures 2.3 and 2.4), is carried into the tube by these sweeping movements of the fimbriae and by the motion of cilia on the epithelial lining. Once in the tube, cumulus cells withdraw their cytoplasmic processes from the zona pellucida and lose contact with the oocyte. Once the oocyte is in the uterine tube, it is propelled by cilia,if with the rate of transport regulated by the endocrine status during and after ovulation. In humans, the fertilized oocyte reaches the uterine lumen in approximately 3 to 4 days.

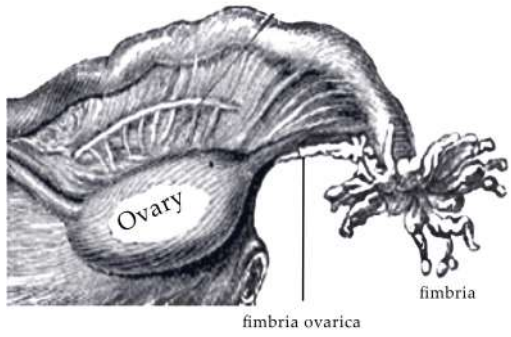


Figure 2.4. *Relation of fimbriae and ovary. Fimbriae collect the oocyte and sweep it into the uterine tube.*

Source: https://simple.wikipedia.org/wiki/File:Fimbria.png.

2.1.5. Corpus Albicans

The corpus luteum reaches its maximum development about nine days after ovulation if fertilization is unsuccessful. It is easily

identifiable as a yellowish protrusion on the ovary's surface. The corpus luteum then contracts as a result of lutein cell degeneration, giving rise to the corpus albicans, a mass of fibrous scar tissue. Menstrual bleeding occurs when progesterone production falls simultaneously.

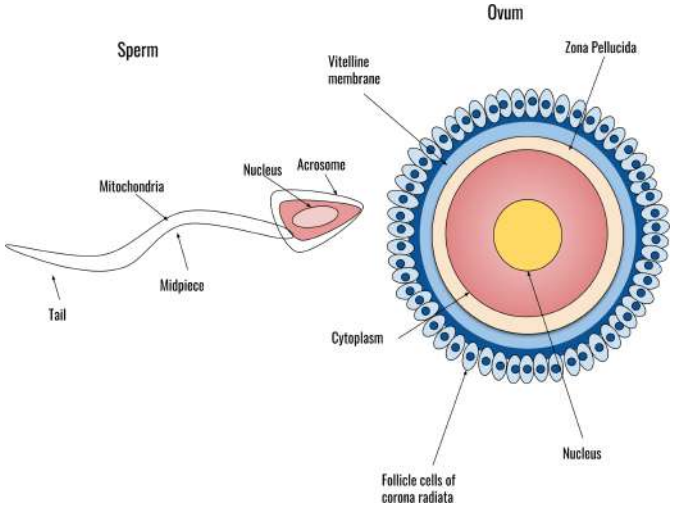


Figure 2.5. *The three phases of oocyte penetration. In Phase 1, spermatozoa pass through the corona radiata barrier; in Phase 2, one or more spermatozoa penetrate the zona pellucida; in Phase 3, one spermatozoon penetrates the oocyte membrane while losing its plasma membrane.*

Source: https://upload.wikimedia.org/wikipedia/commons/5/5f/The_sperm_and_ovum_during_fertilization.svg.

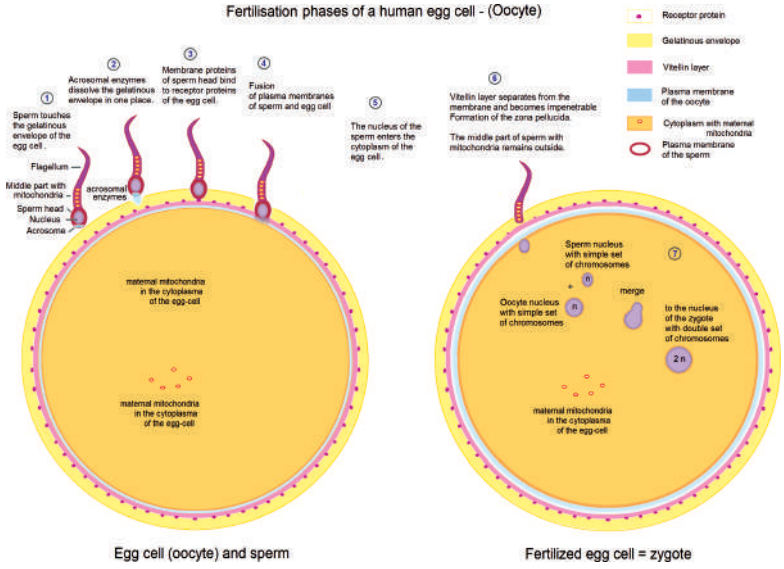


Figure 2.6. *A spermatozoon has penetrated the oocyte, which has finished its second meiotic division. Chromosomes of the oocyte are arranged in a vesicular nucleus, the female pronucleus. The heads of several sperm are stuck in the zona pellucida.*

Source: https://upload.wikimedia.org/wikipedia/commons/e/e7/Egg_cell_fertilization_-_Zygote.png.

The developing embryo's syncytiotrophoblast secretes human chorionic gonadotropin (hCG), a hormone that stops the corpus luteum from degenerating if the oocyte is fertilized. The corpus luteum develops further to become the corpus luteum graviditatis, or corpus luteum of pregnancy. This structure can make up one-third to half of the ovary's overall size by the end of the third month. Up until the end of the fourth month, yellowish luteal cells secrete progesterone; after that, they gradually recede as the placenta's trophoblastic component begins to secrete enough progesterone to sustain pregnancy. Removing the corpus luteum before the fourth month of pregnancy typically results in abortion (Figures 2.5 and 2.6).

2.1.6. Fertilization

Male and female gametes fuse during fertilization in the ampullary region of the uterine tube, which is the widest part of the tube and is closest to the ovary (Figure 2.4). In the female reproductive system, spermatozoa can survive for several days.

Sperm deposited in the vagina only make up 1% of those that reach the cervix, where they may live for several hours. Sperm travel from the cervix to the oviduct mostly by themselves, though uterine cilia-produced fluids may also help. Sperm lose some of their motility and stop migrating after they cross the isthmus. The journey from the cervix to the oviduct takes a minimum of two to seven hours. During ovulation, sperm regain motility, possibly due to the presence of chemoattractants generated by the cumulus cells encircling the egg. They then proceed to the ampulla, where fertilization typically takes place. When spermatozoa enter the female genital tract, they must first go through two processes to become capable of fertilizing the oocyte: (a) capacitation; and (b) the acrosome reaction.

The term "capacitation" refers to the roughly seven-hour conditioning period that occurs in the female reproductive tract in humans. The sperm and the mucosal surface of the tube interact epithelially during a large portion of this conditioning, which takes place in the uterine tube. During this period, the plasma membrane covering the spermatozoa's acrosomal region is stripped of its seminal plasma proteins and glycoprotein coat. Only capacitated sperm can enter the corona radiata cells and proceed through the acrosome reaction. The acrosome reaction, which occurs after binding to the zona pellucida, is induced by zona proteins. This reaction culminates in the release of enzymes needed to penetrate the zona pellucida, including acrosin and trypsin-like substances. The phases of fertilization include phase 1, penetration of the corona radiata; phase 2, penetration of the zona pellucida; and phase 3, fusion of the oocyte and sperm cell membranes.

2.1.6.1. Phase 1: Penetration of the Corona Radiata

Merely 300 to 500 spermatozoa, out of the 200 to 300 million deposited in the female genital tract, make it to the site of fertilization. The egg is fertilized by only one of these sperm cells. It is believed that the other sperm cells assist the fertilizing spermatocide breaking through the barriers that shield the female gamete. Capacitated sperm pass freely through corona cells (Figure 2.5).

2.1.6.2. Phase 2: Penetration of the Zona Pellucida

A glycoprotein shell called the zona pellucida envelops the egg, aiding in sperm binding and triggering the acrosome reaction. The zona pellucida protein-ligand ZP3 mediates both binding and the acrosome reaction. The release of acrosomal enzymes, such as ascrosin, enables sperm to pass through the zona pellucida

and make contact with the oocyte's plasma membrane (Figure 2.5). When the sperm head touches the surface of the oocyte, the zona pellucida's permeability changes. As a result of this contact, lysosomal enzymes are released from cortical granules that line the oocyte's plasma membrane. These enzymes then modify the zona pellucida (zona reaction) in a way that hinders further sperm penetration and deactivates spermatozoa receptor sites specific to a given species on the zona pellucida surface. The zona pellucida may contain other spermatozoa, but only one appears to be able to enter the oocyte (Figure 2.6).

2.1.6.3. Phase 3: Fusion of the Oocyte and Sperm Cell Membranes

The interaction between integrins on the oocyte and their ligands, disintegrins, on the sperm, mediates part of the initial adhesion of sperm to the oocyte. The sperm and oocyte plasma membranes fuse after adhesion (Figure 2.5).

The oocyte membrane and the membrane covering the posterior region of the sperm head fuse because the plasma membrane covering the acrosomal cap disappears during the acrosome reaction (Figure 2.5). In humans, the spermatozoon's head and tail both enter the oocyte's cytoplasm, but the plasma membrane remains on the surface of the oocyte.

As soon as the spermatozoon has entered the oocyte, the egg responds in three ways:

1. **Cortical and Zona Reactions:** As a result of the release of cortical oocyte granules, which contain lysosomal enzymes, (a) the oocyte membrane becomes impenetrable to other spermatozoa, and (b) the zona pellucida alters its structure and composition to prevent sperm binding and penetration. These reactions prevent polyspermy (penetration of more than one spermatozoon into the oocyte).
2. **Resumption of the Second Meiotic Division:** The oocyte finishes its second meiotic division immediately after entry of the spermatozoon. One of the daughter cells, which receives hardly any cytoplasm, is known as the second polar body; the other daughter cell is the definitive oocyte. Its chromosomes (22 + X) arrange themselves in a vesicular nucleus known as the female pronucleus (Figures 2.6 and 2.7).
3. **Metabolic Activation of the Egg:** The activating factor is probably carried by the spermatozoon. Postfusion activation may be considered to encompass the initial cellular and molecular events associated with early embryogenesis.

In the meantime, the spermatozoon advances until it is in close proximity to the pronucleus of the female. The male pronucleus is formed when its nucleus swells (Figure 2.6); the tail separates and becomes less uniform. The pronuclei of the male and female are identical morphologically. Soon they come into proximity and shed their nuclear envelopes. DNA replication is required for both haploid male and female pronuclei during their growth. Without it, the two-cell zygote would contain half of the normal amount of DNA. Chromosomes assemble on the spindle immediately following DNA synthesis, preparing the cell for a typical mitotic division. Each zygote cell has the typical diploid number of chromosomes and DNA due to the longitudinal splitting of the 23 maternal and 23 paternal (double) chromosomes at the centromere and the movement of sister chromatids to opposite poles. A deep furrow on the cell's surface is

created as sister chromatids travel to opposing poles, gradually dividing the cytoplasm into two sections.

The main results of fertilization are as follows:

- **Restoration of the Diploid Number of Chromosomes:** Half from the father and half from the mother. Hence, the zygote contains a new combination of chromosomes different from both parents.
- **Determination of the Sex of the New Individual:** An X-carrying sperm produces a female (XX) embryo, and a Y-carrying sperm produces a male (XY) embryo. Hence, the chromosomal sex of the embryo is determined at fertilization.
- **Initiation of Cleavage:** Without fertilization, the oocyte usually degenerates 24 hours after ovulation.

Figure 2.7. *Phase contrast view of the pronuclear stage of a fertilized human oocyte with male and female pronuclei.*

Source: By Nina Sesina – File:Zygote.tif, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=67459911.

2.1.7. Cleavage

After reaching the two-cell stage, the zygote divides repeatedly through mitosis to produce more cells. These cells, called blastomeres, get smaller with every cleavage division (Figure 2.8). They cluster loosely up until the eight-cell stage. Following the third cleavage, blastomeres maximize their contact with one another, resulting in the formation of a compact ball of cells joined by tight junctions. Compaction is the process that divides inner cells, which communicate widely through gap junctions, from outer cells. About three days after fertilization, the compacted embryo's cells divide once more to create a 16-cell morula (mulberry). The outer cell mass of a morula consists of surrounding cells, while the inner cell consists of the inner cells. The trophoblast, which subsequently contributes to the placenta, is formed by the outer cell mass, while the inner cell mass gives rise to the embryo's tissues.

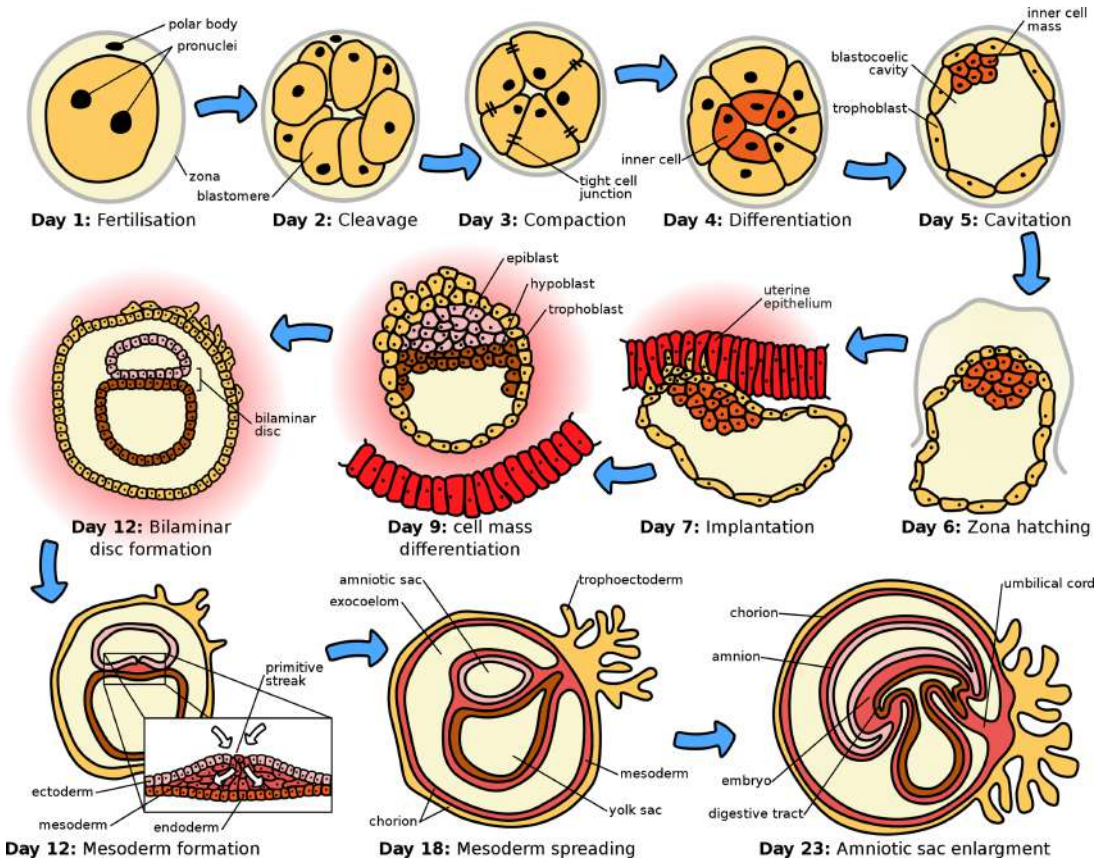


Figure 2.8. *Development of the zygote.*

Source: By Zephyris – SVG version of., CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=10811330.

2.1.7.1. Blastocyst Formation

Fluid starts to seep into the intercellular spaces of the inner mass through the zona pellucida around the time the morula enters the uterus. The intercellular spaces eventually unite to form a single cavity known as the blastocoel. At this point, the embryo is called a blastocyst. The cells of the outer cell mass, known as the trophoblast, flatten and form the epithelial wall, while the cells of the inner cell mass, known as the embryoblast, are positioned at one pole. With the disappearance of the zona pellucida, implantation can begin.

Around the sixth day in humans, trophoblastic cells covering the embryoblast pole start to pierce through the epithelial cells of the uterine mucosa. The attachment and invasion of the trophoblast involve extracellular matrix molecules like laminin and fibronectin, as well as integrins expressed by the trophoblast. Laminin-specific integrin receptors encourage attachment, whereas fibronectin-specific ones drive migration. These molecules also interact via signal transduction pathways to control trophoblast differentiation and ensure that implantation results from both endometrial and trophoblastic activity. As a result, by the end of the first week of development,

the human zygote has started to implant itself in the uterine mucosa after progressing through the morula and blastocyst stages (Figure 2.9).

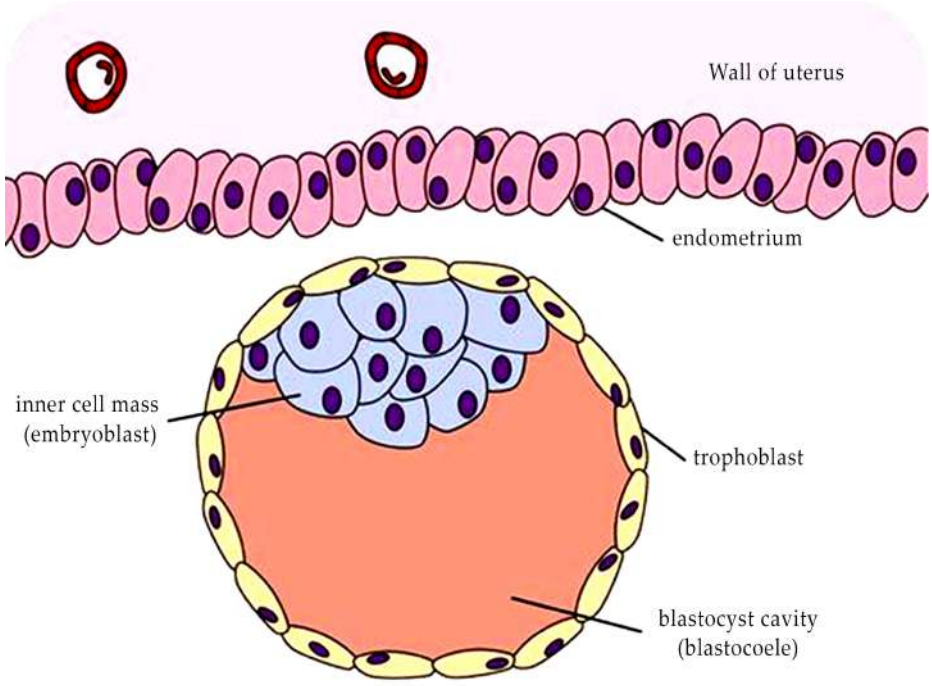


Figure 2.9. *Schematic representation of a blastocyst at the ninth day of development showing trophoblast cells at the embryonic pole of the blastocyst penetrating the uterine mucosa. The human blastocyst begins to penetrate the uterine mucosa by the sixth day of development.*

Source: By Zachary Wilson / CK-12 Foundation – https://www.ck12.org/user:ywviz2vsywluzubnbwfpbc5jb20./book/ck-12-life-science-for-middle-school/section/22.3/, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=125360929.

2.1.8. Uterus at Time of Implantation

The wall of the uterus consists of three layers: (a) the endometrium, or mucosa lining the inside wall; (b) the myometrium, a thick layer of smooth muscle; and (c) the perimetrium, the peritoneal covering lining the outside wall (Figure 2.9). From puberty (11–13 years) until menopause (45–50 years), the endometrium undergoes changes in a cycle of approximately 28 days under hormonal control by the ovary. During this menstrual cycle, the uterine endometrium passes through three stages, the follicular or proliferative phase, the secretory or progestational phase, and the menstrual phase. The proliferative phase begins at the end of the menstrual phase and is under the influence of estrogen, and parallel growth of the ovarian follicles. The secretory phase begins approximately 2 to 3 days after ovulation in response to progesterone produced by the corpus luteum. If fertilization does not occur, shedding of the endometrium (compact and spongy layers) marks the beginning of the menstrual phase. If fertilization does occur, the endometrium assists in implantation and contributes to the formation of the placenta.

The uterine mucosa is in the secretory phase at the time of implantation when the tissue becomes succulent and the uterine glands and arteries coil. Consequently, the endometrium can be divided into three distinct layers: a thin basal layer, an intermediate spongy layer, and a superficial compact layer. Typically, the human blastocyst embeds itself between the gland openings in the endometrium along the anterior or posterior wall of the uterus's body (Figure 2.10).

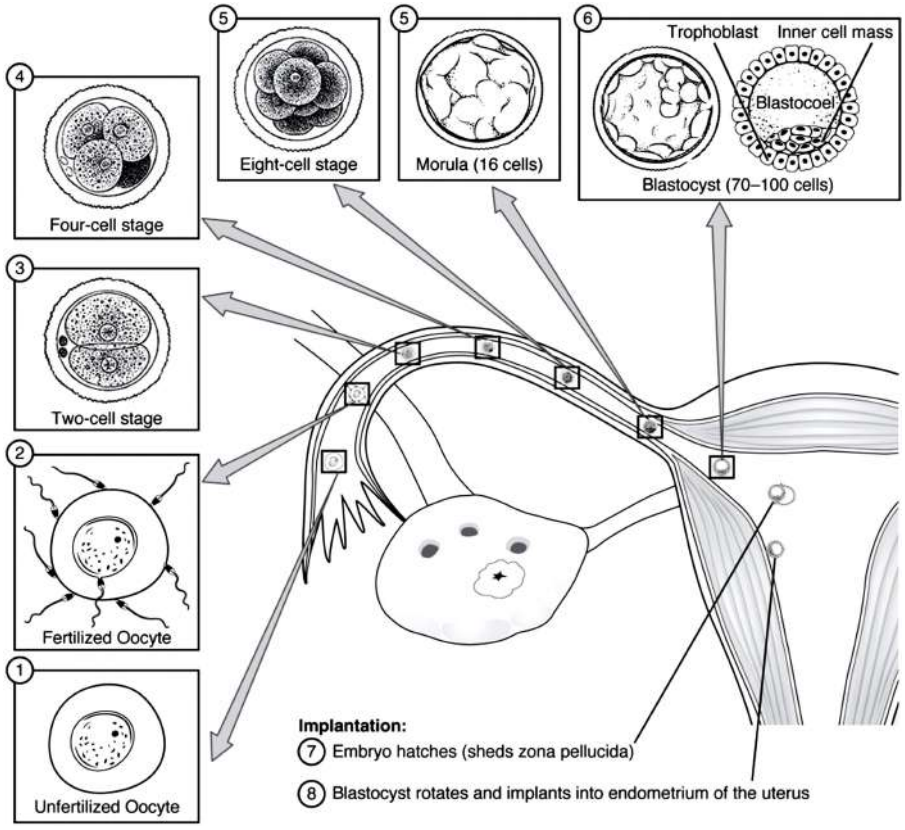


Figure 2.10. *Implantation: Changes in the uterine mucosa correlated with those in the ovary. Implantation of the blastocyst has caused the development of a large corpus luteum during pregnancy. Secretory activity of the endometrium increases gradually as a result of large amounts of progesterone produced by the corpus luteum during pregnancy.*

Source: By OpenStax College – Anatomy & Physiology, Connexions Web site. Embryonic Development https://openstax.org/books/anatomy-and-physiology/pages/28-2-embryonic-development, Jun 19, 2013., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=30148586.

If the oocyte is not fertilized, there will be noticeable extensive diapedesis of blood into the tissue as venules and sinusoidal spaces gradually fill with blood cells. Upon the onset of the menstrual phase, glands and small fragments of stroma separate, allowing blood to exit superficial arteries. The basal layer is the only portion of the endometrium that remains in the uterus after the compact and spongy layers are removed over the course of the next three to four days. This layer serves as the regenerative layer during the proliferative phase when glands and arteries are being rebuilt. It is supplied by its arteries, the basal arteries.

2.2. Gametogenesis and Fertilization

The processes of gametogenesis and fertilization are essential to sexual reproduction because they generate genetically diverse progeny, which guarantees the survival of the species. Gametogenesis is the process by which male and female gametes develop, and fertilization is the joining of these gametes to form a zygote, starting the process of creating a new individual.

The process by which gametes are formed, known as gametogenesis, is an essential part of sexual reproduction in all organisms, including plants and animals. It entails the development of specialized reproductive cells known as gametes, which are carried by both female and male gametes (ova), each of which carries half of the genetic material needed for progeny. Complex cellular processes known as "gametogenesis" lead to the maturation of viable, functional gametes that are ready for fertilization.

2.2.1. Gametogenesis

1. **Male Gametogenesis (Spermatogenesis):** Spermatogenesis is the process by which gametes are formed in the testes of males. It starts during adolescence and lasts until adulthood. In the seminiferous tubules, spermatogonial stem cells divide mitotically to generate primary spermatocytes. These cells go through the first stage of meiosis to become secondary spermatocytes, and the second stage of meiosis results in haploid spermatids. To develop into mature spermatozoa (sperm), spermatids go through additional morphological changes, such as the formation of a head, midpiece, and tail. The seminiferous tubules' lumen is where sperm are released, and they mature in the epididymis before becoming motile and fertile.
2. **Female Gametogenesis (Oogenesis):** In the female body, the process of gametogenesis takes place in the ovaries through a process known as oogenesis. Unlike in males where spermatogenesis produces four functional sperm cells from each spermatogonium, oogenesis typically leads to the development of only one mature egg cell (ovum) per primary oocyte. Oogonia go through mitotic divisions to create primary oocytes, which stay in prophase I of meiosis until puberty. Each month, a few primary oocytes resume meiosis and transform into secondary oocytes under hormonal influence. During ovulation, a secondary oocyte is released from the ovary and travels into the fallopian tube. If fertilization occurs, the secondary oocyte goes through meiosis II and forms a mature egg cell along with a polar body. In the absence of fertilization, the secondary oocyte breaks down.

2.2.1.1. Fertilization

Fertilization is the process through which an egg and sperm cell fuse to form a diploid zygote. It usually happens in the fallopian tube soon after ovulation.

Fertilization involves several key steps:

1. **Sperm Activation and Migration:** During ejaculation, sperm cells are released into the female reproductive tract. They undergo

capacitation, a process that primes them for fertilization by removing glycoproteins from their surface and increasing their motility. Sperm then navigates through the female reproductive tract, guided by chemical signals released by the egg and reproductive tract tissues.

2. **Egg Activation:** Meanwhile, the egg cell undergoes changes upon ovulation, including the release of cortical granules that modify the zona pellucida, the egg's protective layer. This prevents polyspermy, the fertilization by more than one sperm, by creating a barrier to additional sperm entry.
3. **Sperm-Egg Recognition and Fusion:** Once a sperm reaches the egg, it binds to receptors on the zona pellucida and undergoes the acrosome reaction, releasing enzymes that help it penetrate the egg's membrane. The sperm's nucleus enters the egg's cytoplasm, where it fuses with the egg's nucleus to form a diploid zygote.
4. **Zygote Formation:** The fusion of sperm and egg nuclei results in the formation of a zygote, which contains a complete set of chromosomes from both parents. The zygote undergoes rapid cell divisions through mitosis,

2.3. Processes of Spermatogenesis and Oogenesis

Gametogenesis is the process by which a diploid gamete cell divides to produce haploid sperm and egg cells, respectively, in spermatogenesis and oogenesis.

2.3.1. Spermatogenesis

In males, immature germ cells are produced in the testes. These immature germ cells, or spermatogonia, are transformed into sperm in males during puberty through the process of spermatogenesis. Spermatogonia are diploid cells that divide during mitosis, increasing in quantity. Secondary spermatocytes are haploid cells created by the meiosis of primary spermatocytes. To create immature sperm or spermatids, these secondary spermatocytes go through a second meiotic division. To become sperm, these spermatids go through spermiogenesis. Several hormones, including androgens, LH, FSH, and GnRH, are involved in promoting spermatogenesis. Spermatogenesis takes place in the wall of the seminiferous tubules, where spermatozoa are found in the tube lumen and stem cells are located at the tube's periphery. The diploid, undifferentiated cells are located directly beneath the tubule's capsule. These stem cells, known as spermatogonia (plural: spermatagonium), undergo mitosis, whereby one of the progeny develops into a sperm cell and the other produces the subsequent round of sperm (Figure 2.11).

A structure known as a primary spermatocyte initiates meiosis. Following the initial meiotic division, a haploid cell known as a secondary spermatocyte is created. There is another meiotic cell division required for this haploid cell. An endosome produced during meiosis is referred to as a spermatid. It's known as a sperm cell when it enters the tubule lumen and develops a flagellum, or "tail." Every primary spermatocyte that undergoes meiosis yields four sperm. Although they are dormant, stem cells are present from birth until the start of adolescence and are deposited during gestation. Gonadotropic hormones produced by the anterior pituitary during adolescence activate these cells and result in the production of viable sperm.

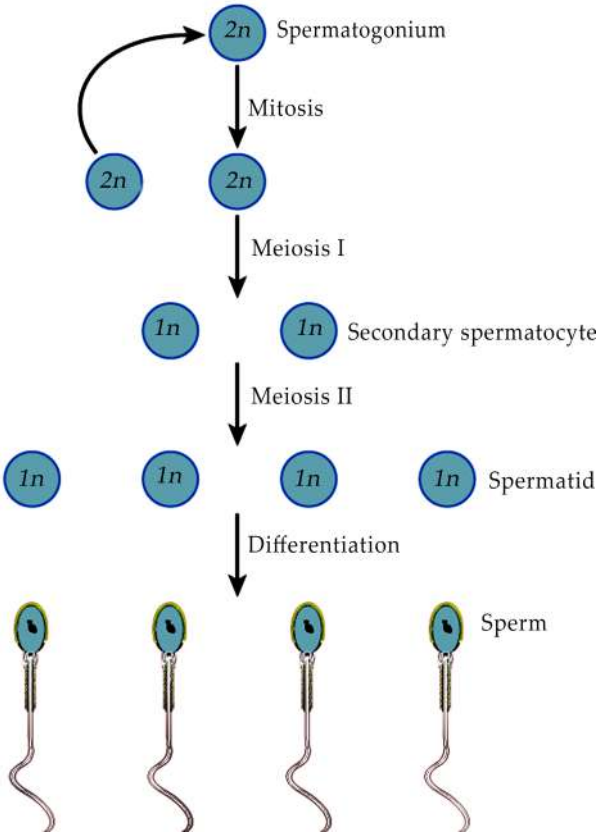


Figure 2.11. *Spermatogenesis: During spermatogenesis, four sperm result from each primary spermatocyte, which divides into two haploid secondary spermatocytes; these cells will go through a second meiotic division to produce four spermatids.*

Source: https://s3-us-west-2.amazonaws.com/courses-images/wp-content/uploads/sites/1223/2017/02/09204014/Figure_43_03_05.jpg.

2.3.1.1. In the Beginning

Males start producing sperm when they reach puberty, which is usually from 10-16 years old. Biological males continually produce sperm in large quantities (~200 million a day). This maximizes the likelihood of sperm reaching the egg following ejaculation. Sperm production occurs in the testes of the male, specifically in the seminiferous tubules. In the testicles, a blood-testis barrier forms to keep the tubules separate from the systemic circulation.

2.3.1.2. Protecting the Sperm

Forming the blood-testis barrier are Sertoli cells. This is crucial to stop chemicals in the blood from having an impact on the sperm's development. Hormones or waste products are examples of these products. It is also significant because it keeps the sperm from being recognized as foreign by the male's immune system because they differ genetically from the male and express different surface antigens.

2.3.1.3. Forming Functional Sperm

The original pool of diploid cells, known as spermatogonia, divides by mitosis to produce two identical cells. These cells are type A1 spermatogonia, and one of them will be utilized to replenish the spermatogonia pool. Because of this spermatogonia replenishment, males remain fertile into adulthood.

The other cell, type B spermatogonium, will eventually form mature sperm. Type B spermatogonia replicate by mitosis several times to form identical diploid cells linked by cytoplasm bridges, these cells are now known as primary spermatocytes.

Primary spermatocytes then undergo meiosis:

- **Meiosis I:** Produces two haploid cells, known as secondary spermatocytes.
- **Meiosis II:** Produces four haploid cells, known as spermatids.

2.3.1.4. Maturation

Spermiation is the process of releasing spermatids into the lumen of the seminiferous tubule after the cytoplasmic bridges disintegrate. As the spermatids move along the seminiferous tubules toward the epididymis,

they go through spermiogenesis, which is the process of remodeling and differentiating into mature spermatozoa. Cells will move from the seminiferous tubule to the rete testis. The removal of extra fluid helps to "concentrate" the sperm. After that, cells travel to the epididymis, where sperm is kept and goes through its last phases of development.

Since spermatogenesis takes about 70 days, multiple spermatogenic processes must be going on simultaneously within a single seminiferous tubule for sperm production to be continuous rather than intermittent. New groups of spermatogonia emerge every 16 days or spermatogenic cycles. These spermatogenic cell populations will all be in distinct phases of spermatogenesis.

2.3.1.5. Following Ejaculation

Keep in mind that sperm undergo capacitation as soon as they leave the male body and enter the female reproductive system. This is the sperm cell's head being cleared of cholesterol and glycoproteins so that it can attach to the egg cell's zona pellucida.

2.3.2. Oogenesis

Oogenesis takes place in the outermost layers of the ovaries. Similar to the process of producing sperm, oogenesis begins with a germ cell known as an oogonium (plural: oogonia). However, this cell divides through mitosis to multiply, ultimately giving rise to 1 or 2 million cells in the developing embryo (Figure 2.12).

The primary oocyte initiates meiosis. This cell will start the first meiotic division, but will stop growing during the first prophase. All future eggs are in the prophase stage at birth. During adolescence, many follicles in an ovary develop as a result of anterior pituitary hormones. As a result, the first meiotic division of the primary oocyte is completed. When the cell divides unevenly, only one set of chromosomes and a small amount of cytoplasm go to one cell, while the majority of the cellular material and organelles go to the secondary oocyte. The second cell, known as a polar body, typically degenerates. Another meiotic arrest occurs at the metaphase II stage. This secondary oocyte will be released during ovulation and move via the oviduct in the direction of the uterus. If the secondary oocyte becomes fertilized, the cell proceeds to meiosis II, completing the process and creating a second polar body and fertilized egg that contains all 46 human chromosomes, half of which come from the sperm.

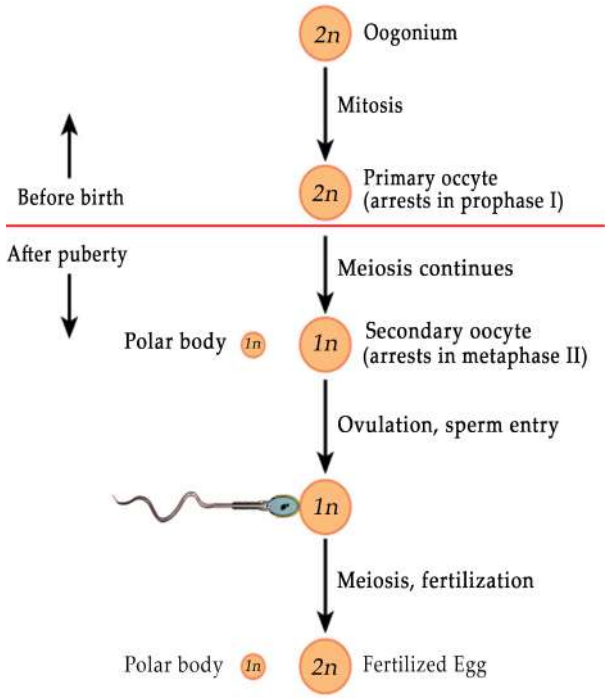


Figure 2.12. *Oogenesis: The process of oogenesis occurs in the ovary's outermost layer. A primary oocyte begins the first meiotic division, but then arrests until later in life when it will finish this division in a developing follicle.*

Source: https://s3-us-west-2.amazonaws.com/courses-images/wp-content/uploads/sites/1223/2017/02/09204044/Figure_43_03_06.jpg.

Oogenesis differs from spermatogenesis in that it begins in the fetus before birth. Primordial germ cells (which originate in the yolk sac of the embryo) move to colonize the cortex of the primordial gonad. Replication by mitosis peaks at approximately 7 million by mid-gestation (~20 weeks).

Cell death occurs after this peak leaving roughly 2 million cells. Meiosis I begins before birth and forms primary oocytes. There is therefore a finite supply of ova.

Primary oocytes are arranged in the gonads as clusters. They have flattened epithelial cells surrounding them, and this is called the primary follicle.

During childhood, further atresia (cell death) occurs, leaving ~40,000 eggs at puberty.

Once puberty begins, several primary oocytes (15-20) begin to mature each month, although only one of these reaches full maturation to become an oocyte.

The primary oocytes undergo three stages:

- Pre-antral;
- Antral; and
- Preovulatory.

The oogonia are converted to the mature ovum. We refer to this process as oogenesis. Millions of mother cells, also known as oogonia, are created in the female ovary during fetal development. Primary oocytes are produced by the meiotic cell division that these mother cells go through. The meiotic division stops at prophase I. On the outer layer, primary follicles contain embedded primary oocytes. More granulosa cell layer surrounds primary follicles, resulting in the formation of secondary follicles. The tertiary follicle is subsequently formed by secondary follicles. When a female reaches puberty, the primary oocytes in her tertiary follicles finish meiosis and divide unevenly to form haploid secondary oocytes and the polar body. Mature Graafian follicles are produced by the tertiary follicle after it experiences certain structural and functional alterations. An ovum is formed when a secondary oocyte completes a second meiotic division. During the menstrual cycle, the Graafian follicle releases the ovum. Ovulation is the process through which an ovum is released from the Graafian follicle. The female reproductive hormone, which is stimulated by the pituitary gland, regulates ovulation.

2.3.2.1. Pre-Antral Stage

Although it is still in meiosis I, the primary oocyte will grow significantly at this point. A layered cuboidal epithelium is formed by the growth and proliferation of the follicular cells. These cells are known as granulosa cells, and they release glycoproteins. The zona pellucida surrounds the primary oocyte and is formed by these substances. Theca folliculi, a specialized layer of surrounding cells that is responsive to LH and can secrete androgens under its influence, is created when surrounding connective tissue cells differentiate further.

2.3.2.2. Antral Stage

Between granulosa cells, fluid-filled spaces develop; these eventually come together to form the antrum, a central fluid-filled space. The follicles are now referred to as secondary follicles. One of these secondary follicles develops into a dominant one during each monthly cycle, with the help of FSH, LH, and estrogen.

2.3.2.3. Pre-Ovulatory Stage

This stage is brought on by the LH surge, and meiosis I have now finished. Two haploid cells with unequal sizes form inside the follicle. With significantly less cytoplasm than the other, one of the daughter cells develops into the first polar body, which will not develop into an ovum.

The secondary oocyte, another haploid cell, is also produced. After that, both daughter cells go through meiosis II. Two polar bodies will result from the replication of the original polar body, but the secondary oocyte stops during meiosis II metaphase. This takes place three hours before ovulation.

2.4. Structure and Function of Male and Female Gametes

Male and female gametes, also known as sperm and egg cells respectively, are specialized reproductive cells with distinct structures and functions tailored to their roles in sexual reproduction.

2.4.1. Structure of Male Gametes (Sperm)

1. **Head:** The head of a sperm cell contains the genetic material (chromosomes) in the form of tightly packed DNA. At the tip of the head is the acrosome, a structure filled with enzymes that aid in penetrating the egg's protective layers during fertilization.
2. **Midpiece:** Following the head is the midpiece, which contains mitochondria responsible for providing energy (in the form of ATP) for the sperm's movement.
3. **Tail (Flagellum):** The tail, or flagellum, is a long, whip-like structure that propels the sperm forward, enabling it to swim through the female reproductive tract towards the egg.

2.4.1.1. Function of Male Gametes (Sperm)

During fertilization, the main function of sperm cells is to transfer genetic material from the male to the female gamete (egg). Because of their specialized motility, sperm can pass through the female reproductive system and reach the egg. Sperm experience the acrosome reaction when they get close to the egg, which releases enzymes that help the egg's protective layers break. The process of embryonic development begins when the sperm and egg combine genetic material to form a zygote after fertilization is successful.

2.4.2. Structure of Female Gametes (Eggs)

1. **Plasma Membrane:** The egg cell is surrounded by a plasma membrane, which serves as a barrier and regulates the passage of molecules in and out of the cell.
2. **Cytoplasm:** Within the egg cell, the cytoplasm contains organelles such as mitochondria for energy production and ribosomes for protein synthesis.
3. **Nucleus:** Like all cells, the egg cell contains a nucleus that houses the genetic material (DNA) necessary for fertilization and embryonic development.

2.4.2.1. Function of Female Gametes (Eggs)

During fertilization, the main function of eggs is to provide the zygote with the female's genetic material. Compared to sperm, eggs are substantially larger and have an abundance of cytoplasm and other organelles that are essential for the early stages of embryonic development. After fertilization, the nuclei of the sperm and the egg combine to form a diploid zygote, which divides into multiple cells to become an embryo.

Gametes, both male and female, have unique structures and functions that are tailored to

their specific roles in sexual reproduction. While egg cells are furnished with nutrients and organelles to facilitate fertilization and the early stages of embryonic development, sperm cells are specialized for motility and delivering the male genetic material. During fertilization, these gametes come together to start the process of creating new life.

2.4.3. Mechanisms of Fertilization and Formation of the Zygote in Animals: A Revision

The complicated process of fertilization, which unites sperm and egg, is necessary for the zygote to form—the first stage of embryonic development.

This intricate process involves several key steps and molecular mechanisms:

1. **Sperm Activation and Capacitation:** Upon ejaculation, spermatozoa are released into the female reproductive tract. They undergo a process called capacitation, involving biochemical and physiological changes that render them capable of fertilizing an egg. Capacitation involves the removal of proteins from the sperm's surface, changes in membrane fluidity, and increased motility, enabling the sperm to swim efficiently through the female reproductive tract.
2. **Sperm Migration:** Sperm must navigate through the female reproductive tract to reach the site of fertilization, typically the ampulla of the fallopian tube where the egg is released during ovulation. Chemotactic signals released by the egg and the female reproductive tract guide sperm migration towards the egg. Sperm also undergo hyperactivation, a vigorous motility pattern, to penetrate the egg's protective layers.
3. **Egg Activation:** At the same time, the released egg undergoes a series of changes known as egg activation. This process includes the resumption of meiosis, the release of cortical granules from the egg's cytoplasm to prevent polyspermy (fertilization by more than one sperm), and the formation of the egg's pronucleus.
4. **Sperm-Egg Recognition and Binding:** The final step involves the recognition and binding of the sperm to the egg's zona pellucida, an extracellular matrix surrounding the egg. Specific molecules on the surface of the sperm, such as sperm receptors, interact with glycoproteins on the zona pellucida, facilitating sperm egg binding. This interaction triggers the acrosome reaction, during which enzymes released from the sperm's acrosome help penetrate the zona pellucida.
5. **Fusion of Sperm and Egg:** Once a sperm successfully penetrates the zona pellucida, it binds to receptors on the egg's plasma membrane, triggering membrane fusion between the sperm and egg. This fusion allows the sperm's genetic material, contained within the sperm head, to enter the egg's cytoplasm.
6. **Formation of the Zygote:** The fusion of sperm and egg nuclei results in the formation of a zygote, which contains a complete set of chromosomes from both parents.

This single-cell embryo undergoes rapid cell division through mitosis, forming a blastocyst as it travels down the fallopian tube toward the uterus for implantation.

Throughout fertilization and zygote formation, precise coordination of molecular and cellular events ensures the successful union of genetic material from both parents, initiating the process of embryonic development. Disruptions in any of these mechanisms can impair fertilization and early embryonic development, leading to infertility or developmental abnormalities.

A Closer Look

Estrogen

Estrogen is an important reproductive hormone in people of all sexes. It's generally known as the 'female' sex hormone, because of its role in the development of the female reproductive system and regulation of the menstrual cycle.

Whilst it's true that estrogen plays a bigger role in those assigned-female-at-birth everybody produces estrogen, regardless of sex.

In those assigned-female-at-birth estrogen is produced mainly in ovaries and depends on other reproductive hormones including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone for both its production and regulation.

Estrone is one of three types of estrogen made by the body. The other types of estrogen are called estradiol and oestriol. Estrone is primarily produced (either directly or from the conversion of other hormones) by the ovaries as well as by adipose (fat) tissue and the adrenal glands. It has a much weaker biological activity than estradiol. Estrone is the major type of estrogen hormone produced in postmenopausal women.

Very little is known about how the production of estrone is controlled. In premenopausal women, some estrone is produced by the ovaries. Estrone is also produced by fat tissue and the adrenal glands, which are the main sources of estrone in children, men, and postmenopausal women. Because estrone is less active than estradiol, it is thought that estrone may act as a reservoir that can be converted into estradiol as needed. As women enter menopause the ovaries stop producing estradiol. At this point, the conversion of adrenal steroid hormones to estrone takes over as the main source of estrogen.

Increased estrone production can occur in women with breast cancer and in men undergoing treatment for testicular or prostate cancer (which reduces testosterone production). Obese women also produce more estrone from their fat tissues. Overproduction of estrone within the breast may be associated with the development of breast cancer in women. Aside from this, estrone production may affect health in both positive and negative ways, but the full extent of this is currently not known.

Low levels of estrogen cause osteoporosis, fatigue, hot flushes, loss of libido, and depression. As estrone is the main estrogen in postmenopausal women, it is thought that low levels may worsen these symptoms (which are also common during menopause), particularly in the case of osteoporosis.

Summary

- The female starts having regular monthly cycles at puberty, regulated by hypothalamus. The hypothalamus releases gonadotropin-releasing hormone (GnRH), stimulating the anterior pituitary gland to release gonadotropins.
- The corpus luteum reaches its maximum development about nine days after ovulation if fertilization is unsuccessful. It is easily identifiable as a yellowish protrusion on the ovary's surface.
- A glycoprotein shell called the zona pellucida envelops the egg, aiding in sperm binding and triggering the acrosome reaction.
- The processes of gametogenesis and fertilization are essential to sexual reproduction because they generate genetically diverse progeny, which guarantees the survival of the species.
- Gametogenesis is the process by which a diploid gamete cell divides to produce haploid sperm and egg cells, respectively, in spermatogenesis and oogenesis.
- Spermiation is the process of releasing spermatids into the lumen of the seminiferous tubule after the cytoplasmic bridges disintegrate.

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Chapter

BILAMINAR AND TRILAMINAR GERM DISC

3

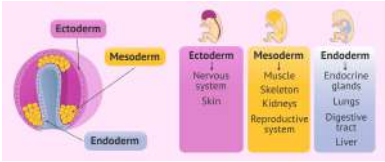
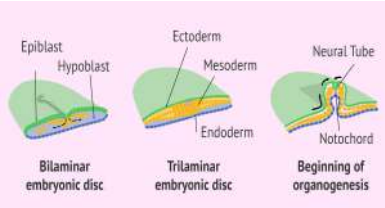
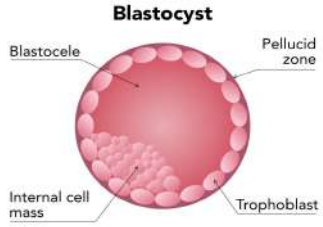
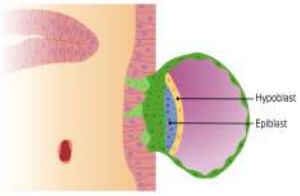
Contents

Unit Introduction

The bilaminar and trilaminar germ discs are crucial for the formation of the embryo and the ectoderm, mesoderm, and endoderm, the three main germ layers during the early stages of embryonic development. These phases signal the start of gastrulation, a complex process where cells differentiate and undergo extensive morphogenetic movements to form the tissues and organs of the developing embryo. After the blastocyst is implanted into the uterine wall, the bilaminar germ disc, also referred to as the bilaminar embryonic disc, forms during the second week of embryonic development. The bilaminar germ disc consists of two main layers: the epiblast and the hypoblast. The embryo proper, comprising the three germ layers and the amnion, a fluid-filled sac that envelops and shields the developing embryo, is derived from the dorsal epiblast. The ventral hypoblast aids in the development of extraembryonic tissues like the yolk sac, which is important for the early exchange of nutrients and the production of blood cells. The bilaminar germ disc, which denotes the beginning of embryonic differentiation and organization, has a flat, disc-like morphology. The trilaminar germ disc, also referred to as the trilaminar embryonic disc, is formed when additional morphological changes and differentiation occur in the bilaminar germ disc as development advances. Gastrulation, a process that takes place during the third week of embryonic development, is responsible for this transition. Gastrulation is the process by which cells migrate inward and reorganize to form the three main layers of the germ: the ectoderm, mesoderm, and endoderm. The ectoderm gives rise to structures like the nervous system, epidermis, and sensory organs. Muscles, bones, blood vessels, and connective tissues are all formed by the mesoderm. The endoderm gives rise to the glands connected to the digestive and respiratory systems, as well as the epithelium lining them.

The ectoderm, mesoderm, and endoderm are represented by discrete regions within the three-layered structure of the trilaminar germ disc. This stage lays the groundwork for the formation of all major organ systems and body structures of the embryo, making it a crucial turning point in embryonic development. The subsequent development and patterning, which give rise to the intricate anatomical and physiological structures of the mature organism, depend on the coordinated differentiation and organization of the three germ layers. The emergence of the three primary germ layers and the start of gastrulation are signified by the bilaminar and trilaminar germ discs, which are important developmental milestones in the early embryo. These phases prepare the ground for the development of all embryonic tissues and organs as well as the complex process of organogenesis and the maturation of the organism.

Orientation and Directional Terms

Terms	Definition	Illustration
Ectoderm	The ectoderm is one of the three primary germ layers formed in early embryonic development.	
Trilaminar germ disc	It is the next stage from the earlier bilaminar embryonic disc. It is an embryo which exists as three different germ layers – the ectoderm, the mesoderm and the endoderm.	
Reticulum	A reticulum is a natural structure that resembles a net or web, like the veins in a leaf or the network of fibers in a cell.	
Blastocyst	A blastocyst is a cluster of dividing cells made by a fertilized egg. It's the early stage of an embryo. A blastocyst is one step among many that lead to a pregnancy.	
Epiblast cells	The epiblast (also known as the primitive ectoderm) is one of two distinct cell layers arising from the inner cell mass in the mammalian blastocyst, or from the blastula in reptiles and birds, the other layer is the hypoblast.	

3.1. Bilaminar Germ Disc

The unique two-layered structure of cells formed in an embryo is known as the bilaminar embryonic disc, also known as the bilaminar germ layers or embryonic disc. This occurs by day eight of the human embryo's development. It develops when the inner cell mass, also referred to as the embryoblast, creates a bilaminar disc with two layers: the primitive endoderm-containing hypoblast layer at the bottom and the upper layer, known as the epiblast (primitive ectoderm), which will eventually give rise to the fetus. The primitive yolk sac and the amniotic sac, two fluid-filled cavities at either end, are where these two layers of cells are stretched.

With its columnar epithelial cells, the epiblast is located next to the trophoblast, while the cuboidal cells of the hypoblast are found closest to the blastocoel, or blastocystic cavity. A base membrane develops between the two layers as they become visible. This bilaminar disc layer division establishes the primitive dorsoventral axis and polarity during development. The amniotic cavity, whose lining is made of amnioblasts that developed from the epiblast, is formed as the epiblast migrates downward and away from the trophoblast. The exocoelomic cavity, or yolk sac, is formed by the hypoblast being forced downward. Certain hypoblast cells secrete extracellular matrix as they move along the inner cytotrophoblast lining of the blastocoel. The yolk sac, also known as the exocoelomic cavity, is formed by the hypoblast cells and extracellular matrix known as Heuser's membrane (also known as the exocoelomic membrane), which covers the blastocoel. The extraembryonic reticulum is disrupted when hypoblast cells migrate along its outer edges to form the extraembryonic mesoderm. The reticulum soon develops pockets, which eventually come together to form the chorionic cavity (extraembryonic coelom).

The second week following fertilization is when the bilaminar germ disc, an important stage in the early development of the embryo, occurs. It denotes the start of cell organization and differentiation within the embryonic structure.

The bilaminar germ disc is characterized by the presence of two primary layers: the epiblast and the hypoblast:

1. **Epiblast:** The epiblast is the upper layer of cells in the bilaminar germ disc. It is a pluripotent layer of cells that will give rise to the embryo proper. The epiblast undergoes further differentiation to form the three primary germ layers: ectoderm, mesoderm, and endoderm. These germ layers will subsequently give rise to all the tissues and organs of the developing embryo.
2. **Hypoblast:** The hypoblast, the lower layer of cells in the bilaminar germ disc, contributes to the formation of extraembryonic structures, such as the yolk sac, rather than being referred to as the primitive endoderm. The yolk sac plays a vital role in early embryonic development by providing nutrients to the developing embryo and serving as a site for the formation of blood cells.

The bilaminar germ disc is arranged in a flat, disc-like structure at this stage. It is encircled by the amniotic cavity, which is lined with the amnion—a membrane made of epiblast—and filled with amniotic fluid. The developing embryo is shielded by the amnion, which also offers a fluid-filled environment conducive to growth. The bilaminar germ disc forms following the process of embryonic cleavage and blastocyst implantation into the uterine wall. Following implantation, the blastocyst's inner cell mass

differentiates to form the bilaminar germ disc, which signals the start of gastrulation and the formation of the embryonic axes.

3.1.1. Day 8

On the eighth day of development, the blastocyst is partially embedded in the endometrial stroma. In the area over the embryoblast, the trophoblast has differentiated into two layers: (a) an inner layer of mononucleated cells, the cytotrophoblast, and (b) an outer multinucleated zone without distinct cell boundaries, the syncytiotrophoblast (Figure 3.1). The cytotrophoblast contains mitotic figures, whereas the syncytiotrophoblast does not. As a result, cytotrophoblast cells split and move into syncytiotrophoblasts, where they merge and separate from one another.

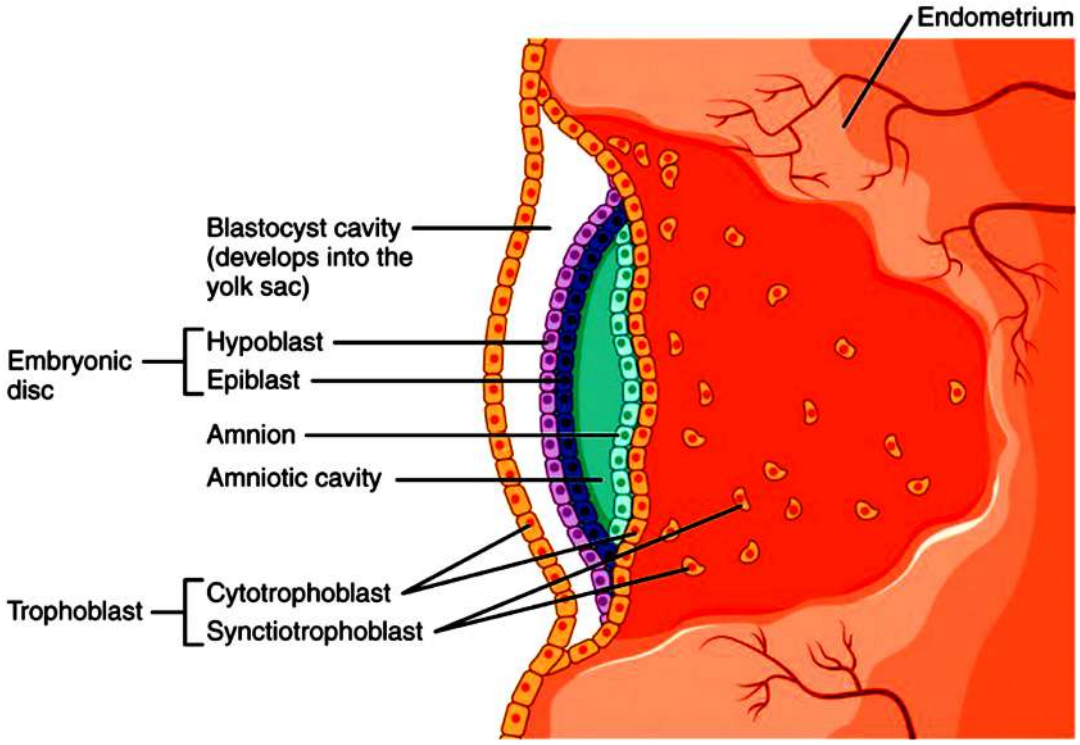


Figure 3.1. *A human blastocysta. The trophoblast consists of an inner layer with mononuclear cells, the cytotrophoblast, and an outer layer without distinct cell boundaries, the syncytiotrophoblast. The embryoblast is formed by the epiblast and hypoblast layers. The amniotic cavity appears as a small cleft.*

Source: https://courses.lumenlearning.com/suny-ap2/chapter/embryonic-development/.

Cells of the inner cell mass, or embryoblast also differentiate into two layers: (a) a layer of small cuboidal cells adjacent to the blastocyst cavity known as the hypoblast layer; and (b) a layer of high columnar cells adjacent to the amniotic cavity, the epiblast layer. Together, the layers form a flat disc. At the same time, a small cavity appears within the epiblast. This cavity enlarges to become the amniotic cavity. Epiblast cells adjacent to the cytotrophoblast are called amnioblasts; together with the rest of the epiblast, they line the amniotic cavity. The endometrial stroma

adjacent to the implantation site is edematous and highly vascular. The large, tortuous glands secrete abundant glycogen and mucus.

3.1.2. Day 9

The blastocyst is more deeply embedded in the endometrium, and the penetration defect in the surface epithelium is closed by a fibrin coagulum. The trophoblast shows considerable progress in development, particularly at the embryonic pole, where vacuoles appear in the syncytium. When these vacuoles fuse, they form large lacunae, and this phase of trophoblast development is thus known as the lacunar stage.

At the abembryonic pole, flattened cells, probably originating from the hypoblast, form a thin membrane known as the exocoelomic (Heuser's) membrane, which lines the inner surface of the cytotrophoblast. This membrane, together with the hypoblast, forms the lining of the exocoelomic cavity, or primitive yolk sac.

3.1.3. Days 11 and 12

By the 11th to 12th day of development, the blastocyst is completely embedded in the endometrial stroma, and the surface epithelium almost entirely covers the original defect in the uterine wall (Figures 3.4 and 3.5). The blastocyst now produces a slight protrusion into the lumen of the uterus. The trophoblast is characterized by lacunar spaces in the syncytium that form an intercommunicating network. This network is particularly evident at the embryonic pole; at the abembryonic pole, the trophoblast still consists mainly of cytotrophoblastic cells.

Simultaneously, syncytiotrophoblast cells erode the endothelium lining the mother capillaries by penetrating deeper into the stroma. The term "sinusoids" refers to these dilated, congested capillaries. Maternal blood enters the lacunar system when the syncytial lacunae unite with the sinusoids (Figure 3.1). Maternal blood starts to flow through the trophoblastic system, establishing the uteroplacental circulation, as the trophoblast continues to erode an increasing number of sinusoids.

Between the inner surface of the cytotrophoblast and the outer surface of the exocoelomic cavity, a new population of cells emerges. These cells, which are derived from yolk sac cells, eventually fill the entire space between the trophoblast externally and the amnion and exocoelomic membrane internally by forming the extraembryonic mesoderm, a fine, loose connective tissue. Large cavities soon form in the extraembryonic mesoderm, and these eventually confluence to form the extraembryonic coelom also called the chorionic cavity. This region encloses the primitive yolk sac and amniotic cavity, except for the location where the connecting stalk connects the germ disc to the trophoblast. The extraembryonic somatopleuric mesoderm is the lining that covers the cytotrophoblast and amnion, while the extraembryonic splanchnopleuric mesoderm layers the yolk sac (Figure 3.2).

The bilaminar disc grows more slowly than the trophoblast, which means that it will always remain very small (0.1–0.2 mm). In the meantime, endometrial cells become polyhedral and lipid- and glycogen-loaded; extravasate fills the intercellular spaces, causing edema in the tissue. Initially limited to the vicinity of the implantation site, these alterations, also referred to as the decidua reaction, eventually spread throughout the entire endometrium.

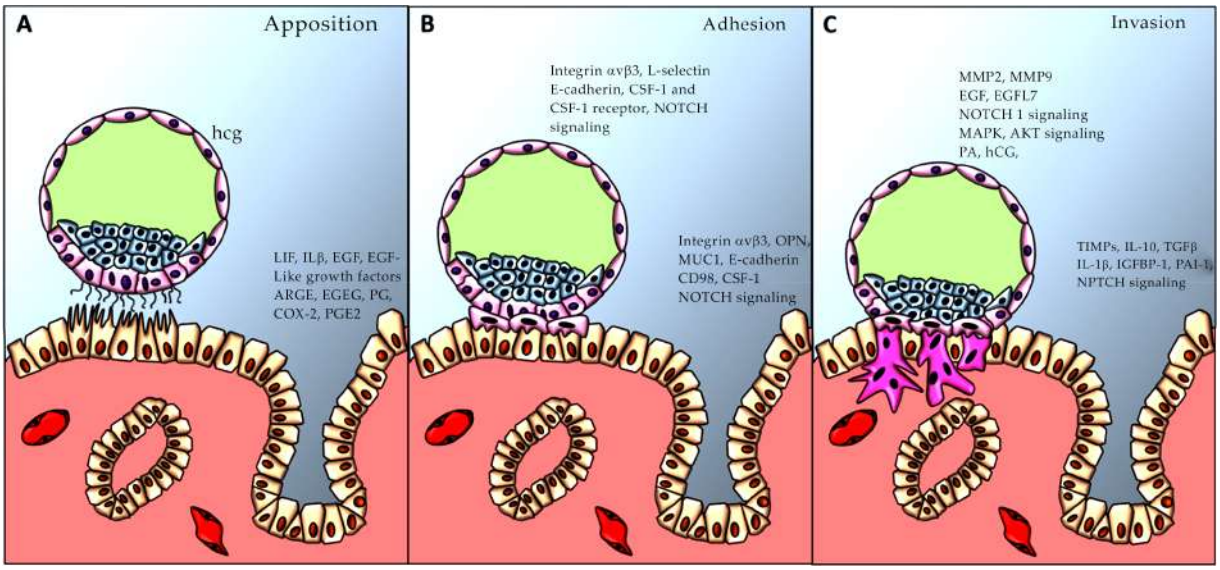


Figure 3.2. *Implantation.*

Source: Massimiani, M., Lacconi, V., La Civita, F., Ticconi, C., Rago, R., & Campagnolo, L., (2020). Molecular signaling regulating endometrium–Blastocyst crosstalk. International Journal of Molecular Sciences, 21(1), 23. https://doi.org/10.3390/ijms21010023.

3.1.4. Day 13

By the 13th day of development, the surface defect in the endometrium typically heals. In some cases, bleeding may happen at the implantation site due to increased blood flow into the lacunar spaces. This bleeding, occurring close to the 28th day of the menstrual cycle, can be mistaken for normal menstrual bleeding, leading to inaccuracies in determining the expected delivery date. The trophoblast is characterized by villous structures, with cytotrophoblast cells proliferating locally and penetrating the syncytiotrophoblast to create cellular columns surrounded by syncytium. These cellular columns covered by syncytium are referred to as primary villi.

In the meantime, the hypoblast produces additional cells that migrate along the inside of the exocoelomic membrane (Figure 3.2). These cells proliferate and gradually form a new cavity within the exocoelomic cavity. This new cavity is known as the secondary yolk sac or definitive yolk sac. This yolk sac is much smaller than the original exocoelomic cavity, or primitive yolk sac. During its formation, large portions of the exocoelomic cavity are pinched off. These portions are represented by exocoelomic cysts, which are often found in the extraembryonic coelom or chorionic cavity.

Meanwhile, the extraembryonic coelom expands and forms a large cavity known as the chorionic cavity. The extraembryonic mesoderm lining the inside of the cytotrophoblast is then known as the chorionic plate. The only place where extraembryonic mesoderm traverses the chorionic cavity is in the connecting stalk (Figure 3.3). With the development of blood vessels, the stalk becomes the umbilical cord.

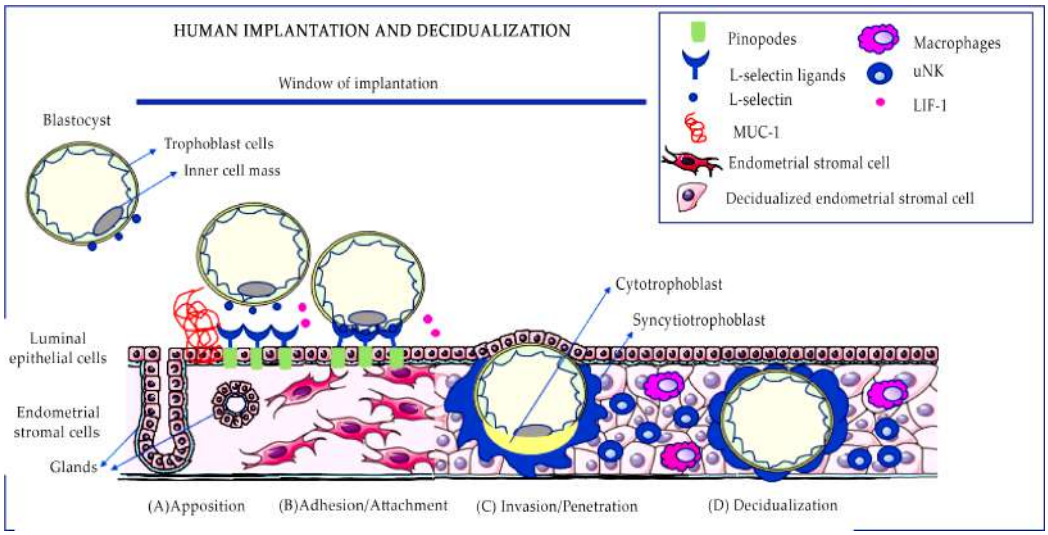


Figure 3.3. *Understanding implantation.*

Source: Ochoa-Bernal, M. A., & Fazleabas, A. T., (2020). Physiologic events of embryo implantation and decidualization in human and non-human primates. International Journal of Molecular Sciences, 21(6), 1973. https://doi.org/10.3390/ijms21061973.

3.2. Trilaminar Germ Disc

A trilaminar embryonic disc, trilaminar germ layers, or trilaminar germ disk is an early stage in the development of triploblastic organisms, which include humans and many other animals. It is the next stage from the earlier bilaminar embryonic disc. It is an embryo that consists of three different germ layers – the ectoderm, the mesoderm, and the endoderm. These layers are arranged on top of each other, giving rise to the name trilaminar, or "three-layered." The mesoderm is segmented further into the paraxial, intermediate, and lateral plate mesoderm. These three layers arise early in the third week (during gastrulation) from the epiblast (a portion of the mammalian inner cell mass).

During the third week after fertilization, the development of the trilaminar germ disc marks an important stage in the embryo's growth. It serves as a crucial turning point in the differentiation and cellular organization of the embryo, establishing the ectoderm, mesoderm, and endoderm as the three main germ layers.

The trilaminar germ disc is characterized by the presence of distinct regions corresponding to each germ layer, each of which will give rise to specific tissues and organs of the developing embryo:

1. **Ectoderm:** The ectoderm is the outermost germ layer of the trilaminar germ disc. It forms a layer of cells that will give rise to structures such as the epidermis, nervous system (including the brain and spinal cord), sensory organs (such as the eyes and ears), and neural crest cells, which migrate to various parts of the embryo and give rise to a diverse array of tissues, including the craniofacial bones and peripheral nervous system.
2. **Mesoderm:** The mesoderm is the middle germ layer of the trilaminar germ disc. It forms between the ectoderm and endoderm and gives

rise to a wide range of tissues and organs, including muscles, bones, connective tissues, blood vessels, kidneys, gonads, and the cardiovascular system. The mesoderm also contributes to the formation of the notochord, a rod-like structure crucial for early embryonic development and serving as a signaling center for patterning the embryo.

3. **Endoderm:** The endoderm is the innermost germ layer of the trilaminar germ disc. It forms a layer of cells that will give rise to the epithelial lining of the respiratory and digestive tracts, as well as associated organs such as the lungs, liver, pancreas, and thyroid gland. The endoderm also contributes to the formation of glands and other structures derived from the digestive and respiratory systems.

Following gastrulation, a complex morphogenetic process in which cells migrate and rearrange to form the three germ layers, the trilaminar germ disc forms. The primitive streak, a structure that develops along the embryo's dorsal surface, is the first sign of gastrulation. The mesoderm is created when epiblast cells move through the primitive streak and enter the area between the layers of epiblast and hypoblast. The endoderm is formed when certain cells move past the hypoblast layer and through the primitive streak. The epiblast layer's remaining cells differentiate into ectoderms in the meantime.

An essential stage in the development of the embryo is the formation of the trilaminar germ disc, which paves the way for the emergence of all the tissues and organs within the growing embryo. The embryo's subsequent patterning and morphogenesis, which give rise to the intricate anatomical structures and physiological systems of the mature organism, depend on the coordinated differentiation and organization of the three germ layers. The formation of the three main germ layers—ectoderm, mesoderm, and endoderm—marks the trilaminar germ disc, a crucial stage in the development of the embryo. This stage determines how all of the developing embryo's tissues and organs develop and lays the groundwork for later embryonic differentiation and organogenesis.

3.2.1. Gastrulation: Formation of Embryonic Mesoderm and Endoderm

The most characteristic event occurring during the third week of gestation is gastrulation, the process that establishes all three germ layers (ectoderm, mesoderm, and endoderm) in the embryo. Gastrulation begins with the formation of the primitive streak on the surface of the epiblast (Figure 3.4). Initially, the streak is vaguely defined, but in a 15- to 16-day embryo, it is visible as a narrow groove with slightly bulging regions on either side. The cephalic end of the streak, the primitive node, consists of a slightly elevated area surrounding the small primitive pit. Cells of the epiblast migrate toward the primitive streak. Upon arrival in the region of the streak, they become flask-shaped, detach from the epiblast, and slip beneath it. This inward movement is known as invagination. Once the cells have invaginated, some displace the hypoblast to create the embryonic endoderm, while others lie between the epiblast and newly created endoderm to form mesoderm. Cells remaining in the epiblast then form ectoderm. Thus, the epiblast, through the process of gastrulation, is the source of all of the germ layers, and cells in these layers will give rise to all of the tissues and organs in the embryo.

Cells start to spread laterally and cephalad as more and more migrate between the layers of epiblast and hypoblast (. They gradually move past the disc's edge and make contact with the extraembryonic mesoderm that covers the amnion and yolk sac. They cross the prechordal plate on both sides in a cephalic direction, contributing to the formation of the prechordal plate which plays a crucial role in the forebrain's induction. The earliest cells to migrate through the node in a cephalic direction give rise to the prechordal plate, which develops between the tip of the notochord and the buccopharyngeal membrane. (The buccopharyngeal membrane at the cranial end of the disc consists of a small region of tightly adherent ectoderm and endoderm cells that represents the future opening of the oral cavity.

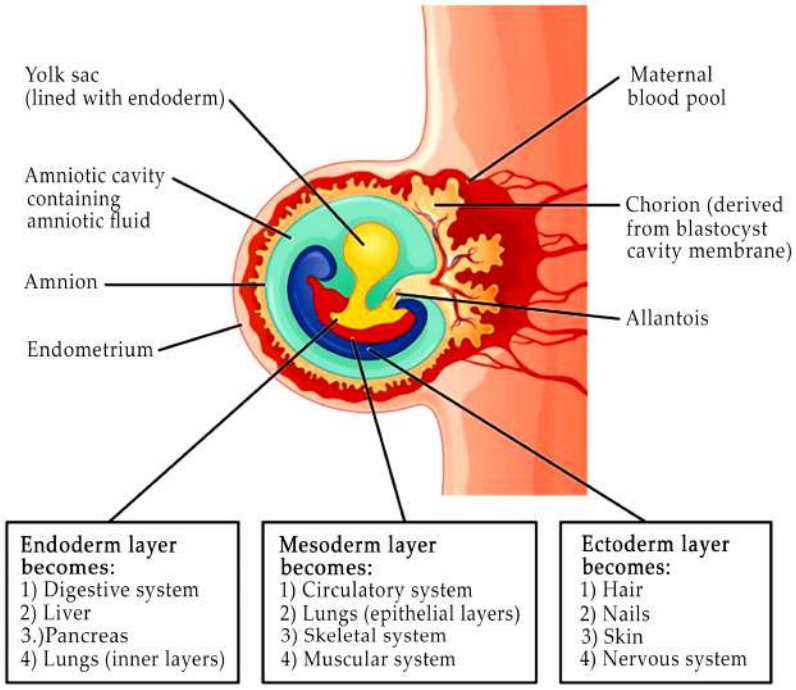


Figure 3.4. *Gastrulation.*

Source: https://courses.lumenlearning.com/suny-ap2/chapter/embryonic-development/.

3.2.2. Formation of the Notochord

The prechordal plate is reached by prenotochordal cells that invade the primitive pit by moving forward cephalad (Figure 3.5). For a brief period, the embryo's midline is made up of two cell layers that make up the notochordal plate because these prenotochordal cells intercalate in the hypoblast. Notochordal plate cells multiply and separate from the endoderm as they move in at the streak, They cross the prechordal plate on both sides in a cephalic direction, contributing to the formation of the prechordal plate which plays a crucial role in the forebrain's induction displacing the hypoblast. After that, they unite to form the definitive notochord, a solid cord of cells, which forms the foundation of the axial skeleton and lies beneath the neural tube. The cranial end forms first due to the dynamic nature of notochord elongation, and caudal regions are added as the primitive streak moves farther to the caudal direction. The prechordal plate, which is located

directly caudal to the buccopharyngeal membrane, and the primitive pit are the cranial destinations of the notochord and prenotochordal cells. The neurenteric canal serves as a temporary bridge connecting the amniotic and yolk sac cavities, where the pit creates an indentation in the epiblast.

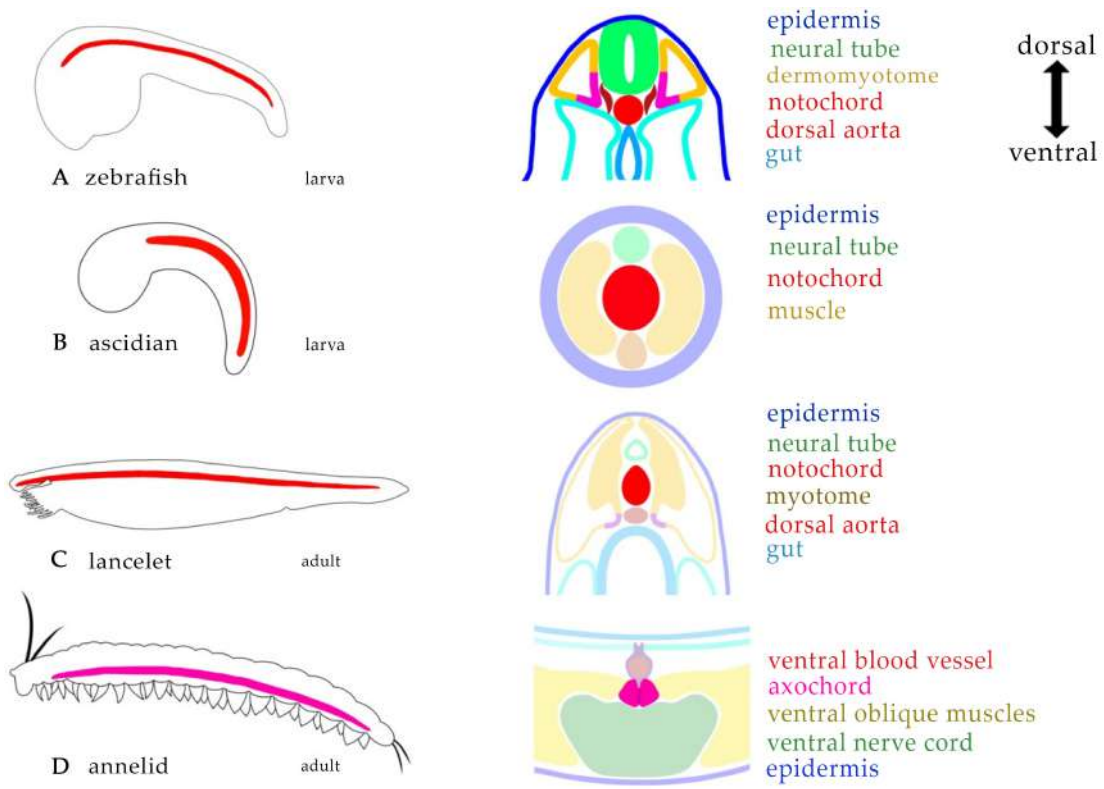


Figure 3.5. *Notochord formation.*

Source: Sui, Z., Zhao, Z., & Dong, B., (2021). Origin of the chordate notochord. Diversity, 13(10), 462. https://doi.org/10.3390/d13100462.

At the caudal end of the embryonic disc, the cloacal membrane forms. This membrane is composed of tightly adherent ectoderm and endoderm cells without any intervening mesoderm, resembling the buccopharyngeal membrane in structure. The posterior wall of the yolk sac forms a tiny diverticulum that extends into the connecting stalk when the cloacal membrane appears. The allantoenteric diverticulum, also known as the allantois, emerges around the 16th day of development. While in certain lower vertebrates, the allantois acts as a reservoir for renal excretion products, in humans it is still primitive and may play a role in abnormal bladder development.

3.2.3. Establishment of the Body Axes

The anteroposterior, dorsoventral, and left-right body axes are established both before and during the gastrulation stage. Cells at the anterior (cranial) margin of the embryonic disc signal along the anteroposterior axis. The anterior visceral endoderm (AVE) is the region where genes necessary for head formation are expressed. These genes include the secreted factor Cerberus and the transcription factors OTX2, LIM1, and HESX1. Before gastrulation, these genes determine the

embryo's cranial end. The expression of Nodal, a member of the transforming growth factor β (TGF-β) family, initiates and sustains the primitive streak itself (Figure 3.12). Numerous genes control the development of the head, tail, and dorsal and ventral mesoderm after the streak has formed. Bone morphogenetic protein-4, or BMP4, is another TGF-β family member that is secreted all over the embryonic disc (Figure 3.6). This protein along with fibroblast growth factor (FGF) will cause mesoderm to ventralize and contribute to mesoderm in the body wall (lateral plate mesoderm), blood, and kidneys (intermediate mesoderm). If its activity were not inhibited by other node-expressed genes, all mesoderm would become ventralized. The node is the organizer as a result. Hans Spemann gave it that name after he initially reported this activity in the dorsal lip of the embryo primitive node in Xenopus, a structure similar to the node. Therefore, its activity is inhibited by chordin (which is stimulated by the transcription factor Goosecoid), noggin, and follistatin. Cranial mesoderm subsequently dorsalizes into somites, somitomeres, and notochord (Figure 3.12). Subsequently, these three genes play a crucial role in neural induction in the cranial region and are expressed in the notochord.

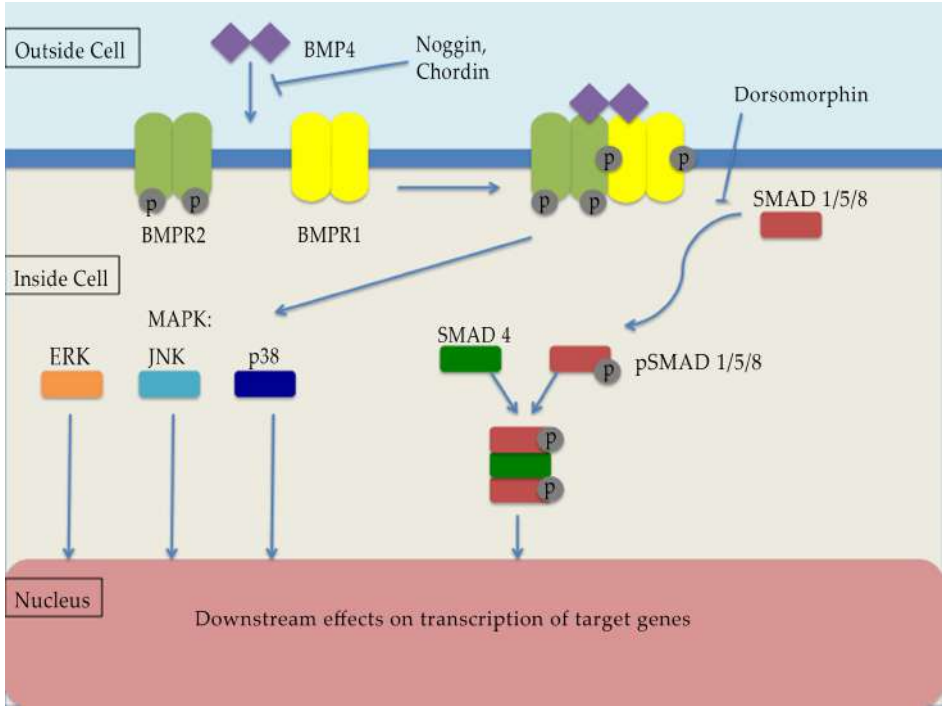


Figure 3.6. *BMP-4.*

Source: By Sarahk90 – Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=22766373

As previously indicated, Nodal plays a role in both starting and sustaining the primitive streak. Similarly, HNF-3β preserves the node in the forebrain and midbrain regions before causing regional specificity. Embryos that lack HNF-3β are unable to gastrulate normally and do not have forebrain or midbrain structures. As was previously mentioned, goosecoid aids in the regulation of head development by activating BMP-4 inhibitors. Serious abnormalities of the head region, including duplications, are caused by either overexpression or underexpression of this gene.

The Brachyury (T) gene regulates the formation of dorsal mesoderm in the middle and caudal regions of the embryo. The presence of this gene product is essential for mesoderm formation in these regions, with its absence leading to a shortened embryonic axis. The extent of shortening is determined by when the protein deficiency occurs.

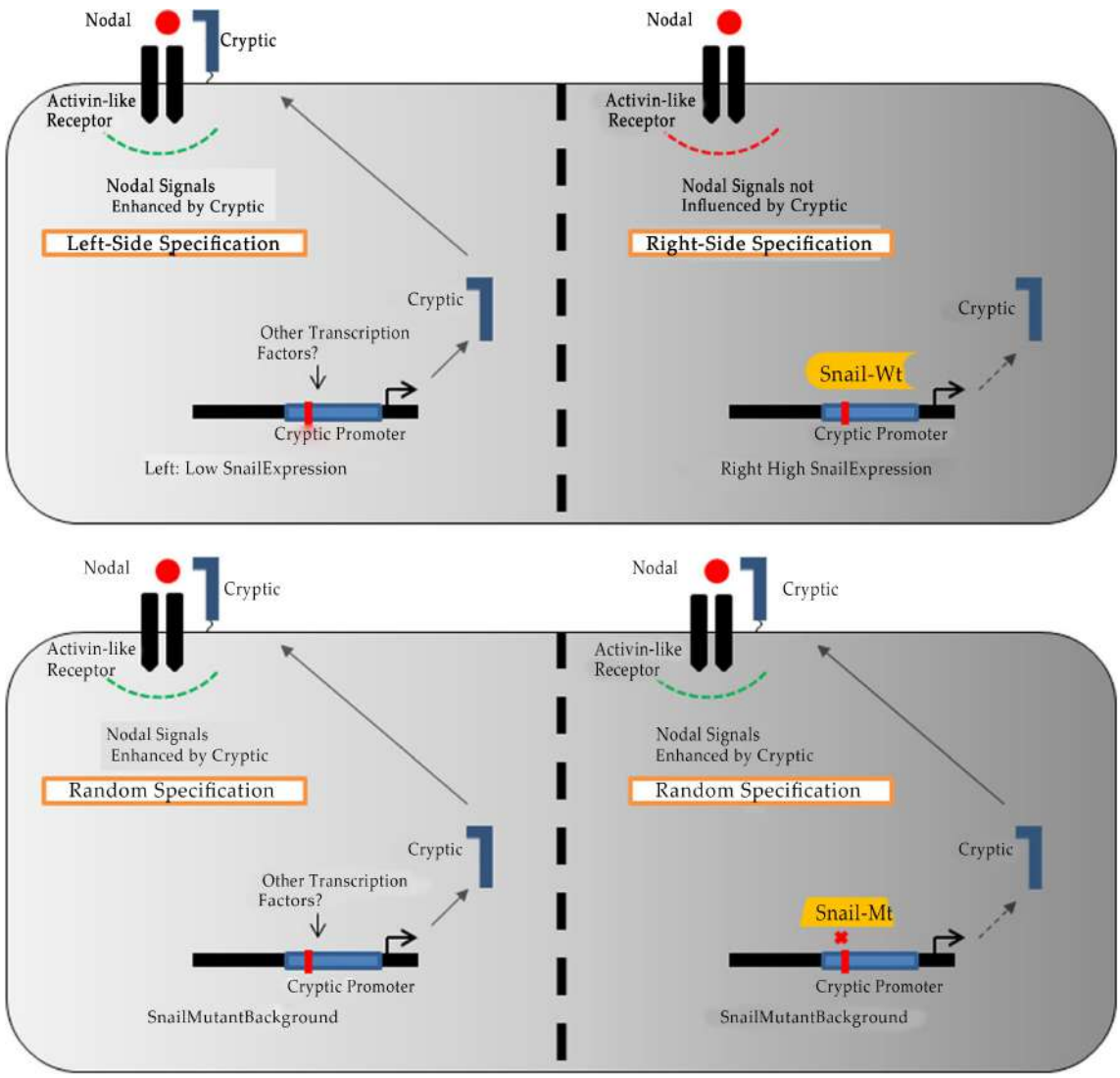


Figure 3.7. *Dorsal views of the germ disc showing gene expression patterns responsible for establishing the left-right body axis.*

Source: Gupta, K., Pilli, V. S. S., & Aradhyam, G. K., (2016). Left-right axis asymmetry determining human cryptic gene is transcriptionally repressed by snail. BMC Dev. Biol., 16, 39. https://doi.org/10.1186/s12861-016-0141-x.

Left-right-sidedness, also established early in development, is orchestrated by a cascade of genes. When the primitive streak appears, fibroblast growth factor 8 (FGF-8) is secreted by cells in the node and primitive streak and induces expression of Nodal but only on the left side

of the embryo. Later, as the neural plate is induced, FGF-8 maintains Nodal expression in the lateral plate mesoderm (Figure 3.7), as well as Lefty-2, and both of these genes upregulate PITX2, a transcription factor responsible for establishing left-sidedness. Simultaneously, Lefty-1 is expressed on the left side of the floor plate of the neural tube and may act as a barrier to prevent left-sided signals from crossing over. Sonic hedgehog (SHH) may also function in this role as well as serving as a repressor for left-sided gene expression on the right.

The Brachyury(T) gene, another growth factor secreted by the notochord, is also essential for the expression of Nodal, Lefty-1, and Lefty-2. Genes regulating right-sided development are not as well defined, although expression of the transcription factor NKX 3.2 is restricted to the right lateral plate mesoderm and probably regulates effector genes responsible for establishing the right side. Why the cascade is initiated on the left remains a mystery, but the reason may involve cilia on cells in the node that beat to create a gradient of FGF-8 toward the left. Indeed, abnormalities in cilia-related proteins result in laterality defects in mice and some humans with these defects have abnormal ciliary function.

3.2.4. Fate Map Established During Gastrulation

The final fates of epiblast regions that migrate and ingress through the primitive streak have been identified and mapped in detail (Figure 3.8). For instance, cells that enter the node through the cranial region give rise to the notochord; those that migrate through the midstreak region give rise to the intermediate mesoderm; those that migrate through the more caudal portion of the streak give rise to the lateral plate mesoderm; and cells that migrate through the caudal-most portion of the streak give rise to the extraembryonic mesoderm (the primitive yolk sac serves as the other source of this tissue).

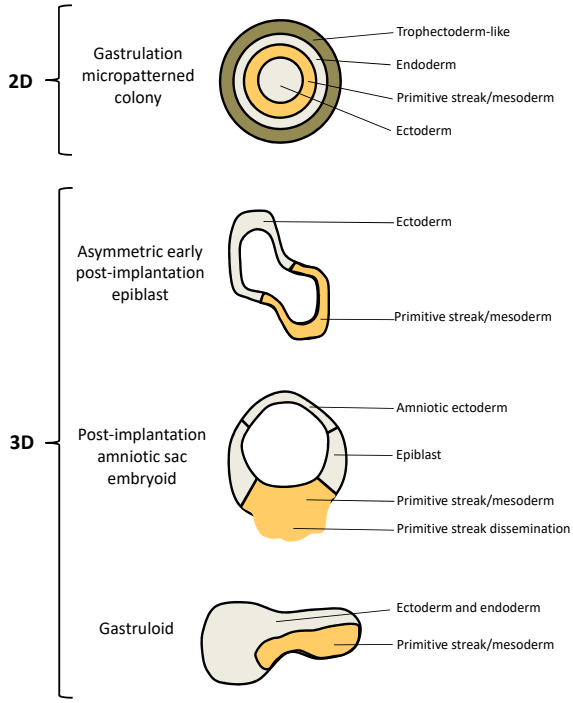


Figure 3.8. *The primitive streak.*

Source: Rosner, M., Reithofer, M., Fink, D., & Hengstschläger, M., (2021). Human embryo models and drug discovery. International Journal of Molecular Sciences, 22(2), 637. https://doi.org/10.3390/ijms22020637.

3.2.5. Growth of the Embryonic Disc

The embryonic disc, which is flat and nearly round at first, progressively lengthens and has a narrow caudal end and a broad cephalic end (Figure 3.9). The primitive streak region mostly stays the same size, while the embryonic disc expands primarily in the cephalic region. A constant migration of cells from the primitive streak region in a cephalic direction is responsible for the growth and elongation of the disc's cephalic portion. Until the end of the fourth week, the primitive streak's surface

cells continue to invaginate and migrate laterally and forward. At that point, the primitive streak exhibits regressive changes, contracts quickly, and eventually vanishes. The embryo's development is significantly impacted by the primitive streak at the caudal end of the disc, which keeps generating new cells until the end of the fourth week. By the middle of the third week, the germ layers in the cephalic portion start to differentiate specifically (Figure 3.9), while differentiation starts at the end of the fourth week in the caudal section. As a result, the embryo develops cephalocaudally, with gastrulation proceeding in caudal segments while cranial structures are differentiating (Figure 3.9).

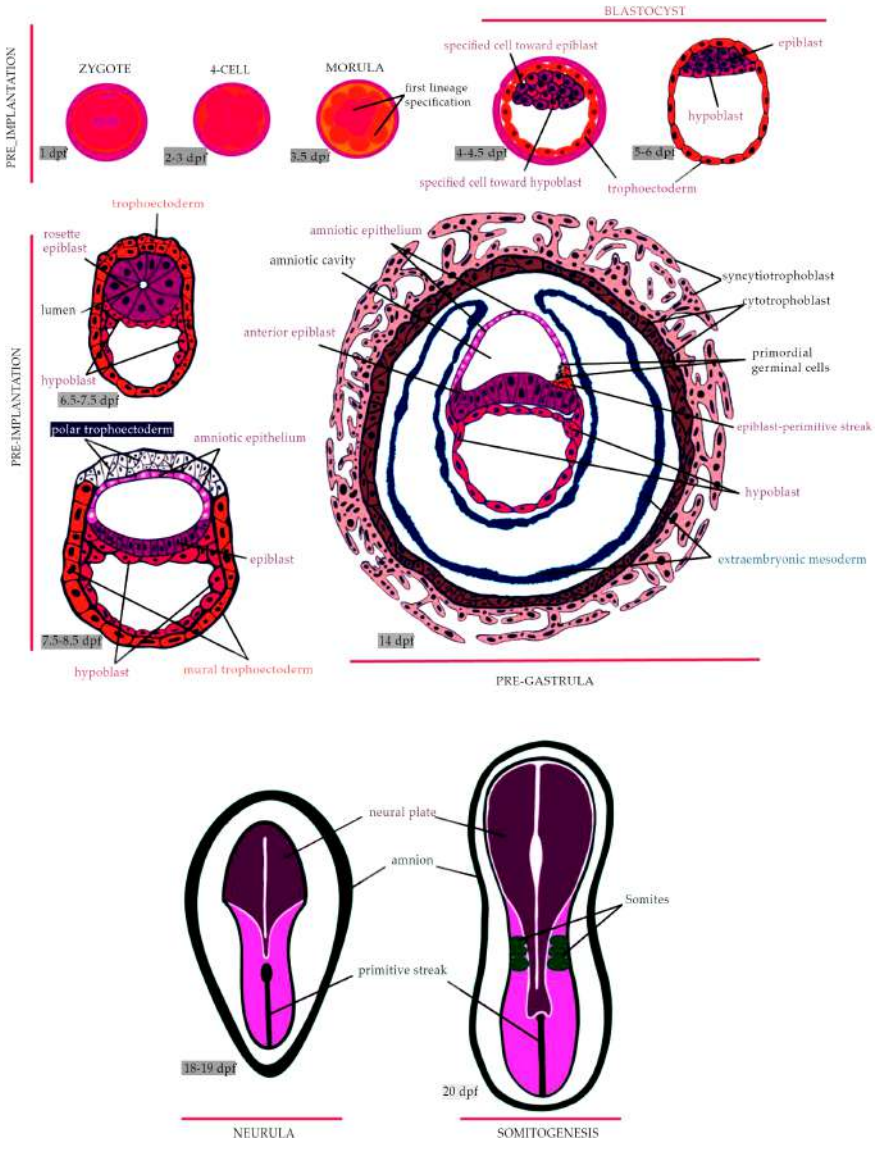


Figure 3.9. *The key events are summarized.*

Source: Ávila-González, D., Gidi-Grenat, M. Á., García-López, G., Martínez-Juárez, A., Molina-Hernández, A., Portillo, W., Díaz-Martínez, N. E., & Díaz, N. F., (2023). Pluripotent stem cells as a model for human embryogenesis. Cells, 12(8), 1192. https://doi.org/10.3390/cells12081192.

3.2.6. Further Development of the Trophoblast

Pregnancy establishment and maintenance depend heavily on the trophoblast, a layer of cells that forms the outer layer of a blastocyst during early embryonic development. The trophoblast develops further to support embryonic growth and facilitate interactions with maternal tissues as the embryo implants into the uterine wall.

Some key aspects of the further development of the trophoblast:

1. **Formation of Trophoblast Subtypes:** After implantation, the trophoblast undergoes differentiation into distinct subtypes, including the cytotrophoblast and syncytiotrophoblast. The cytotrophoblast consists of individual, undifferentiated cells, while the syncytiotrophoblast forms a multinucleated layer that secretes hormones and facilitates nutrient exchange between the embryo and the mother.
2. **Placental Development:** The trophoblast contributes to the formation of the placenta, an essential organ for fetal development. Trophoblast cells invade the maternal endometrium, forming anchoring villi that anchor the embryo to the uterine wall and establish connections with maternal blood vessels. These connections allow for the exchange of nutrients, oxygen, and waste products between the maternal and fetal circulatory systems.
3. **Hormone Production:** The syncytiotrophoblast produces hormones such as human chorionic gonadotropin (hCG), which supports the early stages of pregnancy by maintaining the corpus luteum and stimulating the production of progesterone. Progesterone is essential for maintaining the uterine lining and preventing menstruation, thereby supporting the implantation and early development of the embryo.
4. **Immune Modulation:** Trophoblast cells play a role in modulating the maternal immune response to prevent rejection of the developing embryo. They express molecules that promote immune tolerance, allowing the embryo to evade recognition by the maternal immune system and establish a successful pregnancy.
5. **Maternal-Fetal Communication:** The trophoblast facilitates communication between the developing embryo and maternal tissues through the secretion of signaling molecules and microRNAs. These molecules regulate processes such as angiogenesis, immune tolerance, and tissue remodeling, ensuring proper placental development and fetal growth.
6. **Pathophysiology and Pregnancy Complications:** Dysregulation of trophoblast development and function can lead to pregnancy complications such as preeclampsia, fetal growth restriction, and miscarriage. Understanding the molecular mechanisms underlying trophoblast development is crucial for identifying potential diagnostic markers and therapeutic targets for these conditions.

Establishing and sustaining a successful pregnancy depends on the trophoblast's continued development. The trophoblast is a multifaceted organ that supports embryonic growth and maintains the health of the mother and fetus during pregnancy through differentiation, hormone production, placental development, immune modulation, and communication with maternal tissues in pregnancy.

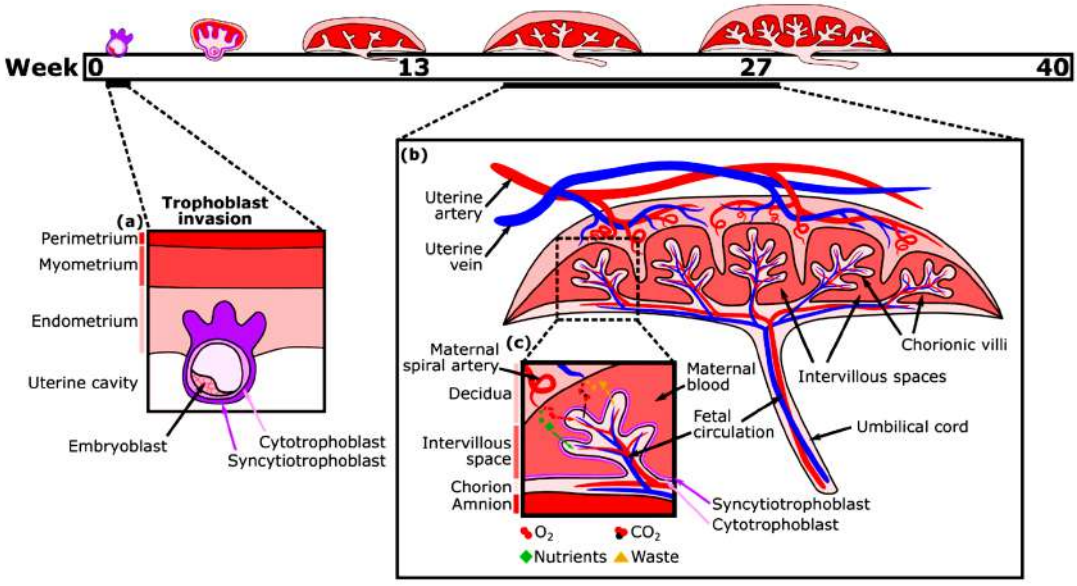


Figure 3.10. *The placenta.*

Source: Cherubini, M., Erickson, S., & Haase, K., (2021). Modeling the human placental interface in vitro: A review. Micromachines, 12(8), 884. https://doi.org/10.3390/mi12080884.

Primary villi, which are made up of a cytotrophoblastic core encased in a syncytial layer, are indicative of the trophoblast. Mesodermal cells enter the core of the primary villi during subsequent development and migrate in the direction of the decidua. A secondary villus is the name given to the recently formed structure. The villous capillary system is formed by mesodermal cells in the villus' core, which start to differentiate into blood cells and tiny blood vessels by the end of the third week. These days, the villus is referred to as a definitive placental villus or a tertiary villus. Developing capillaries in the connecting stalk and the mesoderm of the chorionic plate come into contact with capillaries in the tertiary villi (Figure 3.10). The placenta and the embryo are connected by these vessels, which in turn make contact with the intraembryonic circulatory system. Hence, the villous system is prepared to provide the embryo properly with vital nutrients and oxygen when the heart beats during the fourth week of development.

Meanwhile, the mother's endometrium is reached by the cytotrophoblastic cells in the villi as they gradually pierce the covering syncytium. Here, they make contact with comparable extensions of nearby villous stems, creating a thin cytotrophoblast shell on the outside (Figure 3.10). This shell securely affixes the chorionic sac to the mother's endometrial tissue and gradually envelops the trophoblast (Figure 3.10). Stem or anchoring villi are those that extend from the chorionic plate to the decidua basalis. Nutrients and other elements are exchanged in the free (terminal) villi that branch off the sides of the stem villi.

The chorionic cavity, meanwhile, becomes larger, and by the 19th or 20th day, the embryo is attached to its trophoblastic shell by a narrow connecting stalk (Figure 3.10). The connecting stalk later develops into the umbilical cord, which forms the connection between the placenta and the embryo.

A Closer Look

Blastocyst

A blastocyst is a 5 to 6 day embryo with a complex cell structure consisting of approximately 200 cells. The blastocyst stage is the stage of development prior to the implantation of the embryo in the mother's womb.

This cellular structure differs in two areas that will determine the quality of the embryo and its options to implant and achieve a pregnancy:

- The first is the internal cell mass (ICM), which is a group of cells found inside the blastocyst or cavity that will give rise to the fetus.
- The second is an epithelial cell layer called the trophoblast (TE), which covers the blastocele and will give rise to the extra-embryonic tissues (placenta and amniotic membranes)

Several cells of the TE are usually biopsied when we perform a Preimplantation Genetic Test (PGT-A) and are analyzed by Next Generation Sequencing (NGS), to select those embryos free of chromosomal alterations. To assess and classify the quality of a blastocyst we base it on its size or expansion of the cavity (blastocele) and the morphology of the ICM and TE.

The blastocyst is a distinctive stage of a mammalian embryo. It is a form of blastula that develops from a berrylike cluster of cells, called the morula. A cavity appears in the morula, between the cells of the inner cell mass and the enveloping layer. This cavity becomes filled with fluid. The blastocyst differs from the blastula in that it is composed of two already differentiated cell types, the inner cell mass and the enveloping layer.

Further differentiation produces a thin layer of cells, called the hypoblast, between the inner cell mass and the cavity. These cells contribute to the formation of the embryonic endoderm, which develops the respiratory and digestive tracts.

The enveloping layer is now referred to as the trophoblast. It does not contribute directly to the formation of the embryo but rather serves to establish a connection with the maternal uterus. It is a precursor of the placenta.

SUMMARY

- The bilaminar and trilaminar germ discs are crucial for the formation of the embryo and the ectoderm, mesoderm, and endoderm, the three main germ layers during the early stages of embryonic development.
- The ectoderm, mesoderm, and endoderm are represented by discrete regions within the three-layered structure of the trilaminar germ disc.
- The most characteristic event occurring during the third week of gestation is gastrulation, the process that establishes all three germ layers (ectoderm, mesoderm, and endoderm) in the embryo.
- Pregnancy establishment and maintenance depend heavily on the trophoblast, a layer of cells that forms the outer layer of a blastocyst during early embryonic development.
- Establishing and sustaining a successful pregnancy depends on the trophoblast's continued development.

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Chapter

4

GASTRULATION AND FORMATION OF THE GERM LAYERS

Contents

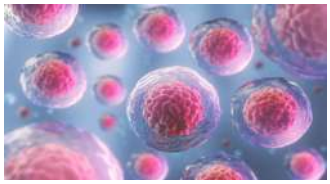
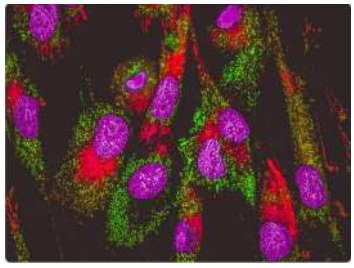
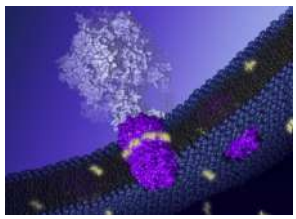
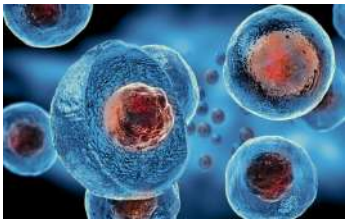
Unit Introduction

Gastrulation, a crucial stage in the development of an embryo, creates the framework for the formation of complex organ systems in vertebrates by transforming the blastula from a single-layered structure into a multi-layered one. Invagination, migration, and differentiation of cells to form the ectoderm, mesoderm, and endoderm are the three main germ layers that are established during this process. The process of gastrulation starts at the primitive streak, a structure that appears on the embryo's surface and typically runs along the future posterior end. Through the epithelial-to-mesenchymal transition (EMT), cells at the primitive streak can penetrate the underlying layers and separate from the epithelial layer. This cellular movement forms the primitive node, a furrow that, depending on the organism's developmental fate, will eventually give rise to the mouth or anus.

Through a process called involution, cells from the primitive streak move toward the interior of the embryo as gastrulation advances, aiding in the formation of the three germ layers. The endoderm, which makes up the innermost layer of the embryo and gives rise to the epithelial linings of the digestive and respiratory tracts as well as related organs like the liver and pancreas, is formed by cells that enter through the primitive streak. Simultaneously, cells at the embryo's dorsal midline migrate laterally to form the mesoderm, an intermediate layer that gives rise to a wide range of structures, such as the kidneys, reproductive organs, cardiovascular system, and musculoskeletal system. The ectoderm, the outermost layer of the embryo that gives rise to the nervous system, sensory organs, and epidermis, is finally formed by cells that are still in the outer layer of the embryo.

For the subsequent development of the embryo, the formation of the three germ layers during gastrulation is crucial because it lays the foundation for the patterning and differentiation of tissues and organs. Understanding this essential process in embryology and developmental biology is crucial because disruptions in gastrulation can result in serious developmental abnormalities and congenital malformations. Ultimately, the process of gastrulation is a crucial turning point in the development of the embryo, coordinating the change from a simple, one-layered creature to a complex, multi-layered creature with distinct body axes and organ systems.

Orientation and Directional Terms

Terms	Definition	Illustration
Gastrulation	Gastrulation is the stage in the early embryonic development of most animals, during which the blastula, or in mammals the blastocyst, is reorganized into a two-layered or three-layered embryo known as the gastrula.	
Epithelial-to-mesenchymal transition	The epithelial–mesenchymal transition (EMT) is a process by which epithelial cells lose their cell polarity and cell–cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells; these are multipotent stromal cells that can differentiate into a variety of cell types.	
Nervous system	The nervous system is the highly complex part of an animal that coordinates its actions and sensory information by transmitting signals to and from different parts of its body.	
Molecular mechanisms	Molecular mechanisms of diseases is one of five areas of expertise in the Pharmacy, Pharmacology and Biomedical Sciences research area.	
Embryonic stem cells	Embryonic stem cells are pluripotent stem cells derived from the inner cell mass of a blastocyst, an early-stage pre-implantation embryo.	

4.1. Gastrulation and Germ Layer Formation

Most animals go through a stage called gastrulation in which the blastula, a single-layered hollow sphere of cells (or the blastocyst in mammals), reorganizes to become the gastrula, a two- or three-layered embryo. The embryo is a continuous epithelial sheet of cells prior to gastrulation. By the end of the gastrulation, the embryo has started to differentiate to form distinct cell lineages and establish the fundamental axes of the body (e.g., internalized one or more cell types, including the potential gut, and internalized dorsal-ventral and anterior-posterior structures).

An animal embryo with a double or triple germ layer is referred to as a gastrula. This is a crucial stage in the development of animal embryos. It originates from the blastocyst's development. To form the gastrula of the double or triple germ layer, a portion of the blastocyst's cells migrate internally through a variety of channels. Many higher animals form mesoderm between the meat ectoderm, whereas lower animals, like coelenterates, only have two germ layers. The gut lumen is the endodermis-enclosed cavity. The gut effect refers to the cell migration that occurs during gastrulation. There are several approaches, including migration, concentration, outsourcing, inset, stratification, and extension. The nucleus started to take the lead in the synthesis of new proteins during this time, and cells underwent significant differentiation, setting the stage for the development of tissues and the creation of organs.

4.1.1. Gastrulation

Most animal embryos go through the stage of gastrulation. Only one layer of blastocysts recombines at this point to create a gastrula with three germ layers (i.e., cells of the ectoderm, mesoderm, and endoderm. Following the cleavage is the process of gastrulation. The embryo enters the gastrula after it forms, and the process of organogenesis gets started. Organs will form from the fusion of the three germ layers' newly formed cells. Each germ layer's cells have the potential to develop into distinct organs and tissues. The ectoderm gives rise to the neural crest, epidermis, and tissue that eventually becomes the nervous system. Mesoderm cells can develop into somites, muscles, and cartilage that make up the ribs and vertebrae. They are found in the space between ectodermal and endodermal cells. Furthermore, the mesoderm can give rise to the spinal cord, dermis, blood vessels, bone, and connective tissue. The epithelium of the respiratory and digestive systems, including the liver and pancreas, is formed from endoderm cells. Following the endocytic formation process, body cells arrange themselves into a group that is encircled by epithelium-related cells.

Different organisms require different times for gastrulation due to differences in molecular mechanisms. Nonetheless, there are some commonalities among gastrulation in diverse organisms. For example, the embryo's topology shifts from a single connected surface, such as a spherical surface, to a non-single connected surface, such as a ring surface. Second, ectodermal, mesodermal, and endodermal cells (as well as certain lower organisms lacking mesodermal cells) develop from embryonic cells. Third, the function of endoderm cells will be digestion. Furthermore, in general, the movement of cells during the process of gastrulation can be categorized into five types: invagination, involution, ingression, delamination, and epiboly. This is true even though the specific patterns of gastrulation in animals vary greatly. The embryo forms an anterior-posterior axis and a proximal-distal axis during the preparation stage of gastrulation. These two axes also result in asymmetry. The

proximal extraembryonic tissue forms the placenta-like tissue, and the formation of the embryonic egg cylinder signifies the formation of the far and near axes. This process involves signal transduction pathways that are mediated by signaling molecules like Wnt, FGF, Nodal, and bone morphogenetic protein (BMP). The epidermis is surrounded by the visceral endoderm. The symmetry before and after is broken when the distal visceral endoderm (DVE) migrates to the anterior region of the embryo to form the anterior visceral endoderm (AVE). The Nodal signaling pathway controls the previously mentioned process. In the first phase of gastrulation, the original strip is created. The original strip is situated where the internal migration happens, at the intersection of the epidermis and posterior extraembryonic tissue.

The Nodal signaling pathway in Coriolis-region cells and the BMP4 signaling pathway triggered by extra-embryonic tissues are closely linked to the formation of the original streak. Cer1 and Lefty1 can inhibit the Nodal signaling pathway, which restricts the formation of primitive streaks in particular areas. After formation, the original strip area will keep expanding in a distal direction. In an effort to learn more about the process of gastrulation, numerous scientists are attempting to compare studies conducted in embryos with those conducted in vitro. Researchers typically cultivate embryonic stem cells (ESC) or artificially induced pluripotent stem cells (iPSC) using 2D (traditional) or 3D (autologous cell culture methods). In comparison to the in vivo experimental method (in the intestinal embryogenesis period in vivo), the tissue culture method-based in vitro culture approach is less expensive, adheres to the 3R principle, and can precisely use the agonist/antagonist in a spatially and temporally specific manner. The third point is challenging to accomplish. Nonetheless, there are some differences between in vivo and in vitro research, so a comparison with the bodily development of embryos is required.

4.1.2. Germ Layer Formation

When an animal embryo forms, a collection of cells known as the germ layer, or reproductive epithelium, is created. This layer is less frequently used. Every animal has a germ layer, but the structure of the vertebrate germ layer is the most noticeable. The sponge (Porifera) germ layer is the most basic, typically producing two to three major tissue layers (also known as primary germ layers). Bilaterally symmetrical animals have three germ layers—endoderm, mesoderm, and ectoderm—unlike radially symmetric animals, which typically have only two germ layers. Radiation-symmetric animals, such as coelenterates, have two germ layer structures, including endoderm and ectoderm. Every cell in the germ layer eventually gives rise to the animal's different tissues and organs. Depending on their location in the embryo, the inner, middle, and outer layers of the germ layers are given different names. Every layer of cells has unique properties beyond their spatial arrangement. For instance, ectodermal cells are small and divide quickly, while endoderm cells are typically larger and contain more yolk. The early distribution of the three germ layers in the gastrula or blastocyst stage can be identified by in vivo staining, which illustrates their expected fate. This map illustrates the possibility that distinct germ layers are connected to egg heterogeneity. It is well known that the quality of an animal's eggs varies depending on its habitat. Eggs, for instance, move, and different parts of the egg have different distributions of macronuclei, such as pigment particles, organelles, nucleic acid proteins, and yolk particles. The uneven oocyst is dispersed into various lobes when the cleavage splits the egg into numerous tiny pieces. The materials that were initially allocated to various lobes are dispersed into various germ layers as gastrointestinal motility advances. These

compounds might have an impact on each germ layer's subsequent differentiation.

The lobes that contain the yellow crescent region of the stalk, for instance, will eventually form muscle and interstitial cells; the lobes that contain the gray crescent region will eventually form the notochord and nerve tissue; and the lobes that contain the transparent material will eventually form the epidermis. In the future, plant polar matter blastomeres will form endoderm. The ectoderm typically forms the nerve tissue and epidermis. The intestinal and digestive gland epithelium, which gives rise to bone, muscle, blood, lymph, and other connective tissues, is formed by the endoderm. The mesoderm is the source of others. Essentially, the germ layer differentiation follows the path shown in the drawing. However, there are some exceptions. The sphincter of the eye's iridescence originates from the ectoderm, a portion of the retina, rather than the mesoderm or mesenchyme. The mesenchyme itself may originate from the ectoderm, mesoderm, or even the endoderm; however, the smooth muscle of the sweat gland is derived from the ectoderm rather than the mesoderm. Regarding regeneration, dedifferentiation cells can reverse the direction of differentiation, making it more challenging to discern the germ layer that is attached to it. The development of the germ layer does not always follow one path. Certain mitotic balls are removed from the echinodermal embryo, allowing the remaining blastomeres to compensate for tissue differentiation into different kinds.

The structure of the sea urchin's mesoderm is formed by lithium ions, whereas the structure of the ectoderm is formed by thiocyanate or sulfate from the mesoderm and endoderm. Comparable adjustments can be made to the research on chicken and fish embryos. Before differentiation, the germ layer is merely a preliminary division. The environment in which the embryonic cells are found, certain cytoplasmic elements within the cells, and the interactions between the cells all have a significant impact on the direction of differentiation. The study of ontogeny and phylogeny can be accessed through the notion of the germ layer. Understanding the inherent relationship between each person's developmental changes and the development of different organs is helpful. For instance, the retina of the eyeball and the brain are two structures where the ectoderm is induced. Other structures where ectoderm is induced under different circumstances include the olfactory sac and the ear sac. The endocrine properties of the cortex and adrenal gland pith are very different because the cortex originates from the mesoderm and the adrenal gland pith from the ectoderm. Understanding the evolutionary relationship between ontogeny and phylogeny is further aided by the notion of the germ layer. A monolayer of cells, such as a group of algae, can be compared to the blastocyst stage. A two-layer structure forms from a portion of the internal and intracellular pleats of the blastocyst and coelenterates. The endoderm digestive tract is located inside, and the ectoderm wall is located outside.

4.1.3. Events and Processes of Gastrulation

Gastrulation is characterized by a series of coordinated cellular movements and morphogenetic events. The emergence of a structure on the embryo's surface known as the primitive streak usually marks the start of the gastrulation process. Gastrulation is driven by morphogenetic changes and cellular movements that are centered around the primitive streak. Epithelial-to-mesenchymal transition (EMT) is the process by which cells next to the primitive streak change from being epithelial cells to being more motile mesenchymal cells. This makes it

possible for these cells to penetrate the embryo's interior and separate from the epithelial layer.

Through a process called involution, cells that penetrate the primitive streak give rise to the three germ layers. The endoderm, which makes up the innermost layer, is produced by the first cells to enter the embryo through the primitive streak and migrate toward the anterior end of the embryo. The epithelial lining of the gastrointestinal tract, respiratory tract, and related organs like the thyroid, pancreas, and liver are all influenced by the endoderm. The mesoderm, a layer in between the endoderm and ectoderm, is created currently by cells that enter through the primitive streak and move laterally toward the sides of the embryo. Numerous structures, such as the musculoskeletal system, cardiovascular system, kidneys, and reproductive organs, are produced by the mesoderm. Furthermore, the mesoderm aids in the development of the notochord, a temporary structure that is essential for establishing the body axis and initiating the formation of the neural tube.

The ectoderm, which forms the outermost layer of the embryo, is ultimately produced by cells that are still in the outer layer. The neural system, sensory organs like the eyes and ears, and the epidermis, hair, nails, and other integumentary structures are all products of the ectoderm. The three germ layers are established during gastrulation by the careful spatiotemporal regulation of gene expression patterns and signaling pathways, which control cell specification, migration, and differentiation. Understanding the events and processes of gastrulation in embryonic development is crucial because disruptions in these processes can result in congenital malformations and abnormalities in development. All things considered, the process of gastrulation marks a significant turning point from a basic, single-layered embryo to a complex, multi-layered creature with distinct body axes and organ systems.

4.1.4. Formation and Differentiation of the Three Embryonic Germ Layers (Ectoderm, Mesoderm, and Endoderm)

The diverse array of tissues and organs in the developing organism results from the formation and differentiation of the three primary germ layers—the endoderm, mesoderm, and ectoderm—during embryonic development. During gastrulation, an important stage of embryogenesis, these layers are formed. Later, they differentiate to form specialized cell types and tissues.

1. Ectoderm:
    - **Formation:** The ectoderm is the outermost germ layer, derived from cells located on the surface of the embryo during gastrulation. These cells remain in the outer layer as other cells ingress through the primitive streak to form the mesoderm and endoderm.
    - **Differentiation:** The ectoderm gives rise to various tissues, including the epidermis (outer layer of skin), hair, nails, and sweat glands. Additionally, the ectoderm contributes to the formation of the nervous system, including the brain, spinal cord, and peripheral nerves. Specialized regions of the ectoderm, called neural crest cells, migrate to different parts of the embryo and give rise to a diverse range of cell types, including craniofacial bones, pigment cells, and

neurons of the peripheral nervous system.

2. Mesoderm:
    - **Formation:** The mesoderm is derived from cells that ingress through the primitive streak during gastrulation, migrating laterally to occupy the space between the ectoderm and endoderm.
    - **Differentiation:** The mesoderm gives rise to a wide variety of tissues and organs, including the musculoskeletal system, cardiovascular system, urogenital system, and connective tissues. It also contributes to the formation of the notochord, a transient structure that induces the development of the nervous system. Specialized regions of the mesoderm, called somites, give rise to segments of the axial skeleton (e.g., vertebrae) and muscles of the body wall and limbs.
3. Endoderm:
    - **Formation:** The endoderm is derived from cells that ingress through the primitive streak and migrate towards the anterior end of the embryo during gastrulation, forming the innermost layer.
    - **Differentiation:** The endoderm gives rise to the epithelial linings of the respiratory tract, gastrointestinal tract, and associated organs such as the liver, pancreas, and thyroid. These organs play essential roles in digestion, nutrient absorption, and metabolism.

As they give rise to the wide variety of tissues and organs required for survival and appropriate physiological function, the formation and differentiation of the three embryonic germ layers are ultimately essential for the development of a functional organism. It is crucial to comprehend these processes in embryonic development because disruptions in the establishment or differentiation of these germ layers can result in developmental abnormalities and congenital malformations.

4.2. Induction and Patterning of Embryonic Tissues

To ensure appropriate spatial organization and functional differentiation, induction and patterning are essential processes in the shaping of the developing tissues and organs. Induction is the process by which signals from one group of cells affect the fate and behavior of nearby cells, resulting in the formation of unique cell types and structures. Growth factors and morphogens are examples of signaling molecules that are secreted during this process and which set off gene expression cascades and cellular reactions in recipient cells. Contrarily, patterning entails the creation of spatial gradients and cues within developing tissues to direct tissue morphogenesis and cell fate specification. Organ primordia, limb buds, body axes, and other complex structures are precisely patterned from embryonic tissues through complex interactions between regulatory networks and signaling pathways. Understanding these basic mechanisms in embryonic development and their relevance to human health and disease is crucial, as disruptions in the induction and patterning processes can result in developmental defects and congenital malformations.

In animal development, the careful planning of cell differentiation from initially identical naïve cells is crucial. Tissue patterning was thought to be underpinned by the concept of

induction (Figure 4.1), which states that nearby tissues and cells instruct one another to carry out different developmental programs, at the beginning of the 20th Century. The earliest known instances of induction in science came from traditional transplantation research, where a segment of one embryo was inserted into a different location on a host embryo. For instance, ectopic lens formation was observed upon transplanting an optic cup into the epidermis, and the formation of a second embryonic axis was noted upon transferring the dorsal pole of one embryo onto the ventral side of another embryo.

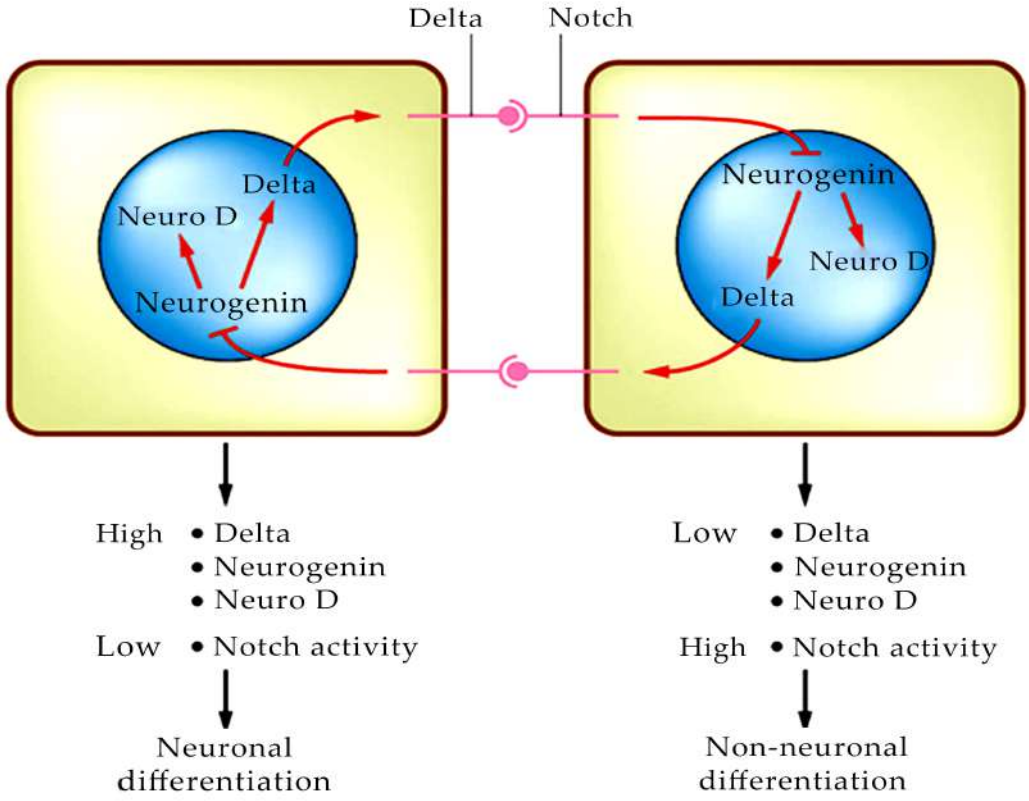


Figure 4.1. *Tissue patterning.*

Source: By JMWSlack – Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=40897255.

Later, researchers postulated and proved that this "induction" is caused by specific molecular actors known as morphogens that are released from cells and tissues. The majority of current models propose that morphogens, which are molecular signals released from signaling sources, are what give individual cells in developing tissues different instructional cues. Tissue patterning is the outcome of the responding cells' interpretation of these instructions, which differ in how certain gene sets are expressed.

Subsequent research revealed that a second possibility exists for classifying phenotypically identical cells into different domains. Cells in this scenario pick their fates in a spatially random way (e.g., randomly) and actively divide into discrete domains to minimize the number of interactions

among phenotypically disparate cells. This mechanism is demonstrated by the formation of blastocysts in mice, wherein cells are somewhat randomly specified as either primitive endoderm or epiblast cells, and then these cell types are segregated into distinct domains. Furthermore, there are emerging cases where this tissue patterning mechanism is combined with morphogen-guided tissue patterning. We do not address this mode of tissue patterning in the remainder of this review; instead, we concentrate on morphogen-guided tissue patterning, as it appears to be used less frequently.

4.2.1. Model Systems for Understanding Morphogen-Guided Tissue Patterning

The discovery and characterization of morphogens and their patterning action in vivo occurred well before the theoretical framework of morphogen-induced tissue patterning, including both the morphogen gradient formation and cell fate specification by morphogens. The discovery that high levels of Bicoid are necessary for the expression of anterior marker genes in Drosophila syncytial germ layers and low levels of Bicoid are linked to the expression of posterior genes provided the first conclusive evidence of the formation of molecular gradient-instructing patterns. More morphogens and their patterning activities were soon identified after this discovery.

Since the discovery of the first morphogen, our understanding of morphogen gradient generation and the morphogenetic action of these molecules has advanced tremendously. Examples of experimental models in which morphogen-guided tissue patterning has been extensively studied include (*a*) anterior-posterior and dorsal-ventral patterning of the *Drosophila* imaginal disc, (*b*) vertebrate limb buds, and (*c*) patterning of the early *Drosophila* embryo. These examples demonstrate how the patterning of gene expression is used to drive the morphogenesis of primordial organs and tissues. The wealth of information gathered from these model systems has revealed a set of shared principles for setting up the structure and architecture of primordial organs.

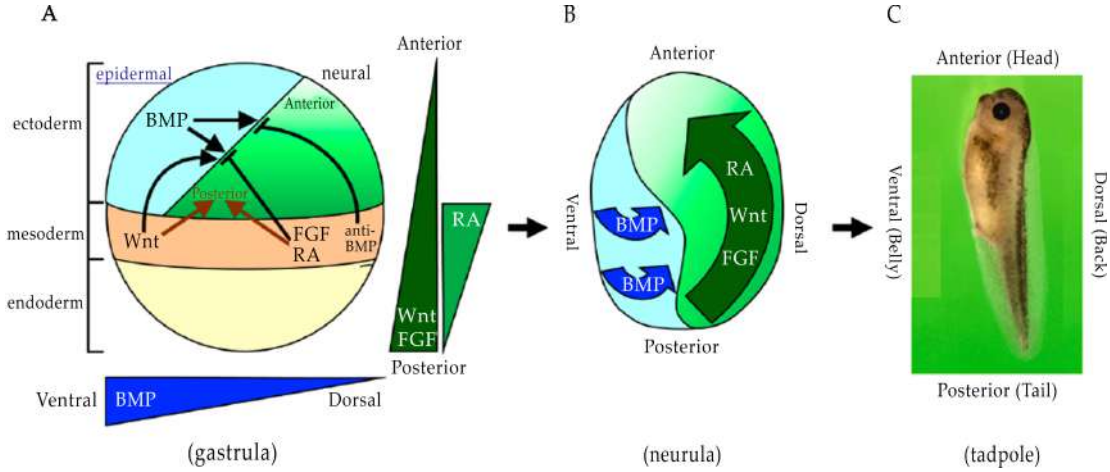


Figure 4.2. *Interpretation of morphogen signals.*

Source: Takebayashi-Suzuki, K., & Suzuki, A., (2020). Intracellular communication among morphogen signaling pathways during vertebrate body plan formation. Genes, 11(3), 341. https://doi.org/10.3390/genes11030341.

One thing that these and other model systems have in common is that morphogens that control tissue patterning are frequently members of the signaling families that include the Wnt, hedgehog (Hh), and transforming growth factor β (TGFβ) families. The majority of morphogens control tissue patterning by attaching to transmembrane receptors and starting signaling cascades. This allows the morphogen's target genes to be transcribed under control by the action of the proper morphogen effectors, which are typically transcription factors (Figure 4.2).

4.2.2. Pattern Induction

In the late 1960s, Wolpert proposed a straightforward model to describe how morphogens communicate positional information to specific cells within the growing embryo. According to Wolpert's "French flag model," cells respond to morphogens at various concentrations based on a range of thresholds. Cells at different distances from the morphogen source are exposed to different concentrations of the morphogen as it diffuses away from its source, creating a gradient (Figure 4.2). The genes with the highest threshold for morphogen, known as blue genes, can be activated by high concentrations of the morphogen in the cells closest to the source; genes with an intermediate threshold, known as white genes, can be activated by intermediate concentrations of the morphogen; and the genes with the lowest threshold, known as red genes, can only be activated by concentrations of the morphogen in the cells farthest from the source.

If red gene promoters have a high affinity for the morphogen effector and can be activated even at low morphogen concentrations, and if the so-called blue gene promoters have the lowest affinity and must be activated at high concentrations of the morphogen, then the French flag response may occur. In fact, studies have revealed that a wide range of morphogens exhibit three to seven thresholds for inducing gene expression.

Another general rule is that distinct morphogen response thresholds are frequently triggered by the same receptors and signaling cascades; therefore, the response is regulated by altering the activity of the same molecular actors (Figure 4.3(a)) rather than by triggering different pathways (Figure 4.3(b)). According to this method, an intracellular gradient of the morphogen effector's activity—typically a transcription factor—is produced by the extracellular morphogen gradient (Figure 4.4). This method is probably going to use the cell's molecular machinery more effectively, but it's also going to be more susceptible to inherent noise in the system. Therefore, the questions of how simple gradients of morphogens impose gene expression patterns and how robust and precisely controlled tissue patterning remain perplexing. Even Wolpert stated that the French flag model's most basic form—gene expression patterning by diffusible morphogen gradients—is unlikely to drive tissue patterning in vivo because diffusible gradients are "too messy," and this approach would lack precision. However, the model's simplicity is what gives it its elegance.

Even though the free diffusion French flag model of morphogen gradient formation is strongly supported by experiments, many scientists have argued that random walk diffusion of a morphogen is unlikely to produce gradient formation that results in tissue patterning as robust and repeatable as that which has been observed. Researchers have suggested that morphogens can be "trapped" by the extracellular matrix, transferred directly from one cell to another, facilitated by lipoproteins, transcytosis, and argosomes, among other methods that could lead to more morphogen gradient precision. It is not necessary for these methods of guaranteeing the high precision of morphogen gradients to be mutually exclusive.

It is also common for additional controls at the level of interpretation of morphogen instructions to further improve the robustness and precision of morphogen-facilitated tissue patterning. Improved interpretation of morphogen instructions and their controlled conversion into appropriate transcriptional responses are aided by (*a*) integration of instructional cues with multiple positive and negative inputs, (*b*) cross-repression of morphogen-regulated genes (e.g., blue genes repressing white genes and vice versa), (*c*) positive feedback, (*d*) feed-forward loops, and (*e*) the presence of inverse antagonist gradients. Additionally, there is accumulating evidence to suggest that individual cells in the embryo (and nuclei in the syncytial *Drosophila* embryo) are responsible for more than simply interpreting morphogen gradients in that they also refine the signal to help improve the robustness and precision of a tissue-level graded response. Therefore, morphogens may provide crude cues for positional information and instruction of cell fate, which are then refined into more precise and robust inputs during the interaction with the responding tissue.

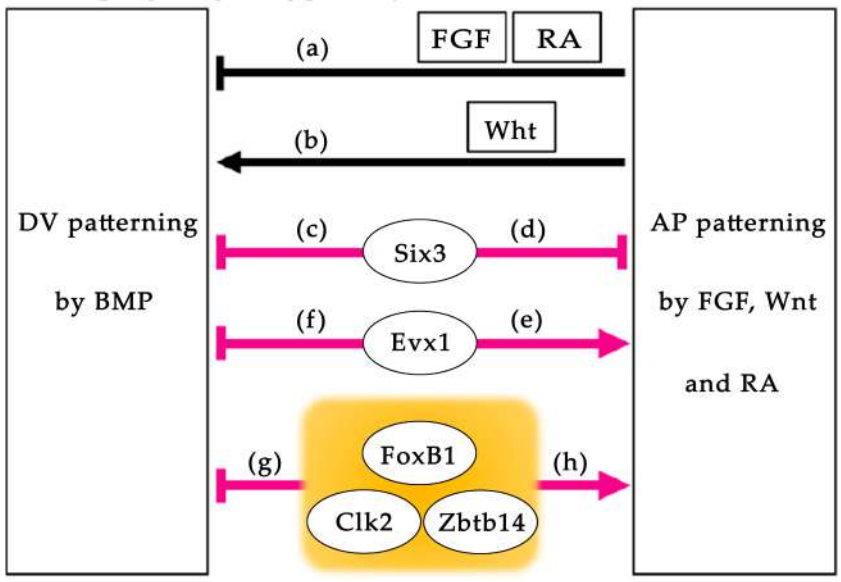


Figure 4.3. *Interpretation of morphogen gradients.*

Source: Takebayashi-Suzuki, K., & Suzuki, A., (2020). Intracellular communication among morphogen signaling pathways during vertebrate body plan formation. Genes, 11(3), 341. https://doi.org/10.3390/genes11030341.

Recently, more noteworthy findings about the significance of the length of morphogen exposure have been made. While most of the research being done today focuses on the cellular response to morphogen concentration, there is mounting evidence that suggests the duration and history of a cell's exposure to a morphogen also matter for tissue patterning and may be crucial in mitigating the impact of noise on tissue patterning. To sum up, in the 30 years since the first morphogen was discovered, tremendous progress has been made in understanding the general principles of morphogen-guided tissue patterning. Future tissue engineers will be able to design bioartificial organs with greater precision thanks to the wealth of knowledge that has been gathered about the function of morphogens and the genes that they target. Nonetheless, there are still a lot of unanswered

questions regarding morphogens and how they work. For instance, the transcriptional and translational regulation of morphogens remains largely unknown to us. Questions remain regarding whether morphogens are released in their free form or as a component of a larger cargo. Furthermore, the specifics of this regulation are still mostly unknown, despite the fact that we are aware that positive and negative feedback systems play a significant role in tissue patterning. Ultimately, there are still unanswered concerns about the interpretation of morphogen gradients, the regulation of morphogen receptors, and the specifics of signaling morphogen occupancy level.

4.2.3. Tissues

Tissues are composed of a mixture of intercellular materials and cells in different ratios, with one component taking center stage. For instance, nerve cells predominate in nervous tissue, whereas intercellular fibrous materials predominate in connective tissues like ligaments and tendons. Therefore, one could define a tissue as being made up of cells that are similar to one another in terms of structure, function, and intercellular materials. Throughout the body's development, cells specialize before aggregating to form body tissues based on shared structural and functional characteristics. The body's high degree of organization and labor distribution results from this arrangement. An organ is formed when different proportions of tissues are put together to create a functional entity. An organ's structure and functional capabilities are determined by the arrangement of its tissues.

As its name suggests, connective tissue serves to integrate, support, and bind the body's cells and organs together as well as provide protection for each part. There are three main types of muscle tissue: smooth muscle, cardiac muscle in the heart, and skeletal (voluntary) muscle. Muscle tissue is excitable, responding to stimulation and contracting to provide movement. Additionally excitable is nervous tissue, which facilitates the transmission of electrochemical signals in the form of nerve impulses that link various bodily parts.

4.2.4. Types of Tissues

There are four main types of tissues within the human body, commonly referred to as the Primary (Basic) tissues of the body. The basic tissues of the body include:

1. **Epithelial (Covering) Tissue:** Epithelial tissue covers the external and internal surfaces, including cavities and tubes of the body. Three different shapes of cells are encountered in the epithelium. These are:
   i. Squamous (flat) cells;
   ii. Cuboidal cells; and
   iii. Columnar cells.

   These three cell types can be arranged in:
   - A single layer to form simple epithelium, e.g., the lining of the stomach (columnar epithelium) or in
   - Several layers form a compound (stratified) epithelium, e.g., the epidermis of the skin (squamous epithelium).
2. **Connective Tissue:** This tissue connects cells and other tissues of the body, offering structural and metabolic support. It also serves as a medium for conveying nutrients to and removing waste from tissues and body organs. It is composed of specialized cells (fibroblasts), intercellular fibrous

materials (collagen, reticular, and elastic fibers), and an extracellular fluid medium called Matrix (Ground substance). The connective tissue is the most abundant in the body.

Examples of connective tissues include:

- Bones;
- Cartilage;
- Ligaments, tendons, and facial sheath;
- Areolar tissue;
- Adipose (fat) tissue;
- Blood;
- Mucous.

3. **Muscle Tissue:** It is composed of highly specialized contractile cells which are often elongated in shape. They are responsible for the movements of body parts relative to each other. Cells of the muscle tissues are referred to as muscle fibers. Muscle tissues occur in three main types:
   - Smooth muscles, which line the walls of tubular (blood vessels) as well as hollow organs (stomach and urinary bladder). These are under involuntary control;
   - Striated skeletal muscles which are attached to bones move at the joints. These are controlled voluntarily;
   - Striated cardiac muscles, which form the wall of the heart and are responsible for the heartbeat. These are also under involuntary control.
4. **Nervous Tissue:** This tissue is responsible for the body's ability to respond to its surroundings appropriately and its awareness of both its internal and external environments. It is composed of cells known as neurons, which are extremely specialized in terms of conductivity and irritability (also known as excitability). It is also made up of neuroglia, which are nourishing and supporting cells for the neurons. The body's nervous system is composed of nerve tissue, which includes the spinal cord, spinal nerve fibers, brain cranial nerves, and various organs and receptor cells.

4.2.5. Epithelial Tissue

An epithelium (ep″ ɪˇ-theʹle-um; "covering") is a sheet of cells that covers a body surface or lines a body cavity (Figure 4.4).

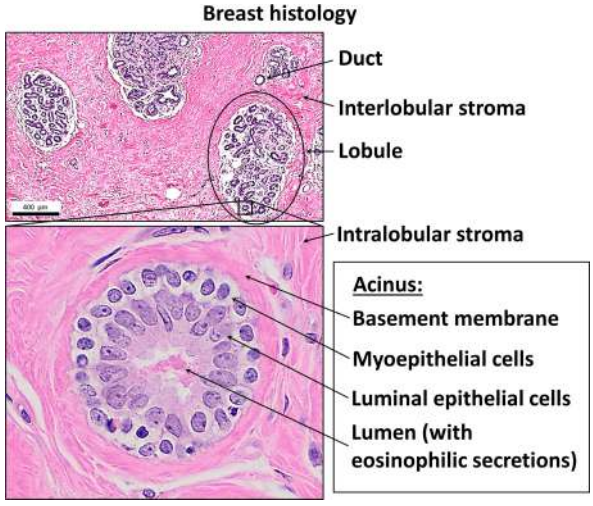


Figure 4.4. *A sheet of closely joined epithelial cells rests on connective tissue proper. Epithelia contain nerve endings but no blood vessels. Note the special features on the epithelial cell surfaces: cilia, microvilli, cell junctions, and basal lamina.*

Source: By Mikael Häggström, M. D. Author info-Reusing images-Conflicts of interest: NoneMikael

Häggström, M.D.Consent note: Consent from the patient or patient's relatives is regarded as redundant, because of the absence of identifiable features (List of HIPAA identifiers) in the media and case information (See also HIPAA case reports guidance). The image integrates a source image by de Bel, T., Litjens, G., Ogony, J., Stallings-Mann, M., Carter, J. M., & Hilton, T. – Own work. Source images: Breast lobules. By: de Bel, T., Litjens, G., Ogony, J., Stallings-Mann, M., Carter, J. M., & Hilton, T. (Attribution 4.0 International License) Normal breast acinus (own work), CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=127049680.

Epithelial tissue occurs in two different forms:

- **Covering and Lining Epithelium: It** covers the outer and inner surfaces of most body organs. Examples include the outer layer of the skin; the inner lining of all hollow viscera, such as the stomach and respiratory tubes; the lining of the peritoneal cavity; and the lining of all blood vessels.
- **Glandular Epithelium:** It forms most of the body's glands.

Epithelia occur at the boundary between two different environments. The epidermis of the skin, for example, lies between the inside and the outside of the body. Most substances that enter the body or are released from the body must pass through epithelium. Therefore, all functions of epithelia reflect their roles as interface tissues.

These functions include:

- Protection of the underlying tissues;
- Secretion (release of molecules from cells);
- Absorption (bringing small molecules into cells);
- Diffusion (movement of molecules down their concentration gradient);
- Filtration (passage of small molecules through a sieve-like membrane);
- Sensory reception.

4.2.6. Special Characteristics of Epithelia

Epithelial tissues have many characteristics that distinguish them from other tissue types (Figure 4.4):

1. **Cellularity:** Epithelia are composed almost entirely of cells. These cells are separated by a minimal amount of extracellular material, mainly projections of their integral membrane proteins into the narrow spaces between the cells.
2. **Specialized Contacts:** Adjacent epithelial cells are directly joined at many points by special cell junctions.
3. **Polarity:** All epithelia have a free apical surface and an attached basal surface. The structure and function of the apical and basal surfaces differ, a characteristic called polarity. The apical surface abuts the open space of a cavity, tubule, gland, or hollow organ. The basal surface lies on a thin supporting sheet, the basal lamina, which is part of the basement membrane (*see* Figure 4.1).
4. **Support by Connective Tissue:** All epithelial sheets in the body are supported by an underlying layer of connective tissue.
5. **Avascular But Innervated:** Whereas most tissues in the body are

vascular (contain blood vessels), the epithelium is avascular (a-vas′ku-lar), meaning it lacks blood vessels. Epithelial cells receive their nutrients from capillaries in the underlying connective tissue. Although blood vessels do not penetrate epithelial sheets, nerve endings do; that is, the epithelium is innervated.

6. **Regeneration:** Epithelial tissue has a high regenerative capacity. Some epithelia are exposed to friction, causing their surface cells rub off. Others are destroyed by hostile substances in the external environment such as bacteria, acids, and smoke. As long as epithelial cells receive adequate nutrition, they can replace lost cells quickly by mitosis, and cell division.

4.2.7. Classification of Epithelia

There are many kinds of epithelia exist in the body. Two features are used to classify and name epithelia: the number of cell layers and the shape of the cells. The terms 'simple' and 'stratified' describe the number of cell layers in an epithelium.

- **Simple Epithelia:** These contain a single layer of cells, with each cell attached to the basement membrane.
- **Stratified Epithelia:** These contain more than one layer of cells. The cells on the basal surface are attached to the basal membrane; those on the apical surface border an open space.

Cell shape is described as squamous, cuboidal, or columnar, referring to the appearance of the cells in the section (Figure 4.2(b)). In each case, the shape of the nucleus conforms to the shape of the cell. This is an important feature to observe when distinguishing epithelial types (Figure 4.5).

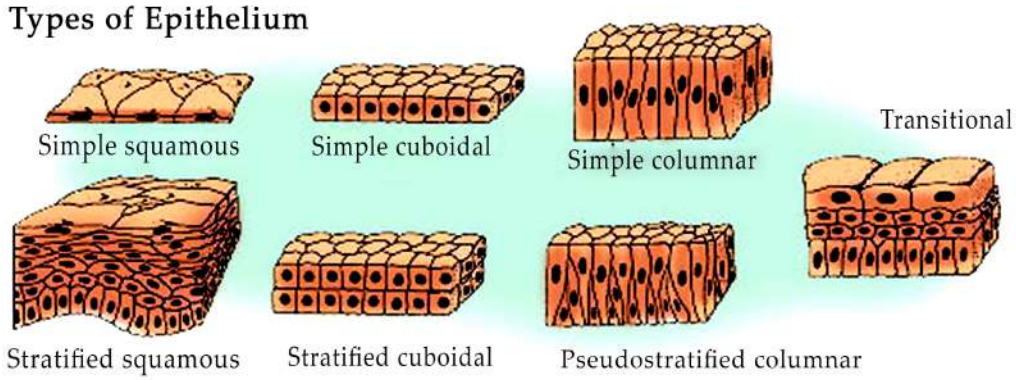
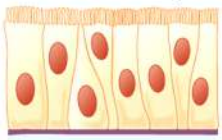
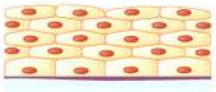
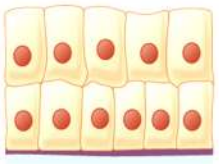
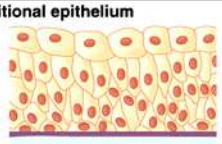


Figure 4.5. *Classification of epithelia.*

Source: By US Government – http://training.seer.cancer.gov/module_anatomy/images/illu_epithelium.jpg,which now seems to appear athttps://training.seer.cancer.gov/images/anatomy/cells_tissues_membranes/epithelium_tissue.jpgon this page: https://training.seer.cancer.gov/anatomy/cells_tissues_membranes/tissues/epithelial.html, Public Domain, https://commons.wikimedia.org/w/index.php?curid=1273805.

Table 4.1. *Function of Epithelial Tissue Related to Tissue Type*

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

Source: By OpenStax College – Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=30131299.

- **Squamous Cells (Sqwa′mus; "Scale"):** These are flat cells with flat, disc-shaped nuclei.
- **Cuboidal Cells:** These are cube-shaped cells with spherical, centrally located nuclei.
- **Columnar Cells:** These are taller than they are wide, like columns. The nuclei of columnar cells are located near the basal surface and are commonly oval and elongated from top to bottom.

Since all of the cells in a layer typically have the same shape, simple epithelia are simple to categorize based on cell shape. However, in stratified epithelia, the various cell layers typically have different cell shapes. Stratified epithelia are named based on the apical layer cell shape to prevent confusion. It is helpful to remember that tissue function is reflected in tissue structure (Table 4.1). The primary purpose of stratified epithelial tissues is protection. In regions where abrasion is frequent, the underlying connective tissues are shielded by several layers of cells. Simple epithelia demonstrate tissue function through the morphology of their cells. Because diffusion and filtration are distance-dependent processes—the thinner the layer, the faster the process happens—squamous cells are found in environments where these processes are significant. Organs involved in secretion and absorption contain columnar and cuboidal cells. The extracellular machinery required to create and package secretions, as well as to generate the energy required for these processes, requires larger cells. The mucus, among other materials is propelled by ciliated epithelia. When you thoroughly examine each kind of epithelial tissue, bear these generalizations in mind. Examine micrographs of various epithelium types (Figure 4.6) and identify individual cells within each. This is not always simple because it is frequently difficult to distinguish the boundaries between epithelial cells. Furthermore, depending on the plane of the cut made to prepare the tissue slides, the nucleus of a specific cell may or may not be visible. Slices from the top of a pear will not contain any seeds when cut transversely; however, slices from the middle will. The same is true for tissue sections: while some cells may have their nuclei cut through, others may not.

4.2.7.1. Simple Epithelia

4.2.7.1.1. Simple Squamous Epithelium

One layer of flat cells makes up a simple squamous epithelium. The closely fitting cells have the appearance of a tiled floor when viewed from above. They have a side-on appearance similar to fried eggs when viewed in the lateral section. This kind of thin, frequently permeable epithelium develops wherever small molecules swiftly diffuse or filter through a membrane. This epithelium is the only material that makes up capillary walls, and because of its extreme thinness, waste products, and nutrients are efficiently exchanged between the surrounding tissue cells and the bloodstream. This epithelium creates the slender walls of the air sacs in the lungs, which are the sites of gas exchange.

4.2.7.1.2. Simple Cuboidal Epithelium

One layer of cube-shaped cells makes up a simple cuboidal epithelium. This epithelium creates the walls of numerous kidney tubules, the secretory cells of numerous glands, and the smallest gland ducts. It performs the same duties as a basic columnar epithelium.

4.2.7.1.3. Simple Columnar Epithelium

A single layer of tall cells arranged in a row like

soldiers makes up the simple columnar epithelium. It covers the tube that transports food from the stomach to the rectum. It is involved in the active transport of molecules, specifically in secretion and absorption. Simple columnar epithelium's structure is perfect for these tasks because it is both thick enough to contain the cellular machinery required to carry out the intricate processes of molecular transport and thin enough to let large numbers of molecules flow through it rapidly. Certain basic columnar epithelia have whip-like bristles called cilia (sil′e-ah; "eyelashes") at the tip of the epithelial cells that beat rhythmically to transfer materials over specific body surfaces. The interior of the uterine tube is lined with a basic ciliated columnar epithelium. The ovum is transported to the uterus by its cilia.

4.2.7.1.4. Pseudostratified Columnar Epithelium

The heights of the cells in pseudostratified (soo-do-strat′˘-f ¯ ı ıd) columnar epithelium vary. Only the tall cells reach the apical surface of the epithelium; all other cells rest on the basement membrane. The tall cells are constantly proliferating from the undifferentiated short cells. The false impression that this epithelium is stratified is caused by the cell nuclei, which are arranged at multiple levels (pseudo = false). Similar to simple columnar epithelium, pseudostratified epithelium is involved in secretion or absorption. The respiratory tubes' interior is lined with ciliated type. Here, the cilia expel sheets of mucus from the lungs that trap dust.

4.2.7.2. Stratified Epithelia

A stratified epithelium has two or more cell layers. They regenerate from below, meaning that the older surface cells are replaced by basal cells that divide and push apically. Compared to simple epithelia, stratified epithelia are more resilient, and one of their main functions—though not the only one—is defense.

4.2.7.2.1. Stratified Squamous Epithelium

Stratified squamous epithelium is made up of numerous cell layers with squamous surface cells, as one might anticipate. The cells are columnar or cuboidal in the deeper layers. This type of epithelium is the thickest and most suited for protection out of all of them. It forms the inner lining of the mouth, esophagus, and vagina as well as the epidermis of the skin, covering the frequently abraded surfaces of our body. Just keep in mind that stratified squamous epithelium makes up the skin's outermost layer and extends into every bodily opening that is directly continuous with the skin. The skin's epidermis is keratinized, which means that keratin, an exceptionally durable protective protein, is present in the surface cells. The body's other stratified squamous epithelia are nonkeratinized, meaning they do not contain keratin.

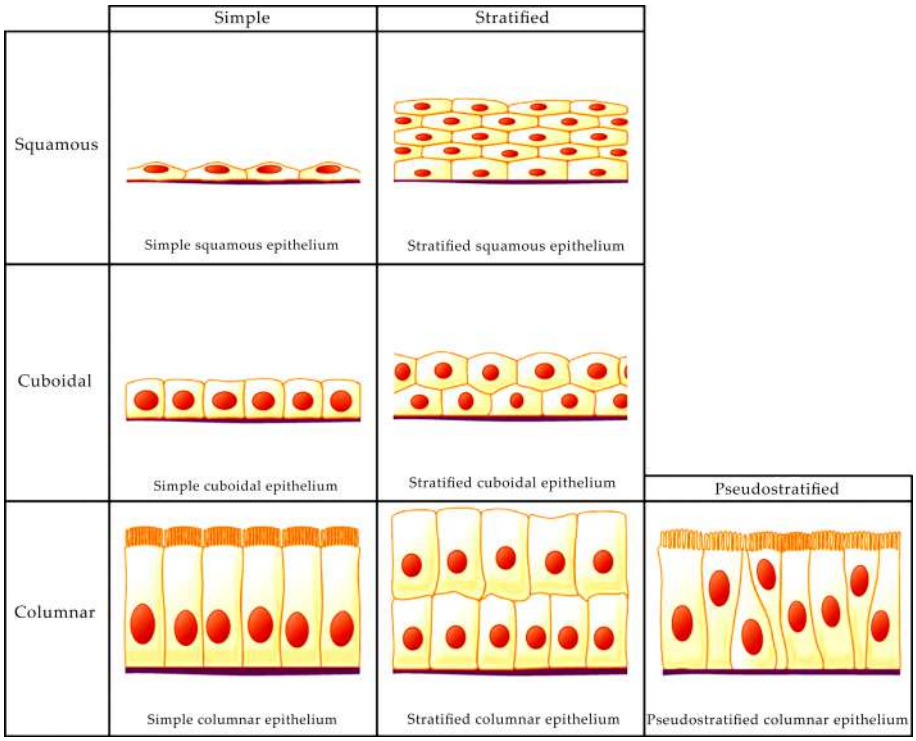


Figure 4.6. *Epithelial tissue.*

Source: https://courses.lumenlearning.com/suny-ap1/chapter/epithelial-tissue/.

4.2.7.2.2. Stratified Cuboidal and Columnar Epithelia

Stratified cuboidal and stratified columnar epithelia are rare types of tissue, located in the large ducts of some glands, for example, sweat glands, mammary glands, and salivary glands. Stratified columnar epithelium is also found in small amounts in the male urethra.

4.2.7.2.3. Transitional Epithelium

Transitional epithelium lines the inside of the hollow urinary organs. Such organs (the urinary bladder, for example) stretch as they fill with urine. As the transitional epithelium stretches, it thins from about six cell layers to three, and its apical cells unfold and flatten. When relaxed, portions of the apical surface invaginate into the cell, giving this surface a scalloped appearance. Thus, this epithelium undergoes "transitions" in shape. It also forms an impermeable barrier that keeps urine from passing through the wall of the bladder.

4.2.8. Glands

Glands are made up of epithelial cells that secrete a product. Aqueous (water-based) fluids, which are produced by glands, typically contain proteins. The process by which gland cells take necessary substances from the blood and convert them chemically into a product that is then

released from the cell is known as secretion. More precisely, the rough endoplasmic reticulum (ER) produces the protein product, which is subsequently assembled into secretory granules by the Golgi apparatus and exocytosed out of the cell. These organelles are present in the majority of gland cells that secrete proteins and are highly developed. Depending on where their product is released, glands are categorized as endocrine (en′do-krin; "internal secretion") or exocrine (ek′so-krin; "external secretion"). They are also categorized based on the number of cells as unicellular ("one-celled") or multicellular ("many-celled"). While most multicellular glands arise through the invagination of an epithelial sheet into the underlying connective tissue, unicellular glands are dispersed throughout epithelial sheets.

4.2.8.1. Endocrine Glands

Endocrine glands are sometimes called ductless glands because they do not have ducts. They release their contents into the surrounding tissue fluid. To be more precise, hormones (hor′m¯onz; "exciters") are messenger molecules that are produced by endocrine glands and released into the extracellular space. The target organs for these hormones are often distant from the endocrine gland that produces them. The hormones then enter adjacent capillaries and move through the bloodstream to reach their target locations. Every hormone instructs the organs it targets to react in a particular way. Endocrine cells found in the intestine, for instance, secrete a hormone that instructs the pancreas to release the enzymes necessary for meal digestion. While epithelia are the source of most endocrine glands, some also come from other tissues.

4.2.8.2. Exocrine Glands

Every exocrine gland secretes its contents onto the skin or into bodily cavities, like the digestive tube. Multicellular exocrine glands also have ducts that transport their contents to the surfaces of the epithelium. Exocrine secretions have localized activity, meaning they act close to the site of release. Exocrine glands are a varied group that includes the liver (which secretes bile), the pancreas (which secretes digestive enzymes), the mammary glands (which secrete milk), the sweat and oil glands of the skin, the salivary glands of the mouth, and many more.

4.2.8.2.1. Unicellular Exocrine Glands

The goblet cell (Figure 4.7) is the primary example of the unicellular exocrine gland.

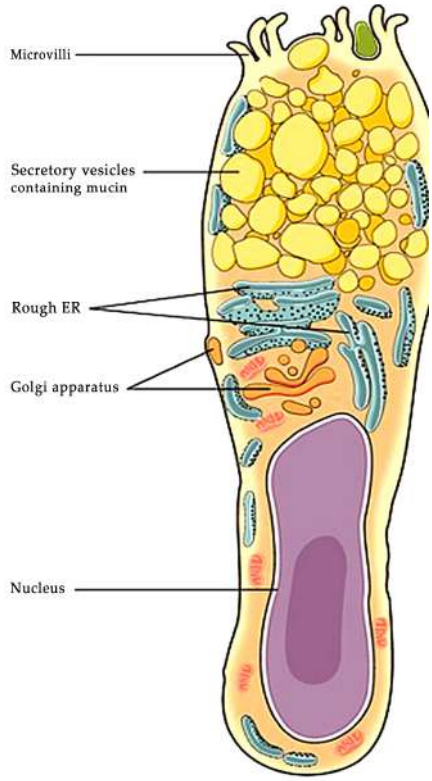


Figure 4.7. Goblet cell (unicellular exocrine gland).

Source: By OpenStax College – Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=30131227.

A goblet cell is shaped like a goblet, which is a drinking glass with a stem, true to its name. Within the intestinal and respiratory tubes' epithelial lining, goblet cells are dispersed in between columnar cells that serve various purposes. They produce a glycoprotein, or sugar protein, called mucin (mu'sin), which, when secreted, dissolves in water. The resultant mucus is a viscous, slimy mixture of mucin and water. Numerous internal body surfaces are covered, shielded, and lubricated by mucus.

4.2.8.2.2. Multicellular Exocrine Glands

An epithelium-walled duct and a secretory unit made up of secretory epithelium comprise each multicellular exocrine gland (Figure 4.8). Additionally, the secretory unit in all but the most basic glands is surrounded by supporting connective tissue that carries nerve fibers and blood vessels. The fibrous capsule that the connective tissue frequently forms divides the gland into sections known as lobes and extends into the gland proper. The ductal structure of multicellular glands is used to classify them (Figure 4.8). Whereas compound glands have a branched duct, simple glands have an unbranched duct. The secretory units of the glands are further divided into two groups: tubular glands, which form tubes, and alveolar glands, which form spherical sacs (an alveolus is a tiny, hollow cavity). Moreover, certain glands are tubuloalveolar, meaning they have both alveolar and tubular secretory units. Alveolar is frequently synonymous with the term acinar (as'-nar; ı acinus = grape or berry).

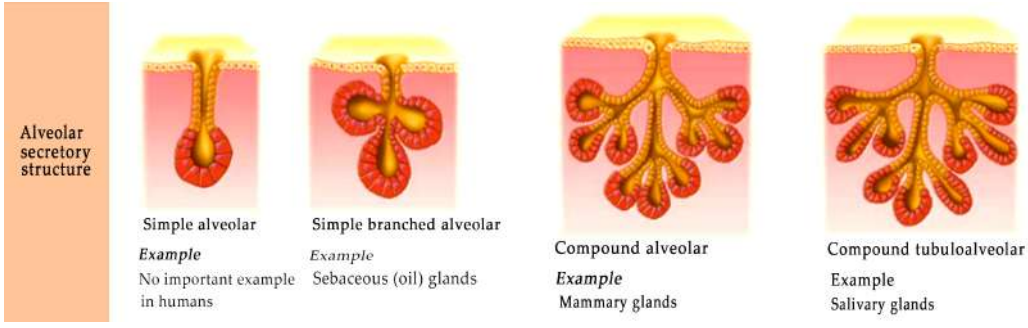


Figure 4.8. *Types of multicellular exocrine glands. Multicellular glands are classified according to the structure of their ducts (simple or compound) and the structure of their secretory units (tubular, alveolar, tubuloalveolar).*

Source: https://courses.lumenlearning.com/suny-ap1/chapter/epithelial-tissue/.

4.2.9. Epithelial Surface Features

Epithelial tissues are composed of numerous cells closely connected by unique cell junctions along their lateral walls. Additionally, the apical and basal regions of epithelial tissues are unique. The underlying connective tissue and basal surface are separated by a specialized boundary; some epithelia have modifications in their apical region that are linked to specific functions.

4.2.9.1. Lateral Surface Features

4.2.9.1.1. Cell Junctions

Three factors contribute to binding epithelial cells to one another:

- *Adhesion proteins* in the plasma membranes of tadjacent cells link together in the narrow extracellular space.
- The wavy contours of the membranes of adjacent cells join in a tongue-and-groove fashion.
- Cell junctions (Figure 4.9), the most important factors, are characteristic of epithelial tissue but are found in other tissue types as well.

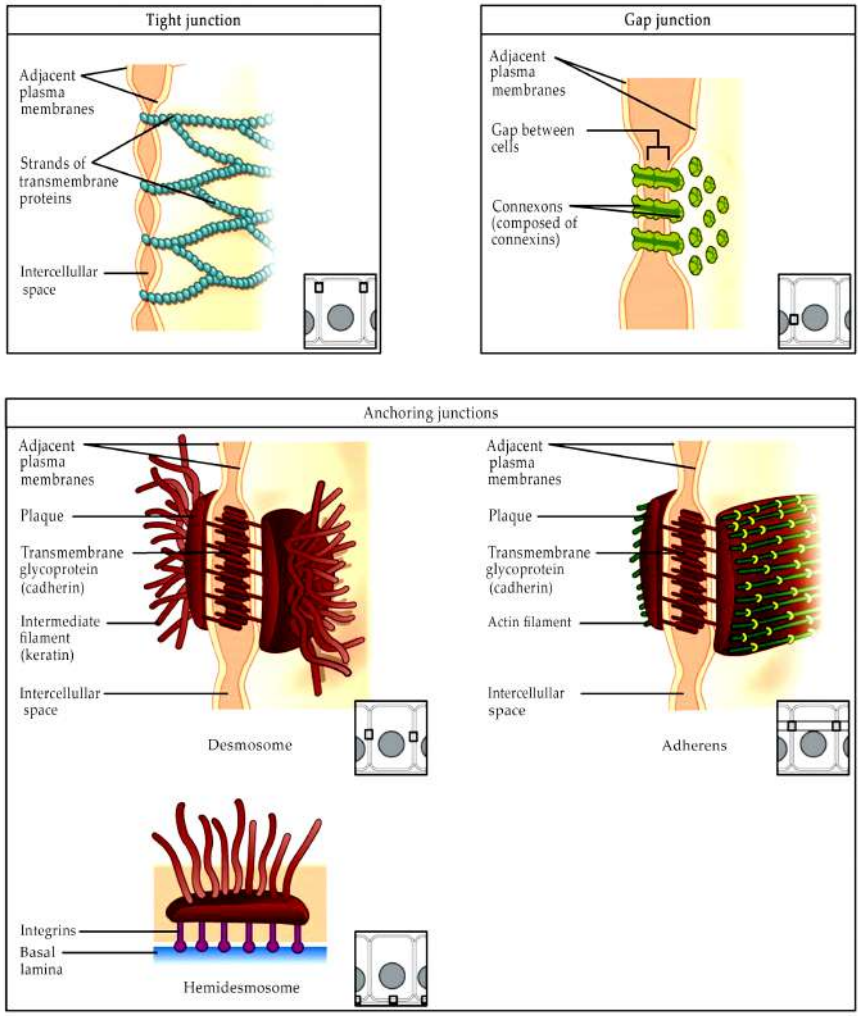


Figure 4.9. *Cell junctions. An epithelial cell shown joined adjacent cells by three common types of cell junction.*

Source: https://courses.lumenlearning.com/suny-ap1/chapter/epithelial-tissue/.

4.2.9.2. Tight Junctions

A belt-like junction encircles each cell's periphery in the apical region of the majority of epithelial tissues. This is a zonula occludens or tight junction (pronounced "small zone that shuts off," z¯on′u-lah o-klood′enz). Certain proteins in the plasma membranes of neighboring cells fuse at tight junctions because of their proximity. Tight junctions stop molecules from moving between the cells that make up the epithelium by creating a seal that closes off the extracellular space as a result of this fusion. For instance, digestive enzymes, ions, and microbes in the intestine are prevented from entering the bloodstream by the tight junctions in the epithelium lining the digestive tract. Tight junctions don't need to be completely impermeable; some can allow certain ions to pass through and are more prone to leakage than others.

4.2.9.3. Adhesive Belt Junctions

Adhesive belt junctions, also known as zonula adherens (z¯on′u-lah ad-hir-ens), are a kind of anchoring junction located directly beneath tight junctions in epithelial tissues. Transmembrane linker proteins bind neighboring cells together by adhering to the cytoskeleton's actin microfilaments. When the tissues are stretched, this junction especially strengthens the tight junctions. Along with tight junctions, make up the tight junctional complex surrounding the apical lateral borders of epithelial tissues.

4.2.9.3.1. Desmosomes

Desmosomes also referred to as anchoring junctions (dez′mo-s¯omz; "binding bodies"), are the primary junctions that hold cells together. These adhesive patches are dispersed along the sides where adjacent cells abut. Desmosomes are complex structures with a circular plaque on the cytoplasmic face of each plasma membrane. Linker proteins bind adjacent cell plaques together. These protrude from both cell membranes and interdigitate in the extracellular space, resembling the teeth of a zipper. Furthermore, from the inner, cytoplasmic side of each plaque, intermediate filaments—the cytoskeletal components that withstand tension—insert themselves. These filaments come in bundles that cross the cytoplasm and attach to desmosomes on the other side of the same cell. Overall, this configuration not only keeps neighboring cells joined together but also joins the intermediate filaments of the entire epithelium into a single, uninterrupted network of robust guy wires. Because the pulling forces are evenly distributed throughout the sheet, the epithelium is therefore less likely to tear when pulled on. Both cardiac muscle tissue and epithelial tissues contain desmosomes. These junctions are typically seen in tissues under a lot of mechanical stress.

4.2.9.4. Gap Junctions

A gap junction, also known as a nexus (nek′sus; 'bond'), can form anywhere along the lateral membranes of neighboring cells. Gap junctions facilitate the direct movement of small molecules between adjacent cells, which is how they function in intercellular communication. Connexons, which are hollow cylinders made of protein, connect the cells at these junctions where the adjacent plasma membranes are extremely close to one another. These cylinders allow small molecules, including ions, to move from one cell to the next. Both embryonic and adult tissues, including connective tissues, frequently contain gap junctions. They are also widely distributed in cardiac and smooth muscle, where ion transport via gap junctions synchronizes contraction.

A Closer Look

Exocrine Glands

Exocrine glands are comprised of an acinus and a duct with different cell types, respectively. These glands are found in many organs within the body and demonstrate a large variety in the function of their secretions. As such, a wide range of cell types exists in exocrine glands.

While the duct functions primarily to transport glandular secretions, the acinus is responsible for the production of glandular secretions, and as such, shows more variety in cellular composition. Typical cell types within the acinus include serous, mucinous, or sebaceous.

- Serous cells secrete an isotonic fluid that contains proteins such as enzymes. Salivary glands are made up of serous cells to a large extent.
- Mucinous glands secrete mucus, a typical example being Brunner glands in the duodenum.
- Sebaceous glands secrete sebum, an oily compound. Sebaceous glands are most prevalent in the face, scalp, groin, and armpits. Cell types can be differentiated histologically as well. Mucous cells typically stain lighter than their serous counterparts when stained with hematoxylin and eosin.

As ducts move from the acinus toward the final target, secretions initially enter the intralobular duct. Intralobular ducts have a simple cuboidal epithelium commonly surrounded by parenchyma. Intralobular ducts drain into interlobular ducts, which are covered by columnar epithelium. The final ductal unit is the interlobar duct, covered by stratified columnar epithelium. Connective tissue surrounds both interlobular and interlobar ducts.

The initial sign of exocrine gland formation is epithelial budding resulting from a complex interaction between mesenchymal and epithelial cell populations. This initial period of ingrowth is influenced by fibroblast growth factors, most notably FGF10 and cadherin-2. Other transcription factors that have been shown to contribute to epithelial budding include HlxB9, Isl1, LEF-1, Msx1/2, Pbx1, Pdx1, and Tbx3.

Following the initial formation of the epithelial bud, ductal elongation occurs. This process undergoes mediation by a large group of molecular signals such as Netrin-1, TIMP1, amphiregulin, IGF1, and leukemia inhibitory factor. Several matrix metalloproteinases (MMPs) contribute assistance with basement membrane renewal and facilitate ductal elongation. After an initial period of ductal elongation, the exocrine gland begins to form ductal branches. NF-kappa-B is thought to play a role, as well as sonic hedgehog and Wnts. As the duct begins to elongate, the acinus undergoes a period of cell proliferation and differentiation. Due to the large variety in exocrine gland function, the exact number of cellular signals and interactions is immense. In general, however, a large role exists for cell adhesion molecules such as laminin and cadherins.

Exocrine morphogenesis is a rapid process. Ductal elongation and branching typically occur in less than a week, with acini formation occurring 5 to 9 days later. In a relatively short developmental period, exocrine glands form and can begin secreting a functional product.

SUMMARY

- Through a process called involution, cells from the primitive streak move toward the interior of the embryo as gastrulation advances, aiding in the formation of the three germ layers.
- Most animals go through a stage called gastrulation in which the blastula, a single-layered hollow sphere of cells (or the blastocyst in mammals), reorganizes to become the gastrula, a two- or three-layered embryo.
- The structure of the sea urchin's mesoderm is formed by lithium ions, whereas the structure of the ectoderm is formed by thiocyanate or sulfate from the mesoderm and endoderm.
- Gastrulation is characterized by a series of coordinated cellular movements and morphogenetic events. The emergence of a structure on the embryo's surface known as the primitive streak usually marks the start of the gastrulation process.
- To ensure appropriate spatial organization and functional differentiation, induction and patterning are essential processes in the shaping of the developing tissues and organs.
- A single layer of tall cells arranged in a row like soldiers makes up the simple columnar epithelium. It covers the tube that transports food from the stomach to the rectum.

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Chapter

DEVELOPMENT OF THE NERVOUS SYSTEM

5

Contents

Unit Introduction

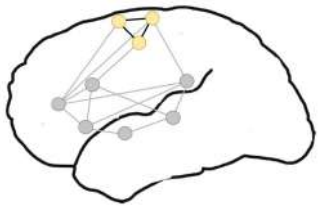
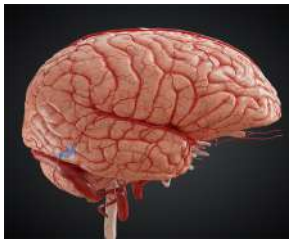
The nervous system takes a long time to fully develop; it starts early in the embryonic stage and continues all the way through adulthood. The complex network of neurons and glial cells that make up the nervous system is the result of a sequence of extremely well-coordinated events. Each stage is essential for the healthy operation of the nervous system, from the development of the neural tube to the creation of synaptic connections. The neural tube forms during the third week of embryonic development, marking the beginning of the nervous system's development. The brain and spinal cord eventually emerge from the neural tube, a hollow structure. Signaling molecules that control the growth and differentiation of neural progenitor cells, such as bone morphogenetic proteins (BMPs) and Sonic hedgehog (Shh), are responsible for its formation. During a process known as neurulation, the neural tube closes and splits into separate regions that will eventually develop into various parts of the central nervous system. Neural progenitor cells within the neural tube continue to proliferate and differentiate after the neural tube is formed, eventually giving rise to neurons and glial cells. Glial cells support and protect neurons, which are the functional units of the nervous system that carry out the task of transmitting electrical signals. Numerous signaling molecules and transcription factors that control the fate of neural progenitor cells—including whether they will develop into neurons or glial cells, as well as their subtype and connectivity—tightly govern the process of neuronal differentiation.

As they differentiate, neurons migrate to their final locations within the nervous system. Numerous chemical cues, such as cell adhesion molecules and chemotactic gradients, aid in this migration and enable neurons to travel through the growing brain and spinal cord to their proper destinations. After arriving at their destinations, neurons start extending processes known as dendrites and axons, which connect with other neurons through synapses. Since it forms the foundation for the neural circuits that mediate motor control, sensory perception, and cognitive function, the formation of these synaptic connections is an essential stage in the development of the nervous system.

Synaptogenesis, the process by which synaptic connections are formed, is a multifaceted interaction between target cells and neurons. It is directed by activity-dependent mechanisms as well as genetic programs, and synaptic activity is essential for improving and fortifying neuronal connections. Neural circuits are formed when redundant or inappropriate connections are removed through a process known as synaptic pruning, which also strengthens important connections. The nervous system is also shaped by experience and external factors during development. The nervous system's structure and function are greatly influenced by sensory experiences and social interactions, especially during the formative stages of development. In addition to potentially having a significant impact on nervous system function, these disruptions may also be a factor in neurodevelopmental disorders like schizophrenia and autism spectrum disorder.

From the time the neural tube forms until the end of life, the nervous system goes through an amazing journey of development. Neural proliferation, differentiation, migration, and synaptogenesis—a sequence of intricately coordinated events—give rise to the complex network of neurons and glial cells that facilitates sensory perception, motor control, and cognitive function. Determining the genesis of neurodevelopmental disorders and creating plans for their prevention and treatment require an understanding of the mechanisms governing nervous system development.

Orientation and Directional Terms

Terms	Definition	Illustration
Bone morphogenetic proteins	Bone morphogenetic proteins (BMPs) are secreted key regulators of an epithelial–mesenchymal interaction in tooth development.	
Synaptogenesis	Synaptogenesis refers to the formation of synapses, the points of contact where information is transmitted between neurons.	
Neural circuits	Neural circuits are more than anatomical structures of connected neurons—they are functional entities that have complex inputs and outputs, regulate their own activity, and ultimately influence behavior.	
Cerebrum	Cerebrum, the largest and uppermost portion of the brain. The cerebrum consists of the cerebral hemispheres and accounts for two-thirds of the total weight of the brain.	
Gyrus	A gyrus is a ridge on the surface of the brain. Each ridge is surrounded by fissures known as sulci (singular: sulcus).	

5.1. Organization of the Nervous System

As the body's communication system, the nervous system is a highly structured and intricate network that enables the coordination of numerous physiological processes and reactions to outside stimuli. The peripheral nervous system (PNS) and the central nervous system (CNS) make up its two primary sections. The brain and spinal cord make up the central nervous system, which controls bodily functions. The peripheral nervous system sends sensory data to the CNS, which processes it to produce the proper motor responses. The brain is further divided into various regions, each of which is in charge of particular abilities like emotion, motor control, thought, and sensory perception. Different regions of the brain, including the cerebral cortex, cerebellum, and brainstem, are involved in processing sensory data, coordinating movement, and controlling autonomic processes like breathing and heart rate. The spinal cord facilitates communication between the brain and the body by sending motor commands from the brain to muscles and glands as well as sensory data from peripheral nerves to the brain.

All of the nerves and ganglia outside of the CNS are part of the peripheral nervous system, which is in charge of sending motor commands from the CNS to muscles and glands as well as sensory data to the brain. The autonomic nervous system and the somatic nervous system are its two further divisions. The somatic nervous system receives sensory information from the outside world, such as touch, pain, temperature, and proprioception, and it also governs voluntary movements. It is made up of sensory neurons that send information from the skin, muscles, and joints to the central nervous system (CNS) and motor neurons that innervate skeletal muscles. On the other hand, the autonomic nervous system, which is further subdivided into the sympathetic and parasympathetic divisions, controls involuntary processes like respiration, heart rate, and digestion. While the parasympathetic division encourages relaxation and preserves energy during rest and digestion, the sympathetic division mobilizes the body's resources in response to stress or danger.

The nervous system is organized hierarchically overall, with the peripheral nervous system functioning as a channel for communication between the CNS and the rest of the body, and the central nervous system acting as the highest level of control and coordination. To maintain survival and homeostasis, this complex organization permits accurate regulation of physiological processes as well as adaptive responses to changes in the internal and external environment.

The nervous system is composed of two main parts, each containing billions of cells called neurons, or nerve cells. These special cells send and receive electrical signals through your body to tell it what to do.

The main parts of the nervous system are:

- Central nervous system;
- Peripheral nervous system.

The nervous system is the organ system in humans that uses electrical signals to coordinate all of the body's voluntary and involuntary movements. In particular, the nervous system uses sensory receptors to gather data from both the internal and external environments. Usually, it then communicates this information to the brain through signals, which the brain interprets and uses to decide how to react. Ultimately, the response is brought about by signals that the brain sends to glands, muscles, or organs. In this scenario, your eyes detect the boy, the information travels to your brain, and your brain instructs your body on what to

do to prevent a collision. The nervous system synchronizes voluntary and involuntary bodily movements through information transmission and reception. More than 100 billion cells make up the nervous system, mostly of two types: neurons, which are the signaling units, and glial cells, which are the supporting units. Neurons play a major role in nervous system function. The nervous system's functional unit, the neuron, is made to move information from one cell to another. Notably, certain neurons are located in specific regions. Because of this structural regularity, neurobiologists are able to classify the nervous system according to its location and purpose.

The central nervous system (CNS) and the peripheral nervous system (PNS) are the two main divisions of the nervous system. Neurons in the brain and spinal cord make up the central nervous system (CNS). The peripheral nervous system (PNS), which connects the central nervous system to every other area of the body, is made up of neurons linked to sensory input (afferent) and motor output (efferent). Put another way, a neuron would be regarded as a component of the central nervous system (CNS) if its whole structure is contained within the brain and/or spinal cord. On the other hand, a neuron is regarded as a component of the PNS if any portion of its structure is found outside of the brain, spinal cord, or both.

The general flow of information between these two systems is as follows: stimulus, receptor, control center, efferent pathway (output signal), effector, and response are the steps in the process. To put it another way, sensory receptors spread throughout the body are always keeping an eye on the surroundings. The PNS then relays this information to the CNS for processing centrally. If an answer is required (i.e., to preserve homeostasis), the CNS will update the target organs' information via the PNS, assisting them in adapting to the initial stimulus. It should be mentioned that certain processes, like thinking, dreaming, and even storing information, can occur solely within the central nervous system.

The somatic nervous system, which regulates skeletal muscle voluntary movement, and the autonomic nervous system, which controls involuntary functions of organs and tissues, are two further subtypes of neurons found in the efferent division of the PNS. Sympathetic and parasympathetic nervous systems are further subdivided into autonomic neurons.

We will cover the autonomic nervous system in a different module. The enteric nervous system, a semi-independent nervous system that regulates the gastrointestinal tract, is a third division of the PNS. Because it can function both independently and through autonomic nervous system modulation, this system is referred to as semi-independent. Interestingly, the amount of neurons in the enteric nervous system is greater than that of the entire spinal cord.

5.1.1. Central Nervous System (CNS)

The central nervous system, which includes the brain and spinal cord, is the nervous system of vertebrates. Both voluntary movements—like walking and speaking—and involuntary movements—like breathing and reflex actions—are managed by the central nervous system. Additionally, it serves as the hub of cognition and emotion. It is one of the two primary nervous system components in humans, along with the peripheral nervous system, which is made up of the nerves that send and receive impulses to and from the central nervous system. The meninges, which act as protective membranes around the brain and spinal cord, are surrounded by a clear fluid called cerebrospinal fluid. The axial skeleton contains the majority of the central nervous system. The brain is housed in the cranium, a bony vault, and the spinal cord, which is elongated and cylindrical, is located in the vertebral canal,

composed of successive vertebrae joined by strong ligaments. The organs of the central nervous system are the brain and spinal cord. The brain and spinal cord are housed in the dorsal body cavity and are protected by bone due to their essential functions. The spinal cord is located in the vertebral canal of the vertebral column, and the brain is housed in the cranial vault. The brain and spinal cord are connected at the foramen magnum, despite the fact that they are regarded as separate organs.

The central nervous organization (CNS) is the control center for the main components of the nervous system. It is responsible for processing and integrating information. It consists of two main components: the brain and the spinal cord.

- **Brain:** It is often called the "command center" of the body. It is a very complex and organized body. The brain controls various cognitive, sensory, and motor functions. It processes and interprets information received from the senses. It allows us to perceive and understand the world around us. The brain plays a critical role in memory, learning, decision-making, emotions, and consciousness.
- **Spinal Cord:** It is a long cylindrical bundle of nerve fibers. It stretches along the spine from the base of the brain to the lower back. It serves as a link between the brain and the rest of the body. It transmits sensory information from the body to the brain. It also transmits movement commands from the brain to muscles and organs. The spinal cord also coordinates reflex actions. This provides quick responses to certain stimuli without involving the brain.

The brain and spinal cord make up your CNS. The brain uses nerves to send messages to the rest of the body. Each nerve has a protective outer layer called myelin. Myelin insulates the nerve and helps the messages get through.

- The central nervous system consists of the brain and spinal cord.
- The brain plays a central role in the control of most bodily functions, including awareness, movements, sensations, thoughts, speech, and memory.
- Some reflex movements can occur via spinal cord pathways without the participation of brain structures.
- The spinal cord is connected to a section of the brain called the brainstem and runs through the spinal canal.
- Cranial nerves exit the brainstem.
- Nerve roots exit the spinal cord to both sides of the body.
- The spinal cord carries signals (messages) back and forth between the brain and the peripheral nerves.
- Cerebrospinal fluid surrounds the brain and the spinal cord and also circulates within the cavities (called ventricles) of the central nervous system.
- The leptomeninges surround the brain and the spinal cord.
- The cerebrospinal fluid circulates between two meningeal layers called the pia matter and the arachnoid

The outer, thicker layer serves the role of a protective shield and is called the dura matter. The basic unit of the central nervous system is the neuron (nerve cell).

- Billions of neurons allow the

different parts of the body to communicate with each other via the brain and the spinal cord.

- A fatty material called myelin coats nerve cells to insulate them and to allow nerves to communicate quickly.

5.1.1.1. Brain and Cerebrum Location

The cerebrum, which makes up the majority of the brain, is responsible for memory, speech, voluntary movements, senses, and thought. The largest sulci, or grooves and infoldings, on the surface of the cerebral cortex, are referred to as fissures. Certain fissures divide the lobes. The cortex appears wormlike due to its gyri. Each convolution is known as a gyrus (plural of gyri) and is defined by two sulci.

The cerebrum is divided into two halves, known as the right and left hemispheres. The corpus callosum, a mass of fibers, connects the two hemispheres. On the left side of the body, voluntary limb movements are regulated by the right hemisphere, while on the right side, they are regulated by the left hemisphere. The majority of people have a single dominant hemisphere.

Each hemisphere is divided into four interconnected lobes, or areas:

- The frontal lobes are located in the front of the brain and are responsible for voluntary movement and, through their connections with other lobes, participate in the execution of sequential tasks, speech output, organizational skills. and certain aspects of behavior, mood, and memory.
- The parietal lobes are located behind the frontal lobes and in front of the occipital lobes. They process sensory information such as temperature, pain, taste, and touch. Additionally, they process information about numbers, body part positioning, spatial awareness, and spatial relationships.
- The temporal lobes are located on each side of the brain. They process memory and auditory (hearing) information and speech and language functions.
- The occipital lobes are located at the back of the brain. They receive and process visual information.

The outermost layer of the brain, known as the cortex or gray matter, is primarily made up of neuronal bodies, which are the portion of neurons that contain the nucleus, which contains DNA. Information processing and storage are actively handled by the gray matter. To distinguish it from a cell nucleus, a nucleus is an isolated cluster of nerve cell bodies in the gray matter. The axons, or projections, of the gray matter cells reach different parts of the brain. Afferent fibers are those that approach the cortex from other parts of the nervous system, whereas efferent fibers depart the cortex to conduct impulses toward other areas (nerves or pathways). Corticopontine tract for the former and corticospinal tract for the latter are the names given to fibers that leave the motor cortex and travel to the brainstem (e.g., the pons) or spinal cord. Myelin, which has a shimmering white appearance and gives rise to the term "white matter," envelops axons as they travel outside of the gray matter.

The lobe name or general function of cortical areas determines their names. The region known as the motor cortex is in charge of motor function. The region is referred to as a sensory or somesthetic cortex if it controls sensory function. The occipital lobe, also known as the occipital cortex, houses the calcarine or

visual cortex, which processes visual information. The auditory cortex interprets sounds or spoken input. It is located in the temporal lobe. Physicians are frequently able to locate an injury and its relative size, sometimes with remarkable precision, thanks to their knowledge of the anatomical projection of the fibers of the various tracts and the relative representation of body regions in the cortex.

5.1.1.2. Central Structures of the Brain

The pituitary gland, thalamus, and hypothalamus are the three main brain structures. Although part of the temporal lobe, the hippocampus is connected to central structures and plays a role in the processing of memories and emotions. The gray matter basal ganglia comprise the putamen and globus pallidus (parts of the lenticular nucleus), the caudate nucleus, and the amygdala, which is situated in the temporal lobe. Neuropathologists have named the putamen and caudate together as striatum due to their structural similarities (Figure 5.1).

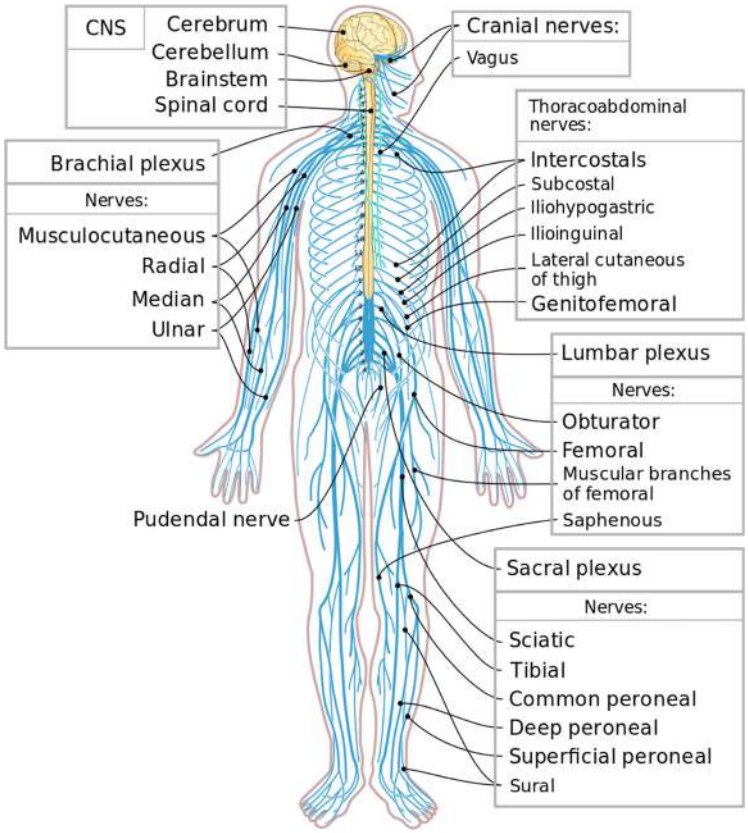


Figure 5.1. *The nervous system.*

Source: https://courses.lumenlearning.com/wm-biology2/chapter/nervous-system/.

- The thalamus integrates and relays sensory information to the cortex of the parietal, temporal, and occipital lobes. The thalamus is located in the lower central part of the brain (the upper part of the brainstem) and medial to the basal ganglia. The brain hemispheres rest on the thalamus, which also plays roles in motor and memory control.

- The hypothalamus, located below the thalamus, regulates automatic functions such as appetite, thirst, and body temperature. It also secretes hormones that stimulate or suppress the release of other hormones, such as growth hormone, in the pituitary gland.
- The pituitary gland is located at the base of the brain. The pituitary gland produces hormones that regulate the functions of many other endocrine glands. It regulates the production of many hormones that have a role in growth, metabolism, sexual response, fluid and mineral balance, and the stress response.
- The ventricles are cerebrospinal fluid-filled cavities in the interior of the cerebral hemispheres.

5.1.2. Peripheral Nervous System (PNS)

In bilateral animals, the nervous system is composed of two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). Outside the brain and spinal cord, the PNS consists of nerves and ganglia. The primary function of the PNS is to serve as a conduit linking the CNS to the limbs and organs. The PNS is vulnerable to toxins because, unlike the CNS, it is not shielded from them by the blood-brain barrier, the skull, or the vertebral column. The PNS is divided into the somatic nervous system and the visceral nervous system. Each of these systems has motor and sensory divisions.

olfactory nerve, optic nerve (cranial nerve II), and retina, which are considered part of the CNS due to their developmental origin, the cranial nerves in the somatic nervous system are part of the PNS. The optic nerve (cranial nerve II) is a tract of the diencephalon rather than a true peripheral nerve. The PNS includes the ganglia associated with the cranial nerves, as well as all other ganglia. The autonomic nervous system controls smooth muscle and glands involuntarily. The system can function in two different ways: sympathetic and parasympathetic, thanks to the connection between the central nervous system and the organs.

The nerves and ganglia are the organs of the peripheral nervous system. Similar to how muscles are bundles of muscle fibers, nerves are composed of nerve fibers. Cranial and spinal nerves extend from the CNS to peripheral organs such as muscles and glands. Outside of the central nervous system, ganglia are groups, or tiny knots, of nerve cell bodies.

The PNS is further divided into an afferent (sensory) division and an efferent (motor) division. The CNS receives impulses from peripheral organs through the afferent, or sensory, division. The CNS sends impulses to the peripheral organs through the efferent or motor division to produce an effect or action.

The efferent division is further divided into the somatic and autonomic nervous systems. The somatic nervous system, also known as the somatomotor or somatic efferent nervous system, sends motor impulses to skeletal muscles. It is sometimes referred to as the voluntary nervous system since these nerves allow for conscious control of the skeletal muscles. The autonomic nervous system, also referred to as the visceral efferent nervous system, provides motor impulses to smooth muscle, glandular epithelium, and cardiac muscle. Sympathetic and parasympathetic divisions are made within it. The autonomic nervous system is also known as the involuntary nervous system because it controls involuntary or automatic functions (Figure 5.2).

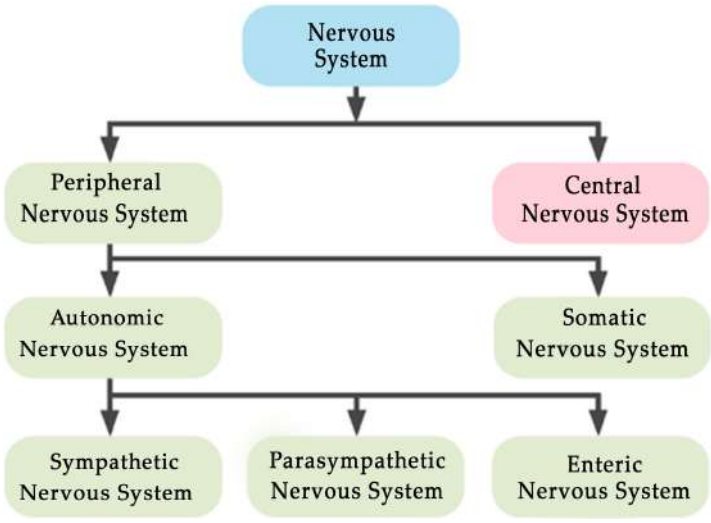


Figure 5.2. *Overview.*

Source: https://humanbiology.pressbooks.tru.ca/wp-content/uploads/sites/6/2019/06/Divisions-of-the-Nervous-System.png.

Your peripheral nervous system consists of many nerves that branch out from your CNS all over your body. This system relays information from your brain and spinal cord to your organs, arms, legs, fingers, and toes. Your peripheral nervous system contains your:

- The somatic nervous system guides your voluntary movements.
- The autonomic nervous system controls the activities you do without thinking about them.

5.2. Neuron Structure and Function

The basic components of the nervous system are neurons, also known as nerve cells. These specialized cells can send chemical and electrical signals throughout the body, enabling various components to communicate and coordinate different physiological processes.

Neurons exhibit a distinctive structure that is highly adapted to their function:

1. **Cell Body (Soma):** The cell body is the central part of the neuron and contains the nucleus, which houses the genetic material (DNA) of the cell. It is responsible for maintaining the metabolic processes necessary for cell survival and function.
2. **Dendrites:** These are branching extensions protruding from the cell body and receive incoming signals from other neurons or sensory receptors. These signals are typically transmitted in the form of chemical messengers called neurotransmitters. Dendrites play a crucial role in integrating incoming signals and determining whether to transmit the signal further along the neuron.
3. **Axon:** The axon is a long, slender projection that extends from the cell body and conducts electrical impulses away from the cell body toward other neurons, muscles,

or glands. Some neurons have a single axon, while others may have multiple branches, enabling for communication with multiple target cells. The axon is insulated by a fatty substance called myelin, which enhances the speed and efficiency of signal transmission.

4. **Axon Terminals:** At the end of the axon, there are specialized structures known as axon terminals. These structures contain synaptic vesicles filled with neurotransmitters. When an electrical signal, known as an action potential, reaches the axon terminals, it triggers the release of neurotransmitters into the synapse, the tiny gap between the axon terminal of one neuron and the dendrite or cell body of another neuron.
5. **Synapse:** The synapse is the junction between two neurons or between a neuron and a target cell, such as a muscle or gland. Neurotransmitters released from the axon terminals of one neuron diffuse across the synaptic cleft and bind to receptors on the membrane of the neighboring neuron or target cell, thereby transmitting the signal.

Neurons are essential to the nervous system's ability to transmit and process information. Using their dendrites, they receive incoming signals from other neurons, integrate these signals in the cell body, and then send an output signal down the axon to interact with target cells or other neurons. This mechanism, called synaptic transmission, is the cornerstone of neural communication and is responsible for many processes, including emotion, motor control, sensory perception, and thought. The structure and function of neurons are remarkably diverse, enabling the sophisticated processing and integration of data necessary for the nervous system's proper operation.

5.2.1. Neuron Functions

Neurons send electrical impulses and chemical signals to and from the brain. Action potentials are the method by which neurons carry out this function. The rapid flow of electrical voltage through the axon of a neuron is known as an action potential. This voltage allows information to be transferred from neuron to neuron throughout the body.

The important functions of a neuron are:

1. **Chemical Synapse:** In chemical synapses, the action potential affects other neurons through a gap present between two neurons known as the synapse. The action potential is carried along the axon to a postsynaptic ending that initiates the release of chemical messengers known as neurotransmitters. These neurotransmitters excite the postsynaptic neurons, causing them to generate their own action potential.
2. **Electrical Synapse:** When two neurons are connected by a gap junction, it results in an electrical synapse. These gaps include ion channels that help in the direct transmission of a positive electrical signal. These are much faster than chemical synapses.

5.2.1.1. Types of Neurons

Neurons differ in structure, function, and genetic composition. Just as there are thousands of species of living things on Earth, there are thousands of different types of neurons.

However, there are five major neuron forms. Each combines several elements of the basic neuron shape.

1. **Multipolar Neurons:** These neurons have a single axon and symmetrical dendrites that extend from them. This is the most common form of neuron in the central nervous system.
2. **Unipolar Neurons:** Usually only found in invertebrate species, these neurons have a single axon.
3. **Bipolar Neurons:** These have two extensions extending from the cell body. At the end of one side is the axon, and the dendrites are on the other side. These types of neurons are mostly found in the retina of the eye. But they can also be found in parts of the nervous system that help the nose and ear function.
4. **Pyramidal Neurons:** These neurons have one axon but several dendrites to form a pyramid shape. These are the largest neuron cells and are mostly found in the cortex. The cortex is the part of the brain responsible for conscious thoughts.
5. **Purkinje Neurons:** These have multiple dendrites that fan out from the cell body. These neurons are inhibitory, meaning they release neurotransmitters that prevent other neurons from firing.

Based on their roles, the neurons found in the human nervous system can be divided into three classes: sensory neurons, motor neurons, and interneurons.

6. **Sensory Neurons:** These get information about what's going on inside and outside of the body and bring that information into the CNS so it can be processed. For instance, if you picked up a hot coal, sensory neurons with endings in your fingertips would convey the information to your CNS that it was really hot.
7. **Motor Neurons:** These get information from other neurons and convey commands to your muscles, organs and glands. For instance, if you picked up a hot coal, the motor neurons innervating the muscles in your fingers would cause your hand to let go.
8. **Interneurons:** These neurons, which are found only in the CNS, connect one neuron to another. They receive information from other neurons (either sensory neurons or interneurons) and transmit information to other neurons (either motor neurons or interneurons).

If you were to grab a hot coal, the sensory neurons in your fingertips would send a signal to the interneurons in your spinal cord. Some of these interneurons would instruct the motor neurons controlling your finger muscles to release the coal, while others would carry the signal up the spinal cord to the neurons in the brain, where it would be interpreted as pain.

The most common type of neurons, interneurons are involved in information processing in both basic reflex circuits (such as those activated by hot objects) and more intricate brain circuits. Your brain's interneurons would work in concert to help you determine that objects that appeared to be hot coals shouldn't be picked up, and ideally store that knowledge for later use.

5.2.1.2. The Basic Functions of a Neuron

Neurons, the fundamental units of the nervous system, perform essential functions for communication within the body and the coordination of physiological processes. These functions include:

1. **Receiving Signals:** Neurons receive signals from other neurons or sensory receptors through specialized structures called dendrites. These signals can be in the form of neurotransmitters released by neighboring neurons or sensory stimuli such as light, sound, touch, or chemicals.
2. **Integrating Signals:** Once received, neurons integrate incoming signals in their cell bodies (soma). This integration process involves combining and processing the incoming information to determine whether to generate an output signal, known as an action potential.
3. **Generating and Propagating of Action Potentials:** If the integrated signals reach a threshold level of excitability, the neuron generates an electrical impulse called an action potential. This action potential travels rapidly along the axon, a long fiber-like projection extending from the cell body, due to sequential depolarization and repolarization of the neuron's membrane.
4. **Transmitting Signals:** Action potentials propagate along the axon toward the axon terminals, which are specialized structures at the end of the axon. At the axon terminals, the action potential triggers the release of neurotransmitters stored in synaptic vesicles into the synaptic cleft, the gap between the axon terminal of one neuron and the dendrite or cell body of another neuron.
5. **Communicating at Synapses:** Neurotransmitters released into the synaptic cleft bind to receptors on the membrane of the postsynaptic neuron or target cell, initiating a series of biochemical events that either excite or inhibit the postsynaptic neuron. This synaptic communication allows for the transmission of signals from one neuron to another or from neurons to target cells such as muscles or glands.
6. **Integrating Inputs and Regulating Outputs:** Neurons receive inputs from multiple sources and integrate them to generate an appropriate output signal. Through this process of synaptic integration, neurons regulate the strength and timing of their output signals, allowing for precise communication within neural circuits and the coordination of complex behaviors and physiological responses.
7. **Modulating Synaptic Strength:** Neurons can modify the strength of their connections with other neurons through processes such as synaptic plasticity. Synaptic plasticity, which includes mechanisms like long-term potentiation (LTP) and long-term depression (LTD), enables the neural circuitry to undergo adaptive changes in response to experience, learning, and memory formation.

The fundamental operations of neurons include the reception, integration, generation, and transmission of electrical signals. These signals facilitate the intricate processes of information processing and neural communication that are essential to the nervous system's operation.

Considering the roles of the three classes of neurons—sensory, motor, and interneurons—all neurons share three basic functions. These are to:

1. Receive signals (or information).
2. Integrate signals (to determine whether or not the information should be passed along).
3. Communicate signals to target cells (other neurons or muscles or glands).

These neuronal functions are reflected in the anatomy of the neuron.

5.2.1.3. Anatomy of a Neuron

Similar to other cells, neurons have a cell body, known as the soma. The soma contains the neuron's nucleus. A large number of proteins are required by neurons, and the majority of these proteins are also produced in the soma. The cell body has several processes that protrude or extend as appendages: several short, branching processes called dendrites and a longer process called an axon.

5.2.1.3.1. Dendrites

Receiving and processing incoming information typically occur in the dendrites and cell body. There are two types of incoming signals: excitatory and inhibitory. Excitatory signals tend to cause a neuron to fire (create an electrical impulse), while inhibitory signals prevent a neuron from firing. Most neurons receive numerous input signals through their dendritic trees. A single neuron can receive thousands of input signals and have multiple sets of dendrites. A neuron fires an impulse based on the sum of excitatory and inhibitory signals it receives. The action potential, or nerve impulse, travels down the axon if the neuron does fire (Figure 5.3).

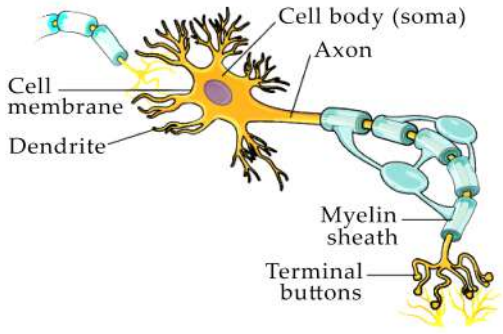


Figure 5.3. *Neuron structure.*

Source: https://courses.lumenlearning.com/waymaker-psychology/chapter/cells-of-the-nervous-system/.

5.2.1.3.2. Other Important Parts of Neuron

1. **Nissl Granules:** A large granular body found in neurons, called a Nissl body (or Nissl substance), is responsible for the synthesis and release of amino acids and proteins.
2. **Schwann Cells:** For the peripheral nervous system (PNS) to remain functional, the Schwann cell is essential. There are two types of Schwann cells—myelinating and non-myelinating—that are derived from neural crest cells. Both are essential for preserving and regenerating axons. Myelinating Schwann cells provide insulation and nutrition to individual nerve fibers, or axons, of the PNS.

3. **Myelin Sheath:** An insulating layer, called myelin develops around nerves, including the spinal cord and brain. It is composed of fatty and protein components. Electrical impulses can travel along nerve cells with speed and efficiency thanks to the myelin sheath.
4. **Node of Ranvier:** A recurring opening in the myelin sheath (insulating layer) of some neurons' axons that promotes quick nerve impulse conduction. This compels the current to flow through the nerve fiber and into the unmyelinated Ranvier nodes, which are rich in ion channels.
5. **Axon Terminal:** It is an enlargement at the end of an axon that is typically club- or button-shaped. It is the region of a nerve cell that forms synaptic connections with another nerve cell.

5.2.1.3.3. Axons

Axons differ from dendrites in several ways:

- Dendrites tend to taper and are often covered with little bumps called spines, while axons generally maintain the same diameter and lack spines.
- Axons originate from the cell body at a specialized area called the axon hillock.
- Many axons are covered with a special insulating substance called myelin, which helps them convey nerve impulses rapidly. Myelin is never found on dendrites.

Towards its end, the axon branches into many segments and develops bulbous swellings known as axon terminals (or nerve terminals). These axon terminals make connections with target cells.

5.2.1.3.4. Cell Body

Also known as a soma, the cell body is the core section of the neuron. It contains genetic information, maintains the neuron's structure, and provides energy for its activities.

Like other cells, a neuron's soma contains a nucleus and specialized organelles. It is enclosed by a membrane that protects it and allows interaction with its surroundings.

5.2.1.4. Neuron Function

Action potentials are used by neurons to send signals. An action potential is a change in the electrical potential of a neuron caused by charged particles moving in and out of the neuron's membrane. An action potential is produced and travels to a presynaptic ending via the axon. Chemical and electrical synapses can both be triggered by action potentials. Neurons can communicate electrically and chemically with one another at synapses. A synapse consists of a presynaptic ending, a synaptic cleft, and a postsynaptic ending.

5.2.1.4.1. Chemical Synapses

At a chemical synapse, the neuron releases chemical messengers known as neurotransmitters. At a chemical synapse, the neuron releases chemical messengers known as neurotransmitters. The postsynaptic neuron may respond to neurotransmitters by producing an action potential of its own. As an alternative, they can stop the postsynaptic neuron from firing. The postsynaptic neuron in that situation is not able to produce an action potential.

5.2.1.4.2. Electrical Synapses

Electrical synapses can fire when a gap junction connects two neurons. Ion channels that facilitate transmission of a positive electrical signal, and this gap is far smaller than a chemical synapse. Signals move across electrical synapses much faster than across chemical synapses due to the nature of these signals' transmission. From one neuron to the next, these signals may, however, become weaker. They are therefore less efficient at sending out repeated signals.

5.2.1.4.3. Transmission and Communication between Neurons

Neurons communicate via chemical and electrical signals. Electrical signals, known as action potentials, are generated in response to sensory stimuli. Chemical or electrical connections called synapses enable electrical signals to travel from neurons to neighboring cells. Muscle movement and contraction are mediated by electrical signals. Synaptic function can be enhanced or diminished by variations in activity level. Neuronal communication can be influenced by lifestyle choices such as exercise, stress management, and drug use. Neuronal signals combine to produce all perceptions, thoughts, and actions.

5.3. Synaptic Transmission

The process by which neurons at specific junctions called synapses communicate with one another is known as synaptic transmission. These synaptic connections enable the transmission of electrical and chemical signals throughout the nervous system, permitting neuronal communication and synchronization of diverse physiological processes.

The process of synaptic transmission involves several key steps:

1. **Action Potential Propagation:** Signals transmission between neurons begins with the generation of an action potential in the presynaptic neuron. When the membrane of the presynaptic neuron depolarizes above a certain threshold, voltage-gated ion channels open, allowing an influx of sodium ions. This depolarization triggers the propagation of an action potential along the axon towards the axon terminals.
2. **Neurotransmitter Release:** As the action potential reaches the axon terminals, it triggers the opening of voltage-gated calcium channels. Calcium ions enter the axon terminal, leading to the fusion of synaptic vesicles containing neurotransmitters with the presynaptic membrane. These neurotransmitters are released into the synaptic cleft, the small gap between the axon terminal of the presynaptic neuron and the dendrite or cell body of the postsynaptic neuron.
3. **Neurotransmitter Binding:** Neurotransmitters diffuse across the synaptic cleft and bind to specific receptor molecules on the membrane of the postsynaptic neuron. Neurotransmitters can excite or inhibit the postsynaptic neuron, depending on the type of receptors they bind to and the neurotransmitter itself. Excitatory neurotransmitters, such as glutamate, typically depolarize the postsynaptic membrane, increasing the likelihood that the postsynaptic neuron will generate an action potential. In contrast, inhibitory neurotransmitters, such as gamma-

aminobutyric acid (GABA) or glycine, hyperpolarize the postsynaptic membrane, decreasing the likelihood that the postsynaptic neuron will generate an action potential.

4. **Postsynaptic Response:** Neurotransmitter binding to receptors on the postsynaptic membrane initiates biochemical events within the postsynaptic neuron, changing membrane potential and neuron excitability. These changes may involve the opening or closing of ion channels, modulating synaptic strength, and generating postsynaptic potentials, such as excitatory postsynaptic potentials (EPSPs) or inhibitory postsynaptic potentials (IPSPs).
5. **Signal Integration:** The postsynaptic neuron integrates the excitatory and inhibitory signals it receives from multiple synapses, determining whether it will generate an action potential. If the net effect of synaptic input is depolarizing and reaches the threshold for action potential generation, an action potential is initiated in the postsynaptic neuron. If the net effect of synaptic input is depolarizing and reaches the action potential threshold, an action potential is initiated in the postsynaptic neuron.
6. **Termination of Transmission:** After neurotransmitters exert their effects on the postsynaptic neuron, they either rapidly degraded by enzymes in the synaptic cleft or actively transported back into the presynaptic neuron or surrounding glial cells for recycling or degradation. This process, known as neurotransmitter reuptake or degradation, terminates the synaptic signal and allows for precise control of synaptic transmission.

Synaptic transmission is a dynamic and controlled process essential to nervous system function, information processing, and neural communication. Deregulation of synaptic transmission is implicated in a number of neurological and psychiatric conditions, underscoring the significance of comprehending the mechanisms behind this essential component of brain activity.

5.3.1. Synapses

Other neurons' dendrites and cell bodies are the sites of neuron-to-neuron connections. Information is transferred from the presynaptic neuron to the postsynaptic neuron at these connections, also referred to as synapses. Neuromuscular junctions are the synaptic connections made by neurons with skeletal muscle cells, and neuroeffector junctions are the connections made by neurons with smooth muscle cells or glands.

Neurotransmitters are chemical messengers that carry information between synapses and junctions. Neurotransmitters are released from the presynaptic cell when an action potential travels down an axon and reaches the axon terminal. Neurotransmitters transmit an excitatory or inhibitory signal by crossing the synapse and attaching to receptors on the postsynaptic cell (Figure 5.4).

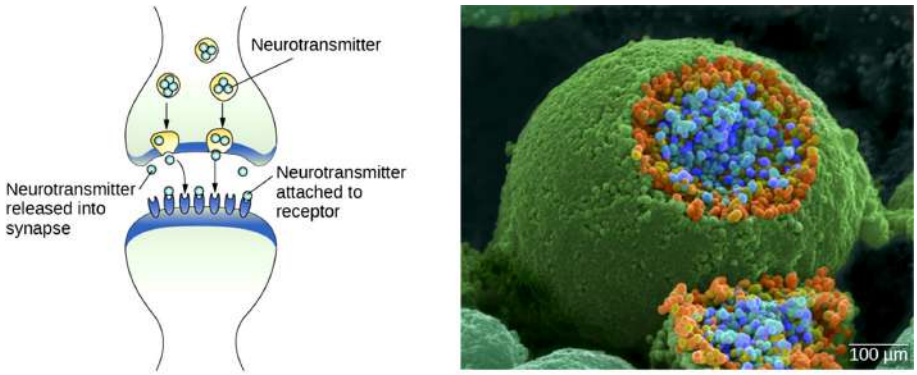


Figure 5.4. *A diagram outlining how synapses are formed.*

Source: https://courses.lumenlearning.com/waymaker-psychology/chapter/cells-of-the-nervous-system/.

Thus, the axon and axon terminals perform the third fundamental neuronal function, which is transmitting information to target cells. A single neuron can form synaptic connections with multiple postsynaptic neurons via various axon terminals, just as it can receive inputs from multiple presynaptic neurons.

5.3.2. Variations on the Neuronal Theme

While most neurons have a similar overall structure, each neuron's structure is unique and tailored to the particular task that neuron (or class of neurons) must perform. Given the complexity and diverse functions of the nervous system, it makes sense that different types of neurons exhibit great diversity in size and shape.

For example, the cerebellum, a region of the brain, contains specialized neurons known as Purkinje cells. Purkinje cells' intricate dendritic tree enables them to receive and process a vast array of synaptic inputs. The unique shapes of other neuronal subtypes in the cerebellum also help in their identification.

Neurons can vary greatly in length. While many neurons are tiny, the axons of the motor neurons that extend from the spinal cord to innervate your toes can be a meter long (or longer, in basketball players like Michael Jordan, LeBron James, or Yao Ming)!

In sensory neurons, the morphological distinction between axons and dendrites is often hazy, illustrating the diversity of neuron form. One myelinated process emerges from the cell body and divides into two branches, one of which travels to the spinal cord to transmit information and the other to peripheral sensory receptors to receive it.

5.3.3. Neuronal Networks

Nervous system function depends on networks of neurons cooperating, as individual neurons cannot function effectively on their own. Neurons form circuits that process incoming information and execute responses by stimulating or inhibiting other neurons. Simple neural circuits consisting of a small number of neurons can exist, as can more intricate neural networks.

5.3.3.1. The Knee-Jerk Reflex

The neuronal circuits responsible for muscle stretch responses, like the knee-jerk reaction triggered by a hammer blow to the patellar

tendon, which is located beneath the knee, are the most basic. Applying pressure to the patellar tendon stretches the quadriceps muscle, causing the sensory neurons that innervate it to fire. These sensory neurons send axons down the spinal cord to motor neurons, which in turn innervate the quadriceps through connections.

The motor neurons fire in response to excitatory signal from the sensory neurons. The quadriceps contract because of the motor neurons' stimulation, straightening the knee. The knee-jerk reflex is a reflex in which a muscle contracts after being stretched because the motor neurons innervating that muscle are directly connected to the sensory neurons of that same muscle.

The hamstring, which opposes the quadriceps, relaxes due to a circuit involving sensory neurons from the quadriceps. If the hamstring contracted, it would oppose the quadriceps, making it difficult for the quadriceps to contract. Therefore, it wouldn't make sense for the sensory neurons in the quadriceps to activate the motor neurons in the hamstring. Rather, an inhibitory interneuron mediates an indirect connection between the motor neurons of the hamstring and the sensory neurons of the quadriceps.

The hamstring muscle relaxes as a result of the interneuron's activation, which inhibits the motor neurons that innervate it. The quadriceps sensory neurons also communicate with the brain, informing it that a tendon was tapped with a hammer, possibly triggering further action. "Why did you do that?" Although very basic behaviors like the knee jerk reflex can be mediated by spinal cord circuits, conscious perception of sensory stimuli and all other higher functions of the nervous system rely on the more intricate neuronal networks found in the brain.

5.3.4. Glial Cells

The nervous system is composed of two cell types: neurons, the primary functional units, and glia, the supporting cells. Glia are vital to the nervous system's operation, akin to supporting actors in a film. The brain contains far more glial cells than neurons. In the adult vertebrate nervous system, glial cells are classified into four major types. Three of these are unique to the central nervous system (CNS) and are called astrocytes, oligodendrocytes, and microglia. Only the peripheral nervous system (PNS) contains the fourth type of cell, known as Schwann cells.

5.3.4.1. Types of Glia and Their Functions

1. **Astrocytes:** These are the most numerous type of glial cell. In fact, they are the most numerous cells in the brain! Astrocytes come in different types and have a variety of functions. They help regulate blood flow in the brain, maintain the composition of the fluid that surrounds neurons, and regulate communication between neurons at the synapse. During development, astrocytes help neurons find their way to their destinations and contribute to the formation of the blood-brain barrier, which helps isolate the brain from potentially toxic substances in the blood.
2. **Microglia:** These are related to the macrophages of the immune system and act as scavengers to remove dead cells and other debris.
3. **Oligodendrocytes:** Oligodendrocytes of the CNS and the Schwann cells of the PNS share a similar function. Both of these types of glial cells produce myelin, the insulating

substance that forms a sheath around the axons of many neurons. Myelin dramatically increases the speed with which an action potential travels down the axon, and it plays a crucial role in nervous system function.

4. **Satellite Glial Cells:** These cover the cell bodies of neurons in PNS ganglia. Satellite glial cells are thought to support the function of the neurons and might act as a protective barrier, but their role is still not well-understood.
5. **Ependymal Cells:** These line the ventricles of the brain and the central canal of the spinal cord, with hairlike cilia that beat to promote the circulation of cerebrospinal fluid (Figure 5.5).

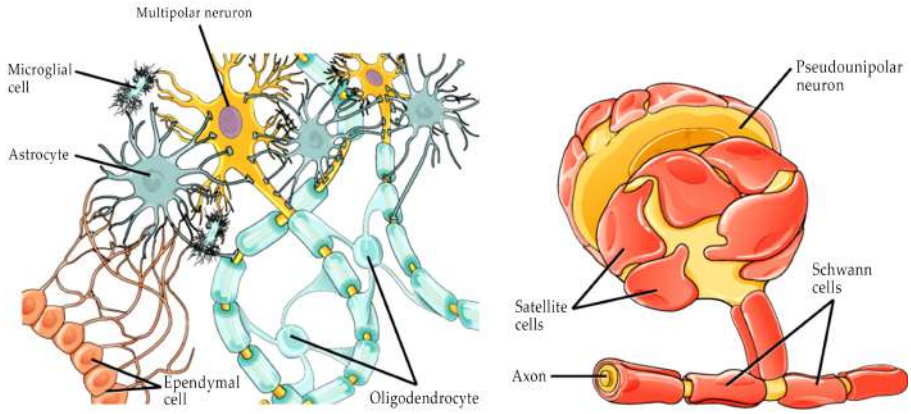


Figure 5.5. *Glial cells.*

Source: https://s3-us-west-2.amazonaws.com/courses-images/wp-content/uploads/sites/1223/2017/02/07195845/Figure_35_01_06.jpg.

5.3.5. Membrane Polarization

Now that we know that neurons possess long-range axons and dendrites that transmit signals both to and from other cells, let's examine a portion of a neuron's dendrite to see how these signals are actually transmitted. A dendrite is in its resting state when it is not transmitting any signals. In this condition, the cell's exterior has a net positive charge and the interior has a net negative charge. The membrane is referred to as polarized because of the positive and negative charges on its opposing sides. The neuron actively maintains membrane polarization through sodium-potassium pumps. For every two potassium ions pumped into the cell, three sodium ions are pumped out. The polarization increases slightly with each pump cycle. Additionally, potassium ions diffuse out of the cell, increasing the negative charge inside and the positive charge outside.

5.3.6. Membrane Depolarization

Depolarization, or the reduction in charge difference across the membrane, results from the opening of sodium channels, allowing a localized influx of positive sodium ions in response to a signal. A chain reaction is initiated when the localized depolarization also causes adjacent sodium channels to open and depolarize the membrane nearby. This sequentially opens additional sodium channels,

spreading depolarization. Depolarization begins at the dendrite, spreading in a wave across the membrane and traveling down the axon.

Depolarization can be compared to spectators rising to do the wave in a football stadium. As the wave reaches seated individuals, it causes them to rise, prompting adjacent individuals to rise as well, continuing the wave through the stands. The membrane then repolarizes, closing sodium channels and activating sodium-potassium pumps to restore the charge difference. At this point, the neuron is prepared to transmit another signal, just like the spectators who take their seats back.

5.4. Central and Peripheral Nervous System

The nervous system is divided into the central nervous system, consisting of the brain and spinal cord, and the peripheral nervous system, consisting of the cranial and spinal nerves and their associated ganglia.

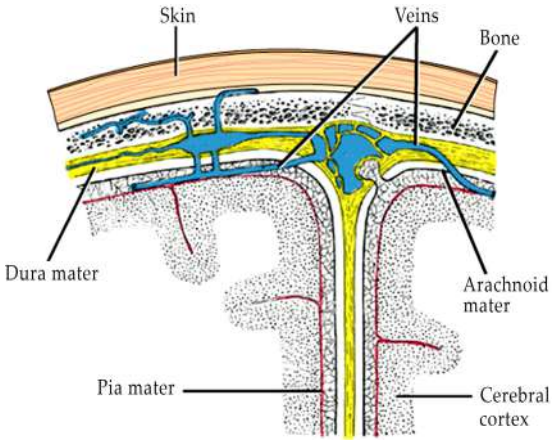


Figure 5.6. *Protective coverings of the brain.*

Source: https://courses.lumenlearning.com/suny-wmopen-biology2/chapter/the-central-nervous-system/.

The brain and spinal cord are the primary sites in the CNS where nerve information is correlated and integrated. The brain and spinal cord are protected by the skull and vertebral column, encased in meninges, and suspended in cerebrospinal fluid. (Figure 5.6).

Large numbers of excitable nerve cells and their processes, known as neurons, make up the central nervous system. These neurons are supported by specialized tissue known as neuroglia (Figure 5.7). Axons, also known as nerve fibers, are a nerve cell's lengthy processes.

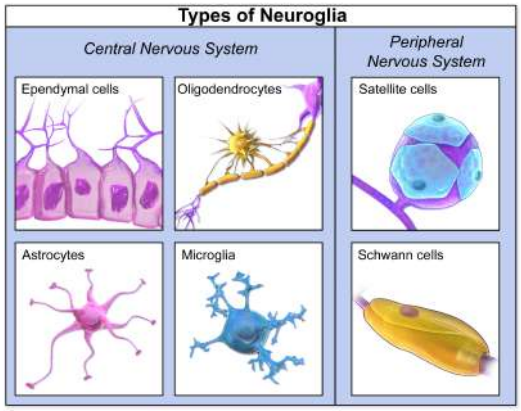


Figure 5.7. *Neuroglia.*

Source: By BruceBlaus. When using this image in external sources it can be cited as: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014." WikiJournal of Medicine, 1(2). doi: 10.15347/wjm/2014.010. ISSN 2002-4436. Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=28761843.

Gray and white matter make up the interior of the central nervous system. Gray matter, composed of nerve cells embedded in neuroglia, is characterized by its gray color. White matter consists of nerve fibers embedded in neuroglia, characterized by the lipid material in the myelin sheaths.

The cranial and spinal nerves, which are made up of bundles of nerve fibers called axons, are part of the peripheral nervous system that transmits and receives information from the

central nervous system. Even though the nerves' fibrous sheaths surround them as they travel to various body parts, trauma frequently causes damage to them because they are comparatively uncovered.

5.4.1. Autonomic Nervous System

The autonomic nervous system is responsible for innervating the body's involuntary structures, including the heart, smooth muscles, and glands. It is present in both the central and peripheral nervous systems. There are afferent and efferent nerve fibers in both the sympathetic and parasympathetic branches of the autonomic nervous system. Sympathetic activity of the autonomic nervous system prepares the body for emergencies. The parasympathetic branch conserves and replenishes energy.

5.4.2. Divisions of the Central Nervous System

Understanding the primary characteristics and general relationships of the brain and spinal cord is crucial before a detailed explanation.

5.4.2.1. Spinal Cord

The spinal cord is situated within the vertebral canal of the vertebral column and is surrounded by three meninges: the dura mater, the arachnoid mater, and the pia mater. Cerebrospinal fluid, which surrounds the spinal cord in the subarachnoid space, provides additional protection.

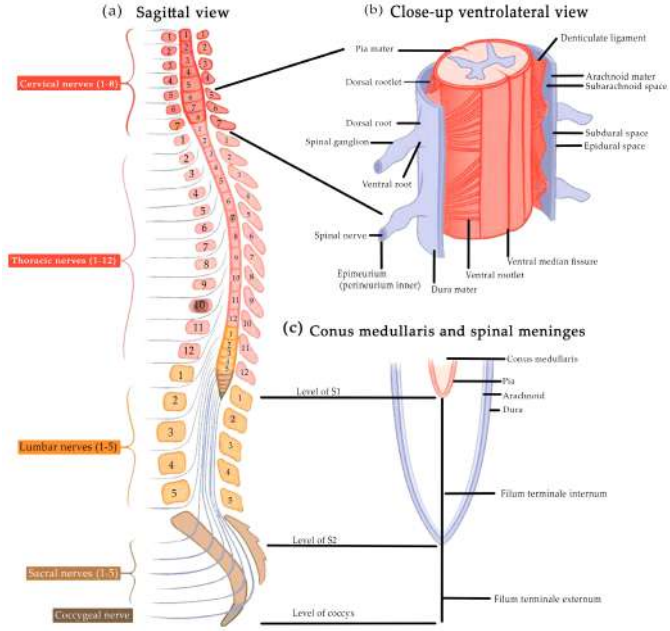


Figure 5.8. *Cord segments, close up of ligaments and conus medullaris.*

Source: https://wikimsk.org/w/img_auth.php/thumb/f/fd/Spinal_cord_anatomy.jpg/825px-Spinal_cord_anatomy.jpg.

The spinal cord is roughly cylindrical, beginning at the foramen magnum in the skull, where it is continuous with the medulla oblongata. It terminates inferiorly in the lumbar region. The spinal cord tapers into the conus medullaris, from which the filum terminale, a prolongation of the pia mater, descends to attach to the coccyx. Thirty-one pairs of spinal nerves are attached to the spinal cord along its length by anterior (motor) roots and posterior (sensory) roots. Each root is attached to the cord by a series of rootlets, which extend the whole length of the corresponding segment of the cord. Each posterior nerve root has a posterior root ganglion, whose cells give rise to peripheral and central nerve fibers (Figure 5.8).

5.4.2.1.1. Structure of the Spinal Cord

The spinal cord consists of an outer layer of white matter surrounding an inner core of gray matter. A thin gray commissure, housing the small central canal, unites the anterior and posterior gray columns (horns) of the gray matter, which appears as an H-shaped pillar in cross-section. For descriptive purposes, the white matter is divided into anterior, lateral, and posterior white columns (Figure 5.9).

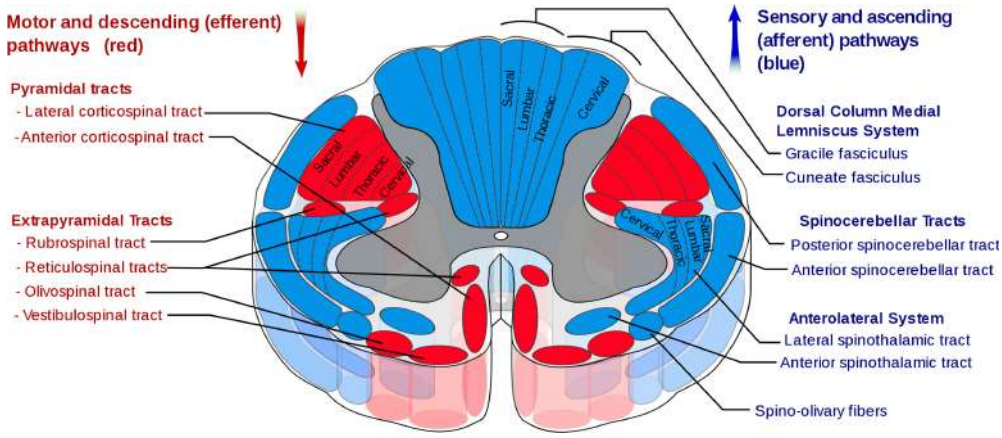


Figure 5.9. *Structure of the spinal cord – transverse section.*

Source: By Polarlys and Mikael Häggström – File:Medulla spinalis – tracts – English.svg by Polarlys (translation by Selket)., CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=10909281.

5.4.2.2. Brain

The brain resides in the cranial cavity and is continuous with the spinal cord through the foramen magnum (Figure 5.10). The brain is surrounded by three meninges – the dura mater, the arachnoid mater, and the pia mater. These meninges are continuous with those of the spinal cord. Cerebrospinal fluid surrounds the brain in the subarachnoid space. The brain is divided into three major parts: the hindbrain, midbrain, and forebrain. The hindbrain consists of the medulla oblongata, pons, and cerebellum. The forebrain consists of the diencephalon and cerebrum. After removing the cerebral hemispheres and cerebellum, the brainstem (medulla oblongata, pons, and midbrain) remains.

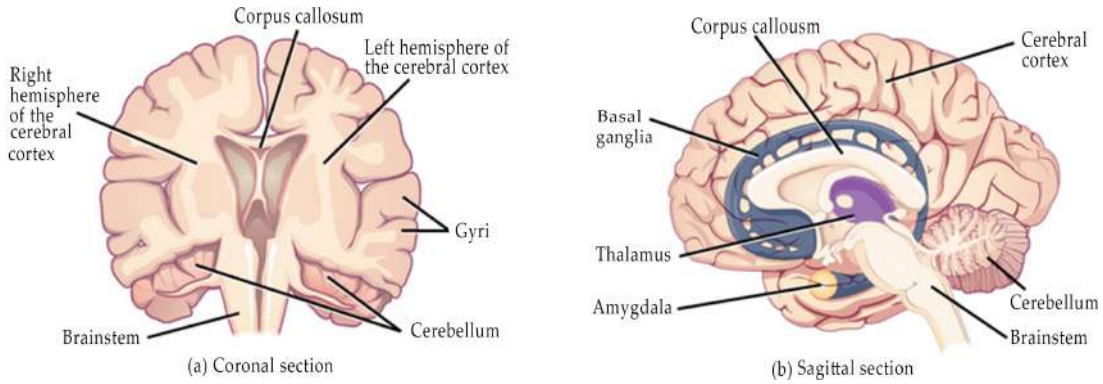


Figure 5.10. *The brain.*

Source: https://courses.lumenlearning.com/suny-wmopen-biology2/chapter/the-central-nervous-system/.

5.4.2.2.1. Hindbrain

1. **Medulla Oblongata:** The medulla oblongata is conical in shape and connects the pons superiorly with the spinal cord inferiorly (Figure 5.10). It contains numerous nuclei and serves as a conduit for ascending and descending nerve fibers.
2. **Pons:** The pons is situated on the anterior surface of the cerebellum, inferior to the midbrain and superior to the medulla oblongata. The pons, or bridge, derives its name from the large number of transverse fibers on its anterior aspect connecting the two cerebellar hemispheres. It also contains many nuclei and ascending and descending nerve fibers.
3. **Cerebellum:** The cerebellum is located within the posterior cranial fossa of the skull, posterior to the pons and the medulla oblongata. It consists of two lateral hemispheres connected by a central region called the vermis. The cerebellum is connected to the midbrain by the superior cerebellar peduncles, to the pons by the middle cerebellar peduncles, and to the medulla by the inferior cerebellar peduncles. The peduncles are large bundles of nerve fibers that connect the cerebellum to the rest of the nervous system. The surface layer of each cerebellar hemisphere called the cortex, is composed of gray matter (Figure 5.16). The cerebellar cortex is thrown into folds called folia, separated by closely set transverse fissures. Masses of gray matter, including the dentate nucleus, are found within the white matter of the cerebellum. The medulla oblongata, the pons, and the cerebellum surround a cavity filled with cerebrospinal fluid, called the fourth ventricle. It connects superiorly to the third ventricle via the cerebral aqueduct and continues inferiorly the central canal of the spinal cord. It communicates with the subarachnoid space through three openings in the inferior part of the roof. It is through these openings that the cerebrospinal fluid within the central nervous system can enter the subarachnoid space (Figure 5.11).

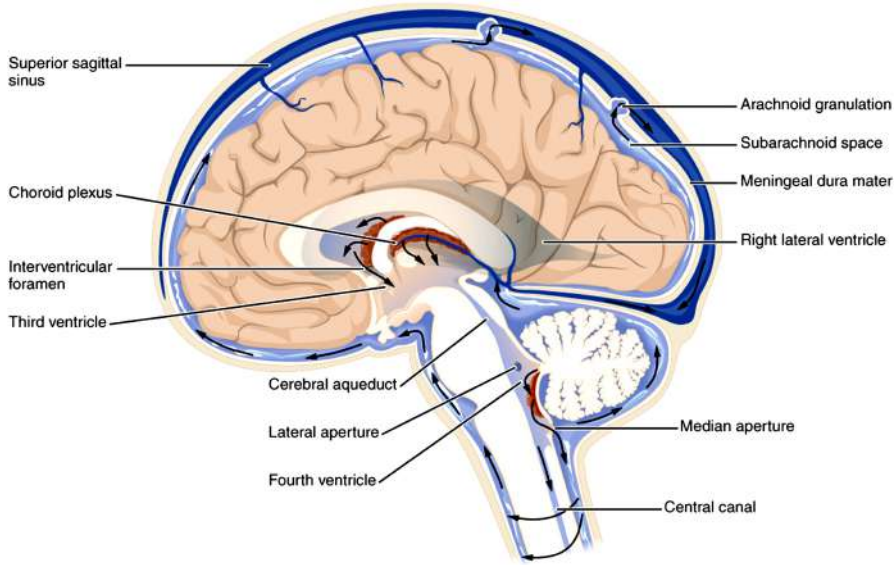


Figure 5.11. *Median sagittal section of the brain to show the third ventricle, the cerebral aqueduct, and the fourth ventricle.*

Source: By OpenStax – https://cnx.org/contents/FPtK1zmh@8.25:fEI3C8Ot@10/Preface, CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=30147960.

5.4.2.2.2. Midbrain

The midbrain is the narrow structure that connects the forebrain to the hindbrain. The narrow cavity of the midbrain is the cerebral aqueduct, which connects the third and fourth ventricles. The midbrain contains numerous nuclei and bundles of ascending and descending nerve fibers.

5.4.2.2.3. Diencephalon

Diencephalon is almost invisible from the brain's surface. It consists of the ventral hypothalamus and the dorsal thalamus. The thalamus, a large egg-shaped mass of gray matter, flanks the third ventricle. The interventricular foramen, which connects the third and lateral ventricles, is formed by the posterior boundary of the thalamus's anterior end. The hypothalamus forms the floor and lower lateral wall of the third ventricle.

5.4.2.2.4. Cerebrum

The two cerebral hemispheres that make up the cerebrum, the largest portion of the brain, are joined by the corpus callosum, a mass of white matter. The cerebrum is located posteriorly above the tentorium cerebelli, and each hemisphere extends from the frontal to the occipital bones, superior to the anterior and middle cranial fossae. The longitudinal fissure, a deep cleft that divides the hemispheres, is where the falx cerebri protrudes. Gray matter makes up the cortex, which is the surface layer of each hemisphere. The cerebral cortex is divided into gyri, or folds,

and sulci, or fissures, that are spaced apart. This significantly increases the cortex's surface area. Each hemisphere's surface is easily divided into lobes by a number of the large sulci. The lobes are named after the cranial bones beneath them. A central core of white matter, known as the basal nuclei or ganglia, contains multiple sizable masses of gray matter within the hemisphere. A group of fan-shaped nerve fibers known as the corona radiata travels through the white matter between the brainstem and the cerebral cortex. The corona radiata converge to form the internal capsule, which passes between the basal nuclei. The caudate nucleus is a tailed structure on the medial side of the internal capsule, while the lentiform nucleus is a lens-shaped nucleus located on the lateral side. Each cerebral hemisphere contains a cavity called the lateral ventricle. The lateral ventricles communicate with the third ventricle through the interventricular foramina. During development, the cerebrum expands significantly, extending beyond the diencephalon, midbrain, and hindbrain.

5.4.2.2.5. Structure of the Brain

The brain is made up of an outer layer of gray matter encircling an inner core of white matter, unlike the spinal cord. As previously mentioned, significant gray matter masses are located deep within the white matter. For instance, the gray cerebellar nuclei are located in the cerebellum, and the gray thalamic, caudate, and lentiform nuclei are located in the cerebrum.

5.4.3. Divisions of the Peripheral Nervous System

The peripheral nervous system consists of the cranial and spinal nerves and their associated ganglia.

5.4.3.1. Cranial and Spinal

Nerves – the nerve fiber bundles that make up the cranial and spinal nerves are held in place by connective tissue. There are 12 pairs of cranial nerves, which exit the brain and enter the skull through foramina, while there are 31 pairs of spinal nerves, which exit the spinal cord through intervertebral foramina in the vertebral column. The spinal nerves are classified as 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal, corresponding to the regions of the vertebral column they are associated with. Note that there is one coccygeal nerve and four coccygeal vertebrae, and eight cervical nerves but only seven cervical vertebrae.

The anterior and posterior roots of each spinal nerve serve as connections between the spinal cord and the spinal nerve1. The anterior root consists of bundles of efferent nerve fibers that carry impulses away from the central nervous system. These nerve fibers are referred to as efferent fibers. Motor fibers are efferent fibers that travel to the skeletal muscles and induce contractions. The anterior gray horn of the spinal cord contains their original cells.

Nerve fiber bundles known as afferent fibers, which transmit nerve impulses to the central nervous system, make up the posterior root. These are called sensory fibers because they transmit information about touch, pain, temperature, and vibration. The posterior root ganglion is a swelling on the posterior root that houses the cell bodies of these nerve fibers. After leaving the spinal cord through their respective intervertebral foramina, the spinal nerve roots combine to form a spinal nerve (Figure 5.12). A spinal nerve is composed of a mixture of motor and sensory fibers because this is where the motor and sensory fibers combine. The length of the roots increases from top to bottom due to the vertebral column growing more in length than the spinal cord during development. The spinal nerve roots in the upper cervical region are short and nearly horizontal, but the lumbar and sacral nerve roots form a vertical bundle

around the filum terminale below the level of the cord's termination (lower border of the adult lumbar vertebra). The cauda equina refers to the collective name for these lower nerve roots.

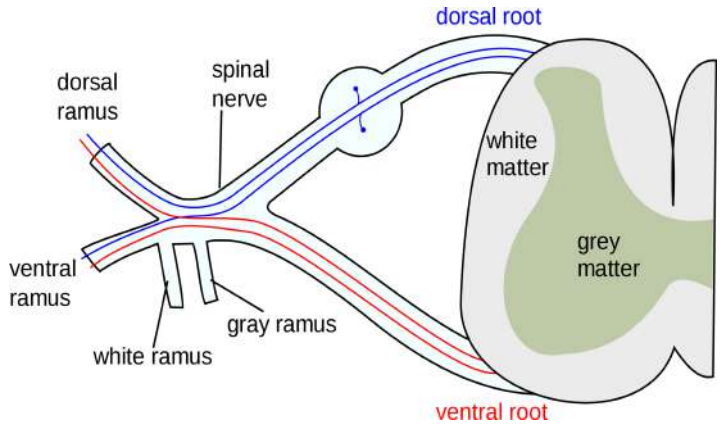


Figure 5.12. *Posterior view of the spinal cord showing the origins of the roots of the spinal nerves and their relationship to the different vertebrae.*

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Each spinal nerve, which contains both motor and sensory fibers, splits into a large anterior ramus and a smaller posterior ramus upon emerging from the intervertebral foramen. The posterior ramus supplies the muscles and skin of the back by circling the vertebral column posteriorly. The anterior ramus extends to supply the muscles and skin of the limbs and the anterolateral body wall. Complex nerve plexuses are formed at the root of the limbs where the anterior rami unite. At the base of the upper limbs are the cervical and brachial plexuses, while the base of the lower limbs is home to the lumbar and sacral plexuses.

5.4.3.2. Ganglia

Ganglia may be divided into sensory ganglia of spinal nerves (posterior root ganglia) and cranial nerves and autonomic ganglia.

1. **Sensory Ganglia:** These are fusiform swellings situated on the posterior root of each spinal nerve just proximal to the root's junction with a corresponding anterior root. They are referred to as posterior root ganglia. Similar ganglia that are also found along the course of cranial nerves V, VII, VIII, IX, and X are called sensory ganglia of these nerves.
2. **Autonomic Ganglia:** These which are often irregular in shape, are situated along the course of efferent nerve fibers of the autonomic nervous system. They are found in the paravertebral sympathetic chains around the roots of the great visceral arteries in the abdomen and close to, or embedded within, the walls of various viscera.

A Closer Look

Somatic Nervous System

The somatic nervous system (SNS) is also known as the voluntary nervous system. It contains both afferent nerves (which send information to the brain and spinal cord), made of sensory neurons that inform the central nervous system about our five senses; and efferent nerves (which send information from the brain), which contain motor neurons responsible for voluntary movements, such as walking or lifting an object.

The nerves in the somatic nervous system are classified based on their location, either in the head or in the spine region. There are 12 pairs of cranial nerves, which send information to the brain stem (base of the brain where the spinal cord connects) or from the brain stem to the periphery.

These nerves are required for the five senses and for the movement of the head, neck and tongue. The spinal nerves are 31 pairs of nerves that send sensory information from the periphery to the spinal cord and muscle commands from the spinal cord to the skeletal muscles.

Interestingly, the neurotransmitter acetylcholine has an excitatory effect in the somatic nervous system but an inhibitory function in the autonomic nervous system. Diseases affecting motor neurons, such as motor neuron disease (MND), cause neurodegeneration, leading to muscle wasting and loss of function. Work at QBI is being conducted to understand the genetics and molecular mechanisms responsible for MND.

Besides regulating voluntary movements, the somatic nervous system is responsible for reflexes, which are involuntary muscle responses controlled by the reflex arc.

A reflex arc involves a sensory neuron sending a signal directly to the spinal cord, which generates a response, such as a quick muscle contraction, that is subconscious. One common example is the knee reflex: hitting the patellar tendon just below the kneecap with a reflex hammer leads to an automatic contraction of the quadriceps – which results in the lower leg kicking out.

SUMMARY

- The nervous system takes a long time to fully develop; it starts early in the embryonic stage and continues all the way through adulthood.
- The cerebrum, which makes up the majority of the brain, is responsible for memory, speech, voluntary movements, senses, and thought.
- The basic components of the nervous system are neurons, also known as nerve cells. These specialized cells can send chemical and electrical signals throughout the body, enabling various components to communicate and coordinate different physiological processes.
- Neurons send electrical impulses and chemical signals to and from the brain. Action potentials are the method by which neurons carry out this function.
- Also known as a soma, the cell body is the core section of the neuron. It contains genetic information, maintains the neuron's structure, and provides energy for its activities.
- The process by which neurons at specific junctions called synapses communicate with one another is known as synaptic transmission. These synaptic connections enable the transmission of electrical and chemical signals throughout the nervous system, permitting neuronal communication and synchronization of diverse physiological processes.
- While most neurons have a similar overall structure, each neuron's structure is unique and tailored to the particular task that neuron (or class of neurons) must perform.
- Depolarization, or the reduction in charge difference across the membrane, results from the opening of sodium channels, allowing a localized influx of positive sodium ions in response to a signal.

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Chapter

DEVELOPMENT OF THE CARDIOVASCULAR SYSTEM

6

Contents

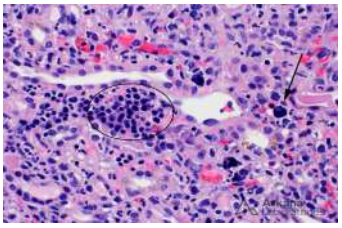
Unit Introduction

From its earliest stages in the embryo to full maturity in the adult, the development of the cardiovascular system is a carefully planned process necessary to maintain life. It starts early in the process of embryogenesis and is characterized by a complex cascade of morphogenetic events that give rise to blood vessels, the heart, and blood cells. Cardiogenesis begins in early embryonic development, approximately three weeks after human conception, when mesodermal cells in the embryonic disc give rise to the primitive heart tube. A network of signaling molecules, such as fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and transcription factors like GATA4 and NKX2.5, control this process. The four-chambered heart, which consists of the ventricles and atria, in addition to the outflow tracts, is formed by looping and segmentation of the primitive heart tube. Vasculogenesis, the simultaneous development of blood vessels, takes place. Blood islands, primitive blood vessels made up of endothelial cells, develop from mesodermal cells. These blood islands come together to form the primary vascular plexus, from which the major blood vessels sprout and remodel. Angiogenesis and vascular patterning are critical processes regulated by important signaling pathways like VEGF and Notch. As development continues, the heart undergoes additional maturation, resulting in the formation of cardiac valves, septation of the atria and ventricles, and remodeling of the outflow tracts to create pulmonary and systemic circulations. Hemodynamic forces, genetic programs, and interactions with neighboring tissues tightly regulate these processes. Congenital heart defects are the most common birth defect affecting newborns and can result from defects in the development of the heart. Concurrently, specialized tissues known as hematopoietic organs are the site of the process of blood cell formation, or hematopoiesis. Primitive hematopoiesis, which results in the production of primitive red blood cells and macrophages, primarily occurs in the yolk sac during embryonic development. Hematopoiesis moves to different locations during development, including the spleen and liver of the fetus, before settling on the bone marrow as the main location in the adult.

The cardiovascular system continues to grow, mature, and remodel throughout fetal development and into postnatal life to meet the evolving physiological needs of the developing organism. This includes the heart's contractility developing, the circulatory system expanding, and the regulation of vascular tone becoming more refined. In addition, the vascular architecture is still being shaped by continuous angiogenesis and vascular remodeling in response to environmental and physiological cues.

The heart, blood vessels, and blood cells are all formed during the highly coordinated and dynamic process of the cardiovascular system's development. Any alterations to this complex process, which is controlled by a complex interaction of genetic, molecular, and environmental factors, can result in congenital heart defects as well as other cardiovascular disorders. Determining the genesis of these illnesses and creating preventative and therapeutic measures require an understanding of the mechanisms underlying cardiovascular development.

Orientation and Directional Terms

Terms	Definition	Illustration
Cardiovascular	Cardiovascular disease (CVD) is a general term for conditions affecting the heart or blood vessels. It's usually associated with a build-up of fatty deposits inside the arteries (atherosclerosis) and an increased risk of blood clots.	
Hemodynamics	Hemodynamics is how your blood flows through your arteries and veins and the forces that affect your blood flow.	
Hematopoiesis	Hematopoiesis is the blood cell production process. Cells that circulate in your blood include immune cells (white blood cells), red blood cells, and platelets.	
Blood-vascular	The vascular system is made up of the vessels that carry blood and lymph fluid through the body.	
Oxygen	Oxygen is a chemical element with an atomic number of 8 (it has eight protons in its nucleus). Oxygen forms a molecule (O_2) of two atoms which is a colorless gas at normal temperatures and pressures.	

6.1. Overview of Cardiovascular System

The human circulatory system transports blood via vessels to and from every area of the body, supplying tissues with nutrients and oxygen while expelling waste products like carbon dioxide. It is a closed tubular system with a muscular heart that pumps blood. Venous, capillary, and arterial components make up the pulmonary and systemic circuits.

The main function of the heart is to pump blood into and out of vessels throughout the body like a muscular pump. The thick walls of the arteries, which carry blood throughout the body at high pressure and velocity, are made of both muscle cells and elastic fibrous tissue. The branching system of arteries known as the arterial tree ends in muscular, short, and narrow vessels called arterioles, from which blood flows into capillaries, tubes made of endothelial cells. These minuscule, thin capillaries while being permeable, receive and distribute essential cellular nutrients and waste products. After leaving the capillaries, the blood moves more slowly and at low pressure through tiny vessels called venules that eventually converge to form veins, which ultimately direct the blood flow back to the heart. At this point, the blood is depleted of oxygen and heavy with waste products.

The circulatory system, or blood-vascular system, is another term for the cardiovascular system. It is made up of the heart, a pumping mechanism made of muscles, and a network of closed vessels known as arteries, veins, and capillaries. As the name suggests, the heart pumps blood through a closed circuit of vessels as it travels through the body's various circulations. The developing embryo's survival, akin to that of an adult, depends on blood circulation to sustain homeostasis and a favorable cellular environment. The cardiovascular system emerges early in development and reaches a functional state ahead of any other major organ system in response to this need. Remarkably, early in the fourth week after conception, the primitive heart starts beating regularly.

Thousands of miles of capillaries penetrate every tissue and reach every cell in the body, and the continuous and regulated flow of blood through them is essential to the cardiovascular system's critical function in preserving homeostasis. The ultimate transport role of blood is carried out in the microscopic capillaries. As waste products are eliminated, nutrients and other necessary materials are transferred from capillary blood into the fluids that surround the cells. The components of the cardiovascular system work together to integrate and regulate functions, including the delivery of blood to different parts of the body as needed. These systems guarantee that every body cell has a consistent internal environment, even in the face of varying nutritional needs or waste product production.

6.1.1. Functions of Cardiovascular System

The human body needs the cardiovascular system to carry out several vital tasks to survive and function optimally. First, it facilitates the delivery of oxygen, nutrition, hormones, and other necessary materials to the body's cells and tissues. The heart pumps oxygenated blood via arteries to tissues and organs, where it is used for the process of cellular respiration, which is how cells produce energy. Simultaneously, the circulatory system carries nutrients from the digestive tract to the cells, providing the building blocks required for development, maintenance, and repair.

Second, the cardiovascular system is primarily responsible for removing carbon

dioxide, a byproduct of cellular metabolism, and other metabolic waste products from tissues and organs. Through veins, deoxygenated blood containing waste products is returned to the heart and pumped to the lungs, where respiration exchanges carbon dioxide for oxygen. The cycle is then completed when the oxygenated blood is put back into the heart and distributed throughout the body. Furthermore, the cardiovascular system helps maintain homeostasis and regulate body temperature by dispersing heat throughout the body. Encouraging the efficient transfer of heat between the body and its surroundings, blood vessels, especially capillaries close to the skin's surface, dilate or constrict in response to changes in environmental temperature or metabolic demands.

The cardiovascular system is also essential for host defense and immune response. As part of the immune system, white blood cells move via the bloodstream to areas of injury or infection where they aid in the fight against foreign substances and pathogens. The lymphatic system, which is intimately linked to the cardiovascular system, filters lymph and collects pathogens in lymph nodes, which enhances immune function. Overall, the cardiovascular system's functions are essential for preserving cellular homeostasis, supporting metabolic activities, and enabling the body to respond to both internal and external threats. Its complex system of organs, veins, and cells ensures constant blood flow and effective exchange of gases, nutrients, and waste products, all of which support life and enhance overall health and well-being.

The cardiovascular system has three major functions: transportation of materials, protection from pathogens, and regulation of the body's homeostasis.

- **Transportation:** The cardiovascular system transports blood to almost all of the body's tissues. The blood delivers essential nutrients and oxygen and removes wastes and carbon dioxide to be processed or removed from the body. Hormones are transported throughout the body via the blood's liquid plasma.
- **Protection:** The cardiovascular system protects the body through its white blood cells. White blood cells clean up cellular debris and fight pathogens that have entered the body. Platelets and red blood cells form scabs to seal wounds and prevent pathogens from entering the body and liquids from leaking out. Blood also carries antibodies that provide specific immunity to pathogens that the body has previously been exposed to or has been vaccinated against.
- **Regulation:** The cardiovascular system is instrumental in the body's ability to maintain homeostatic control of several internal conditions. Blood vessels help maintain a stable body temperature by controlling the blood flow to the surface of the skin. Blood vessels near the skin's surface open during times of overheating to allow hot blood to dump its heat into the body's surroundings. In the case of hypothermia, these blood vessels constrict to direct blood flowing only to vital organs in the body's core. Blood also helps balance the body's pH due to the presence of bicarbonate ions, which act as a buffer solution. Finally, the albumins in blood plasma help to balance the osmotic concentration of the body's

cells by maintaining an isotonic environment.

6.1.2. Components of Cardiovascular System

Together, the organs, tissues, and blood vessels that make up the cardiovascular system circulate blood throughout the body, providing cells and tissues with oxygen, nutrition, hormones, and other necessary materials while expelling waste products from the body's metabolism.

The cardiovascular system consists of several key components:

1. **Heart:** The muscular organ responsible for pumping blood throughout the body. It consists of four chambers: two atria (singular: atrium) and two ventricles. The right atrium receives deoxygenated blood from the body via the superior and inferior vena cavae and pumps it into the right ventricle. The right ventricle then pumps blood to the lungs for oxygenation. The left atrium receives oxygenated blood from the lungs via the pulmonary veins and pumps it into the left ventricle. The left ventricle then pumps oxygen-rich blood to the rest of the body via the systemic circulation.
2. **Blood Vessels:** The conduits through which blood flows throughout the body. They are broadly categorized into three types: arteries, veins, and capillaries.
    i. **Arteries:** Carry oxygen-rich blood away from the heart to various tissues and organs of the body. They have thick, muscular walls that allow them to withstand the high pressure generated by the pumping action of the heart.
    ii. **Veins:** Carry deoxygenated blood back to the heart from the tissues and organs. They typically have thinner walls than arteries and contain valves to prevent the backflow of blood.
    iii. **Capillaries:** Tiny, thin-walled vessels where the exchange of oxygen, nutrients, and waste products occurs between the blood and the surrounding tissues. Capillaries connect arterioles (small arteries) to venules (small veins) and form an extensive network throughout the body.
3. **Blood:** A specialized connective tissue composed of cells suspended in a liquid matrix called plasma. The cellular components of blood include red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes). Red blood cells are responsible for transporting oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. White blood cells play a crucial role in immune response, defending the body against pathogens and foreign substances. Platelets are involved in blood clotting, helping to stop bleeding when blood vessels are damaged.
4. **Lymphatic System:** Although not part of the cardiovascular system itself, the lymphatic system is closely associated with it. It consists of lymphatic vessels, lymph nodes, and lymphoid organs such as the

spleen and thymus. The lymphatic system helps maintain fluid balance in the body, absorbs fats from the digestive system, and plays a vital role in immune function by filtering and trapping pathogens and foreign particles in lymph nodes.

6.2. Heart Structure and Function

The heart pumps blood through the vessels. It pumps blood directly into the arteries, more specifically the aorta or the pulmonary artery.

- The heart pumps oxygenated blood from the left ventricle and into the aorta to begin systemic circulation.
- After supplying cells throughout the body with oxygen and nutrients, the blood returns deoxygenated to the right atrium of the heart.
- Deoxygenated blood flows from the right atrium to the right ventricle.
- The heart then pumps it out of the right ventricle into the pulmonary arteries to begin pulmonary circulation.
- The blood moves to the lungs, exchanges carbon dioxide for oxygen, and returns to the left atrium.
- The oxygenated blood shoots from the left atrium to the left ventricle below, to begin systemic circulation again.
- Each half of the heart has a receiving chamber called an atrium and a pumping chamber called a ventricle.
- Cardiac output in humans is generally 5-6 L/min at-rest and can exceed 35 L/min in elite athletes during exercise.
- The heart weighs about 300 grams.
- Two thin-walled atria are separated by an interatrial septum.
- Two thick-walled ventricles are separated by an interventricular septum.

LV = Left Ventricle
RV = Right Ventricle
LA = Left Atrium
RA = Right Atrium
LV → RA → RV → lungs → LA → LV
LV → Aortic valve → Aorta → Sup. & Inf. Vena Cava → RA → Tricuspid valve → RV → Pulmonary valve → Pulmonary artery → lungs →Pulmonary vein → LA → Mitral valve → LV

1. **Location of the Heart:** The heart is located in the center of the chest. It is attached to your vascular system. Blood vessels travel throughout the body to supply every area of it with nutrients and oxygen. Additionally, they remove waste from all cells in the body.
2. **Pericardium:** The pericardium, a membranous sac, suspends the heart. The diaphragm below, the mediastinal pleura on the side, and the sternum in front are securely attached to the robust outer part of the sac, known as the fibrous pericardium. It eventually melds with the pulmonary (lung) arteries and veins that lead to and from the heart, as well as the coverings of the superior vena cava. The mediastinal pleura, a continuation of the membrane lining the chest, borders

the mediastinum, the area between the lungs. The main vein that carries venous blood from the head, neck, arms, and chest is the superior vena cava. A serous (moisture-exuding) smooth membrane covers the heart after bending back to line the fibrous pericardium. The membrane lining the fibrous pericardium is called the parietal serous layer (parietal pericardium), while the visceral serous layer (also known as the epicardium or visceral pericardium) covers the heart.

The two layers of serous membrane are normally separated by only 10 to 15 ml (0.6 to 0.9 cubic inch) of pericardial fluid, which is secreted by the serous membranes. The space created by the separation is called the pericardial cavity. The pericardial fluid lubricates the two membranes with every beat of the heart as their surfaces glide over each other. Fluid is filtered into the pericardial space through both the visceral and parietal pericardia.

3. **Chambers of the Heart:** The right and left halves of the heart are divided into two chambers each by septa, or partitions. The interventricular septum divides the lower chambers, the ventricles, from the upper chambers, the atria, through a partition known as the interatrial septum. The atria receive blood from different areas of the body and then sent to the ventricles. Blood is then pumped by the ventricles to the lungs and the rest of the body.

   Except for the lungs, all tissues send blood to the right atrium, also known as the right superior portion of the heart. It is a thin-walled chamber. The right atrium receives blood from three veins: the coronary sinus drains blood from the heart itself, and the superior and inferior venae cavae, which bring blood from the upper and lower body, respectively. The right atrium supplies the right ventricle with blood. The chamber from which the pulmonary artery pumps blood to the lungs is the right ventricle or the right inferior section of the heart.

   The left atrium, the left superior chamber of the heart, has a thicker wall and is slightly smaller than the right atrium. The four pulmonary veins, which carry oxygenated blood from the lungs, empty into the left atrium. The left ventricle receives blood from the left atrium. The heart's left ventricle, or inferior left chamber, has walls that are three times thicker than the right ventricle's. All body parts, except for the lungs, receive blood pumped from this chamber via the aorta.

4. **External Surface of the Heart:** Shallow grooves known as the interventricular sulci, filled with blood vessels, mark the border between the ventricles on the front and rear surfaces of the heart. The exterior surface of the heart has two main grooves. One, known as the atrioventricular groove, is located where the right ventricle and right atrium converge. It contains a branch of the right coronary artery,

which supplies blood to the heart muscle.

The anterior interventricular sulcus contains a branch of the left coronary artery and is located between the right and left ventricles. The division of the right and left ventricles on the posterior side of the heart surface is marked by a groove known as the posterior longitudinal sulcus, which also houses an additional branch of the coronary artery. A fourth groove between the left atrium and ventricle houses the coronary sinus, a venous blood channel.

5. **Origin and Development:** The heart first forms in the pharyngeal, or throat, region of the embryo. The embryonic heart first becomes visible as a thickening of invasive cells in the undifferentiated mesoderm, which is in the middle of the embryo's three primary layers. After that, a tube of flattened cells called the endocardial (lining) tube forms. This tube continues differentiating until a tube with anterior and posterior forked ends emerges. As differentiation and growth proceed, this primordial tube starts to fold upon itself, and constrictions along its length result in the formation of four main chambers. These are known as the truncus arteriosus, atrium, ventricle, and sinus venosus, in order of posterior to anterior. The ventricle swings first to the right and then behind the atrium due to the tube's characteristic bending, with the truncus arteriosus falling in between the atrium's lateral dilations. The earliest heartbeats occur at this point in the process of development.

The single opening between the atrium and the ventricle is divided into two sections by endocardial cushions, local thickenings of the endocardium (heart lining). The two atrioventricular valves, or the valves between the atria and ventricles, which control the direction of blood flow through the heart, are also formed as a result of these cushions. Initially, a primary partition with a perforation divides the atrium into right and left halves. Later, a secondary partition with a large opening in its lower part called the foramen ovale separates the two halves. Blood still flows through the two openings, from the right atrium to the left, despite their spatial mismatch. At birth, elevated blood pressure in the atrium forces the primary partition of the left atrium against the secondary partition, resulting in the closure of both openings and complete separation of the atria. Eventually, the two partitions combine.

At its tip, the myocardium (heart muscle) forms indentation that partially divides the ventricle into two chambers. This developing partition is mostly made of muscle, with membranous connective tissue forming concurrently with the division of the truncus arteriosus into two channels: the pulmonary artery and the systemic circulation's aorta and pulmonary artery, respectively. At this point, the heart rotates left and clockwise,

residing in the left thorax, its chambers on the left side being posterior to those on the right. The ductus arteriosus, a blood vessel connecting the pulmonary artery and the aorta, returns most of the blood that passing through the right side of the heart in the fetus to the systemic circulation. This duct's muscular wall contracts violently at birth, closing it off. The blood from the right side of the heart is then forced to the left side for ejection into the systemic circulation after passing via the pulmonary arteries to the lungs for oxygenation. The external division of the ventricle into the right and left chambers is marked by a clear median furrow at the apex of the ventricles.

6.2.1. Structure of Heart

The heart consists of four distinct chambers: two upper chambers called "atria" and two lower chambers called "ventricles." A wall, or septum separates the atria and ventricles. Valves control the flow of blood within the different chambers.

Blood follows this path through the heart:

- Deoxygenated blood returns from the body and enters the right atrium (upper right chamber) via the inferior and superior vena cava veins.
- Blood flows through the tricuspid valve and enters the right ventricle (lower right chamber).
- The right ventricle pumps blood through the pulmonary valve and into the pulmonary artery.
- The blood then flows through the pulmonary arteries into the lungs. In the lungs, oxygen is drawn into the blood, and carbon dioxide is removed. As a result, the blood becomes oxygen-rich.
- The blood returns to the heart and enters the left atrium (upper left chamber) via the pulmonary veins.
- Blood flows through the mitral valve and enters the left ventricle (lower left chamber).
- The left ventricle pumps the blood through the aortic valve into the aorta. This artery delivers blood to the rest of the body.

The adult human heart is normally slightly larger than a clenched fist, with average dimensions of about 13 × 9 × 6 cm (5 × 3.5 × 2.5 inches) and a weight of approximately 300 grams (10.5 ounces). It is shaped like a cone, with the wide base pointing upward and to the right and the apex pointing leftward and downward. It is situated between the lungs and above the diaphragm, which is the muscular wall that separates the chest and abdominal cavities, in the thoracic cavity of the chest. It is located behind the sternum, in front of the windpipe, the esophagus, and the descending aorta. The heart is located to the left of the midline in roughly two-thirds of the chest.

6.2.1.1. Valves of the Heart

To prevent backflow, the heart is equipped with valves that allow the blood to flow in only one direction.

6.2.1.2. Types of Valves

There are two types of valves located in the heart:

1. Atrioventricular Valve (AV Valve):
   - Tricuspid valve;

- Mitral valve.

2. Semilunar Valve:
   - Pulmonary valve;
   - Aortic valve.

Between the atria and the ventricles are thin, leaf-like structures called atrioventricular valves. The tricuspid valve, named for its three irregularly shaped cusps (flaps), guards the right atrioventricular opening. The endocardium, the membrane lining the heart, is essentially folded into leaflets, strengthened by a thin layer of dense connective tissue. The middle supporting flat plate and the dense connective tissue of the ridge surrounding the openings merge at the base of the leaflets.

The ventricular surface of each leaflet's middle supporting layer is connected to tendinous cords of dense tissue (chordae tendineae), covered in a thin layer of endocardium, and originating from the nipple-like papillary muscles. The chordae tendineae and the papillary muscles limit the extent to which the valve portions near their free margin can billow toward the atria. The mitral, or bicuspid valve named for its two flaps—guards the left atrioventricular opening.

The mitral valve is attached in the same way as the tricuspid valve, but because the left ventricle is a more potent pump that operates at high pressure by nature, it is thicker and stronger. When the atria contract, blood is forced through the tricuspid and mitral valves into the ventricles. When the ventricles contract, blood is forced backward, pushing the flaps toward the atria. Consequently, the flaps are forced upward until they come together to form a whole partition that separates the ventricles and the atria. The chordae tendineae and papillary muscles prevent the valve flaps from opening into the atria.

The semilunar valves are pocket-like structures located at the junction where the pulmonary artery and the aorta leave the ventricles. The *pulmonary valve* guards the orifice between the right ventricle and the pulmonary artery. The *aortic valve* guards the orifice between the left ventricle and the aorta. The three leaflets of the aortic semilunar and two leaflets of the pulmonary valves are thinner than those of the atrioventricular valves, but they share the same general construction except for the absence of chordae tendineae.

The heartbeat, an audible sound, is connected to the closure of the heart valves. The closure of the tricuspid and mitral valves produces the first heart sound, and the closure of the pulmonary and aortic semilunar valves produces the second heart sound. It has been found that the major vessels surrounding the heart and the walls of the heart vibrate, producing these distinctive heart sounds. When the ventricles contract and the blood backflows suddenly, the valves close and the ventricles bulge back, producing the low-frequency first heart sound. The blood then returns to each ventricle due to the elasticity of the valves. This phenomenon generates vibrations in the ventricle walls, which radiate outward from the valves. With the use of a stethoscope, sound waves that are produced when the vibrations reach the chest wall where the wall and the heart are in contact can be heard.

As the blood reverberates back and forth between the artery walls and the valves following the sudden closure of the pulmonary and aortic semilunar valves, vibrations are generated in the walls of the aorta, ventricles, and pulmonary artery. These vibrations produce the second heart sound. The chest wall converts these vibrations into sound waves, audible as a high-frequency sound. There is a brief pause before the second heart sound occurs. The start of the next cycle is followed by a pause roughly twice as long as that before the first sound. No sound is produced when the valves open.

6.2.1.3. Wall of the Heart

The heart wall is composed of three layers: the epicardium (outer layer), myocardium (middle layer), and endocardium (inner layer). Coronary vessels supplying arterial blood to the heart pass through the epicardium before entering the myocardium.

The surface of the outer layer, also known as the visceral pericardium, is composed of flattened epithelial (covering) cells that are supported by connective tissue. The heart's contractile components are located in the myocardial layer. Bundles of striated muscle fibers in the myocardium are grouped in a branching pattern that creates a wringing motion, effectively drawing blood from the heart with each beat. The thickness of the myocardium is determined by the pressure needed to pump blood to its destination. The right ventricle's myocardium, which pumps blood to the lungs, is somewhat thicker than the left ventricle's, which must pump blood into the systemic circulation. In contrast, the atrial walls are comparatively thin.

The contractile component of the myocardium consists of muscle fibers made up of cardiac muscle cells. Smaller fibers called myofibrils are found inside each cell and contain well-organized contractile units called sarcomeres. Contractile proteins called myosin (thick filaments) and actin (thin filaments) produce the mechanical function of sarcomeres. Two populations of actin filaments that project from opposing Z lines in an antiparallel manner and are arranged around thick myosin filaments, forming the sarcomere, which is located between two Z lines (Z discs) in a muscle fiber. Each myosin filament contacts actin as actin slides along cross bridges that protrude from myosin filaments at regular intervals. This process results in muscle contraction by shortening the muscle fiber.

Each myosin filament contacts actin as actin slides along cross bridges that protrude from myosin filaments at regular intervals. Large amounts of energy and calcium are needed for actin to slide over myosin. Mitochondria make up about 25% of the cardiac cell volume and supply the energy required for contraction, while the contractile machinery occupies approximately 70% of the cell volume. Intercalated discs, or gap junctions, are special junctions that connect and delineate the boundaries of cardiac muscle cells, facilitating energy and calcium conductance. Intercalated discs are the main conduits for cardiac cell-to-cell communication, necessary for synchronized muscle contraction and circulation maintenance. A thin lining known as the endocardium forms the inner surface of the myocardial wall. This layer is continuous with the lining membrane of the large blood vessels and lines the cavities of the heart, as well as the valves and small muscles involved in valve function.

6.2.2. Function of Heart

The purpose of the cardiovascular system is to ensure that your body receives the oxygen, nutrients, and other substances it requires and eliminates waste products. Your heart pumps blood throughout your body all day and all night, even when you're asleep. This explains how your doctor can hear your heartbeat. That sound is your heart beating normally. Approximately 2,000 gallons of blood are circulated daily by your heart.

Blood is carried by veins to your heart and by arteries away from it. Additionally, your blood vessels remove waste products from your cells, such as carbon dioxide.

The blood flows through your heart in the same way every time. Along the way, valves ensure that the blood is flowing in the proper direction.

6.2.2.1. Types of Circulation

1. **Pulmonary Circulation:** Blood without oxygen comes into the right side of your heart and is sent to the lungs to get oxygen and get rid of carbon dioxide. Then the oxygenated blood comes back through the left side of your heart.
2. **Systemic Circulation:** Blood that has just gotten oxygen from the lungs and returned through your heart's left side is pushed out to the rest of your body's cells so they can receive oxygen and nutrients. The cycle starts again when blood without oxygen goes to the right side of your heart.

6.2.3. Regulations of Heartbeat

The heart beats regularly due to the intrinsic rhythmicity of cardiac muscle, as there are no nerves within the heart and no external regulatory mechanisms required to stimulate its contraction. Observing cardiac development in the embryo provides evidence that these rhythmic contractions originate in the cardiac muscle; cardiac pulsations start before sufficient development of nerve fibers. Furthermore, laboratory experiments have shown that even pieces of cardiac muscle in tissue culture can still contract rhythmically. Moreover, the heart's muscle fibers do not contract to varying degrees, which would be predicted if they were primarily controlled by the nervous system.

However, the heart cannot function effectively solely due to this intrinsic ability. An intricate conducting system within the heart, which is primarily composed of two small, specialized masses of tissue, called nodes, from which impulses originate, and nerve-like conduits for the transmission of impulses, with terminal branches extending to the inner surface of the ventricles, maintains coordination necessary for proper function. Rhythmic cardiac contractions originate from an electrical impulse that moves from the atria at the top of the heart to the ventricles at the bottom. A wave-like propagation of the impulse moves from cell to cell.

The membrane that envelops the muscle fiber, the sarcolemma, has voltage-sensitive protein channels on its surface that facilitate current flow in relation to the flow of particular ions (ion-specific channels). The voltage that is sensed across the membrane (transmembrane voltage) of the sarcolemma, where a difference in electrical potential exists, determines when these voltage-sensitive channels open and close. An excess of negative ions immediately inside the sarcolemma and an equal excess of positive ions outside the sarcolemma (also referred to as the resting potential) combine to form an electrical potential gradient. Muscle cell contraction results from depolarization, which is brought on by positive ions entering the cell in response to an electrical impulse that opens ion channels.

At rest, the heart cell primarily maintains a high intracellular concentration of positively charged potassium ions. In pacemaking cells located in the sinoatrial node, the negative resting potential gradually moves towards the positive threshold potential. Once the threshold potential is surpassed, the cell undergoes depolarization and opens ion channels that bring sodium and calcium into the cell. This sudden increase in membrane potential is transmitted from cell to cell, creating a wave of depolarization that represents the heart's excitation signal. The signal rapidly travels down conduction tissue through specialized atrial cells, the atrioventricular node, and the bundles of His and Purkinje cells, followed by a slower spread in ventricular muscle cells. The rate of spontaneous depolarization plays a crucial role in determining heart rate.

Changes in ion concentration in the extracellular and intracellular fluid, as well as drugs affecting carriers or channels associated with ions, can impact both excitation and propagation mechanisms. After the initial depolarization in cardiac muscle cells, a series of channel openings and closures occur, leading to a return to the resting transmembrane potential. This coordinated interplay of voltage-sensitive channels and resulting changes in transmembrane voltage is known as the cardiac action potential.

The depolarization event in the cardiac muscle cell triggers the opening of a calcium channel, allowing calcium to enter the myocardium. Calcium plays a crucial role in the connection between cardiac depolarization and contraction, known as "excitation-contraction coupling." Normally, the concentration of free calcium ions in the cardiac muscle cell is very low, thanks to the sarcoplasmic reticulum, an internal membrane system that stores calcium ions.

When the cell is excited and depolarized, the calcium channel opens, letting in a small amount of calcium that triggers the release of additional calcium from the sarcoplasmic reticulum. This causes a significant increase in cellular calcium concentration. As the heart repolarizes, the excess calcium is reabsorbed by the sarcoplasmic reticulum, returning the cellular calcium concentration to a low level and allowing the heart muscle to relax.

Reabsorption of calcium by the sarcoplasmic reticulum is vital to prevent muscle tension. In the resting state, troponin and tropomyosin proteins bind to actin molecules, preventing actin from interacting with myosin and blocking muscle contraction. When calcium levels rise during depolarization, troponin and tropomyosin change conformation, allowing actin to bind to myosin and initiate muscle contraction. Once calcium is reabsorbed by the sarcoplasmic reticulum, the myocardial cell relaxes. The regulation of calcium concentrations in the cardiac muscle cell is essential for proper cardiac function. Various factors control the levels of calcium, influencing the contraction and relaxation of the heart muscle.

6.2.3.1. Electrocardiogram

An ECG can be used to analyze and characterize the electrical impulse that the heart produces during each depolarization. The electrocardiogram has proven to be a valuable tool in the clinical diagnosis of cardiac conditions, as it enables the detection of minute voltage variations that coincide rhythmically with cardiac stimulation. Early in the 20th Century, researchers found that by applying leads (wires), to the arms, legs, and chest, they could measure these changes. Potential variations among different lead sets are investigated during the cardiac cycle. Ultimately, the electrocardiogram readout explains how the heart is electrically activated.

Depolarization and repolarization processes in the heart are reflected in the electrocardiogram. When the atria undergo depolarization, it is seen as the P wave, followed by the QRS complex which represents the ventricles depolarizing. The T wave indicates the repolarization of the ventricles. The atria repolarize at the same time as the ventricles depolarize but this wave is usually hidden by the QRS wave. The timing, size, and direction of these waves are crucial in diagnosing heart conditions.

6.2.3.2. Nervous Control of the Heart

The sympathetic nerves and the parasympathetic fibers in the vagus nerve together maintain nervous control of the heart. The sympathetic nerves stimulate the heart, while the vagus nerve inhibits it. The vagus nerve slows the heart rate and decreases cardiac output when it is stimulated. This is achieved by lowering atrial

contractility and impulse formation rates. In heart diseases, parasympathetic stimulation can also result in varied degrees of impaired impulse formation or heart block. The ventricles and the atria beat separately in a total heart block.

The sympathetic nervous system is stimulated to increase the contractility of the ventricles and atria. A period of relaxation known as diastole is followed by a period of contraction known as systole to form the cardiac cycle, which is defined as the duration from the end of one heart contraction to the end of the subsequent contraction. During the entire cycle, pressure is maintained in the arteries; however, this pressure varies during the two periods, the normal diastolic pressure being 60 to 80 millimeters of mercury and the normal systolic pressure being 90 to 120 millimeters of mercury.

6.3. Blood Vessels

The circulatory system is made up of a network of blood vessels that efficiently carry blood throughout the body and back to the heart. The structure and function of these vessels are closely intertwined, with arteries responsible for transporting blood under high pressure from the heart to the body tissues. The elastic walls of the arteries allow blood to flow quickly and efficiently, ensuring proper circulation throughout the body.

An artery's wall is composed of three layers. The innermost layer, known as the tunica intima, is consists of elastic tissues covering a smooth endothelial surface. The middle coat, or tunica media, is made up of elastic fibers mixed in with smooth muscle cells and is thicker in arteries, especially the larger arteries. The vessel is encircled by elastic fibers and muscle cells. Elastic fibers make up the majority of the tunica media in larger vessels. Smooth muscle fibers predominate, while elastic fibers decrease in arteries as they get smaller. Out of the three layers, the outermost layer, or tunica adventitia, is the strongest. It is made up of elastic and collagenous fibers. One protein found in connective tissue is collagen. The tunica adventitia provides a limiting barrier that shields the vessel from overexpansion. This layer also contains the vasa vasorum, tiny blood vessels that supply the walls of larger arteries and veins. As blood travels, diffusion provides nutrition to the inner and middle layers. Arteries can expand and contract with the pulse, returning to their initial size because of their thicker, more elastic wall.

A gradual thinning of the vessel wall and a reduction in lumen size, or passageway, are the hallmarks of the transition from artery to arteriole. The tunica media in arterioles is made up of a single layer of circular or spiral smooth muscle fibers and no longer contains elastic fibers. The tunica intima is still present in arterioles as a lining covered by a layer of thin longitudinal fibers. The connective tissue components make up the tunica adventitia.

Blood is released into the capillaries through pre-capillary sphincters in the arterioles and small arteries. The robust muscle wall has the power to completely block the passageway or to allow it to enlarge to multiple times its original dimensions, significantly changing the way blood flows to the capillaries. This device directs blood flow to the tissues that need it most. The three coats become less distinct as the arterioles get smaller; the smallest arterioles are essentially made up of a layer of smooth muscle encircling the endothelium, or lining. The innermost lining cells of arteries and veins form a single layer of endothelium in the capillary tubules.

Little venules are created as the capillaries converge, and their function is to draw blood from the capillary beds (i.e., the capillary

networks). The venules are made up of an endothelial tube that is supported by a small amount of collagenous tissue as well as a few smooth muscle fibers in the larger venules. The wall structure of venules, though much thinner than that of arteries, starts to show as they get bigger. The tunica media, which has less muscle and elastic tissue than the arterial wall, surrounds the endothelial lining of veins, which carry blood from the peripheral tissues to the heart. The primary component of the outermost layer, known as the tunica adventitia, is connective tissue. Compared to the arterial system, the blood pressure in these vessels is incredibly low, and the blood must exit at an even lower pressure. Because of this, a unique system is required to maintain blood flow when the blood returns to the heart. Many veins have a special valve system that enables them to do this.

These valves, which are found in pairs and are made of semilunar folds in the tunica intima, are responsible for controlling blood flow to the heart, especially when it is flowing upward. The valve flaps flatten against the vein wall as blood moves toward the heart; as the pressure from the blood and surrounding tissues fills the valve pocket, the flaps then blow out to close the opening. The veins in the extremities have more of these valves than any other area of the body.

Veins are more malleable than arteries because of the way their walls are made, which allows them to dilate and constrict. Their contractility appears to play a major role in reducing the cardiovascular system's capacity by causing the peripheral vessels to constrict in response to the heart's inability to pump enough blood.

Though they are more numerous, veins often run parallel to arteries in the body. Their walls are thinner and their channels are bigger than arteries.' 40% of the blood volume is typically found in the veins, with the remaining 60% going into the systemic circulation. The right ventricle, the pulmonary artery and its branches, the lungs' arterioles, capillaries, and venules, and the pulmonary veins that empty into the left atrium make up the pulmonary circuit.

The upper surface of the right ventricle gives rise to the pulmonary trunk, the common stem of the pulmonary arteries, which divides into the left and right pulmonary arteries that supply the lungs four to five centimeters beyond this point. The pulmonary valve, which protects the aperture between the pulmonary trunk and the right ventricle, has three leaflets, or cusps. With walls that are about twice as thick as the vena cava and one-third that of the aorta, the trunk has comparatively thin walls for an artery. Although the pulmonary arteries on the right and left are small in length, their diameters are rather large.

Because the walls can be stretched, the vessels can hold the stroke volume of the right ventricle, which is an essential function that is comparable to that of the left ventricle. The pulmonary trunk crosses the aortic route and ascends diagonally to the left. The trunk splits into the left and right pulmonary arteries, which enter the lungs, between the fifth and sixth thoracic vertebrae (roughly at the level of the bottom of the breastbone). The branches divide after entering the lungs, with capillaries being the last branch to form.

The lungs' alveoli, or air sacs, are surrounded by capillaries that take in oxygen and expel carbon dioxide. The pulmonary veins, which transport oxygenated blood from the lungs to the left atrium of the heart, are reached by the capillaries carrying oxygenated blood as they merge with progressively bigger vessels.

6.3.1. Arteries

Blood vessels called arteries transport blood from the heart. Blood leaving the lungs and traveling to the body's tissues typically has a high oxygen content. However, the pulmonary trunk and arteries of the pulmonary circulation loop transport deoxygenated blood from the heart to the lungs for oxygenation. Because arteries transport blood that is forcefully pushed out of the heart, they are subject to elevated blood pressure. The artery walls are more muscular, elastic, and thicker than those of other vessels to withstand the high pressure. The elastic tissue in arteries allows them to stretch and accommodate the pressure exerted by the heart. The walls of smaller arteries have a more muscular structure.

Smaller arteries have smooth muscles in their arterial walls that contract and expand to control blood flow through their lumen. This mechanism helps regulate blood flow to different body parts as needed. Regulation of blood flow influences blood pressure, as constriction of smaller arteries increases the pressure on arterial walls.

6.3.1.1. Aorta

The aorta, the largest vessel in the systemic circuit, arises from the left ventricle. The ascending aorta, the aortic arch, and the descending aorta—which can be further divided into the thoracic and abdominal aortas—are the three regions that make up this structure. The aorta's ascending segment gives rise to the right and left coronary arteries, which supply oxygen-rich blood to the heart. Three major arteries emerge from the aortic arch: the innominate, the left common carotid, and the left subclavian, named according to their order of origin from the heart. The blood in these three branches provides oxygen to the head, neck, and arms.

The innominate (brachiocephalic) artery splits into the right subclavian and right common carotid arteries as it ascends toward the clavicle (collarbone). The top of the thyroid cartilage, which is the main cartilage in the voice box, or larynx, is where the two common carotid arteries, one branching from the innominate and the other directly from the aorta, extend in parallel on either side of the neck. Here, they split to become the internal and external carotid arteries. The internal carotid arteries supply the forward part of the brain, the eye and its appendages, the forehead and nose, and many branches of the external carotid arteries supply the head and neck.

The basilar artery, which splits into the posterior cerebral arteries, is the result of the union of the two vertebral arteries, one of which originated as a branch of the innominate and the other as a branch of the left subclavian artery, at the base of the brain. The two internal carotid arteries, the two vertebral arteries, and the connecting arteries between them make up the circle of Willis, from which the majority of the blood supply to the brain originates.

The subclavian artery on the left and the innominate's continuation on the right supply the arms. Both of these vessels become known as the axillary artery at the border of the first rib. As the axillary artery travels down the upper arm, it becomes the brachial artery. The brachial artery splits into the radial and ulnar arteries at the elbow's level. The radial artery passes downward on the distal (thumb) side of the forearm, while the ulnar artery passes on the medial side. The hand and wrist are supplied by connections (anastomoses) between the two, with branches at the level of the palm.

The descending aorta's thoracic (chest) section produces branches called visceral branches and parietal branches, which supply the viscera and the walls encircling the thoracic cavity. Blood for the pericardium, lungs, bronchi, lymph nodes, and esophagus is supplied by the

visceral branches. The parietal vessels supply blood to the membrane lining the thoracic cavity, the spinal cord, the vertebral column, and part of the diaphragm. They also supply blood to the intercostal muscles, which are the muscles between the ribs, and the muscles of the thoracic wall. The aorta again produces both visceral and parietal branches as it passes through the diaphragm and is referred to as the abdominal aorta. Visceral vessels comprise the paired renal and testicular or ovarian vessels as well as the unpaired celiac, superior, and inferior mesenteric vessels.

The aorta gives rise to the celiac artery just below the diaphragm. It splits almost instantly into the hepatic (mainly serving the liver) and splenic (supplying the stomach, pancreas, and spleen) arteries, as well as the left gastric (supplying a portion of the stomach and esophagus). Directly beneath the celiac artery in the abdominal aorta is where the superior mesenteric artery originates. The small intestine and a portion of the large intestine are supplied by its branches. The inferior mesenteric artery rises a few centimeters above the aortic end and branches to supply the colon's lower region. The kidneys are reached by the renal arteries. The ovaries in women and the testes in men are supplied by the ovarian or testicular arteries, respectively.

The inferior phrenic, which supplies the lumbar, middle sacral arteries, and suprarenal (adrenal) glands, is one of the parietal branches of the abdominal aorta. The muscles of the abdominal wall, the skin, the lumbar vertebrae, the spinal cord, and the meninges (which cover the spinal cord) are all supplied by the four pairs of lumbar arteries. The common iliac arteries, which each descend laterally and give rise to external and internal branches, split off from the abdominal aorta. The left and right external iliac arteries are the common iliacs' direct descendants.

They pass through the inguinal area and split off to supply the lower limbs and abdominal structures. These arteries are then referred to as femoral arteries. The femoral artery continues as the popliteal artery at a point just above the knee, from which the anterior and posterior tibial arteries emerge. The popliteal artery continues directly into the posterior tibial artery, which travels down the lower leg to supply the posterior leg and foot structures.

The peroneal artery originates from the posterior tibial artery just below the knee. It branches off to supply blood to the lower leg muscles and the fibula, which is the smaller of the two lower leg bones. The branches end in the foot. The dorsalis pedis artery, which supplies the foot, is formed when the anterior tibial artery descends from the lower leg to the ankle.

6.3.1.2. Pulse

An artery that is close to the skin's surface can feel a pulse. The pulse is the result of the artery wall's periodic expansion and contraction brought on by the heartbeat. A pressure wave is created along the arteries when the heart forces blood into the aorta and strikes its elastic walls. The pulse is this impact. Every artery pulses, but it is easiest to detect where the vessel gets closest to the body's surface.

The pulse is readily distinguished at the following locations: (1) at the point in the wrist where the radial artery approaches the surface; (2) at the side of the lower jaw where the external maxillary (facial) artery crosses it; (3) at the temple above and to the outer side of the eye, where the temporal artery is near the surface; (4) on the side of the neck, from the carotid artery; (5) on the inner side of the biceps, from the brachial artery; (6) in the groin, from the femoral artery; (7) behind the knee, from the popliteal artery; (8) on the

upper side of the foot, from the dorsalis pedis artery. The most popular method for checking the pulse is via the radial artery. A few fingers are positioned on the artery near the wrist. Since there is a large, sensitive surface area available to feel the pulse wave, using multiple fingertip placement is preferred. The number and regularity of beats per minute, the force and strength of the beat, and the tension provided by the artery to the finger are all noted while the pulse is being examined. The time interval between beats is typically equal in length.

6.3.2. Veins

Venules draw blood from capillaries and sinusoids, then combine to form progressively larger veins that culminate in the great veins, or venae cavae. In the extremities, deep veins are named after the principal arteries, while superficial veins lie just beneath the skin and drain the skin and superficial fascia (fibrous tissue sheets). Connections often exist between the deep and superficial veins. The right atrium receives venous blood from three sources: the coronary sinus from the heart muscle; the superior vena cava from the upper body; and the inferior vena cava from the lower body.

6.3.2.1. Superior Vena Cava and Its Tributaries

The superior vena cava is formed by tributaries from the head and neck, the arms, and part of the chest. Venous sinuses between the layers of the dura mater allow for venous drainage of the brain without valves. The internal jugular vein continues this system downward through the neck, receiving blood from the face, neck, and brain. It joins with the subclavian vein to form the innominate veins at the collarbone level. The external jugular vein is formed near the lower jaw, draining structures of the head and neck and joining the subclavian vein into the innominate vein. The arm veins are tributaries of the subclavian vein with valves and paired deep veins with connections between them. The superficial venous drainage of the hand is achieved by tiny anastomosing (interconnecting) veins that combine to form the basilic vein, which runs up the ulnar side of the forearm and receives blood from the hand, forearm, and arm, and the cephalic vein, which runs up the radial (thumb) side of the forearm. The radial veins, which are deep anastomosing veins of the hand and wrist, and the ulnar veins, which run parallel to the corresponding artery, are two examples of the forearm's deep veins. The brachial vein, which joins the basilic vein at the level of the shoulder to form the axillary vein, is formed by the convergence of the radial and ulnar veins at the elbow. The axillary vein changes into the subclavian vein at the outer edge of the first rib, marking the end of the upper extremity's venous system.

To form the innominate vein, the subclavian, external, and internal jugular veins converge. The superior vena cava, which opens into the upper posterior region of the right atrium, is where the right and left innominate veins come to an end. Apart from the innominate veins, the azygous vein and minor veins from the pericardium and mediastinum (the space between the two lungs) supply blood to the superior vena cava.

The majority of blood from the back, chest, and abdominal walls flows into veins that are next to the vertebral bodies, which are the parts of the vertebrae that support weight. This group of veins is known as the azygous system, and it connects the inferior vena cava and superior vena cava. This system's azygous, hemiazygous, and accessory hemiazygous veins are its terminal veins. The right ascending lumbar vein continues upward as the azygous vein at the level of the diaphragm. The right intercostal veins, which drain the muscles of the intercostal spaces, are the principal tributaries

of this vein. Along with the pericardium, lymph nodes, esophagus, and right lung as tributaries, it enters the superior vena cava approximately at the level of the fourth thoracic vertebra.

The left side of the azygous system differs widely between people. The hemiazygous vein typically begins as a continuation of the left ascending lumbar vein just below the diaphragm and ends in the azygous vein. The esophagus, the intercostal muscles, and a section of the mediastinum are drained by the hemiazygous tributaries. With tributaries from the left intercostal spaces and the left bronchus, the accessory hemiazygous typically extends downward as a continuation of the fourth intercostal space's vein. It empties just above the hemiazygous entrance into the azygous vein.

6.3.2.2. Inferior Vena Cava and Its Tributaries

The inferior vena cava, a large venous trunk without valves, receives blood from the back, legs, walls, and contents of the abdomen and pelvis. The dorsal venous arch, which passes over the top of the foot not far from the base of the toes, is primarily responsible for draining the foot. Veins draining the sole are connected to the arch. The saphenous veins, both large and small, drain the lower leg superficially. They are extensions of the dorsal venous arch. The popliteal vein is typically where the small saphenous vein ends after extending up the back of the lower leg. There is some correspondence between the great saphenous vein and deep veins. As it ascends the inside of the lower leg and thigh from the dorsal venous arch, the latter vein—the longest vein in the body—takes in venous branches from the knee and thigh region before ending in the femoral vein.

Most of the blood from the lower extremity is carried back through the deep veins, which include the femoral and popliteal veins, as well as the veins that run alongside the anterior and posterior tibial and peroneal arteries. The anterior and posterior tibial veins begin in the foot and meet at the knee to form the popliteal vein, which then becomes the femoral vein as it extends through the thigh.

Once the femoral vein reaches the inguinal ligament (located at the front diagonal border between the trunk and thigh), it becomes the external iliac vein. The external iliac vein then joins with the internal iliac vein to create the common iliac vein. The internal iliac vein drains various parts of the pelvic region, including the pelvic walls, viscera, external genitalia, buttocks, and part of the thigh. The legs and a large portion of the pelvis are drained through the paired common iliac veins, which then merge above the coccyx (the lowest spine bone) to form the inferior vena cava.

As the inferior vena cava travels upwards through the abdomen, it collects blood from the common iliac veins, as well as from the lumbar, renal, suprarenal, and hepatic veins, before finally emptying into the right atrium of the heart.

The ascending lumbar vein, a vertical connecting vein, unites the pairs of lumbar veins on either side, draining blood from the abdominal walls and loins; the left ascending lumbar vein becomes the hemiazygous, and the right ascending lumbar vein becomes the azygous. Normally, these veins enter the inferior vena cava independently. Renal veins are located in front of their corresponding renal arteries; the left renal vein receives blood from various organs, while the right renal vein receives tributaries only from the kidney.

Both the right phrenic and right suprarenal veins end directly in the inferior vena cava, above the gonadal vein. As it passes through the diaphragm, two or three brief hepatic trunks empty into the inferior vena cava.

6.3.2.3. Portal System

One way to think of the portal system is as a specific area of the systemic circulatory system. The portal system differs from other vessels despite having capillary origins because it ends in the liver's capillary-like vascular bed. The liver is the first organ the blood from the spleen, stomach, pancreas, and intestine passes through before entering the heart. The hepatic vein receives blood from the portal vein (80%) and the hepatic artery (20%), while the hepatic vein receives blood from the liver and empties into the inferior vena cava. The blood in the hepatic artery provides the liver with the oxygen it needs. Blood enters the portal vein and subsequently travels to the liver from the abdominal viscera, especially the intestinal tract. The liver processes substances found in the portal blood (see human digestive system).

6.3.2.4. Venous Pulmonary System

The oxygenated blood in veins is collected from the pulmonary capillaries, where blood absorbs oxygen and exhales carbon dioxide. It then moves through venules, gradually larger veins, and four pulmonary veins, two from each lung's hilum. Each lung's hilum serves as the entrance point for the bronchus, blood vessels, and nerves. After that, these veins flow into the left atrium, where the heart receives their contents.

6.3.3. Capillaries

The enormous network of approximately 10 billion microscopic capillaries facilitates the exchange of waste products, nutrients, and fluids between tissues and blood. Despite their tiny size—0.2 mm in diameter at most, roughly the tip of a pin—the capillary network functions as a reservoir, typically holding one-sixth of the blood volume in circulation. Active tissues like muscle, liver, kidney, and lungs have more capillaries than tendon or ligament; additionally, the cornea, epidermis, and hyaline cartilage (semitransparent cartilage found in joints) do not contain any capillaries.

The capillary network that receives blood from arterioles is small and has thin walls made up of a single layer of cells. These vessels are extensions of the inner lining cells of larger blood vessels and are typically three to four endothelial cells in circumference, except near the veins where they may be slightly wider. A basement membrane surrounds these cells and helps support the structure of the vessels.

An average capillary unit consists of vessels that branch off and connect (anastomose), with each ranging in length from 0.5 to 1 millimeter. Because the capillary wall is so thin, it functions as a semipermeable membrane that lets substances that contain small molecules—like water, fatty acids, glucose, oxygen, and ketones—pass through. At the venous end of the capillary bed, waste products and carbon dioxide flow through the membrane into the vessel, while oxygen and nutrients enter the tissues through the wall at the arteriolar end of the capillary unit. The main mechanism that controls blood flow into the capillaries is the dilation and constriction of the arterioles. However, the capillary unit's muscular gatekeepers, or sphincters, guide the flow to the areas that are most in need.

Substances cross the capillary wall's cellular membrane in three ways. Through a process known as diffusion, substances soluble in the capillary cells' lipid (fatty) membrane can go straight through them. Through a process known as ultrafiltration, certain chemicals that are required by the tissues and soluble in water but totally insoluble in the lipid membrane can pass through the tiny pores, or water-filled passageways, in the membranes. These pores make up only 1/1,000th of the surface area of capillaries. Certain endothelium receptors are responsible for the transport of other substances, like cholesterol.

6.4. Blood Flow

The passage of blood through a tissue, organ, or vessel is referred to as blood flow, and it is typically measured in terms of blood volume per unit of time. The heart's ventricles contract first, starting the process. Blood is forced into the major arteries by ventricular contraction, which causes blood to flow from high-pressure areas to low-pressure areas as it passes through capillaries, venules, and veins in the venous system, as well as smaller arteries and arterioles (Figure 6.1).

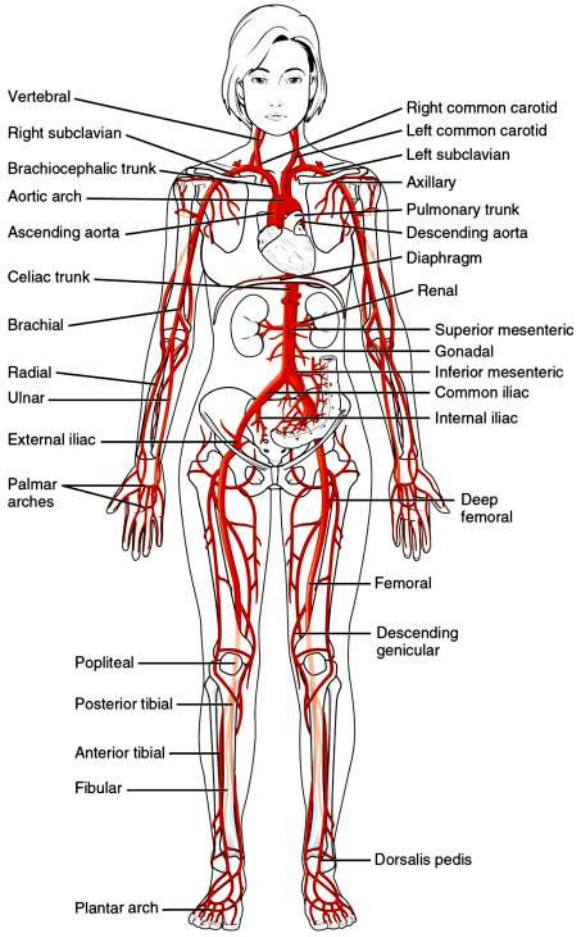
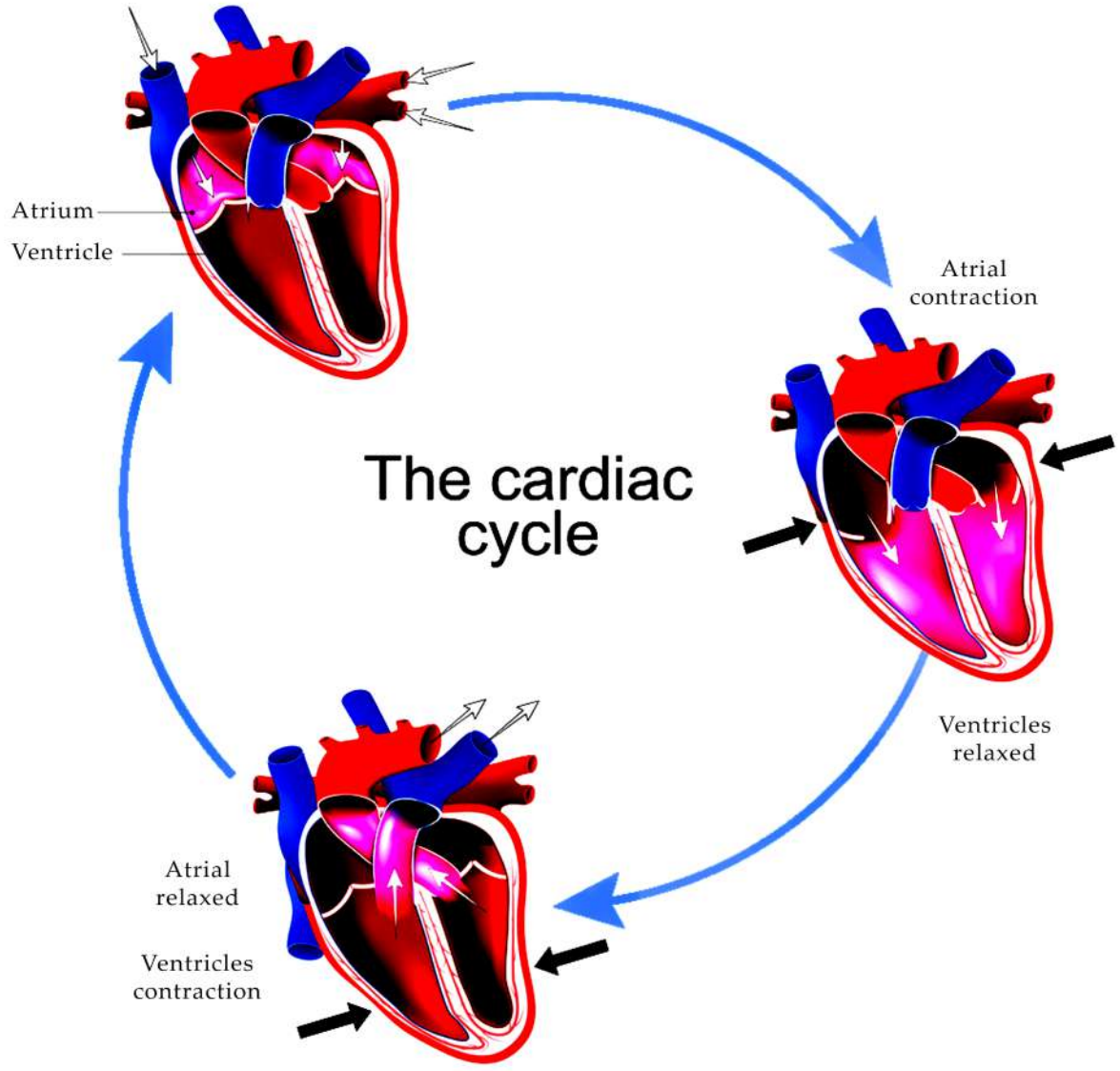


Figure 6.1. *The network of the circulatory system.*

Source: https://courses.lumenlearning.com/suny-ap2/chapter/circulatory-pathways/.

6.4.1. Cardiac Cycle

The cardiac cycle is a series of pressure changes that take place within the heart. These pressure changes result in the movement of blood through different chambers of the heart and the body as a whole. The two main phases of the cardiac cycle are systole (the contraction phase) and diastole (the relaxation phase).



Source: https://www.shutterstock.com/image-vector/diagram-phases-cardiac-cycle-main-parts-1050564824.

6.4.1.1. Diastole

The diastole phase begins with the relaxation of all the heart muscles. During diastole, blood returns to the heart and begins to fill the atria and ventricles. The low pressure in the ventricles allows the mitral and tricuspid valves to open, letting blood flow from the atria into the left and right ventricles respectively (Figures 6.2 and 6.3).

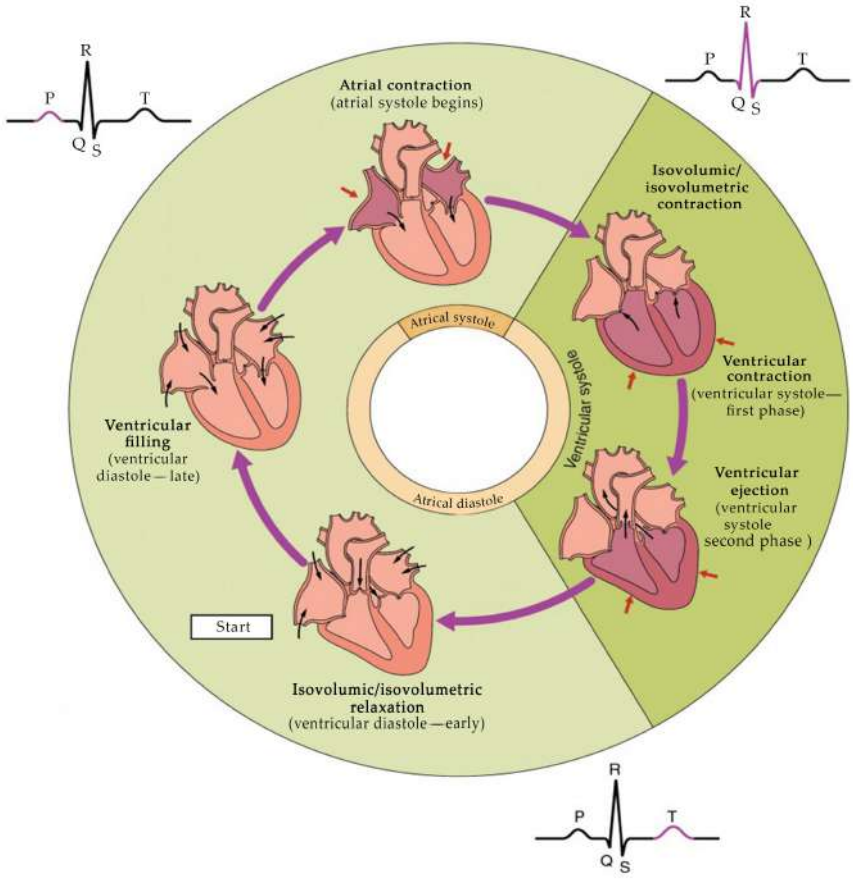


Figure 6.2. *The cardiac cycle.*

Source: https://courses.lumenlearning.com/suny-ap2/chapter/cardiac-cycle/.

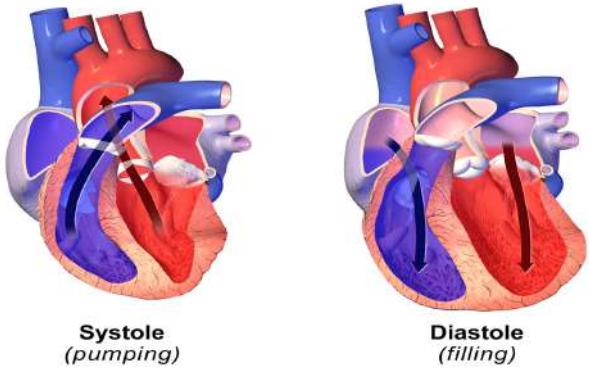


Figure 6.3. *Systole and diastole.*

Source: https://upload.wikimedia.org/wikipedia/commons/thumb/3/34/Heart_systole.svg/300px-Heart_systole.svg.png; https://upload.wikimedia.org/wikipedia/commons/thumb/0/0f/Heart_diasystole.svg/1200px-Heart_diasystole.svg.png.

6.4.1.2. Systole

The ventricles enter the systole and begin contracting, initiating another wave of contraction. The increased pressure in the ventricles closes the mitral and tricuspid valves. The pressure pushes open the aortic and pulmonary valves, starting the systole phase of the cycle (See image below).

6.5. Blood Pressure

The force or pressure of blood within your arteries is measured by your blood pressure. Your heart pumps blood into the arteries that distribute blood throughout your body with each beat. This occurs 60–100 times per minute. Your body needs the oxygen and nutrients carried by the arteries to function. Blood pressure can be influenced by a wide range of factors, including hormones, stress, exercise, diet, sitting, and standing. One-way valves, smooth muscle, blood vessel size, and blood pressure all work together to control how much blood moves through the body.

Systolic blood pressure measures the pressure blood exerts on vessel walls during a heartbeat. A systolic blood pressure of 120 mmHg is ideal. The pressure inside the vessels in between heartbeats is measured by diastolic blood pressure. Around 80 mmHg is the ideal diastolic blood pressure.

6.5.1. Blood Pressure Measured

Blood pressure is measured in millimeters of mercury (mmHg):

- **Systolic Pressure:** The pressure when your heart pushes blood out.
- **Diastolic Pressure:** The pressure when your heart rests between beats.

For example, if your blood pressure is "140 over 90" or 140/90mmHg, it means you have a systolic pressure of 140mmHg and a diastolic pressure of 90mmHg.

As a general guide:

- Ideal blood pressure is considered to be between 90/60mmHg and 120/80mmHg;
- High blood pressure is considered to be 140/90mmHg or higher;
- Low blood pressure is considered to be below 90/60mmHg.

6.5.1.1. High Blood Pressure

High blood pressure is often related to unhealthy lifestyle habits, such as smoking, drinking too much alcohol, being overweight and not exercising enough.

Left untreated, high blood pressure can increase your risk of developing a number of serious long-term health conditions, including coronary heart disease. You also risk damaging the blood vessels in your kidneys or eyes.

6.5.1.2. Low Blood Pressure

Low blood pressure is less common. Some medicines can cause low blood pressure as a side effect. It can also be caused by a number of underlying conditions, including heart failure and dehydration.

6.5.2. Blood Components and Function

The blood volume in an average human body is between 4 and 5 liters. It functions as a liquid connective tissue that carries various substances throughout the body and aids in preserving the equilibrium of gases, nutrients, and waste products. Red blood cells, white blood cells, platelets, and plasma make up blood.

6.5.2.1. Components of Blood

There are four components of blood:

- Plasma;
- Red blood cells;
- White blood cells;
- Platelets.

6.5.2.2. Red Blood Cells

Erythrocytes, another name for red blood cells, account for roughly 45% of the volume of blood and are by far the most prevalent type of blood cell. Erythrocytes are produced at a remarkable rate of approximately 2 million cells per second from stem cells in the red bone marrow. Erythrocytes are biconcave, meaning that they are disks with a concave curve on both sides, with the thinnest part of the disk being in the center. Because of their distinct shape, erythrocytes have a high surface area-to-volume ratio and can fold to fit into tiny capillaries. The nucleus of immature erythrocytes is expelled as the cell matures, resulting in a distinct biconcave shape. Red blood cells have no DNA and cannot heal themselves after being damaged because they do not have a nucleus.

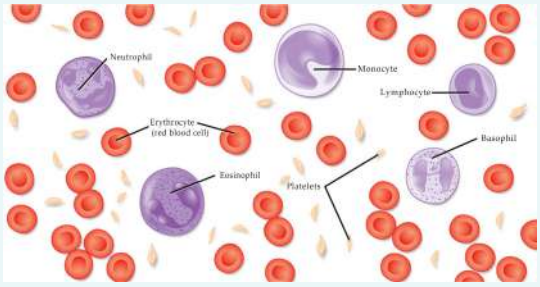


Figure 6.4. *The blood components.*

Source: https://courses.lumenlearning.com/suny-biology2xmaster/chapter/components-of-the-blood/.

Through the red pigment hemoglobin, erythrocytes carry oxygen throughout the blood. The iron and proteins that makeup hemoglobin enable erythrocytes to carry much more oxygen. Oxygen can be easily transported into the lungs and out of the cells in the systemic tissues' capillaries due to the high surface area to volume ratio of erythrocytes (Figure 6.4).

6.5.2.3. White Blood Cells

White blood cells, also known as leukocytes, make up a very small percentage of the total number of cells in the bloodstream but have important functions in the body's immune system. There are two major classes of white blood cells: granular leukocytes and agranular leukocytes.

1. **Granular Leukocytes:** The three types of granular leukocytes are neutrophils, eosinophils, and basophils. Each type of granular leukocyte is classified by the presence of chemical-filled vesicles in their cytoplasm that give them their function. Neutrophils contain digestive enzymes that neutralize bacteria that invade the body. Eosinophils contain digestive enzymes specialized for digesting viruses that have been bound to by antibodies in the blood. Basophils release histamine to intensify allergic reactions and help protect the body from parasites.
2. **Agranular Leukocytes:** The two major classes of agranular leukocytes are lymphocytes and monocytes. Lymphocytes include T cells and natural killer cells that fight off viral infections and B cells that produce antibodies against infections by pathogens. Monocytes develop into cells called macrophages that engulf and ingest pathogens and the dead cells from wounds or infections.

6.5.2.4. Platelets

Platelets, which are tiny cell fragments also referred to as thrombocytes, are in charge of blood clotting and scab formation. Large megakaryocyte cells that periodically burst and release thousands of membrane fragments that eventually become platelets are where platelets originate in the red bone marrow. Without a nucleus, platelets can only endure in the body for a week or less before being taken up and broken down by macrophages.

6.5.2.5. Plasma

About 55% of the volume of blood is made up of plasma, the non-cellular or liquid component of the blood. Plasma is a mixture of dissolved materials, proteins, and water. Water makes up about 90% of plasma, though the precise percentage varies based on the individual's level of hydration. Plasma contains albumins and antibodies among other proteins. The immune system's component antibodies attach themselves to antigens on the surface of pathogens that infect the body. Because albumins give body cells an isotonic solution, they aid in preserving the osmotic balance of the organism. Plasma contains dissolved substances such as glucose, oxygen, carbon dioxide, electrolytes, nutrients, and cellular waste products. These substances travel throughout the body using the plasma as a means of transportation.

6.5.3. Functions of Blood Cells

Blood has many different functions, including:

- Transporting oxygen and nutrients to the lungs and tissues;
- Forming blood clots to prevent excess blood loss;
- Carrying cells and antibodies that fight infection;
- Bringing waste products to the kidneys and liver, which filter and clean the blood;
- Regulating body temperature.

6.5.4. Cardiovascular Disease

The World Health Organization states that cardiovascular disease is the primary cause of death globally. This disease encompasses conditions affecting the heart and blood vessels, such as coronary artery disease, stroke, hypertension, and heart failure:

- **Aging/Hypertension:** Persistently elevated blood pressure (high blood pressure) in the arteries is associated with the development of disorders such as atherosclerosis, heart attack, and stroke, and can cause kidney damage.
    - o There is a decrease in compliance with age due to a loss in elasticity (notably with the aorta).
    - o Increase in fibrotic changes (an increase in collagen fibers and their cross-linking).
    - o With older age, higher blood pressure becomes prevalent.
    - o The pathophysiology of hypertension includes diabetes, hypercholesterolemia, and cigarette smoking (contributing to the arteriosclerotic changes).
- **Coronary Artery Disease (Heart Disease):** Narrowing or blockage in the coronary arteries, which supply blood directly to the heart muscle. Complete blockage of blood flow will cause a heart attack.
- **Stroke:** It is the death of brain cells

(neurons) due to the lack of blood supply.

- **Heart Failure:** The heart is not able to supply enough blood to body tissues. It is caused by conditions such as hypertension, heart disease, and cardiomyopathy (a chronic disease of the heart muscle).
- **Vessel Aneurysm:**
  - With a loss or defective elastic components of a vessel, the outward transmural pressure (distension) can be unbalanced with an inadequate tension force allowing for an aneurysm to form (susceptible to rupture).
  - The aneurysmal rupture in the brain results in life-threatening subarachnoid hemorrhage.
- **Atherosclerosis:** A form of arteriosclerosis characterized by the deposition of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries.
- **Dissection:** The abnormal, and usually abrupt formation of a tear along the inside wall of an artery. As the tear becomes larger, it forms a small pouch which is called a "false lumen." The blood that accumulates inside this false lumen can generate blood clots or otherwise block blood flow, leading to a stroke.

A Closer Look

Human Heart

With its complicated nature, the human heart is the very essence of life. This vital organ, safely nestled in the chest, continuously pumps blood throughout the body, keeping us alive and functioning. Its intricate structure and vital functions make it a fascinating biological marvel.

To truly grasp the heart's complexities, we must first analyze its physical structure. The human heart has four cardiac chambers: two atria and two ventricles. The atria are the upper chambers in charge of receiving blood, while the ventricles, the lower chambers, are in charge of pumping blood to the rest of the body. These cardiac chambers work in unison to ensure that blood circulates freely throughout the circulatory system. The anatomy of the heart is a feat of engineering, and any disruption can have serious consequences for our health.

The rhythmic pumping action of the heart, known as the cardiac cycle, is what keeps us alive. It consists of several phases, including diastole and systole, in which the heart relaxes and contracts. The electrical system of the heart is critical in regulating this rhythm and keeping the heartbeat steady. Arrhythmias and other cardiac complications can result from any irregularities in this system.

The heart acts as a powerful pump, pushing blood throughout the circulatory system and supplying oxygen and nutrients to every cell in the body. This constant blood flow is critical for our health and vitality. Understanding blood flow through the heart highlights the significance of each heartbeat and how disruptions can lead to various heart conditions.

The heart valves serve as the heart's gatekeepers. With each heartbeat, they open and close, enabling blood to flow in one direction while restricting backflow. Their proper operation is critical for maintaining proper blood circulation. Heart valve problems, such as stenosis or regurgitation, can significantly impact heart health and may require medical intervention.

Unfortunately, heart disease is common in today's society. Cardiovascular disorders include a wide range of conditions such as coronary artery disease, heart failure, and arrhythmias. Understanding common heart diseases and their risk factors enables us to make educated lifestyle decisions to protect our heart health.

Our lifestyle choices can have a significant impact on the health of our hearts. A heart-healthy diet high in fruits and vegetables, whole grains, and lean proteins can lower the risk of heart disease. Regular exercise not only aids in weight maintenance but also solidifies the heart muscle and improves circulation.

Cardiology has seen groundbreaking advances in the form of modern diagnostics and treatment options in recent years. MRI and CT scans, for example, provide detailed insights into heart conditions, allowing for early detection and intervention. Furthermore, novel treatments, such as

minimally invasive procedures and novel medications, provide hope to patients suffering from heart disease. Telemedicine and remote monitoring are also changing how we manage heart disease. Patients can now receive virtual consultations and have their heart conditions remotely monitored using wearable devices. This trend allows for more frequent monitoring and prompt interventions, which is especially beneficial for those who live in remote areas or have limited access to healthcare facilities.

Heart disease prevention should be a top priority. Adopting a heart-healthy lifestyle and controlling risk factors like high blood pressure, high cholesterol, and diabetes are critical first steps. Regular heart checks and screenings can detect any problems early on, allowing for timely intervention and complications prevention.

Public awareness is critical in promoting heart health. Educational campaigns and initiatives can empower people to make informed lifestyle choices, resulting in a significant decrease in heart disease cases. Understanding the symptoms of a heart attack, such as chest pain, shortness of breath, and dizziness, can prompt people to seek medical attention immediately, potentially saving lives.

Furthermore, addressing risk factors such as smoking, obesity, and stress is critical in lowering the prevalence of heart disease. Community-based programs that promote heart-healthy behaviors and regular heart screenings can help to create a healthier population while reducing the strain on healthcare systems.

Summary

- The cardiovascular system continues to grow, mature, and remodel throughout fetal development and into postnatal life to meet the evolving physiological needs of the developing organism.
- The human circulatory system transports blood via vessels to and from every area of the body, supplying tissues with nutrients and oxygen while expelling waste products like carbon dioxide.
- The cardiovascular system is also essential for host defense and immune response. As part of the immune system, white blood cells move via the bloodstream to areas of injury or infection where they aid in the fight against foreign substances and pathogens.
- The contractile component of the myocardium consists of muscle fibers made up of cardiac muscle cells.
- The heart beats regularly due to the intrinsic rhythmicity of cardiac muscle, as there are no nerves within the heart and no external regulatory mechanisms required to stimulate its contraction.
- Changes in ion concentration in the extracellular and intracellular fluid, as well as drugs affecting carriers or channels associated with ions, can impact both excitation and propagation mechanisms.
- The circulatory system is made up of a network of blood vessels that efficiently carry blood throughout the body and back to the heart.
- The passage of blood through a tissue, organ, or vessel is referred to as blood flow, and it is typically measured in terms of blood volume per unit of time.
- The force or pressure of blood within your arteries is measured by your blood pressure. Your heart pumps blood into the arteries that distribute blood throughout your body with each beat.

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Chapter

7

DEVELOPMENT OF THE RESPIRATORY SYSTEM

Contents

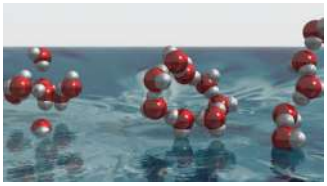
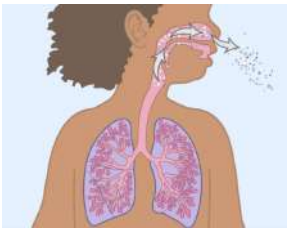
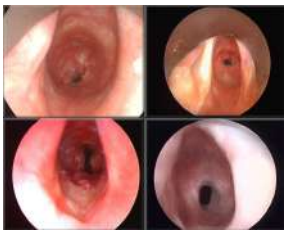
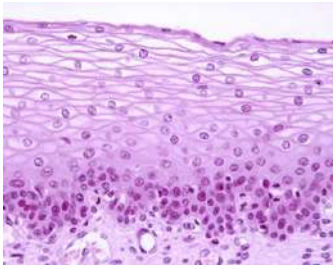
Unit Introduction

Early in the embryonic stage and continuing into the postnatal period, the respiratory system's development is a complicated and tightly controlled process. It involves the development of numerous structures involved in breathing and gas exchange, allowing the body to exchange carbon dioxide and oxygen with the outside world. The respiratory system originates from the foregut endoderm, a layer of cells in the developing embryo, during embryonic development. A sequence of morphogenetic processes culminates in the development of the primitive respiratory diverticulum, also known as the lung bud, which originates from the foregut endoderm during the fourth week of human gestation. To form the respiratory tree, which includes the trachea, bronchi, and bronchioles, the lung bud goes through a process called branching morphogenesis, which is characterized by repeated branching and elongation of epithelial tubes.

The surrounding mesodermal cells also give rise to the blood vessels and lymphatics that supply the lungs, as well as the supporting structures of the respiratory system, including the cartilage, smooth muscle, and connective tissue of the airways. A complex interplay of signaling molecules and transcription factors, such as fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and members of the Sonic hedgehog (Shh) and Wnt signaling pathways, controls the coordinated development of the endodermal and mesodermal components of the respiratory system. As the embryo develops, the respiratory system undergoes further differentiation and maturation. The major structural elements of the respiratory system are established by the end of the embryonic period, or around the eighth week of gestation, and the lung tissue starts to differentiate into distinct regions, including the conducting airways and gas exchange units known as alveoli. However, because the lungs continue to grow and develop throughout the fetal life, functional gas exchange does not occur until late in gestation. The switch to breathing air after birth marks a significant stage in the development of the respiratory system. Many physiological changes are brought about by the first breath, including the lungs expanding, fetal shunts like the ductus arteriosus and foramen ovale closing, and the onset of pulmonary circulation. These modifications allow the baby to start breathing air on its own and adjust to life outside of the womb.

During the postnatal period, the respiratory system grows and matures in response to growth, aging, and environmental factors such as exposure to tobacco smoke and air pollution, undergoing both structural and functional changes. A healthy respiratory system is vital for survival from infancy to adulthood, as well as for maintaining appropriate gas exchange and promoting general health and well-being. It is crucial to comprehend the mechanisms underlying respiratory system development for preventive and therapeutic interventions, as disruptions to this process can result in congenital abnormalities, respiratory diseases, and impaired lung function.

Orientation and Directional Terms

Terms	Definition	Illustration
Molecules	A molecule is a group of two or more atoms held together by attractive forces known as chemical bonds; depending on context, the term may or may not include ions which satisfy this criterion.	
Respiratory system	The respiratory system is a biological system consisting of specific organs and structures used for gas exchange in animals and plants.	
Syndrome	A syndrome is a set of medical signs and symptoms which are correlated with each other and often associated with a particular disease or disorder.	
Laryngotracheal Tube	The laryngotracheal tube then grows caudally into the splanchnic mesoderm on the ventral surface of the foregut, dividing into the right and left lung buds.	
Epithelium	Epithelium or epithelial tissue is a thin, continuous, protective layer of compactly packed cells with little extracellular matrix.	

7.1. Overview of Development of the Respiratory System

The development of the digestive system is closely linked to that of the respiratory system from the start. Thus, abnormalities in the foregut frequently affect both systems at the cranial level. Understanding this subject will help clarify the complexities involved in the formation of the respiratory tree. The pseudo glandular period, the canalicular period, and the saccular period are the three distinct stages of lung development. In a human fetus, the respiratory system is dormant during pregnancy.

The development of the lungs occurs in three phases. The developing lung resembles an endocrine gland during weeks six through 16 of the pseudo-glandular period, also called the glandular period. By the end of this period, all significant lung components, except for those needed for gas exchange (e.g., alveoli), have developed. During this stage, breathing is impossible, and fetuses born during this time cannot live.

The canalicular period, which lasts from weeks 16 to 26, is characterized by an increase in lung tissue vascularization, bronchial lumen enlargement, and the development of respiratory bronchioles and alveolar ducts from terminal bronchioles. Near the end of this stage, breathing becomes feasible, but few fetuses born during this time will make it. The final stage of lung development, the saccular period, lasts from week 26 to birth. The crucial blood-air barrier is formed during this period. Type II alveolar cells, which secrete pulmonary surfactant, are among the specialized cells of the respiratory epithelium that emerge.

This surfactant plays a crucial role in lowering surface tension at the air-alveolar surface, allowing the terminal saccules to expand. At this point, the lungs resemble rocks and will sink in water but expand after taking their first breath—a characteristic that was once used to identify whether or not a baby was alive (Figure 7.1).

Figure 7.1. *The right and left lung buds from which the bronchi and lungs will develop.*

Source: https://upload.wikimedia.org/wikipedia/commons/7/71/Gray948.png.

Respiratory buds: Lung buds from a four-week-old human embryo, showing the beginning of lobulation. When exposed to air at birth, the respiratory system fully develops, although growth and development continue throughout childhood. Premature babies may have immature alveolar type II cells, leading to insufficient surfactant in the alveoli. This raises surface tension, causing alveoli to collapse and lose their ability to exchange gases. This condition is known as respiratory distress syndrome. Finally, the alveolar period, lasting from birth to age eight, is characterized by an increase in the number of alveoli, alveolar ducts, and terminal saccules. Septa form to create wall divisions, and true alveoli appear as indentations in the saccular wall.

The trachea, bronchi, larynx, nose, pharynx, and lungs, which are divided into the upper and lower respiratory tracts. The nose, pharynx, and larynx make up the upper respiratory tract, which is the region above the throat. The trachea, bronchus, and lungs are all included in the lower respiratory tract, which is the region below the larynx. The primary functions of the

respiratory system include defense, respiration, metabolism, and endocrine regulation. The respiratory system reaches maturity by the age of 20, and as people age, its anatomical features progressively deteriorate. The lungs developed and grew before the age of 20, with the number of alveoli peaking between ages 10 and 12. The respiratory system reaches peak functionality between the ages of 20 and 25. Afterward, it starts to deteriorate; otherwise, it continues to provide sufficient gas exchange throughout an individual's lifetime, barring illness. Chronic respiratory damage in the elderly is often attributed to various factors, including environmental influences, immune system status, nutrition, smoking, sleep patterns, and other bodily systems such as the endocrine, nervous, digestive, and cardiovascular systems.

The impact of aging on the respiratory system is difficult to predict, but as we age, the respiratory system's composition and capabilities will progressively alter. The tracheal groove, a shallow longitudinal groove, first appears in the middle of the bottom wall of the original pharyngeal end at the start of the fourth week. The laryngotracheal diverticulum, also known as the laryngotracheal tube, is a blind sac that forms on the ventral side of the esophagus as a result of the gradual deepening of the stenosis. The tracheal esophageal septum is the interstitial space that separates the esophagus from the laryngotracheal diverticulum.

The laryngotracheal diverticulum swells into two left and right lung buds at the end of the fourth week. These lung buds are the primordium of the bronchi and lungs. The bronchial tree in the lungs is formed by the repeated branching of the lung buds. The number of alveoli increases in the seventh month, and the alveolar epithelium secretes surfactant and displayed type 2 cells in addition to type 1 cells. Infants born prematurely at 7 months gestation can survive due to the large number of capillaries in the alveolar septum. The lungs go through a rapid survival phase in the first few weeks, during which the number of alveoli increases, the alveolar wall thins, the fluid in the alveolar cavity is gradually absorbed, the number of type 2 cells increases, and the amount of surfactant released increases. The lungs continue to grow, and the quantity of alveoli keeps rising from birth into early childhood.

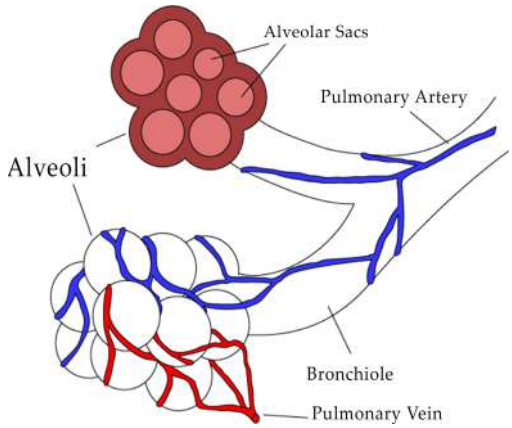
7.1.1. Aging and the Respiratory System

Mammals breathe by expanding their lungs and flattening their diaphragm. As we age, our lung elasticity decreases. Mammals breathe (inhale) when the diaphragm, a domed muscle that separates the thorax and abdomen, contracts and flattens. When the diaphragm relaxes, more air enters to compensate for the drop in thoracic pressure. Lung elasticity allows air to be expelled when the diaphragm relaxes. It takes little energy to be in this calm, relaxed breathing state. As demands increase, the abdominal muscles resist expansion. Increased abdominal pressure tilts the diaphragm and ribcage upward, increasing volume and air entry.

The diaphragm and abdominal muscles relax to allow expiration, which can be accelerated by the abdominal muscles pulling down on the rib cage. Forced expiration raises the pressure across the airway walls, which may cause the airways to narrow or even wheeze. Auxiliary intercostal muscles form and stiffen the rib cage. The equilibrium between the two breathing patterns is necessary for speech. Conscious changes in breathing often alter the autonomous response, influenced by factors such as anxiety, fear, aging-related lung elasticity loss, pulmonary conditions like emphysema, or obesity-related abdominal expansion.

Certain forms of emphysema develop naturally with aging, usually in people over

85. Humans stop producing new alveolar tissue at the age of 20. Lung tissue then starts to deteriorate slowly. Lung elastin starts to degrade, and the number of lung capillaries decreases as alveoli die, reducing lung elasticity. This is a normal aspect of aging for healthy individuals.



Source: https://upload.wikimedia.org/wikipedia/commons/d/db/Alveoli_diagram.png.

Aging also decreases the mass and strength of chest muscles, weakens bones and cartilage, and alters posture. Emphysema can be brought on by or assisted by these age-related alterations in the architecture of the respiratory system. All elderly people are at risk of decreased respiratory function, restricting maximum lung performance and causing discomfort at higher exertion levels, though not all will develop clinically evident emphysema.

7.1.1.1. Respiratory System Development Research Status

The nasal cavity, sinuses, and outer nose form the entrance of the respiratory system. The mucous membrane lining the nasal cavity consists of the lamina propria and epithelium. The periosteum, skeletal muscle, and perichondrium are all connected to the deep section of the mucosa. The vestibular, respiratory, and olfactory portions of the nasal mucosa can be divided based on their respective structures and functions. In elderly people, nasal cartilage becomes less elastic, the tip droops slightly, the nasal cavity deforms and widens, and the turbinate atrophy. The inferior turbinate blood vessels undergo cavernous-like degeneration, and the middle and lower turbinate narrow. The nasal mucosa becomes thin, atrophied, pale, or slightly reddish. The rate of cilia transmission is slowed; the maxillary sinus mucosal epithelial cells, the mucous gland, and the blood vessel wall have fat deposits; the anterior nasal opening shifts from a forward horizontal opening to a lower side. Glandular atrophy occurs in the lamina propria of the nasal mucosa.

1. **Throat:** The throat is a vital organ for voice and breathing. The aging process causes the laryngeal cartilage to calcify or ossify; men experience this condition earlier than women, and by age 80, it is almost entirely ossified. Other changes include thyroid cartilage ossification, collagen fiber degeneration of the sacral cartilage, atrophic changes in the elastic tissue, diminished elastic and muscle fibers in the vocal cords, proliferating collagen fibers, and structural disorganization. The laryngeal mucosa is thinned, and the epithelium frequently exhibits parakeratosis or hyperkeratosis, along with fat loss in the lamina propria.
2. **Thoracic:** The vertebrae, ribs, sternum, and scapula comprise the thorax. The thoracic vertebrae bend backward, and the sternum protrudes as the age-related degenerative changes become more apparent. The ribs slant from the

upper back to the lower front, the upper rib gap widens, rib cartilage calcifies, rib cage joints calcify, joint ligaments harden, and elasticity decreases. These changes cause the diaphragm to lose function, worsening with age.

In the elderly, thorax has a larger anterior and posterior diameter, a smaller left and right diameter, a wider upper part, a narrower lower part, and a flattened shape that resembles a barrel. This is a typical aging-related chest manifestation for the barrel chest. Aging-related pleural fibrous tissue hyperplasia can result in pleural thickening, thinning and drying of the pleural layers, decreased transparency, and calcification. Small airway, bronchus, and trachea: The trachea is a tubular structure that divides into the left and right bronchi at its lower end. It begins at the annular cartilage and extends downward through the neck into the chest. Aging causes degenerative changes to the bronchi, small airways, and trachea.

In the elderly, the tracheal lumen dilates, and the internal diameter increases, more so in females. The elastic tissue of the wall decreases, collagen fibers increase with hyaline degeneration, the bronchial lumen narrows, the small airway lumen narrows or collapses, and mucosal atrophy and loss of wall elasticity are more pronounced. The tracheal and bronchial mucosa show epithelial atrophy or local hyperplasia, with mucosal damage prone to squamous metaplasia. Mucosal cells shrink, cilia progressively shed, and adhesion and lodging occur. Reduced goblet cells in the airways grow. Decreased smooth muscle of the submucosa, lymphocyte infiltration, and degenerative alterations in the tracheal and bronchial mucosal glands are documented. The lung is an elastic, spongy organ that resembles a cone. The tip of the lung is at the top, the base of the lung is at the bottom, the mediastinum is on the inside, and the rib surface is on the outside. A pleural visceral layer covers the lung surface, and a polygonal shape is visible through this layer.

7.1.1.2. Respiratory System Development Clinical Applications

One of the primary targets for the treatment of asthma and chronic obstructive pulmonary disease is the β2 adrenergic receptor. The symptoms of asthma can be effectively relieved and controlled with the help of β2 adrenergic receptor agonists. In addition to reducing vascular exudation, relaxing airway smooth muscle, increasing mucociliary clearance, controlling mast cell and eosinophil mediator release, and preventing allergic asthma, these agonists can also provide significant relief from asthma symptoms. As per the pipeline database, inhaled long-acting β2 receptor agonists (LABA) account for the greatest number of newly developed drugs for this target, with 45 β2 adrenergic receptor agonists currently on the market. Inflammation, which is difficult to manage, often leads to the onset of respiratory illnesses. Drugs that target glucocorticoid receptors are effective in reducing airway inflammation. Inhaled glucocorticoids can improve lung function, reduce seizures, and effectively treat asthma. It is now used as an initial asthma treatment. Mometasone furoate, Fluticasone furoate, and Cysteinide are the three recently released inhaled glucocorticoids (ICS). Extensive research is being conducted on novel glucocorticoids, with many medications undergoing preclinical and clinical development. Histamine, an appealing chemical, is present early in the inflammatory process. The human body contains at least three different subtypes of histamine receptors in various tissues. An allergic reaction of type I is closely associated with the histamine H1 receptor. H1 receptor blockers are useful for treating moderate allergic asthma and allergic asthma with rhinitis due to their inhibitory effect on allergic reactions. Astemizole, Avastin, and ketotifen are among

the available medications. Phosphodiesterase 4 (PDE4) has emerged as a potential new treatment target for respiratory disorders in recent years. PDE4 selective inhibitors can generate inflammatory cytokines, downregulate the release of inflammatory mediators, and raise intracellular cAMP levels. Cilomilast and roflumilast are two recently developed PDE4 inhibitors. However, some of the Phase III trial's findings regarding the safety and efficacy of cilastatin had some issues, which prompted the medication's further development. Currently, only two medications targeting PDE4 are in preclinical stages.

In recent years, a novel class of medications known as leukotriene modulators has been discovered to treat bronchial asthma. Zafirlukast, pranlukast, and montelukast are examples of representative drugs that are cysteinyl leukotriene receptor antagonists and whose target is a cysteine leukotriene receptor. Currently, few medications are being researched for these targets. It is noteworthy that some medications target the muscarinic choline receptor (M receptor). These medications constitute a significant portion of the study's total variations, despite variations in other targets.

Recent research on selective M3 receptor antagonists has focused on their strong therapeutic potential for treating smooth muscle pathophysiology. Significant progress has been made in the development of specific M receptor antagonists in recent years. Respiratory medicine research and development have unique characteristics due to the specific organs and tissues involved and the unique administration methods. To achieve high efficacy and low toxicity, respiratory drugs are often administered locally, necessitating unique dosage forms in addition to conventional oral and injectable forms. Many novel respiratory medication formulations, including transdermal patches, nasal inhalants, oral inhalers, sustained release formulations, and controlled release formulations, have been created in recent years. The new product combines antitussive, antiasthmatic, and antihistamine preparations, along with a single paeoniflorin preparation. Yamaguchi Company Ltd. (Japan) together with East Asia Pharmaceutical Co, Ltd has introduced amphoteric hydrochloride oral fast-disintegration tablets, an oral medication that dissolves in the mouth. The FDA approved BioMarin's oral disintegrating tablet, prednisolone sodium, in 2006 as an adrenal corticosteroid for use in conditions like asthma. Five varieties of ICS/LABA compound preparations are currently listed globally, and they have emerged as the hot topic in clinical research. The recent introduction of new products, such as combination therapy and one-time/d administration, will encourage the use of asthma medications, increase patient compliance, and lessen adverse reactions.

7.2. Developmental Processes and Events in Respiratory System Formation

The respiratory system starts to develop early in the fetal stage. Most structures in this process originate from the endoderm. The fetus can be seen breathing toward the end of development. However, before delivery, the mother supplies all the fetus's oxygen and eliminates its carbon dioxide through the placenta.

- **Timeline:** Around week four of pregnancy is when the respiratory system starts to develop. By week 28, a premature baby can typically breathe on its own because enough alveoli have developed. However, the respiratory system is not fully developed until early childhood, when a full complement of mature alveoli is present.

- **Weeks 4–7:** In the embryo, respiratory development starts at week four. Olfactory pits form when ectodermal tissue from the anterior head region invaginates posteriorly and fuses with endodermal tissue from the developing pharynx. One of the two structures that will grow to become the nasal cavity is the olfactory pit. Around this same period, the lung bud develops. The lung bud protrudes from the foregut and is a dome-shaped structure made of tissue. Pharyngeal pouches are superior to endodermal foregut. As development proceeds, the longitudinal extension of the lung bud gives rise to the laryngotracheal bud. The distal end of this structure becomes more bulbous and forms bronchial buds, while the portion closest to the pharynx becomes the trachea. The bronchial buds will eventually give rise to the bronchi and all other lower respiratory structures (Figure 7.2).

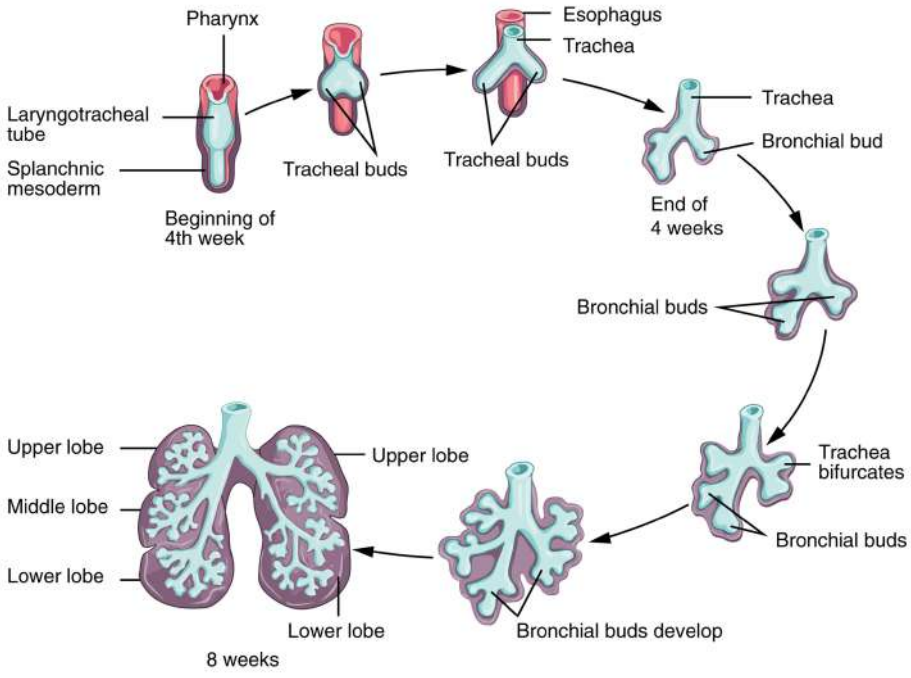


Figure 7.2. *Development of the lower respiratory system.*

Source: By OpenStax College – Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=30148400.

- **Weeks 7–16:** As development moves forward, bronchial buds keep branching until every segmental bronchus has been formed. The diameter of the bronchi's lumens starts increasing at week 13. Respiratory bronchioles begin forming by week 16. Every major lung structure involved in the airway is now present in the fetus.
- **Weeks 16–24:** After the formation of the respiratory bronchioles, the next stage of

development involves the formation of alveolar precursors and ducts as well as extensive vascularization, or the growth of blood vessels. The respiratory bronchioles have formed by week 19. Furthermore, type I and type II pneumocytes are formed by the differentiation of cells lining the respiratory structures. Following differentiation, type II cells begin releasing trace amounts of pulmonary surfactant. Fetal breathing movements may start at week 20.

- **Weeks 24–Term:** From week 24 to term, the respiratory system undergoes significant development and growth. Alveolar precursor development and pulmonary surfactant production increase. Surfactant levels usually become high enough to produce meaningful lung compliance by the eighth month of pregnancy. As the respiratory system grows, the surfaces that will form the respiratory membrane continue to develop. Pulmonary capillaries develop and continue growing, providing a large surface area for gas exchange. The primary turning point in respiratory development occurs around week 28, at which point enough alveolar precursors have developed to allow a premature infant to breathe on its own. Alveoli, however, continue to grow and develop throughout childhood. A full complement of functioning alveoli develops by about age 8.
- **Fetal "Breathing:"** Fetal breathing movements can be seen as early as 20–21 weeks of development, though their exact purpose is still unknown. Muscle contractions during fetal breathing movements result in the inhalation of amniotic fluid and the exhalation of the same fluid along with mucus and pulmonary surfactant. The breathing movements of a fetus are not constant and can alternate between periods of high and low activity. Breathing movements can vary in frequency depending on maternal factors. For instance, hyperglycemia, or elevated blood glucose, can increase respiration rate. On the other hand, hypoglycemia, or low blood sugar, can reduce fetal breathing movements. It is also known that smoking tobacco lowers fetal breathing rates. Fetal breathing may help tone the muscles for breathing after birth. It might also aid in the development and maturation of the alveoli. Breathing movements in fetuses are regarded as an indication of good health.
- **Birth:** Before birth, the lungs are packed with surfactant, mucus, and amniotic fluid. Much of this fluid is expelled from the fetal thoracic cavity as the fetus is compressed and forced through the birth canal. Some fluid remains but is quickly absorbed after birth. Within ten seconds of birth, the first breath is taken, the first breath inflates the lungs and acts as the body's first inspiration. Because pulmonary surfactant lowers the surface tension of the alveoli, it is essential for inflation to happen. At approximately 26 weeks of

pregnancy, severe respiratory distress is common; however, recent medical advancements have improved survival rates. Survival is poor before 26 weeks due to insufficient pulmonary surfactant and underdeveloped gas exchange surfaces.

7.2.1. Differentiation of Respiratory Structures and Establishment of Gas Exchange Function

Intricate processes essential to maintaining life include the differentiation of respiratory structures and the establishment of gas exchange function in the developing respiratory system. These processes result in specialized structures that can help the body and the external environment exchange carbon dioxide and oxygen.

They include a sequence of morphogenetic events and cellular differentiation steps:

1. **Formation of the Respiratory Diverticulum:** The foregut endoderm, a layer of cells in the developing embryo, is where the respiratory system starts to develop during embryogenesis. In humans, the lung bud or respiratory diverticulum is a tiny protrusion that originates from the foregut's ventral wall during the fourth week of pregnancy. This bud forms the first primordium of the respiratory tract and then branches out during morphogenesis to create the complex system of gas exchange units and airways.
2. **Branching Morphogenesis:** A crucial stage in the formation of the respiratory system is known as branching morphogenesis, and it is typified by the repeated branching and elongation of lung bud-derived epithelial tubes. The respiratory tree is a highly branched structure resembling a tree that develops when the lung bud experiences successive bifurcations to form the trachea, bronchi, and bronchioles during branching morphogenesis. Numerous signaling pathways, such as those involving fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and members of the Sonic hedgehog (Shh) pathway, are involved in the precise regulation of branching morphogenesis.
3. **Differentiation of Airway Epithelium:** The epithelial cells lining the developing airways differentiate to take on specialized roles as branching morphogenesis moves forward. Within the airway epithelium, various cell types such as basal cells, secretory cells, and ciliated cells emerge. While secretory cells create mucus to lubricate and shield the surface of the airway, ciliated cells are in charge of producing coordinated movements that push mucus and foreign particles out of the airways. As progenitor cells, basal cells can regenerate other cell types and restore damaged epithelium.
4. **Development of Gas Exchange Units:** The lung bud gives rise to specialized structures known as gas exchange units, or alveoli, where the exchange of carbon dioxide and oxygen takes place, concurrently with airway development. During alveolar development, thin-walled

sacs with a vast capillary network surrounding them form, offering a lot of surface area for effective gas exchange. The primitive epithelium lining the developing lung bud gives way to type I alveolar epithelial cells, which form the thin barrier across which gases are exchanged. Surfactant, a lipoprotein complex secreted by type II alveolar epithelial cells, is what lowers surface tension in the alveoli during exhalation, preventing the alveoli from collapsing and facilitating effective gas exchange.

5. **Establishment of Gas Exchange Function:** In the latter stages of pregnancy and the first few months after delivery, the gas exchange function is established. Fetal lungs are filled with fluid before birth, and the placenta is mainly responsible for gas exchange. But as labor begins and the baby takes its first breaths, several physiological changes take place to help the baby adjust to breathing on air and create a stable pulmonary gas exchange. The absorption of fetal lung fluid, alveolar expansion, and surfactant synthesis and secretion by type II alveolar epithelial cells are some of these alterations. Furthermore, blood flow is redirected to the pulmonary circulation upon closure of fetal shunts like the ductus arteriosus and foramen ovale, enabling oxygenation of blood in the lungs. When combined, these adjustments help the baby adjust to life outside of the uterus and exchange gases efficiently.

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7.2.2. Fetal Lung Development and Adaptations for Postnatal Respiration

The establishment of efficient gas exchange and the transition to postnatal respiration depend on the intricate and dynamic process of fetal lung development. Throughout the course of gestation, a number of morphological, cellular, and physiological changes take place to prepare the lungs for breathing and life outside the uterus.

1. **Embryonic and Pseudoglandular Stages:** The respiratory diverticulum, also known as the lung bud, forms early in embryogenesis from the foregut endoderm, marking the beginning of lung development. The trachea, bronchi, and bronchioles are formed by branching morphogenesis that occurs in the developing lungs during the embryonic and

pseudoglandular stages (up to about 16 weeks gestation in humans). The surrounding mesenchyme gives rise to supporting structures like cartilage, smooth muscle, and connective tissue, while the lung epithelium differentiates into different cell types such as ciliated cells, secretory cells, and basal cells.

2. **Canalicular and Saccular Stages:** In the canalicular stage (approximately 16-28 weeks gestation), further branching of the airways occurs, leading to the formation of respiratory bronchioles and the onset of vascularization. Capillaries invade the developing lung tissue, establishing the pulmonary circulation necessary for gas exchange. Meanwhile, in the saccular stage (approximately 28-36 weeks gestation), the terminal sacs or alveoli begin to emerge, and type I and type II alveolar epithelial cells differentiate. Type II cells produce surfactant, a lipoprotein complex that reduces surface tension within the alveoli, preventing their collapse during exhalation.
3. **Alveolar Stage:** The alveolar stage (approximately 36 weeks gestation to early childhood) is characterized by continued alveolarization and maturation of the lung tissue. Alveolar septa thin and elongate, increasing the surface area available for gas exchange. Surfactant production increases, enhancing lung compliance and reducing the risk of respiratory distress syndrome (RDS) after birth. Lung growth and development continue into early childhood, with alveolar number reaching its peak around 2-3 years of age.
4. **Adaptations for Postnatal Respiration:** The fetal lungs undergo a number of adaptations to support gas exchange after birth and ease the transition to postnatal respiration. One essential adaptation is the absorption of fetal lung fluid, which fills the alveoli and airways during gestation. Hormonal shifts and labor-related mechanical factors encourage the removal of lung fluid from the airspaces prior to birth, which permits lung expansion and air entry during the first breath. Furthermore, when breathing begins, a series of physiological events take place, such as the closure of fetal shunts like the foramen ovale and ductus arteriosus, which reroute blood flow to the pulmonary circulation and improve pulmonary perfusion.

The progressive formation and maturation of the respiratory structures required for postnatal respiration characterize the dynamic process of fetal lung development. The fetal lungs undergo adaptations such as surfactant production and lung fluid clearance to prepare them for the shift to breathe air and the establishment of efficient gas exchange following birth. Understanding fetal lung development and adaptation mechanisms is essential for managing respiratory disorders in neonates and improving outcomes.

7.2.3. Fetal Lung Development

The development of fetal lungs is a carefully planned process that starts early in embryogenesis and moves through several phases to prepare the lungs for postnatal life. A sequence of morphogenetic processes, cellular differentiation, and physiological adaptations

that leads to the formation of the mature respiratory system, capable of maintaining gas exchange after birth. The respiratory diverticulum, also known as the lung bud, forms from the foregut endoderm during the embryonic period, approximately four weeks into a human pregnancy. This initial growth acts as the respiratory tract's primordium and establishes the framework for later branching morphogenesis. The lung bud divides into the trachea, bronchi, and bronchioles in a series of bifurcations during branching morphogenesis. A network of signaling molecules, such as fibroblast growth factors (FGFs), sonic hedgehog (Shh), and bone morphogenetic proteins (BMPs), which coordinate the temporal and spatial patterning of lung development, tightly regulate this process.

The development of specific cell types within the epithelium occurs alongside lung development and the airways. Within the airway epithelium, different cell populations, such as ciliated cells, secretory cells, and basal cells, emerge. Each of these cell populations has a specific function that contributes to respiratory physiology. While secretory cells produce mucus to lubricate and protect the surface of the airways, ciliated cells, for example, produce coordinated movements that drive mucus and foreign particles out of the airways. As progenitor cells, basal cells ensure the preservation of airway integrity and function by regenerating other cell types and mending damaged epithelium.

Concurrently with airway development, the lung bud forms specialized structures called gas exchange units, or alveoli, where carbon dioxide and oxygen are exchanged. The formation of respiratory bronchioles and the appearance of terminal sacs, also known as primitive alveoli, are two hallmarks of the canalicular and saccular stages of alveolar development. Type I and type II alveolar epithelial cells differentiate during the alveolar stage, and alveolar septa thin and lengthen to increase the surface area available for gas exchange. Surfactant, a lipoprotein complex that lowers surface tension in the alveoli and prevents them from collapsing during exhalation, is produced and secreted by type II cells, also referred to as surfactant-producing cells. This process facilitates effective gas exchange.

The lungs undergo vascularization and perfusion during fetal lung development, which is necessary to maintain gas exchange. As the lung tissue develops, capillaries infiltrate it, initiating the pulmonary circulation required for blood oxygenation and carbon dioxide elimination. The optimal gas exchange efficiency in the developing fetus is ensured by the precise coordination of lung epithelial and vascular development, which also guarantees appropriate matching of ventilation and perfusion.

Numerous intrinsic and extrinsic factors, such as genetic programs, maternal-fetal interactions, and environmental cues, influence the development of the fetal lung as gestation progresses. Understanding the mechanisms underlying fetal lung development is crucial for identifying potential therapeutic targets and interventions, as disruptions to these processes can result in congenital lung abnormalities and respiratory disorders. In summary, fetal lung development is intricate and crucial for establishing respiratory function and adapting to life outside the uterus.

7.2.4. Adaptations for Postnatal Respiration

Important physiological changes in the newborn that support efficient breathing and gas exchange during the transition from intrauterine to extrauterine life are known as adaptations for postnatal respiration. A crucial stage of neonatal adaptation is the switch to air breathing, which

necessitates a number of intricate modifications to the respiratory, cardiovascular, and metabolic systems. The removal of fetal lung fluid from the alveoli and airways is one of the most important adaptations for postnatal respiration. The fluid that fills the fetal lungs during gestation is vital to lung development and safeguards the vulnerable respiratory epithelium.

However, the newborn's lungs must quickly clear this fluid after birth to expand and breathe. The onset of the newborn's breathing efforts, the mechanical compression of the chest during vaginal delivery, and hormonal changes linked to labor all play a role in the clearance of fetal lung fluid. These coordinated mechanisms aid in the removal of fluid from the alveoli and airways, enabling the establishment of efficient gas exchange.

The initiation of breathing simultaneously sets off a series of physiological adjustments in the cardiovascular system that enhance oxygen delivery to tissues and maintain pulmonary circulation. Blood flow from the placenta is redirected to the lungs upon closure of fetal shunts like the ductus arteriosus and foramen ovale, which facilitates gas exchange in the pulmonary circulation. Blood in the lungs is better oxygenated when pulmonary vascular resistance decreases, and pulmonary blood flow increases. These modifications promote the oxygenation of systemic arterial blood, ensuring essential organs and tissues receive enough oxygen. Furthermore, the production and secretion of pulmonary surfactant—a lipoprotein complex that lowers surface tension in the alveoli and keeps them from collapsing during exhalation—are necessary for the establishment of efficient gas exchange.

Surfactant production begins in the late stages of fetal lung development and continues into the early postnatal period. Premature babies who are born before surfactant production reaches maturity are susceptible to respiratory distress syndrome (RDS), a potentially fatal illness marked by hypoxemia and alveolar collapse. Exogenous surfactant therapy may be used to enhance lung function and surfactant production in premature infants to improve respiratory outcomes. In addition, the respiratory muscles adjust to sustain respiration and preserve sufficient ventilation. As the main breathing muscle, the diaphragm contracts rhythmically to open the thoracic cavity and lower intrathoracic pressure, which allowing air to enter the lungs. The intercostal and abdominal muscles are examples of additional accessory respiratory muscles that help with inspiration and expiration by expanding the lung volume. For the newborn to breathe and exchange gases efficiently, coordination of these respiratory muscles is necessary.

Additionally, the newborn's respiratory control system develops to regulate breathing and respond to variations in oxygen and carbon dioxide levels. The central chemoreceptors of the brainstem regulate breathing rate and depth in response to variations in blood pH and carbon dioxide levels. Changes in arterial oxygen levels are detected by peripheral chemoreceptors in the aortic arch and carotid bodies, which then provide feedback to control ventilation.

The integration of these brain processes contributes to the preservation of tissue oxygenation levels and the acid-base balance. The physiological alterations required for postnatal respiration are crucial for the newborn's successful transition from intrauterine to extrauterine life, as well as for the establishment of efficient breathing and gas exchange. These adaptations include the elimination of fetal lung fluid, modifications to cardiovascular function, production of pulmonary surfactant, development of respiratory muscles and control systems, and synchronization of respiratory efforts. Optimizing respiratory outcomes in

newborns and managing neonatal respiratory disorders require an understanding of the mechanisms underlying these adaptations.

7.3. Respiratory Anatomy

The exchange of carbon dioxide and oxygen between the body and its surroundings is carried out by the intricate network of organs and structures that makes up the respiratory system. The respiratory tract, which consists of the upper and lower respiratory passages, is at its center. The pharynx, larynx, nose, and nasal cavity are all parts of the upper respiratory tract, while the trachea, bronchi, bronchioles, and lungs make up the lower respiratory tract.

Air primarily enters the respiratory system through the nose and nasal cavity. Mucous membranes with ciliated cells and goblet cells that produce mucus line their interiors. These membranes trap impurities and warm, humidify, and filter incoming air. Olfactory receptors, which are responsible for the sense of smell, are also found in the nasal cavity. Food and air share a common pathway through the pharynx, which allows air to enter the lower respiratory tract. The vocal cords are housed in the larynx, also referred to as the voice box, which is connected to the pharynx and is essential for producing speech as well as protecting the airways. The larynx connects to the trachea, a stiff tube made of cartilaginous rings that offers structural support and prevents collapse during respiration.

Within the lungs, the trachea divides into the left and right primary bronchi, which then branch into smaller bronchi and bronchioles. These airways regulate airflow and remove mucus and debris, as they are surrounded by smooth muscle and lined with ciliated epithelial cells. Gas exchange takes place in groups of tiny air sacs called alveoli where the bronchioles terminate.

The thoracic cavity houses the two cone-shaped lungs, protected by the rib cage. The pleura, a double-layered membrane that surrounds each lung, aids in lowering friction during breathing motions. To accommodate the heart, the left lung has two lobes (upper and lower), while the right lung has three lobes (upper, middle, and lower). A vast network of pulmonary capillaries surrounds the alveoli in the lungs, serving as the site of the exchange of carbon dioxide and oxygen between the blood and the surrounding air.

Diffusion between the surrounding capillary endothelium and the thin alveolar walls facilitates this process, which is referred to as external respiration. While carbon dioxide is exhaled from the body through the alveoli, oxygen is taken up by the bloodstream. The respiratory anatomy consists of many interrelated structures that cooperate to enable gas exchange, which is necessary for both the maintenance of physiological homeostasis and cellular respiration. Every part of the respiratory system, from the upper respiratory passages to the lungs' alveoli, is essential to maintaining effective gas exchange and oxygen delivery to all of the body's tissues. The respiratory system consists of the nose, pharynx (throat), larynx (voice box), trachea (windpipe), bronchi and lungs.

1. **Nose:** It is the only externally visible organ of the respiratory system.

   Nose can be divided into two parts:

   i. **External Nose:** The external nose consists of a framework of bones and hyaline cartilage covered with muscle and skin and lined by a mucous membrane. The frontal bone, nasal bones and maxillae form the bony framework of the external nose. The undersurface of the external

nose has two openings called the external nares or nostrils. Interior to the external nostrils is the nasal vestibule which has coarse hairs that filter out dust particles.

ii. **Internal Nose:** The internal nose is a larger cavity located inferior to the nasal bone and superior to the mouth. Anteriorly it merges with the external nose and posteriorly joins with the pharynx through two openings called internal nares. The space within the internal nose is called the nasal cavity. A vertical partition called the nasal septum divides the nasal cavity into right and left sides. The superior surface of the nasal cavity contains olfactory epithelium, which provides the sense of smell. The nasal cavity is lined internally with a mucous membrane which contains goblet cells and cilia. Goblet cells produce mucous, which moistens the respiratory system and entraps dust particles. Cilia cells move mucous and dust particles toward the oral cavity so that they can be swallowed or spit out.

The nose has three functions:

a. Warming, moistening, and filtering incoming air;

b. Detecting olfactory stimuli;

c. Modifying speech vibrations.

2. **Pharynx:** The internal nares mark the beginning of the funnel-shaped tube that forms the pharynx, or throat, and ends at the larynx, or voice box. The pharynx is situated anteriorly to the cervical vertebrae, superior to the larynx, and posterior to the nasal and oral cavities. The tonsils, which are involved in immunological responses against foreign invaders, are housed in the pharynx, which also serves as a passageway for food and air and a resonating chamber for speech sounds.

   The pharynx can be divided into three anatomical regions:

   i. **Nasopharynx:** The superior portion of the pharynx extends from internal nares to the soft palate. It has respiratory function only.

   ii. **Oropharynx:** The middle part of the pharynx which extends from the soft palate to the hyoid bone. It has both respiratory and digestive functions as air, food and liquid pass through it.

   iii. **Laryngopharynx:** The inferior portion of the pharynx. It starts from the hyoid bone and connects with the esophagus and larynx. It has both respiratory and digestive functions.

3. **Larynx:** The larynx or voice box is a short passageway that connects the laryngopharynx with the trachea. It lies in the midline of the neck anterior to the esophagus. It is made up of 9 cartilages.

   One of the cartilages, called epiglottis extends superiorly and forms a lid over the trachea during swallowing so that liquid and food do not enter the windpipe. The

larynx acts as a passageway and produces sound by modifying air vibrations (Figure 7.3).

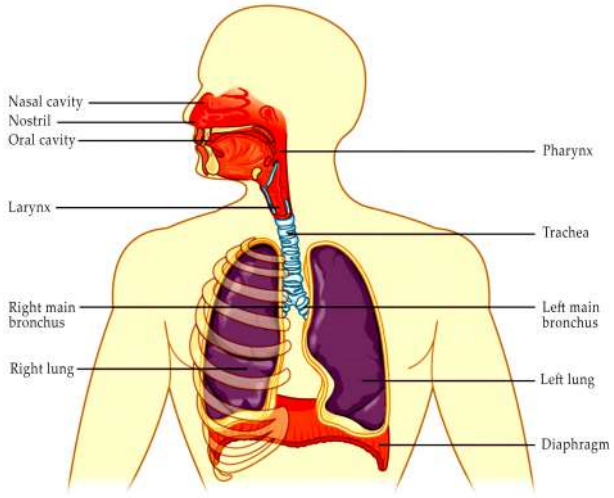

Figure 7.3. *Respiratory system.*

Source: https://courses.lumenlearning.com/suny-ap2/chapter/organs-and-structures-of-the-respiratory-system/.

4. **Trachea:** The trachea or windpipe, is a tubular passageway for air, approximately 12 cm (5 in.) long and 2.5 cm (1 in.) in diameter. It is located anterior to the esophagus and extends from the larynx to the superior border of the fifth thoracic vertebra (T5), where it divides into right and left primary bronchi.

   Goblet cells and ciliated columnar cells make up the tracheal mucosa, which shields the airway from dust. The trachea consists of 16–20 incomplete horizontal rings of hyaline cartilage, stacked and joined by dense connective tissue. These C-shaped rings are spanned by a fibro-muscular membrane on the open side, which faces posteriorly toward the esophagus. Maintaining effective airflow depends on the ability of the trachealis muscle to slightly alter the trachea's diameter during inhalation and exhalation. The semi-rigid support provided by the solid C-shaped cartilage rings prevents the tracheal wall from collapsing inward and obstructing the airway, particularly during inhalation.

5. **Bronchi:** The trachea splits into a left primary bronchus that goes into the left lung and a right primary bronchus that goes into the right lung at the superior border of the fifth thoracic vertebra. Similar to the trachea, the primary bronchi are lined by pseudostratified ciliated columnar epithelium and have incomplete cartilage rings. The main bronchi split as they enter the lungs, producing smaller bronchi called secondary (lobar) bronchi, one for each lung lobe. There are three lobes in the right lung and two in the left. The secondary bronchi keep branching, creating tertiary (segmental) bronchi, which are even smaller bronchi that split into bronchioles. Repeatedly, bronchioles split into smaller tubes known as terminal bronchioles. The bronchial tree is the term for this broad branching that emerges from the trachea and has an inverted tree-like appearance. Respiratory bronchioles are the microscopic branches that split off from terminal bronchioles. Respiratory bronchioles lead to alveolar ducts. Alveoli and alveolar sacs abound around the alveolar ducts. Pulmonary capillaries are a network of blood vessels located

around the alveoli. Diffusion across the alveolar and capillary walls facilitates the exchange of O2 and CO2 between the blood and the air spaces in the lungs.

6. **Lungs:** Within the thoracic cavity are two conical-shaped organs called the lungs. The heart and other structures in the mediastinum divide them from one another. The pleural membrane, a double-layered membrane, encloses and protects each lung. The pleural cavity is the small space between the two layers of the pleural membrane. The pleural cavity contains a small amount of lubricating fluid. The pleural fluid facilitates easy passage of the membranes over one another during breathing by lowering friction between them. The lungs rest against the ribs on both the anterior and posterior surfaces, extending from the diaphragm to a point just superior to the clavicles. The base, a broad inferior portion of the lung, overlies the diaphragm. The term "apex" refers to the lung's narrow upper segment. The hilum, a region on the medial surface of each lung, is the entrance and exit point for bronchi, pulmonary blood vessels, lymphatic vessels, and nerves. The cardiac notch, a concavity in the middle of the left lung where the heart rests, is also present. The fissures further divide each lung into lobes. The superior, middle, and inferior lobes of the right lung are separated by an oblique and horizontal fissure. An oblique fissure separates the left lung into the superior and inferior lobes. Each lobe is composed of many tiny lobules.
7. **Respiration:** The process of gas exchange in the body is called respiration. It has three basic steps:
    - **Pulmonary Ventilation or Breathing:** The inhalation (inflow) and exhalation (outflow) of air and involves the exchange of air between the atmosphere and the alveoli of the lungs.
    - **External (Pulmonary) Respiration:** The exchange of gases between the alveoli of the lungs and the blood in pulmonary capillaries across the respiratory membrane. In this process, pulmonary capillary blood gains O2 and loses CO2.
    - **Internal (Tissue) Respiration:** The exchange of gases between blood in systemic capillaries and tissue cells. In this step, the blood loses O2 and gains CO2.

Within cells, the metabolic reactions that consume O2 and produce CO2 during the production of ATP are termed cellular respiration.

7.3.1. Pulmonary Ventilation

Air enters the lungs when the air pressure within the lungs is lower than the air pressure outside the body. When the air pressure inside the lungs is higher than the air pressure outside the atmosphere, air moves out of the lungs.

It involves two steps:

- **Inhalation:** Or inspiration, is the process of breathing in. The air pressure inside the lungs is equal to

that of the atmosphere just before each inhalation; at sea level, this equals approximately 760 mmHg or 1 atmosphere (atm). The pressure inside the alveoli must drop below the atmospheric pressure for air to enter the lungs. This requires enlarging the lungs. The lungs must expand for inhalation to take place, which raises lung volume and lowers lung pressure to below atmospheric pressure (758 mmHg). The diaphragm, a dome-shaped skeletal muscle that forms the floor of the thoracic cavity, is the most significant muscle used during inhalation. When the diaphragm contracts, it flattens and lowers its dome. This increases the vertical diameter of the thoracic cavity. About 75% of the air that enters the lungs during quiet breathing is caused by the diaphragm contracting. The external intercostals are the other muscles involved in inhalation. These muscles contract, causing the ribs to rise and increasing the chest cavity's lateral and anteroposterior diameters.

- **Exhalation:** Also known as breathing out, is a result of a pressure differential. When exhaling, the pressure in the lungs exceeds the atmospheric pressure. The process of exhaling normally involves no muscular contractions, making it a passive action. Exhalation results from the elastic recoil of the lungs and chest wall, which naturally want to return to their unstretched state. When the inspiratory muscles relax, exhalation begins. Due to its elasticity, the diaphragm's dome moves superiorly as it relaxes. The ribs are depressed as the external intercostal muscles relax. These movements reduce the thoracic cavity's anteroposterior, lateral, and vertical diameters, thereby reducing lung volume. The alveolar pressure then rises to roughly 762 mmHg. The air then moves from the alveolar region of higher pressure to the atmospheric region of lower pressure (Figure 7.4).

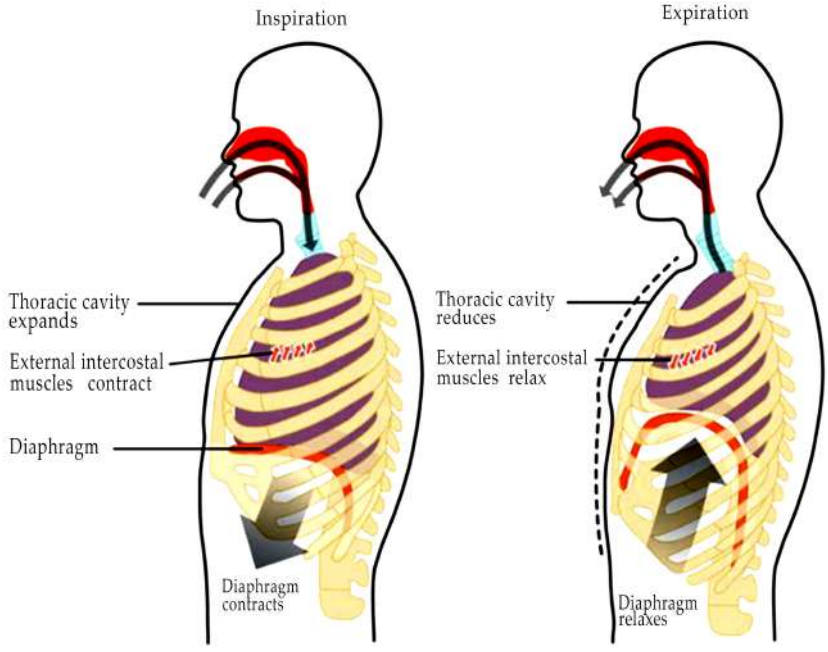

Figure 7.4. *Inspiration and expiration.*

Source: https://courses.lumenlearning.com/suny-ap2/chapter/the-process-of-breathing-no-content/.

7.3.2. Lung Volumes and Capacities

While at rest, a healthy adult averages 12 breaths a minute. The apparatus used to measure the volume of air exchanged and respiration rate is called a spirometer or respirometer.

The record is called a spirogram:

- **Tidal Volume (VT):** The volume of air that moves in and comes out with each inhalation and exhalation. It is approximately 500 ml.
- **Minute Ventilation (MV):** The total volume of air inhaled and exhaled each minute. It is calculated as respiratory rate multiplied by tidal volume: MV = 12 breaths/min X 500 mL/breath = 6 liters/min
- **Inspiratory Reserve Volume:** The additional amount of air other than 500 ml that can be inhaled with a deep breath. It is approximately 3,100 ml in males and 1,900 ml in females.
- **Expiratory Reserve Volume:** The volume of air in addition to 500 ml that can be expelled by a forceful exhalation after a normal inhalation. It is approximately 1,200 ml in males and 700 ml in females.
- **Forced Expiratory Volume in 1 Second (FEV1.0):** The volume of air that can be exhaled from the lung in 1 second with maximal effort after a maximal inhalation.
- **Residual Volume:** Even after a strong exhalation, some volume of air remains inside the lungs which cannot be exhaled out. This is called the residual volume, and it cannot be measured with a spirometer. It is approximately 1,200 ml in males and 1,100 ml in females.
- **Inspiratory Capacity:** The sum of tidal volume and inspiratory reserve volume. It is 3,600 ml in males and 2,400 ml in females.
- **Functional Residual Volume:** The sum of residual volume and expiratory reserve volume. It is 2,400 ml in males and 1,800 ml in females.
- **Vital Capacity:** The sum of inspiratory reserve volume, tidal volume, and expiratory reserve volume. It is approximately 4,800 ml in males and 3,100 ml in females.
- **Total Lung Capacity:** The sum of vital capacity and residual volume; 6,000 ml in males and 4,200 ml in females.

7.3.3. Regulation of Respiration

Humans can significantly maintain and regulate the respiratory rhythm to meet the needs of various body tissues. The neural system is responsible for this. This regulation is mainly carried out by a specialized center called the respiratory rhythm center, which is located in the brain's medulla. The respiratory rhythm center's activities can be modulated by the pneumotaxic center, a different brain region located in the pons area. This center's neural signal has the ability to shorten inspiration times, which changes breathing rate. Adjacent to the rhythm center is a chemosensitive region that is extremely sensitive to hydrogen ions and CO2. An increase in these substances may trigger this center, which may then instruct the rhythm center to modify the respiratory process to remove the substances. Aortic arch and carotid artery receptors are also capable of detecting variations in CO2 and H+ concentrations and informing the rhythm center of the need for corrective action. Oxygen has very little effect on how the respiratory rhythm is regulated.

The physiological process of regulating respiration is intricate and involves the synchronization of various systems to ensure sufficient oxygenation of tissues and elimination of carbon dioxide from the body. This regulation involves involuntary mechanisms managed by the respiratory centers of the brainstem and voluntary mechanisms influenced by conscious control and feedback from peripheral receptors.

1. **Central Respiratory Centers:** The primary respiratory centers responsible for regulating breathing are located in the medulla oblongata and pons of the brainstem. The medullary respiratory center consists of the dorsal respiratory group (DRG) and ventral respiratory group (VRG). The DRG primarily controls inspiration, while the VRG is involved in both inspiration and expiration. The pontine respiratory centers, including the pontine respiratory group (PRG) and pneumotaxic center, provide modulatory input to regulate respiratory rhythm and pattern.
2. **Chemoreceptors:** Peripheral chemoreceptors located in the carotid bodies and aortic bodies, as well as central chemoreceptors located in the medulla, monitor changes in blood pH, carbon dioxide (CO2), and oxygen (O2) levels. Elevated levels of CO2 and decreased pH (acidosis) stimulate increased ventilation, while decreased CO2 levels and increased pH (alkalosis) suppress ventilation. Low arterial oxygen levels (hypoxemia) also stimulate ventilation, primarily through the peripheral chemoreceptors.
3. **Lung Stretch Receptors:** Lung stretch receptors, or pulmonary stretch receptors, are located in the smooth muscle of the airways and respond to changes in lung volume and inflation. Activation of these receptors during lung inflation inhibits further inspiration, preventing overinflation of the lungs. This protective mechanism is known as the Hering-Breuer reflex and helps regulate tidal volume and respiratory rate.
4. **Proprioceptors:** Located in skeletal muscles and joints provide feedback on body movement and activity levels to the respiratory centers. Increased physical activity and muscle exertion stimulate ventilation to meet the increased metabolic demand for oxygen and removal of CO2 produced during cellular respiration.
5. **Voluntary Control:** Conscious control over breathing patterns and depth is exerted through higher brain centers, including the cerebral cortex. While breathing is predominantly under involuntary control, voluntary adjustments can be made, such as holding one's breath (apnea) or altering breathing rate and depth. Voluntary control allows for adaptations to specific activities, such as breath-holding during swimming or adjusting breathing patterns during speech or singing.

In general, a complex interaction between proprioceptors, lung stretch receptors, peripheral chemoreceptors, central respiratory centers, and voluntary control mechanisms governs

respiration. To meet the body's metabolic needs and preserve physiological homeostasis, these regulatory mechanisms make sure that blood gas levels, breathing rhythm, and ventilation are maintained at the proper levels. It is crucial to comprehend these regulatory processes because dysregulation of respiratory control can result in respiratory disorders like hypo- or hyperventilation and impair oxygen delivery to tissues.

7.3.4. Disorders of Respiratory System

Many conditions can affect the organs and tissues of the respiratory system. Some conditions develop due to inhaled irritants, including viruses or bacteria causing infections. Others occur as a result of disease or getting older.

Conditions that can cause inflammation (swelling, irritation, and pain) or affect the respiratory system include:

- **Allergies:** Inhaling proteins, such as dust, mold, and pollen, can cause respiratory allergies in some people. These proteins can cause inflammation in your airways.
- **Asthma:** A chronic (long-term) disorder, asthma causes inflammation in the airways that can make breathing difficult.
- **Infection:** Infections can lead to pneumonia (inflammation of the lungs) or bronchitis (inflammation of the bronchial tubes). Common respiratory infections include the flu (influenza) or the common cold.
- **Disease:** Respiratory diseases include lung cancer, chronic obstructive pulmonary disease (COPD), pulmonary edema, pulmonary fibrosis, sarcoidosis, cystic fibrosis etc. These illnesses can harm the respiratory system's ability to deliver oxygen throughout the body and filter out waste gases.
- **Aging:** Lung capacity decreases as you get older.
- **Damage:** Damage to the respiratory system can cause breathing problems.

7.4. Gas Exchange in the Lungs

The physiological process of gas exchange in the lungs is essential for cellular respiration and the maintenance of the body's acid-base balance. It permits the uptake of oxygen (O2) from inhaled air and the removal of carbon dioxide (CO2) from the bloodstream. The respiratory membrane enables the diffusion of gases between the pulmonary capillary blood and the alveolar air within the pulmonary alveoli, which are tiny air sacs grouped at the distal ends of the respiratory bronchioles. This complex process takes place within these air sacs.

The respiratory membrane is a thin, delicate interface that forms between the vast network of pulmonary capillaries surrounding the pulmonary alveoli. The respiratory membrane consists of three layers: the alveolar epithelium, the interstitial space with connective tissue and basement membranes, and the capillary endothelium. Rapid gas exchange is made possible by the respiratory membrane's thinness and large surface area, which maximize the area of contact between pulmonary capillary blood and alveolar air and reduce the diffusion distance.

Several physiological factors affect gas exchange during external respiration, which is the process by which carbon dioxide is released from the bloodstream into the alveoli

and oxygen is absorbed into the bloodstream. First, partial pressure of oxygen, or PO2, the difference in partial pressure between alveolar and capillary oxygen, causes oxygen to diffuse from the alveolar air across the respiratory membrane and into the pulmonary capillary blood. After returning via the pulmonary veins to the heart, oxygenated blood is pumped to the systemic circulation, where it is distributed to all of the body's tissues and organs. Due to the partial pressure differential between capillary and alveolar carbon dioxide (also known as the partial pressure of carbon dioxide, or PCO2), carbon dioxide diffuses from the pulmonary capillary blood across the respiratory membrane and into the alveoli. During expiration, carbon dioxide is then exhaled from the lungs. The elimination of carbon dioxide from the bloodstream contributes to the maintenance of the acid-base balance, supports cellular activity, and helps control blood pH by preventing the accumulation of acidic metabolic byproducts.

The surface area and thickness of the respiratory membrane, as well as the perfusion of pulmonary capillaries and alveolar ventilation, all affect how efficiently gases are exchanged in the lungs. Any interference with these processes, such as diseases of the lungs that impact pulmonary circulation or alveolar integrity, can impede gas exchange and worsen respiratory function. Diseases like pulmonary edema, pulmonary embolism, and emphysema can limit the surface area available for gas exchange or obstruct blood flow through the pulmonary vasculature, which can result in hypercapnia (high blood carbon dioxide levels) or hypoxemia (low blood oxygen levels).

Gas exchange in the lungs is a basic physiological function necessary to ensure tissues receive enough oxygen and eliminate carbon dioxide from the blood. Efficient gas exchange supports cellular respiration and overall physiological function. It is ensured by the highly specialized structure of the respiratory membrane and the precise regulation of ventilation and perfusion. Understanding the principles of gas exchange in the lungs is essential for identifying and treating respiratory conditions and enhancing respiratory well-being.

The respiratory system regulates blood pH and facilitates gas exchange to maintain homeostasis. The lungs carry out gas exchange by removing carbon dioxide, a waste product released during cellular respiration. Through the lungs, the body absorbs oxygen required for cellular respiration as carbon dioxide leaves. The body uses ATP, which is produced during cellular respiration, to power a variety of processes, including muscle contraction and nerve transmission. A shortage of oxygen has a variety of negative effects on brain activity, judgment, and other areas.

7.4.1. External Respiration

External respiration is the exchange of gas between the air in the alveoli and the blood within the pulmonary capillaries. A normal respiratory rate is 12-25 breaths per minute. In external respiration, gases diffuse in either direction across the walls of the alveoli. Oxygen diffuses from the air into the blood and carbon dioxide diffuses out of the blood into the air. Most of the carbon dioxide is carried to the lungs in plasma as bicarbonate ions ($HCO3^-$). When blood enters the pulmonary capillaries, the bicarbonate ions and hydrogen ions are converted to carbonic acid (H_2CO_3) and then back into carbon dioxide (CO_2) and water. This chemical reaction also uses hydrogen ions. The removal of these ions gives the blood a more neutral pH, allowing hemoglobin to bind up more oxygen. Deoxygenated blood, also known as "blue blood," coming from the pulmonary arteries, generally has an oxygen partial pressure (pO2) of 40 mmHg and a carbon dioxide partial pressure (pCO2) of 45 mmHg. Oxygenated blood

leaving the lungs via the pulmonary veins has an oxygen partial pressure (pO2) of 100 mmHg and a carbon dioxide partial pressure (pCO2) of 40 mmHg. It should be noted that alveolar pO2 is 105 mm Hg, and not 100 mmHg. The reason pulmonary venous return blood has a lower-than-expected pO2 can be explained by a ventilation-perfusion mismatch.

7.4.2. Internal Respiration

Internal respiration is the exchanging of gases at the cellular level.

1. **The Passage Way from the Trachea to the Bronchioles:** At the lower end of the trachea, it divides into two directions, forming the right and left primary bronchi. This division point is known as the carina, a keel-shaped cartilage plate. This marks the beginning of the Bronchial Tree, a system of respiratory tubes that progressively split into smaller tubes within the lungs.
2. **Right and Left Lungs:** The right primary bronchus is the first part we encounter. It then divides into the lobar (secondary) and segmental (tertiary) bronchi, and finally, the bronchioles, which are lined by simple cuboidal epithelium and have little cartilage. Pseudostratified ciliated columnar epithelium lines the bronchi. Because of the vertical structure, objects will probably lodge here at the intersection of the Right Primary Bronchus and the Carina. Things tend to fall into it, whereas objects would find it difficult to lodge in the Left Primary Bronchus due to its more curved shape.

The trachea and heart are connected to the lungs by anatomical features known as the roots of the lungs. The bronchi, pulmonary vessels, bronchial vessels, lymphatic vessels, and nerves are the roots of the lungs. The hilus of the lung, which is the depression on the medial surface of the lung that serves as the opening for the bronchus, blood vessels, and nerves, is where these structures enter and exit the body. Numerous respiratory bronchioles are connected to terminal bronchioles, which progress into alveolar ducts and eventually form alveolar sacs. Every bronchiole ends in an extended area that is encircled by numerous alveoli, which are blood capillaries that enclose air sacs. Alveolar Macrophages are also present there; they consume any microorganisms that make it into the alveoli. The pulmonary alveoli are microscopic, membranous air sacs found within the lungs that are only visible under a microscope. They serve as both the units of the respiratory system and the site of the circulatory system gas exchange.

7.5. Transport of Gases in the Blood

Before entering the capillaries, oxygen must diffuse from the alveolus. Because the capillaries are permeable to oxygen, it can accomplish this. Approximately 5% of the oxygen will dissolve in the blood plasma once it enters the capillary. Red blood cells bind to the other oxygen. The oxygen-carrying protein hemoglobin is found in red blood cells. Hemoglobin-containing blood can carry 26 times the amount of oxygen compared to plasma that lacks the protein. Without hemoglobin, our bodies would have to work much harder to pump more blood to meet our cells' oxygen needs. It combines with hemoglobin to form oxyhemoglobin after diffusing through the respiratory membrane. The oxygen-carrying blood is now circulated throughout the body by the heart. Blood carries

oxygen into arteries, arterioles, and finally, capillaries, where it is close to bodily cells. Now that the temperature and pH are different—warmer and more acidic than in the lungs—and that the cells are under pressure, the hemoglobin will release its oxygen and diffuse to the cells for cellular respiration, also known as aerobic respiration. Moving energy from one chemical form (glucose) to another (ATP) is known as cellular respiration because ATP is needed by all cells for all metabolic processes. The mitochondria are where carbon dioxide is created and oxygen is consumed in cells. At the end of the electron transport chain, oxygen is created when it reacts with hydrogen ions to form water. Carbon dioxide is released by cells during the breakdown of glucose's carbon molecules. Because body cells have higher levels of carbon dioxide than blood, each one diffuses carbon dioxide into neighboring capillaries. The majority of the carbon dioxide in the capillaries enters the red blood cells where it combines with water to form carbonic acid. Some of the carbon dioxide is absorbed by hemoglobin and some is dissolved in plasma. It makes its way to the capillaries encircling the lung, where it is reverted to carbon dioxide by a water molecule that has left. After that, it goes into the lungs and is exhaled into the atmosphere.

The process of respiration, or gas exchange, is the other main function of the lungs. The purpose of respiration is to remove carbon dioxide from the body, which is a waste product of cellular respiration, and to supply oxygen for body cells to use during cellular respiration. Both oxygen and carbon dioxide must be moved between the internal and external respiration sites for the exchange to take place. Both gases need a specific transport system in order for the majority of the gas molecules to be transferred between the lungs and other tissues, even though carbon dioxide is more soluble in blood than oxygen.

7.5.1. Oxygen Transport in the Blood

A vital mechanism that guarantees the transfer of oxygen (O2) from the lungs to tissues throughout the body—where it is necessary for energy production and cellular respiration—is oxygen transport in the blood. Hemoglobin, a protein present in red blood cells, binds oxygen during this process, allowing oxygenated blood to circulate throughout the body. When oxygen is inhaled, it diffuses across the respiratory membrane and enters the alveolar capillaries, where it binds to hemoglobin molecules in red blood cells. Four subunits make up the tetrameric protein hemoglobin, and each one has an iron (Fe) atom that can attach itself to oxygen molecules. Up to four oxygen molecules can be bound by a single hemoglobin molecule to form oxyhemoglobin (HbO2).

The oxygen-hemoglobin dissociation curve, which depicts the relationship between the saturation of oxygen (SaO2) in hemoglobin and the partial pressure of oxygen (pO2) in the blood, facilitates the binding of oxygen to hemoglobin. Hemoglobin shows a strong affinity for oxygen at higher pO2 levels, such as those found in the lungs, and becomes saturated with oxygen (oxyhemoglobin). As oxygen is delivered to tissues by the systemic circulation and blood, hemoglobin releases oxygen molecules and becomes deoxygenated (deoxyhemoglobin) when pO2 falls.

The partial pressure of oxygen, pH, temperature, and the amount of carbon dioxide (CO2) in the blood all have an impact on how much oxygen hemoglobin can carry. The oxygen-hemoglobin dissociation curve shifts to the left in response to changes in temperature, CO2 concentration, and pH (alkalosis). This increases hemoglobin's affinity for oxygen and improves oxygen uptake in the lungs. On the other hand, lowering the pH (acidosis), raising the temperature, and increasing the

CO2 concentration cause the curve to move to the right, decreasing hemoglobin's affinity for oxygen and encouraging the release of oxygen into the tissues.

A tiny amount of oxygen is dissolved directly in the plasma, mostly as molecular oxygen (O2), in addition to binding to hemoglobin. While dissolved oxygen makes up only a small portion of the total oxygen transport, it is essential for preserving the partial pressure gradient that allows oxygen to diffuse into tissues. After blood has been oxygenated, the heart pumps it through the arteries to the body's tissues and organs. From the capillaries, oxygen diffuses into the tissues, where it is utilized by the cells for ATP synthesis and oxidative metabolism. The cycle of oxygen transport in the blood is completed when deoxygenated blood is pumped back to the heart via the venous system and reoxygenated in the lungs.

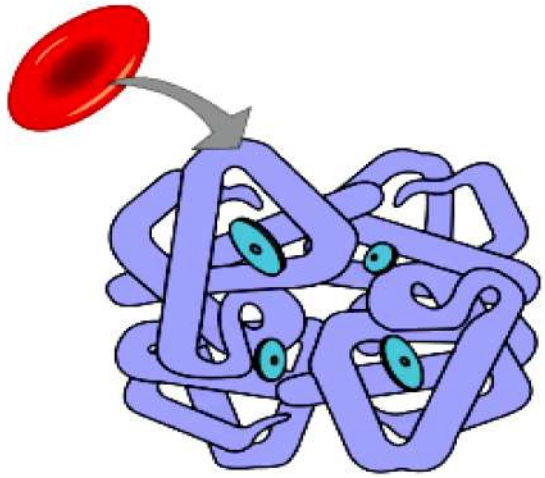

Figure 7.5. *Hemoglobin consists of four subunits, each of which contains one molecule of iron.*

Source: https://s3-us-west-2.amazonaws.com/courses-images-archive-read-only/wp-content/uploads/sites/403/2015/05/21032107/Screen-Shot-2015-05-21-at-12.19.07-PM-300x257.png.

The binding of oxygen to hemoglobin in red blood cells and the movement of oxygenated blood through the systemic circulation facilitate the transport of oxygen in the blood. This procedure guarantees that oxygen reaches tissues, where it is necessary for metabolic and cellular respiration. The diagnosis and treatment of respiratory and cardiovascular diseases, as well as the optimization of oxygen delivery to tissues in a variety of physiological and pathological conditions, depend heavily on our understanding of the mechanisms underlying oxygen transport (Figure 7.5).

You may remember that oxygen is not very soluble in liquids, despite the fact that oxygen is carried by blood. Only around 1% and a half of the total amount of oxygen is dissolved in the blood and carried through the bloodstream. A specialized transport system that depends on erythrocytes, or red blood cells, transports most oxygen molecules from the lungs to the body's tissues. Hemoglobin, a metalloprotein found in erythrocytes, is responsible for attaching oxygen molecules to the erythrocyte (Figure 7.3). Heme is the iron-containing part of hemoglobin, and it is the heme that binds oxygen. Because each erythrocyte contains four iron ions, it can carry up to four molecules of oxygen. Hemoglobin-bound oxygen diffuses into red blood cells as it passes from the alveolus to the capillary through the respiratory membrane. Oxyhemoglobin (Hb–O2), the end product formed when oxygen binds to hemoglobin, is produced by the following reversible chemical reaction. The bright red color of oxygenated blood is attributed to the molecule known as oxyhemoglobin.

$$Hb + O_2 \leftrightarrow Hb - O_2$$

In this formula, Hb represents reduced hemoglobin, that is, hemoglobin that does not have oxygen bound to it. There are multiple factors involved in how readily heme binds to

and dissociates from oxygen, which will be discussed in the subsequent sections.

7.5.2. Function of Hemoglobin

Subunits, a type of protein structure known as a quaternary structure, make up hemoglobin. An iron atom is covalently bound to the heme in the center of each of the four subunits that make up hemoglobin, arranging them in a ring-like pattern. Hemoglobin undergoes a conformational change upon binding of the first oxygen molecule, which facilitates the easier binding of the subsequent oxygen molecules. Up until all four heme sites are occupied by oxygen, the binding of one oxygen molecule helps the binding of the subsequent molecule. The opposite also happens: The subsequent oxygen molecule dissociates more easily after the initial oxygen molecule dissociates and is "dropped off" at the tissues. Hemoglobin is considered saturated when all four heme sites are occupied. Hemoglobin is deemed partially saturated when one to three heme sites are occupied. Hemoglobin saturation is therefore defined as the percentage of available heme units that are bound to oxygen at a given time when looking at the blood as a whole. When the body's erythrocytes have 100% hemoglobin saturation, all of their heme units are bound to oxygen. Hemoglobin saturation normally ranges from 95% to 99% in a healthy person with normal hemoglobin levels.

7.5.3. Oxygen Dissociation from Hemoglobin

One important mechanism that controls the release of oxygen (O2) to tissues according to their metabolic needs is the oxygen dissociation from hemoglobin. The oxygen-hemoglobin dissociation curve, which illustrates the connection between blood oxygen partial pressure (pO2) and hemoglobin saturation with oxygen (SaO2), controls this process. Hemoglobin shows a strong affinity for oxygen in the lungs, where the partial pressure of oxygen (pO2) is high. This leads to the maximum saturation of hemoglobin with oxygen, or oxyhemoglobin. This guarantees effective uptake of oxygen in the lungs, where it combines with hemoglobin in red blood cells and diffuses from the alveoli into the pulmonary capillaries.

Oxygen is released from hemoglobin to tissues with lower pO2 levels as oxygenated blood travels throughout the body. The oxygen-hemoglobin dissociation curve shows that at lower PO2 levels, oxygen unloading occurs more easily, facilitating effective oxygen delivery to metabolically active tissues. This phenomenon is referred to as the Bohr effect, and it occurs when the blood's concentration of carbon dioxide (CO2) rises, temperature rises, or the pH falls (acidosis). On the other hand, conditions like low CO2 concentration, elevated pH (alkalosis), and lowered temperature improve hemoglobin's affinity for oxygen, which lowers the amount of oxygen released into tissues. The cooperative binding behavior wherein the binding of one oxygen molecule to hemoglobin increases the affinity of the remaining binding sites for oxygen is reflected in the sigmoidal shape of the oxygen-hemoglobin dissociation curve. Over a broad range of oxygen tensions, this cooperative binding enables quick and effective oxygen uptake and release, guaranteeing sufficient oxygen delivery to tissues.

The oxygen-hemoglobin dissociation curve controls the dynamic process of oxygen dissociation from hemoglobin, which is impacted by temperature, CO2 concentration, pH, and other variables. This procedure supports cellular respiration and physiological function throughout the body by ensuring that tissues receive the optimal amount of oxygen based on their metabolic needs. For an understanding of respiratory physiology and the control of oxygen transport in health and disease, one must grasp the mechanisms behind oxygen dissociation from

hemoglobin. An essential component of oxygen binding to and dissociation from heme is partial pressure. A graph that illustrates the relationship between partial pressure and oxygen's binding to heme and subsequent dissociation from heme is called an oxygen-hemoglobin dissociation curve (Figure 7.5). Keep in mind that gases move from a higher partial pressure region to a lower partial pressure region. Furthermore, the greater the number of bound oxygen molecules, the greater the affinity of an oxygen molecule for heme. Therefore, a proportionately larger number of oxygen molecules are bound by heme in the oxygen–hemoglobin saturation curve as the partial pressure of oxygen increases. The oxygen–hemoglobin saturation/dissociation curve predictably demonstrates that less oxygen molecules are bound to heme the lower the partial pressure of oxygen. Therefore, both the degree of oxygen binding to heme at the location of the respiratory membrane and the degree of oxygen dissociation from heme at the location of body tissues are significantly influenced by the partial pressure of oxygen (Figure 7.6).

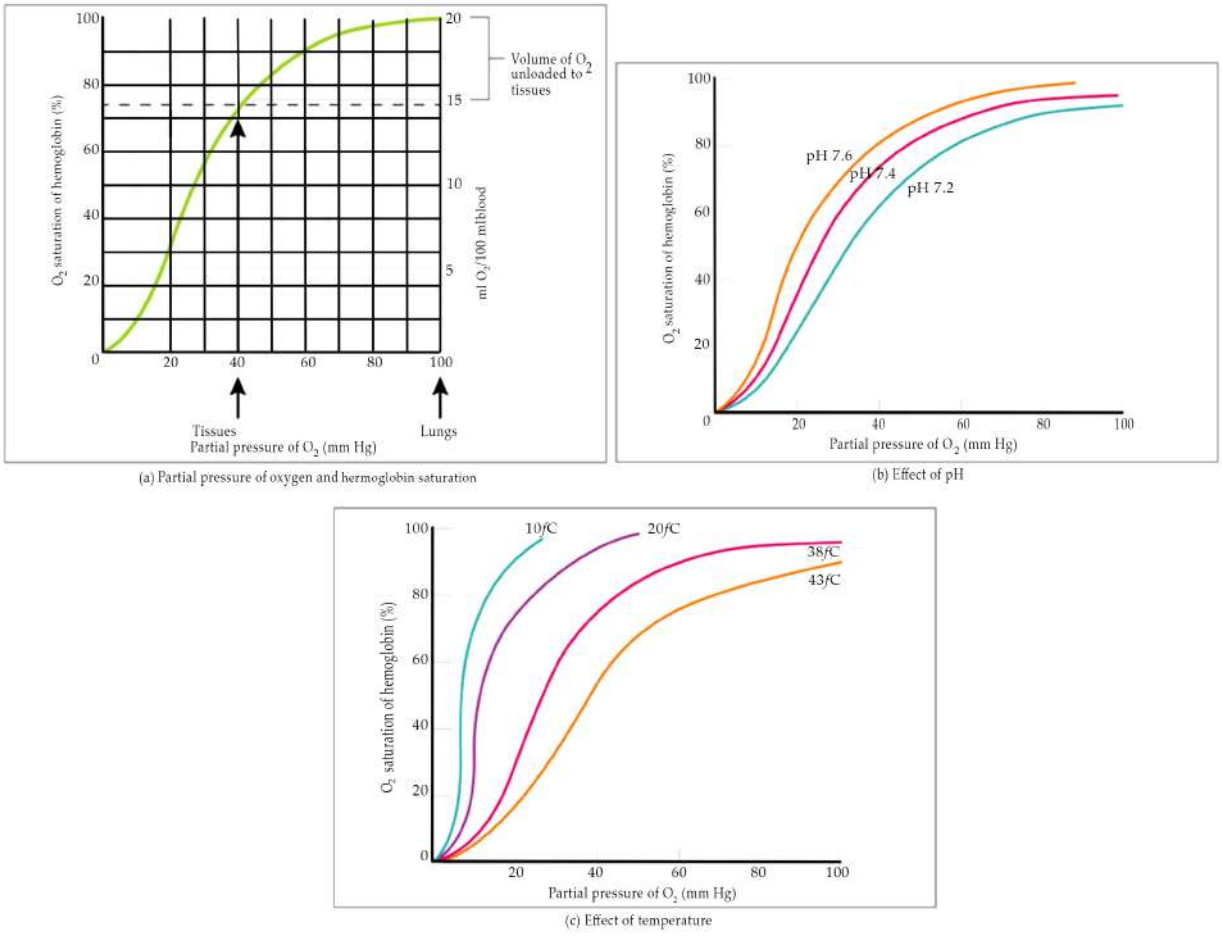

Figure 7.6. *The oxygen-hemoglobin dissociation curve.*

Source: https://bio.libretexts.org/@api/deki/files/25470/2323_Oxygen-hemoglobin_Dissociation-1024x782.jpg?revision=1.

Because some tissues have a higher metabolic rate than others, this is significant. Muscles and other highly active tissues quickly use oxygen to make ATP, bringing the partial pressure of oxygen in the tissue down to around 20 mm Hg. The difference between the two becomes fairly high, about 80 mm Hg because the partial pressure of oxygen inside capillaries is approximately 100 mm Hg. More oxygen molecules separate from hemoglobin and enter the tissues as a result. Conversely, tissues with lower metabolic rates, like adipose (body fat), have the opposite effect. Since these cells use less oxygen, the partial pressure of oxygen in these tissues stays relatively high, which prevents as many oxygen molecules from separating from hemoglobin and penetrating the interstitial fluid within the tissue.

Despite being considered deoxygenated, venous blood still contains some oxygen bound to hemoglobin in its red blood cells. This creates a reserve of oxygen that can be drawn upon in the event that tissues require an increase in oxygen. The saturation/dissociation curve of oxygen-hemoglobin is influenced by factors other than partial pressure. For instance, a greater temperature encourages hemoglobin and oxygen to separate more quickly, whereas a lower temperature prevents this from happening (*see* Figure 7.4(b)). The human body controls its temperature very carefully, so this element might not have an impact on how gases are exchanged throughout the body. Highly active tissues are an exception to this rule, as they may release more energy than they give off as heat. Because of this, oxygen and hemoglobin separate easily, which serves as a mechanism to increase the amount of oxygen that reaches active tissues.

Some hormones, including growth hormone, epinephrine, thyroid hormones, and androgens, can alter the oxygen-hemoglobin saturation/disassociation curve by encouraging erythrocytes to produce a substance known as 2,3-bisphosphoglycerate (BPG). Glycolysis produces BPG as a byproduct. Since erythrocytes lack mitochondria, the only way these cells can make ATP is through glycolysis. BPG encourages hemoglobin and oxygen to separate from one another. Therefore, despite hemoglobin's partial pressure, oxygen dissociates from it more easily the higher the BPG concentration. Another factor influencing the oxygen-hemoglobin saturation/dissociation curve (*see* Figure 7.6) is the blood pH. The relationship between pH and oxygen's affinity for hemoglobin gives rise to the Bohr effect, a phenomenon wherein a lower, more acidic pH encourages oxygen to dissociate from hemoglobin. On the other hand, oxygen dissociation from hemoglobin is inhibited by a higher pH, or more basic. The more carbon dioxide there is in the blood, the more molecules need to be converted, which drops the pH of the blood by producing hydrogen ions. Furthermore, when specific byproducts of cell metabolism, like lactic acid, carbonic acid, and carbon dioxide, are released into the bloodstream, blood pH may become more acidic.

7.5.4. Hemoglobin of the Fetus

Although the fetus has its own erythrocytes and circulatory system, it depends on the mother for oxygen. The umbilical cord, which is attached to the placenta and separated from mother blood by the chorion, provides blood to the developing fetus. Gas exchange at the respiratory membrane and the chorion operate via comparable mechanisms. Nonetheless, the partial pressure of oxygen in the mother's blood within the placenta is lower compared to maternal arterial blood, ranging from 35 to 50 mm Hg. Given that the partial pressure of oxygen in fetal blood at the placenta is only 20 mm Hg, there is not a significant difference in partial pressures between maternal and fetal blood. As a result, the oxygen does not diffuse as

much into the fetal blood supply. This issue is solved by the fetal hemoglobin, which has a higher affinity for oxygen than that of the mother (Figure 7.6). Fetal hemoglobin has four subunits, just like adult hemoglobin, but two of the subunits in fetal hemoglobin are structurally different, giving fetal hemoglobin a higher affinity for oxygen than adult hemoglobin (Figure 7.7).

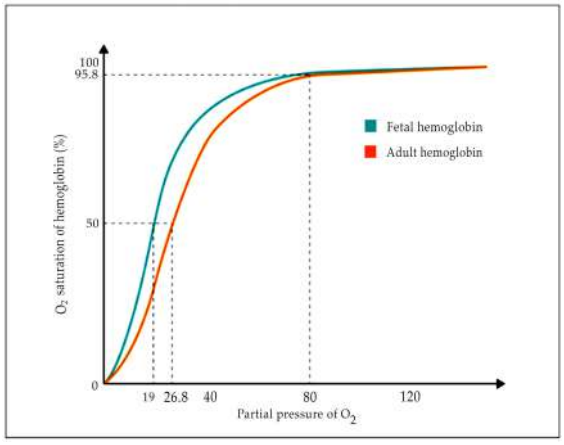

Figure 7.7. *Oxygen-hemoglobin dissociation curves in fetus and adult. Fetal hemoglobin has a greater affinity for oxygen than adult hemoglobin.*

Source: https://bio.libretexts.org/@api/deki/files/25469/Screen-Shot-2015-05-21-at-12.30.58-PM.png?revision=1.

7.5.5. Carbon Dioxide Transport in the Blood

There are three main ways that carbon dioxide is moved. Some carbon dioxide molecules dissolve in blood plasma, which serves as the first mechanism of carbon dioxide transport. Transport in the form of bicarbonate (HCO_3^-), which also dissolves in plasma, is the second mechanism. The third mechanism of carbon dioxide transport is similar to how erythrocytes carry oxygen. (Figure 7.8).

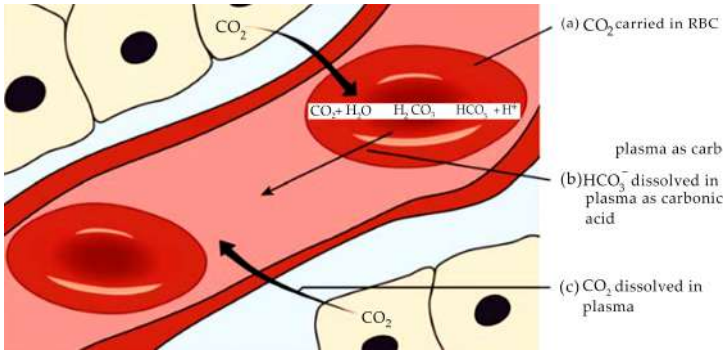

Figure 7.8. *Carbon dioxide is transported by three different methods: (a) in erythrocytes; (b) after forming carbonic acid (H_2CO_3), which is dissolved in plasma; (c) and in plasma.*

Source: https://bio.libretexts.org/@api/deki/files/25471/Screen-Shot-2015-05-21-at-12.34.05-PM.png?revision=1.

7.5.5.1. Dissolved Carbon Dioxide

While carbon dioxide is not thought to be highly soluble in blood, a tiny portion—roughly 7% to 10%—dissolves in plasma when it diffuses from the tissues into the blood. After entering the bloodstream, the dissolved carbon dioxide diffuses across the respiratory membrane into the alveoli, where it is exhaled during pulmonary ventilation. This process occurs when the blood reaches the pulmonary capillaries.

7.5.5.2. Bicarbonate Buffer

A large fraction—about 70%—of the carbon dioxide molecules that diffuse into the blood is transported to the lungs as bicarbonate. Most bicarbonate is produced in erythrocytes after carbon dioxide diffuses into the capillaries, and subsequently into red blood cells. Carbonic anhydrase (CA) catalyzes the reaction between carbon dioxide and water to form carbonic acid (H2CO3), which then dissociates into two ions: bicarbonate (HCO3–) and hydrogen (H+). The following formula depicts this reaction:

$$CO_2 + H_2O \xleftrightarrow{CA} H_2CO_3 \rightarrow H^+ + HCO_3^-$$

Bicarbonate tends to accumulate in erythrocytes, where it is found in higher concentrations than in the surrounding blood plasma. As a result, in exchange for chloride (Cl^-) ions, some bicarbonate will leave the erythrocytes and travel into the plasma along its concentration gradient. Because neither the electrical charge of the blood nor the erythrocytes is changed by swapping one negative ion for another, this phenomenon—known as the chloride shift—occurs. The above-depicted chemical reaction that produces bicarbonate is reversed at the pulmonary capillaries, yielding carbon dioxide and water as the end products.

In exchange for chloride ions, a large portion of the bicarbonate in the plasma re-enters the erythrocytes. Carbonic acid is created when hydrogen and bicarbonate ions combine. Carbonic anhydrase then breaks this acid down into carbon dioxide and water. After leaving the erythrocytes, carbon dioxide diffuses into the plasma and then into the alveoli, where it can pass through the respiratory membrane and be exhaled during pulmonary ventilation.

7.5.6. Carbaminohemoglobin

Carbon dioxide (CO2) and hemoglobin in the blood combine to form carbaminohemoglobin, a substance that helps move CO2 from tissues to the lungs for exhalation. While most CO2 is carried in the blood as bicarbonate ions (HCO3-) after CO2 has been hydrated, some CO2 combines directly with hemoglobin to form carbaminohemoglobin. This reversible reaction occurs primarily during cellular metabolism, where CO2 is produced as a byproduct of aerobic respiration, in the systemic capillaries of tissues. Carbon dioxide encounters hemoglobin in red blood cells as it diffuses from metabolically active cells into the systemic capillaries. Hemoglobin's globin chain amino groups bind to a carbamino group (-NHCOO-) to initiate the reaction between hemoglobin and CO2.

Since CO2 binds to different amino groups than oxygen, this reaction does not affect hemoglobin's ability to bind oxygen. It does, however, compete with oxygen for hemoglobin binding sites, changing the oxygen-hemoglobin dissociation curve and the way oxygen is released into tissues. By facilitating the extraction of CO2 from tissues, carbaminohemoglobin helps to sustain the partial pressure gradient required for CO2 diffusion into the bloodstream. CO2 is released from hemoglobin in the pulmonary capillaries and diffuses into the alveolar spaces, where it is exhaled during expiration, as blood containing carbaminohemoglobin returns to the lungs via the venous system.

The partial pressure of CO2 in the blood, temperature, and pH all affect hemoglobin's

affinity for gas. During metabolism, tissues exhibit increases in CO2 partial pressure, which facilitates the production of carbaminohemoglobin and improves CO2 transport. On the other hand, lowering the pH (acidosis) and raising the temperature encourage the release of CO2 from hemoglobin, which makes it easier for the lungs to expel CO2.

All things considered, carbaminohemoglobin is a vital part of the blood's buffering system and is essential for moving carbon dioxide from metabolically active tissues to the lungs where it is exhaled. Comprehending the synthesis and functioning of carbaminohemoglobin is fundamental to understanding respiratory physiology and blood gas exchange regulation in a range of physiological and pathological circumstances. Hemoglobin binds to about 20% of carbon dioxide and carries it to the lungs.

Unlike oxygen, which binds to iron, carbon dioxide binds amino acid moieties on the globin portions of hemoglobin to form carbaminohemoglobin, which is formed when carbon dioxide and hemoglobin bind together. Hemoglobin typically has a bluish-purple tone when it is not carrying oxygen, giving blood the darker maroon color that is indicative of deoxygenated blood.

The following formula depicts this reversible reaction:

$$CO_2 + Hb \leftrightarrow HbCO_2CO_2 + Hb \leftrightarrow HbCO_2$$

The partial pressure of carbon dioxide affects the binding and dissociation of carbon dioxide to and from hemoglobin, just like it does for the transport of oxygen by heme. Blood that exits the lungs and enters bodily tissues has a lower partial pressure of carbon dioxide than that which is present in the tissues because carbon dioxide is released from the lungs. Because of its increased partial pressure, carbon dioxide consequently escapes the tissues, enters the blood, travels into red blood cells, and attaches itself to hemoglobin. In contrast to the alveoli, the partial pressure of carbon dioxide in the pulmonary capillaries is higher. Because of this, carbon dioxide and hemoglobin separate easily and diffuse into the air through the respiratory membrane.

The partial pressure of oxygen in the blood and the oxygen saturation of hemoglobin, in addition to the partial pressure of carbon dioxide, affect hemoglobin's affinity for carbon dioxide. The connection between hemoglobin's affinity for carbon dioxide and the partial pressure of oxygen gives rise to the Haldane effect. Carbon dioxide is not easily bound by oxygen-saturated hemoglobin. Hemoglobin, however, binds to carbon dioxide easily when oxygen is not bound to heme and the partial pressure of oxygen is low.

A Closer Look

Respiratory System and Breathing

The respiratory system comprises of the lungs, airways, and breathing muscles. Healthy lungs are vital to effective oxygen exchange, which benefits every cell in our body. When we inhale, air enters our lungs, where oxygen is absorbed, and carbon dioxide is expelled. This process ensures that our organs get the oxygen they require to function properly.

Lung diseases are a group of conditions that interfere with the proper functioning of the lungs. These ailments are classified into three categories:

- **Airway Diseases:** These conditions affect the airways that carry oxygen and gases to and from the lungs. These diseases, which frequently cause airway constriction or blockage, include asthma, chronic obstructive pulmonary disease (COPD), bronchiolitis, and bronchiectasis (a central disorder in cystic fibrosis). Those who suffer from it frequently describe the sensation as if they were exhaling through a narrow straw.
- **Lung Tissue Diseases:** These conditions compromise the structural integrity of the lung tissue. Scarring or inflammation limits lung expansion, making oxygen intake and carbon dioxide release difficult. Individuals suffering from this disorder compare their experience to wearing a constricting garment that prevents them from taking deep breaths. Pulmonary fibrosis and sarcoidosis are examples of lung tissue diseases.
- **Lung Circulation Diseases:** These conditions, caused by clotting, scarring, or inflammation, affect the blood vessels in the lungs. This influences oxygen uptake and carbon dioxide release, as well as heart function. Pulmonary hypertension is a form of lung circulation disease. Those who are affected frequently experience substantial shortness of breath during physical exertion.

- **Common Lung Diseases:**
  - **Chronic Obstructive Pulmonary Disease (COPD):** It is a common lung disease that is frequently caused by long-term contact with harmful irritants such as cigarette smoke and air pollutants. This illness disrupts airflow, making breathing difficult. Coughing and wheezing are common symptoms, as is an increased sensitivity to respiratory infections. Early detection and treatment are critical for slowing disease progression and improving lung function.
  - **Asthma:** It is a chronic inflammatory disease that affects the airways, allowing them to narrow and making breathing difficult. Allergens, pollution, and cold air can all aggravate symptoms. Asthmatic people experience shortness of breath, coughing, and chest tightness. Differentiating asthma from other lung conditions is critical for effective treatment.

- **Pulmonary Fibrosis:** The formation of scar tissue in the lungs causes pulmonary fibrosis, hampering their capacity to expand and contract during breathing. This reduces oxygen exchange and causes shortness of breath. Environmental exposure, certain medications, and autoimmune disorders are all common causes. Early diagnosis employing lung function tests and imaging is critical for effective management of the condition.

- **Effects of Common Lung Diseases on Breathing:**
  - **Shortness of Breath (Dyspnea):** Dyspnea, or shortness of breath, is a characteristic symptom of many lung diseases. Airflow restriction caused by inflammation, scarring, or obstruction makes even routine activities difficult. Climbing stairs, walking, and other daily activities become arduous, lowering your quality of life. Seeking medical attention and implementing effective management strategies are critical.
  - **Decreased Oxygen Levels (Hypoxemia):** Hypoxemia, or low blood oxygen levels, can have serious repercussions for the body's functioning. Lung diseases impair oxygen exchange, resulting in fatigue, confusion, and other symptoms. Sustaining overall health involves observing your oxygen saturation and tackling underlying lung issues.
- **Preventive Measures and Healthy Lung Practices:**
  - **Smoking Cessation:** Smoking is a major cause of lung diseases such as COPD, lung cancer, and asthma. Quitting smoking can improve lung health and lower the likelihood of further progression of disease. Psychotherapy, support groups, and nicotine replacement therapy are all available to help you quit smoking.
  - **Regular Exercise and Physical Activity:** Physical activity on a regular basis improves lung function and capacity. Aerobic exercises, such as brisk walking, swimming, and cycling, aid in building respiratory muscles and improve lung efficiency. Including these activities in your daily routine improves your breathing and overall well-being.
  - **Indoor Air Quality:** Indoor air quality is extremely important for lung health. Pollutants such as dust, pet dander, and mold can aggravate lung conditions and cause symptoms. Use air purifiers and ensure proper ventilation to reduce potential irritants and allergens.

Summary

- The development of the digestive system is closely linked to that of the respiratory system from the start.
- The respiratory system starts to develop early in the fetal stage. Most structures in this process originate from the endoderm.
- Intricate processes essential to maintaining life include the differentiation of respiratory structures and the establishment of gas exchange function in the developing respiratory system.
- The development of fetal lungs is a carefully planned process that starts early in embryogenesis and moves through several phases to prepare the lungs for postnatal life.
- The exchange of carbon dioxide and oxygen between the body and its surroundings is carried out by the intricate network of organs and structures that makes up the respiratory system.
- Gas exchange in the lungs is a basic physiological function necessary to ensure tissues receive enough oxygen and eliminate carbon dioxide from the blood. Efficient gas exchange supports cellular respiration and overall physiological function.
- One important mechanism that controls the release of oxygen (O2) to tissues according to their metabolic needs is the oxygen dissociation from hemoglobin.

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Chapter

DEVELOPMENT OF THE GASTROINTESTINAL SYSTEM

8

Contents

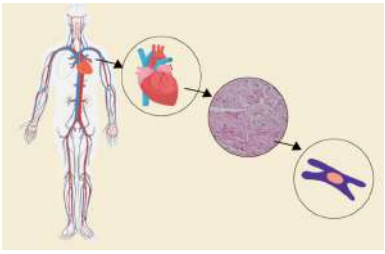
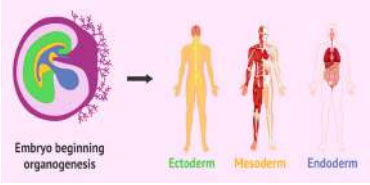
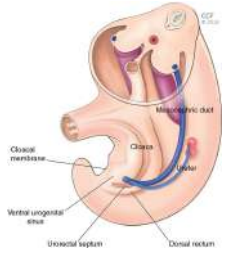
Unit Introduction

The intricate and meticulously planned process of developing the gastrointestinal (GI) system begins early in embryonic development and continues throughout fetal growth and postnatal life. Under complex morphological and functional changes, this system—which is in charge of digestion, nutrient absorption, and waste removal—adapts to the changing nutritional requirements of the developing organism. The gastrointestinal tract emerges from the endodermal germ layer during embryonic development through a complex series of processes. During the third week of pregnancy, the primitive gut tube begins to form, which is the first stage. This tube runs from the cloacal membrane, which forms the anus, to the buccopharyngeal membrane, which eventually becomes the mouth. After that, the gut tube continues to differentiate into different regions that give rise to different GI tract structures: the foregut, midgut, and hindgut.

Organogenesis is the process by which the basic gut tube is transformed into the different parts of the gastrointestinal system as development proceeds. Important organs like the pancreas, liver, intestines, and stomach form as a result of a mix of budding, folding, and differentiation processes. The correct development and functionality of these organs are ensured by tightly regulating the spatial and temporal patterning of these structures through signaling pathways involving growth factors, transcription factors, and morphogens. The development of neural and vascular networks is also essential for the growth of the gastrointestinal tract. Blood vessels, such as the umbilical and vitelline arteries and veins, provide growing gut tissues with nutrition and oxygen. To independently regulate digestive processes, the enteric nervous system (ENS), a sophisticated network of neurons located within the GI tract, goes through simultaneous processes of differentiation and migration. The gastrointestinal system continues to develop and adapt in the later stages of fetal development and in the postnatal period to meet the evolving nutritional requirements of the developing organism. Nutrient absorption and digestive efficiency are improved by structural changes such as the lengthening and coiling of the intestines and the development of villi and microvilli, which increase absorptive surfaces.

The introduction of oral feeding and the colonization of the gut microbiota aid in the postnatal functional maturation of the GI system. The development of a varied microbial community in the intestines is essential for immunological response, nutrition metabolism, and general health. Even though the process of gastrointestinal development is incredibly complex, anomalies or disturbances in it can result in functional disorders or congenital malformations. Hirschsprung's disease, intestinal malrotation, esophageal atresia, and congenital deficiencies in digestive enzymes are common examples. The process of developing the gastrointestinal system is complex and dynamic, encompassing various stages of growth during the embryonic, fetal, and postnatal stages. This system develops from a basic primitive gut tube into a complex network of organs necessary for waste removal, nutrient digestion, and absorption through precise morphological and functional changes regulated by genetic and environmental factors. Determining the cause of congenital defects and formulating preventative and therapeutic measures require an understanding of the mechanisms underlying gastrointestinal development.

Orientation and Directional Terms

Terms	Definition	Illustration
Morphological	Morphology in biology is the study of the form and structure of organisms and their specific structural features.	
Organogenesis	Organogenesis is the process of formation of organs from three germ layers. It concerns cell-cell interaction, cell fate determination, cell proliferation and survival, cell and tissue shape and size, and arrangement of cells into tissues and ultimately functional organs.	
Cloacal membrane	The cloacal membrane is the membrane that covers the embryonic cloaca during the development of the urinary and reproductive organs.	
Gastrointestinal tract	The gastrointestinal tract is the tract or passageway of the digestive system that leads from the mouth to the anus.	
Esophagus	The esophagus, colloquially known also as the food pipe, food tube, or gullet, is an organ in vertebrates through which food passes, aided by peristaltic contractions, from the pharynx to the stomach.	

8.1. Development of Digestive Organs, Including the Stomach, Liver, Pancreas, and Intestines

Initially, the digestive system starts as a basic tube with no clear opening. The other digestive organs develop as extensions from this tube, while the intestines must temporarily extend into the umbilical cord before moving back into the abdomen. Understanding the early development of the foregut, midgut, and hindgut, as well as their associated structures, is crucial for comprehending the complex blood supply and connective tissues within the abdomen.

8.1.1. Formation and Differentiation of the Primitive Gut Tube

An important early stage in the development of the gastrointestinal (GI) system is the formation and differentiation of the primitive gut tube, which lays the groundwork for the complex structures that will facilitate digestion, absorption, and waste elimination. This complex process, which entails several carefully planned morphogenetic events, takes place during embryonic development. The three germ layers—ectoderm, mesoderm, and endoderm—are established during the process of gastrulation, which the trilaminar embryonic disc goes through around the third week of gestation. The epithelial lining of the digestive tract and related organs develops from the endoderm, the innermost layer. The folding of the embryo into a cylindrical shape during embryonic folding is the first sign that the gut is beginning to form.

The primitive streak, a depression formed by this process, is the location of gastrulation and the start of germ layer differentiation. After migrating through the primitive streak, endodermal layer cells form the notochord, a structure that offers structural support and developmental cues. The primitive gut tube is then shaped by significant morphological changes that the endoderm goes through. The primitive gut tube is first formed by a longitudinal invagination that runs from the buccopharyngeal membrane (future mouth) to the cloacal membrane (future anus). The structure of this tube is uniform at first, but it soon divides into the foregut, midgut, and hindgut, three distinct regions along the anterior-posterior axis.

The foregut, located at the front end of the embryo, gives rise to structures such as the pharynx, esophagus, stomach, liver, pancreas, and the beginning of the small intestine. The midgut, situated between the foregut and hindgut, forms the rest of the small intestine, as well as the cecum, appendix, and parts of the large intestine. The hindgut, found at the back end, contributes to the formation of the remaining parts of the large intestine.

During development, the gut tube elongates and matures, with signals from surrounding tissues helping to specify cell types and organ formation. For example, the pancreas develops with input from neighboring tissues like the notochord and dorsal mesentery, which prompt endodermal cells to become pancreatic precursors. Overall, the creation and differentiation of the gut tube are critical parts of embryonic development, laying the groundwork for the gastrointestinal system and the formation of digestive organs and tissues. Understanding this process is key to unraveling the causes of congenital gastrointestinal issues and developing ways to prevent and treat them.

8.1.2. Gut Tube

Due to the embryo's lateral and cephalocaudal folding, a portion of the yolk sac is incorporated

into the developing embryo, forming the primitive gut. The yolk sac and the allantois are the parts that remain outside the embryo. The primitive gut creates the foregut and hindgut, respectively, as a blind-ended tube on the embryo's cephalic and caudal ends. While the vitelline duct (yolk stalk) temporarily connects the middle section to the yolk sac, it forms the midgut.

The development of the primitive gut and its derivatives are generally divided into four sections:

- the proximal foregut;
- the distal foregut;
- the midgut;
- the hindgut.

The pharyngeal gut, or pharynx, which runs from the oropharyngeal membrane to the respiratory diverticulum, makes up the first part of the proximal foregut. The development of the pharyngeal apparatus, and eventually the head and neck, depends on this area. Secondly, the distal foregut connects the liver bud to the pharyngeal tube. Third, the midgut connects the left third of the transverse colon with the right two-thirds at the liver bud. Fourth, the hindgut connects the cloacal membrane to the left third of the transverse colon.

8.1.3. Mesenteries

The mesenteries, which are two layers of peritoneum that enclose organs and connect them to the body wall, suspend the gut tube and its derivatives from the dorsal and ventral body wall in the abdominal cavity. We refer to these organs as intraperitoneal organs (i.e., stomach), while retroperitoneal organs are those that lie directly on the posterior body wall and have peritoneum covering their anterior surface (i.e., kidneys. Peritoneal ligaments are the mesenteries that connect one organ to the body wall or between two organs. Blood vessels, nerves, and lymphatic pathways are carried to and from the abdominal organs by the mesenteries and peritoneal ligaments working together.

Initially, in contact with the posterior abdominal wall, the dorsal mesentery suspends the gut tube from it. The dorsal mesentery forms the dorsal mesogastrium, also known as the greater omentum, at the stomach; the mesoduodenum forms the duodenum; the mesentery proper forms the jejunum and ileum; and the dorsal mesocolon forms the colon.

Conversely, the upper duodenum, stomach, and lower esophagus are the only anatomical structures that are suspended from the ventral body wall by the ventral mesentery. The septum transversum, a mass of splanchnic mesoderm that divides the pericardial and peritoneal cavities, is the source of the ventral mesentery. Eventually, the growing liver divides it into the lesser omentum and the falciform ligament; the former runs from the liver to the lower esophagus, stomach, and upper duodenum, while the latter runs from the liver to the ventral body wall.

The umbilical vein, which is obliterated after birth to form the round ligament of the liver, passes through the free margin of the falciform ligament. The portal triad—the bile duct, the portal vein, and the hepatic artery—is formed by the free margin of the lesser omentum that joins the duodenum and the liver (hepatoduodenal ligament). The omental bursa and the remainder of the peritoneal cavity are connected by the epiploic foramen of Winslow, which is formed by this free margin.

8.1.4. Foregut

The anterior portion of the alimentary canal in humans, which extends from the distal esophagus to the first half of the duodenum at the bile duct entrance, is known as the

foregut. The mesentery connects the foregut to the abdominal walls beyond the stomach. The foregut develops from the folding primitive gut of the endoderm and is different from the midgut and hindgut in terms of development. While the anterior region of the primitive gut is usually referred to as the "foregut," other parts of the adult gut can also be classified as such. Structures derived from the adult foregut are usually involved when pain occurs in the epigastric area, which is located directly below the ribs' intersection.

The foregut gives rise to the:

- pharynx;
- the lower respiratory system;
- the esophagus;
- the stomach;
- the proximal half of the duodenum;
- the liver;
- the biliary apparatus;
- the pancreas.

The derivatives of the foregut, except for the pharynx and the lower respiratory system, are mostly supplied by the celiac artery (trunk).

1. **Esophagus:** A respiratory diverticulum, also known as a lung bud, emerges from the proximal foregut's ventral wall during the third week of pregnancy. The esophagus forms when the lung bud separates from the foregut as it grows larger. The esophagus is short at first but grows quickly due to the expansion and movement of the heart and lungs.
2. **Stomach:** The rudimentary stomach appears as a fusiform-shaped dilatation of the distal foregut during the fourth week of pregnancy. Its position and appearance then undergo significant changes; the latter can be better comprehended by imagining the stomach rotating around two axes: a longitudinal axis and an antero-posterior axis.

The stomach's left side faces anteriorly and its right-side faces posteriorly after rotating 90° clockwise around its longitudinal axis. This explains why the right vagus nerve innervates the posterior wall after having previously innervated the right side of the stomach, whereas the left vagus nerve innervates the anterior wall. Alongside this rotation, the stomach's posterior wall experiences much faster cellular proliferation than its anterior wall, which gives rise to the creation of the larger and lesser curvatures, respectively.

Additionally, the stomach rotates around its antero-posterior axis, causing the cranial end (cardiac part) to move slightly downward and to the left and the caudal end (pyloric part) to move upward and to the right. As a result, the stomach takes on its final configuration, with the cardia inferior to the right and the pylorus superior to the left.

The position of the mesenteries is also modified by the rotational changes of the stomach. Remember that the dorsal mesogastrium and the ventral mesentery connect the stomach to the dorsal and ventral walls, respectively (mesogastrium), in that order. The omental bursa, also known as the lesser peritoneal sac, is a space created behind the

stomach by the rotation of the stomach around its longitudinal axis, which pulls the ventral and dorsal mesogastrium to the right and left, respectively.

3. **Duodenum:** The duodenum develops from two sources during the fourth week of pregnancy: the cranial part of the midgut and the caudal portion of the foregut, where they converge slightly distal to the origin of the bile duct. The duodenum develops into a C-shaped loop that initially extends ventrally. The duodenum, on the other hand, rotates to the right and presses up against the posterior abdominal wall when the stomach rotates, making it retroperitoneal. The duodenum receives blood supply from both the superior mesenteric artery and branches of the celiac trunk because of its dual origin.

4. **Liver and Biliary Apparatus:** The liver starts to develop in the fourth week of pregnancy when the liver bud, or hepatic diverticulum, emerges from the distal foregut's ventral wall. The gallbladder and the cystic duct form as a ventral outgrowth from the bile duct, while the stalk that connects the diverticulum and the foregut narrows to form the bile duct. Due to the rotational changes in the duodenum, the bile duct, which originally opens anteriorly into the duodenum, ends up opening posteriorly.

   The hepatic diverticulum extends into the ventral mesentery, as was previously mentioned. This splits the ventral mesentery into the lesser omentum and the falciform ligament and places the future liver between the foregut and ventral abdominal wall. The liver takes up a lot of space in the upper abdomen during the ensuing weeks. The oxygenated blood that enters the liver through the umbilical vein determines the subsequent growth and division of the organ. Like the stomach, the right lobe grows larger than the left due to cellular proliferation, which is much faster on one side.

   Additionally, the mesoderm surrounding the liver's surface, with the exception of its cranial surface, differentiates into the visceral peritoneum. The latter is near the septum transversum, where the central tendon of the diaphragm originates. This surface, which is referred to as the bare area of the liver, is therefore in constant contact with the developing diaphragm and is never covered in visceral peritoneum. The mesenchyme of the septum transversum is the source of Kupffer cells, connective tissue cells, and hematopoietic cells, despite the fact that the foregut makes up a large portion of the liver. Therefore, both the foregut and the septum transversum are necessary for the development of a functional liver.

5. **Pancreas:** Two distinct pancreatic buds subsequently unite to form the pancreas. In particular, the ventral pancreatic bud emerges from the ventral wall along with the bile duct, whereas the dorsal pancreatic bud develops from the dorsal wall of the duodenum. The ventral pancreatic

bud is pulled dorsally and inferiorly by the duodenum as it rotates and assumes a C-shaped shape. The pancreas is then formed by the fusion of the pancreatic buds and their primitive duct systems.

The inferior portion of the pancreatic head and the uncinate process are formed by the ventral pancreatic bud. The superior portion of the head, neck, and pancreatic body is formed by the dorsal pancreatic bud. The main pancreatic duct (of Wirsung) is made up of the entire ventral pancreatic duct and the distal portion of the dorsal pancreatic duct.

The dorsal proximal portion of the pancreatic duct either disappears or continues as the accessory pancreatic duct (of Santorini). As a result, the pancreas and its duct systems take on their final form. The accessory duct, if it exists, enters the duodenum at the minor papilla, while the main pancreatic duct joins the bile duct and enters the major papilla.

8.1.5. Midgut

The superior mesenteric artery supplies the derivatives of the midgut, which include the distal half of the duodenum, jejunum, ileum, cecum, appendix, ascending colon, and the proximal two-thirds of the transverse colon.

The derivatives of the midgut are supplied by the superior mesenteric artery. The primary intestinal loop forms during the fifth week of pregnancy as a result of the midgut's rapid elongation, which occurs much faster than the growth of the abdominal cavity. The superior mesenteric artery runs along the loop's axis, and at its apex, the vitelline duct maintains open communication between the loop and the yolk sac. The jejunum, proximal half of the ileum, and inferior half of the duodenum will all develop from the loop's cranial limb. The distal half of the ileum, the cecum, the ascending colon, and the proximal two-thirds of the transverse colon are all developed from the loop's caudal limb.

By the sixth week, the primary intestinal loop protrudes into the umbilicus (a physiological herniation) due to the continued elongation of the midgut and the pressure from the dramatic growth of abdominal organs. In parallel, the loop revolves around the superior mesenteric artery's axis 90° counterclockwise. This causes the cranial limb to move caudally, to the embryo's right, and the caudal limb to move cranially, to the embryo's left. The rotation continues until the eighth week of pregnancy, at which point the expanding cecum gives rise to the vermiform appendix, a worm-like diverticulum, while the lengthening jejunum and ileum form a series of folds known as the jejunal-ileal loops.

The herniated midgut retracts into the abdomen during the tenth week. Although the exact mechanism causing this retraction is unknown, it is thought to be related to the increase in the size of the abdominal cavity. The intestinal loops travel a total of 270° as they reenter the abdomen, rotating 180° counterclockwise around the superior mesenteric artery axis. Consequently, the cecum—which was originally located beneath the liver—becomes inferiorly displaced and pulls the proximal hindgut down to form the ascending colon.

The intestines have fully receded into the abdomen by the eleventh week. The ascending and descending colon's dorsal mesenteries shorten and fold, attaching these organs to the dorsal body wall, where they secondarily become retroperitoneal. The jejunum, ileum,

cecum, transverse colon, and sigmoid colon become intraperitoneal because they are still suspended from the dorsal body wall by a brief mesentery.

8.1.6. Hindgut

This posterior, or caudal, portion of the alimentary canal is called the hindgut, or epigaster. It encompasses the splenic flexure, the distal third of the transverse colon, the descending colon, the sigmoid colon, and the anorectal junction in mammals. In zoology, the cecum and ascending colon are also referred to as part of the "hindgut."

The derivatives of the hindgut are supplied by the inferior mesenteric artery. During the initial weeks of development, the allantois enters the anterior part of the cloaca while the terminal portion of the hindgut enters the posterior portion; these two structures eventually form the urogenital sinus and the future anorectal canal, respectively. Endoderm lines the cloacal cavity, while surface ectoderm lines its ventral boundary; the latter is referred to as the cloacal membrane. The mesodermal layer known as the ureorectal septum develops between the allantois and the hindgut by the seventh week of pregnancy. Its tip forms the future perineal body, and it divides the cloaca into the urogenital sinus and the anorectal canal. While the anorectal canal develops into the rectum and most of the anal canal, the urogenital sinus forms the future bladder, portions of the urethra, and the phallus. In particular, the surface ectoderm of the cloaca is the source of the lower third of the anorectal canal, whereas the upper two-thirds originate from the hindgut's endoderm.

The pectinate line, an uneven fold of the mucosa, marks the location of the juncture where the degeneration of the cloacal membrane connects the upper and lower portions of the anorectal canal. Additionally, this is the point at which the epithelium lining changes from columnar to stratified squamous. The vasculature of the anorectal canal is consistent with its dual origin: the inferior rectal arteries, which are branches of the internal pudendal arteries, supply the lower one-third of the canal, which is inferior to the pectinate line, while the superior rectal arteries, which are branches of the inferior mesenteric artery, supply the upper two-thirds.

8.2. Congenital Anomalies and Developmental Disorders of the Gastrointestinal Tract

The gastrointestinal tract (GIT) is composed of the stomodeum, an ectodermal depression at the cranial end of the embryo, and the proctodeum, an ectodermal depression at the caudal end. Therefore, the endoderm of the yolk sac forms the remaining portion of the lining of the terminal parts, which has ectodermal origins.

The splanchnic mesenchyme that surrounds the gut wall forms the muscular and connective tissue components. Congenital malformations affecting the gastrointestinal tract (GIT) can be categorized into upper and lower gut anomalies (Table 8.1). Upper pathology affects the esophagus, stomach, duodenum, pancreas, and hepatobiliary tract, which are the foregut tubes closest to the Treitz ligament. Lower GIT anomalies include colon, anorectal malformations, and mid- and hindgut structures such as the jejunum and ileum, which make up the small bowel. Congenital anomalies can be further classified as structural or functional. Defective embryogenesis or intrauterine complications like ischemia can lead to structural abnormalities. Normal anatomy is present in functional defects, but the GIT's contents flow is disrupted. Structural flaws usually have a negative effect on functional capability.

Table 8.1. *Embryologic Derivates of the Gastrointestinal Tract*

Gastrointestinal Tract	Anatomic Relation	Embryonic Source	Blood Supply	Viscera
Upper gastrointestinal tract.	Proximal to the ligament of Treitz	Foregut	Celiac axis	• Esophagus • Stomach • Duodenum • Biliary ducts • Liver • Pancreas
Lower gastrointestinal tract	Distal to the ligament of Treitz	Midgut	SMA	• Jejunum • Ileum • Cecum • Ascending colon • Proximal 2/3 transverse colon
		Hindgut	IMA	• Distal 1/3 transverse colon • Descending colon • Sigmoid colon • Rectum • Anal canal

8.2.1. Foregut Disorders

Disorders affecting the esophagus, stomach, duodenum, liver, gallbladder, and pancreas—structures derived from the embryonic foregut—are collectively referred to as foregut disorders. These disorders can result in a variety of symptoms and complications that may call for medical or surgical intervention. They can also be caused by acquired conditions, developmental defects, or congenital abnormalities.

Esophageal atresia (EA) with or without tracheal fistula (TEF)

The condition known as esophageal atresia/tracheoesophageal fistula (EA/TEF) is caused by abnormal development of the esophageal tube, which is the tube that carries food from the mouth to the stomach. Between four and eight weeks after conception, the esophagus and windpipe (trachea), which begin as a single tube, usually split into two adjacent passages.

8.2.1.1. Embryology

The embryonic ventral foregut differentiates into the esophagus and trachea during the fourth week of pregnancy. By the end of the ninth week of pregnancy, the esophagus has finished developing its muscles and neurons. Esophageal malformations most likely stem from mistakes made during this stage of development.

8.2.1.2. Clinical Presentation

EA/TEF is categorized into five types and clinical presentation varies depending on the type of pathology (Figure 8.1). Type A is the most common (90% of cases) and consists of proximal EA with a distal TEF. Type B consists solely of proximal EA (no fistula) whereas type C only has a TEF (no atresia). Type D has both a proximal and distal TEF in the setting of atresia. Type E consists of proximal EA with TEF and a distal esophageal pouch. Types D and E are exceedingly rare.

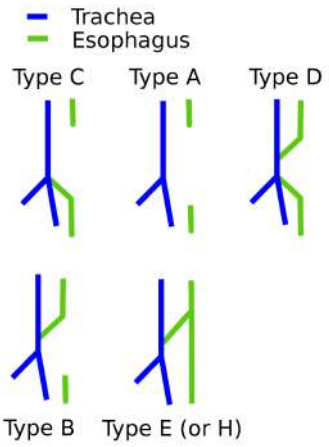


Figure 8.1. *Types of tracheoesophageal fistulae depicted in figures A–E.*

Source: By Jmarchn – Own work and Tracheoesophageal Fistula Types.JPG, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=63893867.

The baby will start to drool and will choke, cough, and regurgitate when trying to feed themselves. The infant will have a scaphoid abdomen and there won't be any gas in the bowel distally on the radiograph because types B and E have a proximal obstruction without distal fistulization. Recurrent aspiration pneumonia may be the presenting symptom of type C, and diagnosis may not occur until later in life.

8.2.1.3. Diagnosis

Prenatal ultrasound can show the blind end of the esophageal pouch and show polyhydramnios. An unsuccessful attempt to pass a nasogastric or oro-gastric tube after delivery serves as a diagnostic. On radiography, the tube's tip will be visible in the esophageal pouch. To ascertain the existence of any additional anomalies, renal and cardiac ultrasounds as well as plain films of the spine and limbs must be obtained due to the VACTERL phenomenon (vertebral, anal, cardiac, tracheoesophageal, renal, and limb deformities). Because this affects operative planning, an echocardiogram is especially necessary to confirm that the aortic arch is in its typical left-sided anatomic location. Among anomalies linked to EA/TEF, ventricular septal defect is the most prevalent type.

8.2.1.4. Surgical Management

Correcting EA/TEF should ideally be done in a single step. A staged procedure is used for patients with respiratory or cardiac defects who are too unstable to tolerate general anesthesia. It starts with a decompressive gastrostomy and fistula takedown and ends with esophageal reconstruction later. To facilitate the elongation of the proximal and distal esophageal ends, infants with long gap atresia also experience delayed repair. Open thoracotomy is no longer the preferred method in practice, as video-assisted thoracoscopy is a less invasive approach. The serratus anterior and latissimus dorsi muscles are spared when

a right posterolateral thoracotomy incision is made at the fourth intercostal space when the open approach is used. After carrying out extrapleural dissection up until the azygous vein is reached, it is divided. The lower esophageal pouch and related fistula are identified in type A cases. There is a fistula resection. The next step is to mobilize the proximal esophageal pouch to create tension-free continuity between the two ends. Before mobilization, a proximal fistula is ligated if one is present. By means of a single layer end-to-end anastomosis, the esophagus is rebuilt. A chest tube is inserted and is left in place until the anastomosis's patency is confirmed by a post-operative esophogram. Anastomotic leaks are treated with antibiotics and a chest tube, and they usually resolve on their own.

8.2.1.5. Outcomes

The thoracic approach has improved results, and since there are fewer concomitant abnormalities like cardiac defects, the majority of infants go on to lead fairly normal lives. The majority of patients live with their esophageal strictures and gastroesophageal reflux disease (GER) for the rest of their lives. GER may not cause any symptoms at all or result in esophageal stricture, respiratory issues, or a chronic cough. Prokinetics and anti-reflux drugs are used in medical primary care. The last option for treating GER is surgery with a fundoplication. Endoscopic dilatation is the most effective treatment for esophageal strictures, which can develop years after repair. Surgery is needed for resection and anastomosis in cases of recurrent or resistant esophageal strictures.

8.2.2. Duodenal Atresia

Duodenal atresia is a congenital condition in which the duodenum is narrowed or blocked. This blockage prevents liquids and food from passing through the stomach into the rest of the intestine.

8.2.2.1. Embryology

It results due to the failure of duodenal recanalization and most commonly occurs in the second portion of the duodenum distal to ampulla of Vater but any segment can be affected.

8.2.2.2. Clinical Presentation

Emesis and intolerance to food happen within the first 24 to 48 hours of life. Depending on where atresia is in relation to the major duodenal papilla, there can be two types of emesis: benign and malignant. If the obstruction is farther away from it, the baby will vomit bilirubin. Non-bilious emesis is brought on by obstruction close to the ampulla. Because the obstruction is proximal, the abdomen won't swell. A physical examination may reveal a palpable mass in the epigastrium.

8.2.2.3. Diagnosis

The abdominal x-ray's "double bubble" denotes the presence of air in the duodenum and stomach but not in the colon or distal small bowel. To rule out malrotation, which can also present with bilious emesis in infancy and is a surgical emergency, a UGI series needs to be obtained. A duodenal web, an intraluminal diverticulum that resembles an elongated, conical silhouette resembling a "windsock," may be seen during a UGI. Since trisomy 21 and its associated complications have been linked to other defects, an echocardiogram and renal ultrasonography are performed to rule out any other defects.

8.2.2.4. Surgical Management

"The diamond D," or diamond duodenoduodenostomy involves making a longitudinal incision in the duodenum's distal tapering section and a transverse incision in its proximal widened duodenum. To enable mucosal abutment between the two incongruent

duodenal diameters, the anastomosis is shaped like a diamond. Because duodenal webs are not always visible on pre-operative UGI and can result in persistent obstruction if left uncorrected, evaluation for them must be done during repair. If the web is found, it is excised by performing a longitudinal duodenotomy over the affected area. Its placement in relation to the major duodenal papilla needs to be carefully considered to preserve the ampulla of Vater's integrity. To prevent lumen narrowing, the duodenotomy is closed transversely.

8.2.2.5. Outcome

After duodenal atresia is corrected, long-term complications are typically rare, if they occur at all. A persistent obstruction might mean that the duodenal web was missed and needs to be reoperated. Early postoperative delayed gastric emptying is common and does not require treatment; most cases go away on their own with time, and enteral feedings can be advanced in small amounts as tolerated.

8.2.3. Pyloric Stenosis

Pyloric stenosis is an uncommon condition in infants where food cannot pass through the small intestine. Food is normally held in the stomach until it is prepared for the next phase of the digestive process by a muscular valve that exists between the stomach and the small intestine. This valve is known as the pylorus. Food cannot pass through the pylorus muscles of pyloric stenosis because they thicken and enlarge abnormally. The symptoms of pyloric stenosis include weight loss, dehydration, and forceful vomiting. Infants suffering from pyloric stenosis might exhibit constant hunger.

8.2.3.1. Embryology

The exact etiology is unknown. Exposure to erythromycin has been implicated as a risk factor.

8.2.3.2. Clinical Presentation

It is characterized by feeding intolerance and non-bilious emesis that becomes projectile over time; usually presenting around 2–4 weeks of life, however, may not present up until 6–12 weeks. Emesis is non-bilious because the site of obstruction, the pylorus, is proximal to the ampulla of Vater. It tends to occur in firstborn Caucasian males.

8.2.3.3. Diagnosis

On physical exam, may be able to palpate an "olive-like" firm, mobile mass in the right upper quadrant or epigastrium, however, this is often difficult to appreciate on a restless infant. The abdomen is otherwise soft and non-distended. Ultrasound is diagnostic and demonstrates a pyloric channel length ≥ 16 mm, a wall ≥4 mm in thickness.

Frequent vomiting of hydrochloric acid (HCl) causes dehydration, hypochloremia, and alkalosis. Hypovolemia causes an increase in aldosterone secretion, which in turn causes potassium and sodium resorption. The baby will therefore have hypochloremic, hypokalemic metabolic alkalosis, according to the laboratory panel. In exacerbating hypokalemia, extracellular hydrogen is exchanged for potassium to correct the acid-base imbalance. Acidic urine eventually results from the renal hydrogen-potassium pump being stimulated to resorb potassium and secrete hydrogen as hypokalemia worsens. This is known as "paradoxical aciduria" because, in an alkalotic state, bicarbonate secretion ought to be prioritized; however, the nephrons put potassium correction ahead of hydrogen loss.

8.2.3.4. Surgical Management

Pyloric stenosis is not a surgical emergency and operative intervention is deferred until electrolytes have normalized, ideally, chloride >95, bicarbonate <30. As the primary metabolic derangements are caused by volume and gastric

juice loss, resuscitation should be initiated with 10-20 cc/kg normal saline boluses. Once volume status has been adequately restored and urine output robust, potassium containing fluids (D5 1/2NS + 10 K/L) are administered at a maintenance rate.

In the past, a right subcostal transverse incision was made to perform a Ramstedt pyloromyotomy; however, laparoscopic surgery is increasingly being used nowadays. An incision is made longitudinally along the anterior surface of the pylorus, passing through the serosa and hypertrophied muscle before the submucosa emerges. This process is similar to slicing a grape's tough outer skin to reveal its smooth inner flesh. The myotomy's length indicates the location of the pylorus and proximal duodenum, which is marked by the antrum of the stomach proximally and the pyloric vein of Mayo distally. After surgery, oral feeding can begin 6-7 hours later and be progressed as tolerated.

8.2.3.5. Outcomes

Long-term results from pyloromyotomy are excellent and few infants, if any, have residual complications. Incomplete myotomy can present with persistent feeding intolerance in the peri-operative period and requires re-operation.

8.2.4. Biliary Atresia

Biliary atresia is a condition in infants in which the bile ducts outside and inside the liver are scarred and blocked. Bile cannot flow into the intestine, leading to a buildup in the liver, which causes damage. The damage leads to scarring, loss of liver tissue and function, and cirrhosis.

8.2.4.1. Embryology

The pathophysiology is unknown. Between 4 and 10 weeks of gestation, the extrahepatic biliary tract develops from the hepatic diverticulum. This occurs normally. In the post-natal period, there appears to be an inflammatory process that causes fibrosis of the extrahepatic biliary ducts.

8.2.4.2. Clinical Presentation

During the first two weeks of life, worsening jaundice that is not responsive to phototherapy and persistent direct hyperbilirubinemia are typical. Laboratory results show direct hyperbilirubinemia, and elevated alkaline phosphatase, and are consistent with biliary obstruction. There are indications of cholestasis, including dark urine and light- or gray-colored stools.

8.2.4.3. Diagnosis

The most sensitive and specific technetium-99 iminodiacetic acid scan (99-Tc IDA) is performed on the hepatobiliary system. Normally, the hepatocytes absorb the radiotracer, which is then easily eliminated into the intestines through the biliary ducts. Technetium will be absorbed by the liver in biliary atresia as usual, but the duodenum cannot receive radiotracer because of extrahepatic duct blockage. A small or completely destroyed gallbladder may be seen on an abdominal ultrasound. In addition, magnetic resonance cholangiopancreatography (MRCP) can be useful in ruling out choledocal cysts or intrahepatic atresia.

8.2.4.4. Surgical Management

Quick surgical intervention is essential because early biliary decompression increases the likelihood of survival and can even reverse liver damage. If the treatment is not successful after 3.4–5.6 months, irreversible liver damage may occur. The preferred procedure is the Kasai portoenterostomy. Initially, an intraoperative cholangiogram is carried out to confirm the diagnosis and outline the biliary tree's anatomy. The extent of liver damage is measured with a liver biopsy. The fibrotic common bile duct

is then excised after being separated from the hepatoduodenal ligament at the level of the porta hepatis. A Roux-en-Y hepaticojejunostomy is created and a 20 cm segment of the jejunum is brought up retrocolically.

8.2.4.5. Outcomes

Successful, long-term establishment of bile flow correlates with earlier surgical intervention. Infants aged <60 days at the time of surgery have the best results. Of children who have a portoenterostomy, about one-third survive for 10 years or longer; the remaining children eventually die of liver failure and need to be transplanted. Additional signs that a liver transplant is necessary include intrahepatic atresia, deficiencies in fat-soluble vitamins that prevent a person from thriving, and variceal hemorrhage brought on by portal hypertension. After a liver transplant, the 5-year survival rate varies from 75% to 95%. In addition to progressive liver failure, cholangitis is a significant post-operative complication that affects up to 50% of patients undergoing portoenterostomy surgery. Until proven otherwise, decreased bile flow, as shown by elevated total bilirubin in the presence of fever and leukocytosis, is essentially indicative of cholangitis. IV antibiotics and fluid resuscitation are used to treat it.

8.2.5. Choledochal Cysts

A choledochal cyst is a congenital abnormality of the duct that carries bile from the liver to the gallbladder and small intestine. Bile is produced by the liver to aid in food digestion. Bile can back up in the liver of a child who has a choledochal cyst, a swelling of that duct.

8.2.5.1. Embryology

The etiology is unknown. An aberrant pancreaticobiliary junction near the duodenal wall has been suggested.

8.2.5.2. Clinical Presentation

The signs of biliary obstruction in infants include light-colored stools, dark urine, and progressive jaundice. One may palpate a sore spot in the upper right quadrant of the abdomen. Laboratory results will show elevated levels of alkaline phosphatase and direct bilirubin, which are indicative of biliary obstruction. Additionally, pancreatitis or cholangitis may be present in patients.

8.2.5.3. Diagnosis

While abdominal ultrasound and hepatobiliary 99-Tc IDA scan are useful, MRCP best delineates the anatomy of the biliary tree and is the diagnostic test of choice.

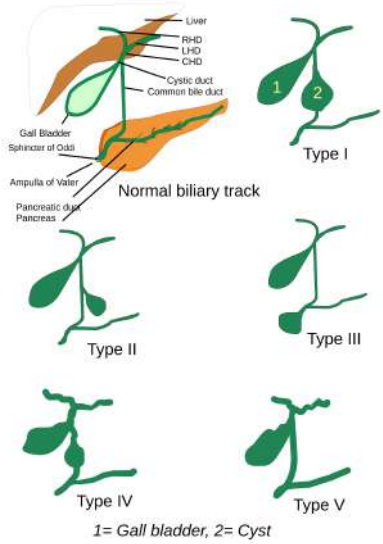


Figure 8.2. Normal anatomy of the hepatobiliary tree and its relationship to the pancreas and duodenum.

Source: By Drriad, I., CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2309266.

The types of choledochal cysts are: (A) Type 1: Fusiform dilation of the common bile duct, which is an extrahepatic duct. (B) Type 2:

Isolated diverticulum off the common bile duct. (C) Type 3: Supraduodenal choledococele. (D) Type 4: Cystic dilation of both the intrahepatic and extrahepatic bile ducts. (E) Type 5: Dilation of only the intrahepatic ducts.

There are five types (Figure 8.2). Type 1 is the most common and presents as saccular or fusiform dilation of the common bile duct (CBD). Intrahepatic ducts are normal. Type 2 is an isolated CBD diverticulum. Type 3 is a choledochocele, in which there is cystic dilation of the supra-duodenal CBD, prior to its junction with the pancreatic duct. In type 4 disease, intra- and extra-hepatic bile ducts are dilated whereas in type 5 disease only intra-hepatic ducts are dilated.

8.2.5.4. Surgical Management

Given the risk of cholangiocarcinoma, highest in types I and IV, surgical intervention is indicated at the time of diagnosis of any type of choledochal cyst. The approach depends on the type of lesion. For type 1 cysts, primary cyst excision with cholecystectomy and roux-en-Y hepaticojejunostomy reconstruction is the procedure of choice. Type 2 disease is managed by simple diverticulectomy. Type 3 is managed by transduodenal cyst excision or marsupialization and sphincteroplasty. Types 4 and 5 may be treated by anatomic hepatic resection based on the extent and location of the disease, however, liver transplantation is ultimately required in most cases.

8.2.5.5. Outcomes

Choledocal cyst excision has good long-term results and few significant side effects. The most dangerous consequence, biliary tract cancer, can arise from incomplete excision. Less serious complications include cholangitis, stricture formation, and choledocolithiasis, which are treated medically and endoscopically, respectively.

A Closer Look

Gut's Nervous System

The nervous system of the gut, known as the enteric nervous system (ENS), is a complex network of neurons embedded in the walls of the gastrointestinal (GI) tract, extending from the esophagus to the anus. Often referred to as the "second brain" due to its intricate structure and extensive capabilities, the ENS operates independently of the central nervous system (CNS) but communicates bidirectionally with it via the vagus nerve and other neural pathways.

Comprising approximately 500 million neurons, the ENS regulates various GI functions, including motility, secretion, blood flow, and immune response, to facilitate digestion and maintain gut homeostasis. It consists of two main plexuses: the myenteric plexus (located between the longitudinal and circular muscle layers) and the submucosal plexus (found in the submucosal layer). These plexuses coordinate muscle contractions, regulate glandular secretions, and monitor the chemical composition of luminal contents.

The ENS integrates sensory information from the GI tract, including mechanical distension, chemical stimuli, and the presence of nutrients, bacteria, and toxins, to modulate gut function and signal the CNS when necessary. This bidirectional communication enables the gut to respond adaptively to changes in its environment and maintain digestive efficiency.

Moreover, the ENS interacts closely with the gut microbiota, a diverse community of microorganisms residing in the GI tract, influencing each other's activities and contributing to gut health. The microbiota produces neurotransmitters, such as serotonin and gamma-aminobutyric acid (GABA), that modulate ENS activity, while the ENS regulates gut motility and mucosal integrity, shaping the composition and function of the microbiota.

Dysfunction of the ENS is implicated in various GI disorders, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and gastroparesis, highlighting its crucial role in gut health and disease. Therapeutic approaches targeting the ENS, such as neuromodulation, pharmacological agents, and lifestyle interventions, offer promising avenues for the management of GI disorders and the restoration of gut function.

The gut's nervous system, or enteric nervous system, is a sophisticated neural network that governs gastrointestinal function and interacts dynamically with the central nervous system and gut microbiota. Understanding the complexities of the ENS provides insights into the mechanisms underlying gut-brain interactions and opens new avenues for the development of therapies targeting GI disorders and promoting gut health.

Summary

- An important early stage in the development of the gastrointestinal (GI) system is the formation and differentiation of the primitive gut tube, which lays the groundwork for the complex structures that will facilitate digestion, absorption, and waste elimination.
- Due to the embryo's lateral and cephalocaudal folding, a portion of the yolk sac is incorporated into the developing embryo, forming the primitive gut.
- The superior mesenteric artery supplies the derivatives of the midgut, which include the distal half of the duodenum, jejunum, ileum, cecum, appendix, ascending colon, and the proximal two-thirds of the transverse colon.
- The gastrointestinal tract (GIT) is composed of the stomodeum, an ectodermal depression at the cranial end of the embryo, and the proctodeum, an ectodermal depression at the caudal end.
- Pyloric stenosis is an uncommon condition in infants where food cannot pass through the small intestine. Food is normally held in the stomach until it is prepared for the next phase of the digestive process by a muscular valve that exists between the stomach and the small intestine.
- Biliary atresia is a condition in infants in which the bile ducts outside and inside the liver are scarred and blocked. Bile cannot flow into the intestine, leading to a buildup in the liver, which causes damage.

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Chapter

DEVELOPMENT OF THE URINARY SYSTEM

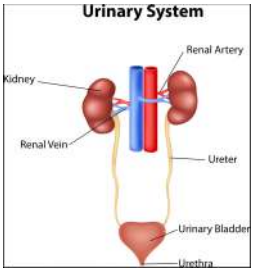
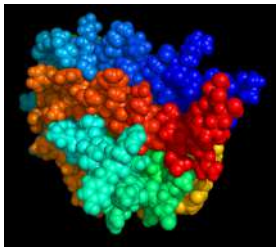
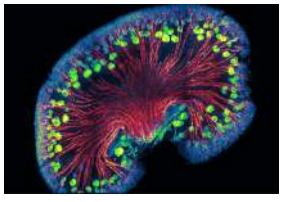
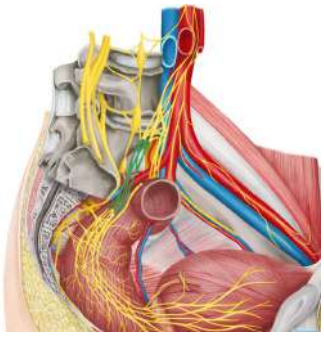
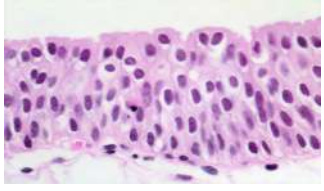
9

Contents

Unit Introduction

The urinary system serves several purposes, including blood purification and waste removal from the body. Additionally, the system performs other equally significant tasks. Consider pH regulation, which is regulated by both the lungs and the blood's buffers. Furthermore, the heart and blood vessels both play a part in blood pressure regulation. The urinary system also controls the solute concentration in the blood. Did you know that the kidneys play a significant role in determining the concentration of red blood cells? The kidneys produce 85% of the erythropoietin (EPO) that stimulates the production of red blood cells. The kidneys also perform the final synthesis step of vitamin D production, converting calcidiol to calcitriol, the active form of vitamin D. Serum chemistry profiles, urinalysis, aerobic bacterial urine culture, history and physical examination findings, and signalment can all be used to diagnose a variety of urinary system abnormalities. Changes in water intake, frequency of urination, amount of urine produced, urine appearance, and behavior should all be documented in the history. Acquiring information regarding past and present medication administration, appetite, diet, changes in body weight, and injuries or illnesses is also crucial.

Orientation and Directional Terms

Terms	Definition	Illustration
Urinary system	The urinary system's function is to filter blood and create urine as a waste by-product. The organs of the urinary system include the kidneys, renal pelvis, ureters, bladder and urethra.	
Erythropoietin	Erythropoietin is a hormone that your kidneys naturally make to stimulate the production of red blood cells. High or low levels of erythropoietin can cause health problems.	
Nephrogenesis	Nephrogenesis refers to the process of kidney development. It encompasses the formation and maturation of nephrons, which are the functional units of the kidney responsible for filtering blood and producing urine.	
Ureteric plexus	The ureteric plexus is a nerve plexus covering and innervating the ureter. The plexus can be graduated into three parts, as the ureter itself can be divided: In the upper part of the ureter, the plexus gets its nerve fibers mainly from the renal plexus, but also from the abdominal aortic plexus.	
Urothelium	The urothelium is a highly specialized type of tissue that lines the inside of your urinary tract. It serves as a barrier, preventing urine (pee) from leaking out into your body.	

9.1. Anatomy and Physiology of Urinary System

The urinary system is in charge of producing and secreting urine as well as filtering waste products from the blood. These processes support the preservation of bodily fluid volume and composition.

Although it has far-reaching effects, the urinary system is relatively simple anatomically and consists of:

- Kidneys;
- Ureters;
- Bladder;
- Urethra.

The kidneys, which create urine and filter blood, are the primary organs. The remaining components are merely supporting structures for the movement and holding of urine. Nitrogen enters the circulation when protein and nucleic acids break down normally. Most of this nitrogen is disposed of, but some is recycled to create new cellular products. Nitrogen is wasted, and the body needs a way to get rid of it because blood levels of it can be hazardous, so it combines with hydrogen to form NH_3, or ammonia, which dissolves easily in water.

9.1.1. Processes and Events in Kidney Development

The formation of kidneys, also known as nephrogenesis, is a carefully orchestrated process that begins in the embryonic stage and continues into postnatal development. It involves a series of ordered events and communication between various cell types and signaling pathways, resulting in the creation of fully functional kidneys that can filter waste from the blood and regulate fluid and electrolyte levels. The development of the kidneys begins around the fifth week of gestation and proceeds through several distinct stages:

1. **Pronephros Formation:** The pronephros, a temporary embryonic structure that acts as a forerunner to the final kidneys, forms at the earliest stage of kidney development. Prosphric tubules and nephric ducts make up the pronephros, which originates from intermediate mesoderm. The pronephros regresses and has little effect on kidney function.
2. **Mesonephros Development:** Early in embryonic development, the mesonephros develops and becomes functional as a stand-in kidney after the pronephros retreats. Mesonephric tubules and nephric ducts, which make up the mesonephros, are involved in excretion and fluid balance in the growing embryo.
3. **Metanephros Induction:** Beginning around the fifth week of gestation, the ureteric bud (derived from the Wolffian duct) and the metanephric mesenchyme (derived from the intermediate mesoderm) interact reciprocally to form the metanephros, the definitive kidney in mammals. In this process, signaling molecules like Wnt, GDNF (glial cell-derived neurotrophic factor), and BMP (bone morphogenetic protein) are essential. The collecting duct system is created by the branching morphogenesis of the ureteric bud, and the kidney's functional units, nephrons, are formed by the mesenchymal-to-epithelial transition of the metanephric mesenchyme.
4. **Nephrogenesis:** The process

of nephrogenesis includes the development of nephrons, which are made up of a renal tubule (which includes the distal tubule, loop of Henle, proximal tubule, and collecting duct) and a renal corpuscle (which includes a glomerulus and Bowman's capsule). Nephrogenesis proceeds in a stepwise fashion, beginning in the kidney's cortical region and ending in the medulla. The process includes the formation of cap mesenchyme, renal vesicles, S-shaped bodies, comma-shaped bodies, and intricate interactions between the ureteric bud and the metanephric mesenchyme. Nephron formation and patterning are crucially regulated by signaling pathways like Notch, FGF (fibroblast growth factor), and RAAS (renin-angiotensin-aldosterone system).

5. **Maturation and Differentiation:** Nephrons mature and differentiate during the course of nephrogenesis to acquire their specific functions, such as filtration, reabsorption, and secretion. Different cell types within the nephron, including podocytes, proximal tubule cells, loop of Henle cells, distal tubule cells, and intercalated cells in the collecting duct, develop during this process.

Kidney development is a meticulously planned process with several phases and complex molecular mechanisms. Understanding the procedures and occurrences involved in kidney development is crucial for both preventing and treating diseases related to the kidneys. Abnormalities or disruptions in nephrogenesis can result in congenital kidney anomalies and renal disorders.

9.1.2. Kidneys

Mammals have spherical or bean-shaped kidneys. They are situated outside the membrane known as the peritoneum, which encloses the abdominal cavity's organs. They are called "retroperitoneal" due to their position. "Perirenal fat" is the term for the fat tissue that surrounds them. The kidney is encapsulated in fibrous tissue. The term "hilum" refers to the bean shape's indentation. The renal vein and ureter exit the kidney at the hilum, which is also the site where the renal artery enters the kidney. The outer cortex and the inner medulla are the two separate sections that make up the kidney. Blood is filtered in the cortex by microscopic structures known as glomeruli.

Urine is concentrated in the medulla via a sophisticated tubule network. By absorbing the water and electrolytes and keeping waste materials from being reabsorbed, they achieve this. The term "nephron" refers to a single glomerulus and the associated set of tubules that make up the microscopic functional unit of the kidney.

Multiple nephron tubules are arranged into larger, visible kidney regions known as pyramids. The gaps between the renal pyramids, known as the renal columns, give blood vessels a path to the cortex. The pyramids' tips, known as papillae, are responsible for draining urine from nephron tubules into bigger passageways called minor calyces. The minor calyces merge to form the major calyces, which are even larger vessels. These enlarge to form the ureters aperture. The renal pelvis is the term for this collection chamber.

9.1.3. Nephrons

The actual filtration components of the kidneys are called nephrons. Via the renal artery, blood enters the kidneys and passes through branching arteries. These arteries eventually shrink to become known as afferent arterioles as they

enter the nephron. There is a lot of pressure on the blood in these vessels. The glomerulus, a collection of capillaries housed in a shell is called Bowman's capsule. It receives the afferent arteriole branch. Salts, glucose, amino acids, and water are forced out of the blood vessels and into the Bowman's capsule by the blood pressure. Because most proteins and blood cells are too large to be filtered out, they remain inside the blood vessel and exit the glomerulus through the efferent arteriole.

Microscopic anatomy of a nephron:

- Bowman's capsule;
- Glomerulus;
- Afferent arteriole;
- Efferent arteriole;
- Proximal convoluted tubule;
- Distal convoluted tubule;
- Collecting duct;
- Loop of Henle;
- Peritubular capillary.

The network of tubules that concentrates the filtrate into urine is accessed through Bowman's capsule. Capillaries, which are tiny blood vessels, encircle the tubules. Materials are reabsorbed back into the blood in this capillary. Due to its twisted shape, the first segment of the tubule is appropriately called the proximal convoluted tubule. Here, all of the glucose and amino acids are reabsorbed along with 99% of the water. Urine containing glucose or amino acids indicates a medical condition. For example, excessive blood glucose in diabetics is excreted in the urine because they are unable to reabsorb it. The proximal convoluted tubule leads to the loop of Henle, a lengthy looping structure that descends into the kidney's medulla. Here, more electrolytes (salts) and water are absorbed. The distal convoluted tubule, where extra potassium ions, hydrogen ions, and certain medications or toxins are transferred from the blood into the filtrate, is the next structure the filtrate passes through. The finished product is subsequently discharged into a sizable collecting duct, where several nephrons empty. This collecting duct travels via the calyxes, the pyramidal papillae, and the renal pelvis before exiting through the ureter.

9.1.4. Ureters

The ureters are tubes made of smooth muscle that propel urine from the kidneys to the urinary bladder. In a human adult, the ureters are usually 20–30 cm (8–12 in) long and around 3–4 mm (0.12–0.16 in) in diameter. The ureter is lined by urothelial cells, a type of transitional epithelium, and has an additional smooth muscle layer that assists with peristalsis in its lowest third.

Numerous conditions, such as kidney stones and urinary tract infections, can harm the ureters. The development of two ureters on the same side or ureters positioned abnormally are examples of congenital abnormalities affecting the ureters. In addition, children frequently experience reflux—the backflow of urine up the ureters from the bladder.

The ureters have been identified for at least 2,000 years, with the word "ureter" stemming from the stem uro-relating to urinating and seen in written records since at least the time of Hippocrates. It is, however, only since the 1500s that the term "ureter" has been consistently used to refer to the modern structure, and only since the development of medical imaging in the 1900s that techniques such as X-ray, CT, and ultrasound have been able to view the ureters.

The ureters are muscular tubes that transport urine from the kidneys to the urinary bladder. Ureters have three layers of tissue:

Microscopic anatomy of the ureter:

1. Fibrous outer coat;
2. Muscular layer;

3. Inner mucosal layer.

The muscle layer is the functional layer, using peristalsis to move the urine along. Peristalsis is a waving contraction of the muscles to propel the contents of a tube in one direction. In this case, the urine is propelled to an opening at the base of the bladder.

9.1.4.1. Structure

The ureters are tubular structures, approximately 20–30 cm (7.9–11.8 in) in adults, that pass from the pelvis of each kidney into the bladder. From the renal pelvis, they descend on top of the psoas major muscle to reach the brim of the pelvis. Here, they cross in front of the common iliac arteries.

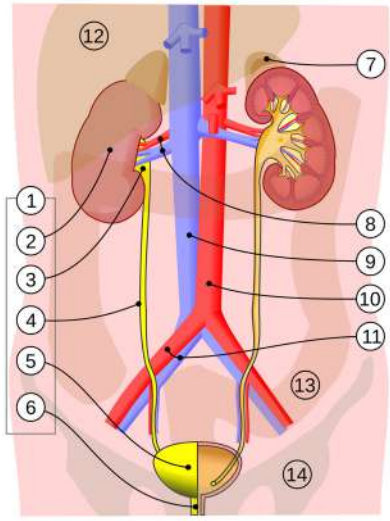


Figure 9.1. *Structures that are near the ureters. (1) Human urinary system: (2) Kidney; (3) renal pelvis; (4) ureter; (5) urinary bladder; (6) urethra. (left side with frontal section); (7) adrenal gland vessels: (8) Renal artery and vein; (9) inferior vena cava; (10) abdominal aorta; (11) common iliac artery and vein with transparency: (12) liver; (13) large intestine; and (14) pelvis.*

Source: https://upload.wikimedia.org/wikipedia/commons/thumb/3/30/Urinary_system.svg/1200px-Urinary_system.svg.png.

They then pass down along the sides of the pelvis and finally curve forward and enter the bladder from its left and right sides at the back of the bladder. The ureters are 1.5–6 mm (0.059–0.236 in) in diameter and surrounded by a layer of smooth muscle for 1–2 cm (0.39–0.79 in) near their ends just before they enter the bladder (Figure 9.1).

The ureters enter the bladder from its back surface, traveling 1.5–2 cm (0.59–0.79 in) before opening into the bladder at an angle on its outer back surface at the slit-like *ureteric orifices*. This location is also called the vesicoureteric junction. In the contracted bladder, they are about 25 mm (1 in) apart and about the same distance from the internal urethral orifice; in the distended bladder, these measurements may be increased to about 50 mm (2 in).

Several anatomical features traverse the ureters as they descend from the kidneys to the bladder, passing by, above, and around them. The ureter passes through the psoas major muscle and ends up directly behind the peritoneum in its upper portion. It crosses the genitofemoral nerve as it moves through the muscle. The midline of the right and left ureters is where the inferior vena cava and abdominal aorta are located, respectively. The right ureter is located in the lower abdomen behind the terminal ileum and lower mesentery, while the left ureter is situated behind the sigmoid colon and jejunum. The ureters pass in front of the internal iliac veins and arteries as they enter the pelvis, where they are encircled by connective tissue and travel back and forth. Subsequently, they traverse the inferior vesical, middle rectal, and umbilical arteries as they move inward and forward. From here, in males, they enter the bladder close to the trigone by passing in front of the seminal vesicles and beneath the vas deferens. The ureters in females pass behind the ovaries and proceed through the lower midline segment of the uterine broad ligament. For a

short part, the uterine arteries travel on top for a short (2.5 cm (0.98 in) period. They then pass by the cervix, traveling inward towards the bladder.

9.1.4.2. Blood and Lymphatic Supply

Along its course, the ureter receives supply from a variety of arteries. The renal arteries supply the portion of the ureter that is closest to the kidney, or its upper third. The gonadal arteries—which are the ovarian artery in women and the testicular artery in men—as well as direct branches from the abdominal aorta supply the middle portion of the ureter. The inferior and superior vesical arteries are the principal branches of the internal iliac arteries that supply the lower third of the ureter, which is closest to the bladder.

The middle rectal artery, branches straight from the aorta, and, in women, the uterine and vaginal arteries are some of the arteries that can contribute to the varying arterial supply. The arteries that supply the ureters terminate in an intricate network of vessels found in the advententitia off ureters. Due to the numerous connections (anastamoses) among the arteries, especially in the adventitia, damage to one vessel does not affect the ureter's ability to supply blood. Venous drainage starts as a network of smaller veins in the adventitia and primarily follows the pattern of arterial supply.

The renal veins drain the upper ureters, while the vesicular and gonadal veins drain the lower ureters. The location of lymphatic vessels in the ureter affects lymphatic drainage. Submucosal, intramuscular, and adventitial lymphatic vessels are where lymph gathers. The lateral aortic nodes close to the gonadal vessels receive the drainage from the vessels that are closer to the kidney, which then flows into renal collecting vessels. The right paracaval and interaortocaval nodes on the right and the left paraaortic nodes on the left receive the middle section of the ureter's drainage. Lymph from the lower ureter may empty into the external, internal, or common iliac lymph nodes in the pelvis, or it may empty into the common iliac lymph nodes.

9.1.4.3. Nerve Supply

The ureteric plexus, located in the adventitia of the ureters, is a network (plexus) of nerves that supply the ureters abundantly. The plexus is comprised of several directly connected nerve roots (T9–12, L1, and S2-4) as well as branches from other nerve plexuses and nerves. Specifically, the aortic plexus, upper hypogastric plexus, and middle ureter receive branches from the nerve, while the lower ureter receives branches from the lower hypogastric plexus and nerve. The adventitia contains the plexus. The ureteric plexus is formed by these nerves traveling in separate bundles along small blood vessels. The amount of sensation is greatest near the bladder and least near the kidneys.

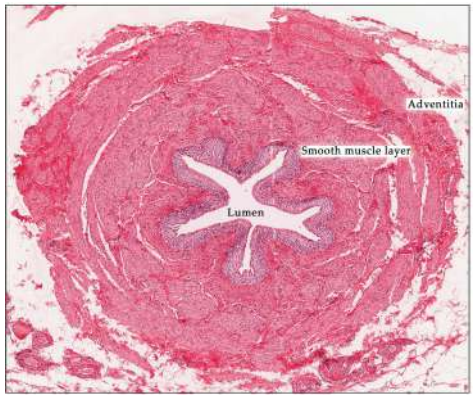
Sensation to the ureters is provided by nerves that come from T11–L2 segments of the spinal cord. When pain is caused, for example by a spasm of the ureters or by a stone, the pain may be referred to the dermatomes of T11–L2, namely the back and sides of the abdomen, the scrotum (males) or labia majora (females) and upper part of the front of the thigh.

9.1.4.4. Microanatomy

The epithelium is surrounded by a significant number of muscle fibers, and the adventitia lies beyond this. A microscopic view of the ureter, displaying the purple cells that make up the epithelium adjacent to the lumen is shown here.

The urothelium, a type of transitional epithelium that can adapt to ureteric stretches, lines the inside of the ureter. When the transitional epithelium is relaxed, it can take the form of a layer of columnar cells; when it

is distended, it takes the form of flatter cells. The lamina propria is located beneath the epithelium. The lamina propria is composed of lymphatics, veins, and blood vessels scattered throughout a loose connective tissue layer with numerous elastic fibers. Two layers of muscle encircle the ureter: an outer, circular, or spiral layer of muscle and an inner, longitudinal layer. A third layer of muscle surrounds the lower portion of the ureter. An advententitia with veins, lymphatic vessels, and blood vessels is located beyond these layers.



Source: https://upload.wikimedia.org/wikipedia/commons/thumb/1/17/2607_Ureter.jpg/1073px-2607_Ureter.jpg.

9.1.4.5. Development

The ureteric buds, which protrude from the mesonephric duct, give rise to the ureters. This is a mesoderm-derived duct that is present in the early embryo. With time, the buds dilate, become longer, and split into the left and right ureters. They also move into the surrounding mesodermal tissue. Subsequent divisions from these buds eventually form the kidney's collecting ducts, pelvis, major and minor calyces, and ureters.

The cloaca, which divides into the anorectal canal and the urogenital sinus during development, is linked to the mesonephric duct. The urogenital sinus gives rise to the bladder. With time, the surrounding portions of the primitive ureters are absorbed by the expanding bladder. Ultimately, because of the kidneys' upward migration during development, the ureters' entry points into the bladder migrate upward (Figure 9.2).

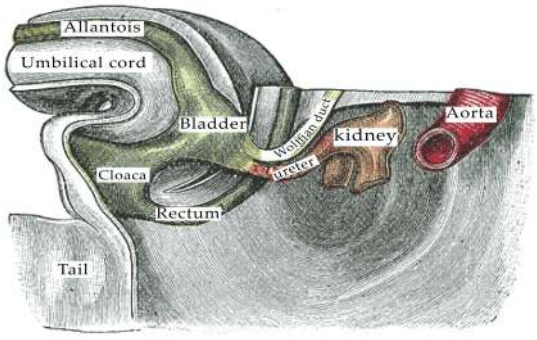


Figure 9.2. *Image showing the bottom part of an 4–5 weeks old embryo. Here, the ureter (in orange) can be seen emerging from the bottom of the mesonephric duct (labelled "Wolffian duct"), connected to the primitive bladder.*

Source: Image from Gray's Anatomy 1918 edition; https://upload.wikimedia.org/wikipedia/commons/a/a6/Gray1116.png.

9.1.5. Urinary Bladder

The urinary bladder temporarily stores urine. It is situated in the pelvic cavity. The fibrous connective tissue covers the exterior. The detrusor muscle is a layer of muscle found inside the connective tissue. This smooth muscle contracts, causing the bladder to release urine. The mucosa, which lines the inside of the bladder, is supported by the submucosa, an elastic fibrous membrane, which is the next tissue layer.

The specialized cells known as transitional epithelium make up the mucosa. The mucosa of the bladder has numerous folds known as rugae when it is empty. When the bladder is filled with urine, the rugae and transitional epithelium allow the bladder to expand. The openings of the

two ureters and the urethra combine to form the trigone, a triangular structure at the base of the bladder. An internal urethral sphincter is formed when a band of detrusor muscle surrounds the urethra's opening. When the bladder is about halfway full, this sphincter, which is innervated, relaxes due to involuntary muscle control.

9.1.6. Urethra

The urethra, which has thin walls, is the final channel through which urine exits the bladder. This tube connects the exterior of the body to the base of the bladder. In females, the urethra is relatively short, connecting the external urethral sphincter to the bladder. However, it is longer in males. It travels the entire length of the penis after passing through the prostate gland and arriving at the external sphincter.

Interesting facts:

- Each kidney has over a million nephrons.
- The male urethra is also the pathway for products of the reproductive system.
- Even if 75% of the nephrons are lost, the kidney will still function. It is possible to live a healthy life with only one kidney.
- Urine was once used as a cleaning product!
- Normal urine is sterile (germ-free). It is composed of water, salts, and waste products.
- Reptiles have adapted a very long loop of Henle to facilitate more water reabsorption to prevent dehydration.

9.1.7. Formation of the Nephron and Establishment of Renal Function

Nephrogenesis, the process that forms the nephron, the kidney's functional unit, occurs during kidney development and is essential to the establishment of renal function. Nephrogenesis involves complex interactions between various cell types and signaling pathways, starting during embryonic development and continuing into the postnatal period.

The process of nephron formation can be divided into several key stages:

1. **Induction and Specification:** The ureteric bud, which develops from the Wolffian duct, and the metanephric mesenchyme, which comes from the intermediate mesoderm, engage in reciprocal interactions to initiate the development of the nephron. Wnt, BMP, and GDNF are examples of signaling molecules that are important in causing the metanephric mesenchyme to differentiate into cells that are precursors to the nephron.
2. **Condensation and Mesenchymal-to-Epithelial Transition (MET):** Under the influence of signaling cues from the ureteric bud, the metanephric mesenchyme undergoes condensation, forming aggregates known as cap mesenchyme. Subsequently, cap mesenchyme cells undergo MET, transitioning from a mesenchymal to an epithelial phenotype. This transition is characterized by changes in cell shape, cell-cell adhesion, and expression of molecular markers such as Pax2 and Wt1.
3. **Renal Vesicle Formation:** Following MET, additional morphological changes in the cap mesenchyme result in the formation of renal vesicles, the precursors of the renal

tubules. The proximal convoluted tubule, loop of Henle, distal convoluted tubule, and connecting tubule are all produced by renal vesicles, which are composed of an epithelial monolayer encircling a central lumen.

4. **Comma-Shaped and S-Shaped Bodies:** Renal vesicles develop further, going through structural changes that result in comma-shaped bodies with an indentation on one side. S-shaped bodies, which symbolize later phases of nephron development, develop from comma-shaped bodies. S-shaped bodies have a characteristic curvature that makes the proximal and distal segments of the nephron visible.
5. **Glomerular Development:** The vascularization of the nephron takes place concurrently with tubular morphogenesis, resulting in the formation of the glomerulus, which is the site of blood filtration. Renal vesicles develop when endothelial cells from the metanephric mesenchyme invade and form capillary loops. Podocytes from the epithelial cells of the renal vesicle then envelop these capillary loops. The generation of filtration slits and specialized intercellular junctions—both necessary for the selective filtration of blood components—are involved in this complex process.
6. **Maturation and Differentiation:** Nephron segments develop specific functions as a result of the differentiation of various cell types during the course of nephrogenesis. Reabsorbing water and other solutes is the responsibility of proximal tubule cells, whereas the medulla's loop of Henle cells creates an osmotic gradient. Through secretion and reabsorption processes, collecting duct cells and distal tubules control acid-base homeostasis and electrolyte balance.

As nephrogenesis advances and nephrons integrate into the renal architecture, renal function is established. The development of the glomerular filtration, tubular reabsorption, and secretion mechanisms required for urine production and the preservation of bodily homeostasis constitute functional maturation of the nephron. The significance of nephron formation in renal physiology and general health is highlighted by the coordinated development of nephrons, which guarantees the kidneys' correct functioning in filtration, excretion, and regulation of fluid and electrolyte balance. Understanding the mechanisms underlying nephron development is crucial for the prevention and treatment of kidney-related diseases, as disruptions or abnormalities in nephrogenesis can result in congenital kidney anomalies and renal disorders.

9.2. Composition of Urine

Urination is the process by which the kidneys produce and expel urine, a liquid byproduct of the body, through the urethra. Urine's typical chemical makeup consists primarily of water, but it also contains nitrogenous molecules like urea, creatinine, and other waste products. Damage or infection to the kidney's glomeruli may cause other substances to be expelled in the urine, changing the nephron's capacity to filter or reabsorb the various components of blood plasma.

- Ø **Normal Chemical Composition of Urine:** Urine is an aqueous

solution of greater than 95% water, with a minimum of these remaining constituents, in order of decreasing concentration:

- Urea 9.3 g/L.
- Chloride 1.87 g/L.
- Sodium 1.17 g/L.
- Potassium 0.750 g/L.
- Creatinine 0.670 g/L.
- Other dissolved ions, inorganic and organic compounds (proteins, hormones, metabolites).

Up until it enters the urethra, where facultatively anaerobic gram-negative rods and cocci colonize the epithelial cells lining the urethra, urine is sterile. While ammonia can be extremely toxic to mammals, urea is essentially a processed form of ammonia that is not. The liver uses carbon dioxide and ammonia as raw materials to produce urea.

Ø **Abnormal Types of Urine:** Urine can exhibit abnormal characteristics or contain components that are not normal under many conditions. Most people refer to them with the suffix -uria.

Some of the more common types of abnormal urine include:

- **Proteinuria:** Protein content in urine, often due to leaky or damaged glomeruli.
- **Oliguria:** An abnormally small amount of urine, often due to shock or kidney damage.
- **Polyuria:** An abnormally large amount of urine, often caused by diabetes.
- **Dysuria:** Painful or uncomfortable urination, often from urinary tract infections.
- **Hematuria:** Red blood cells in urine, from infection or injury.
- **Glycosuria:** Glucose in urine, due to excess plasma glucose in diabetes, beyond the amount able to be reabsorbed in the proximal convoluted tubule.

Ø **Urine Composition: What's Normal?:** Urine is a liquid waste product that the body produces and eliminates. It is excreted through the urethra after being secreted by the renal tubules and building up in the bladder. Although water makes up 91–96% of its composition, it also contains a variety of other liquid and solid substances (Figure 9.3).

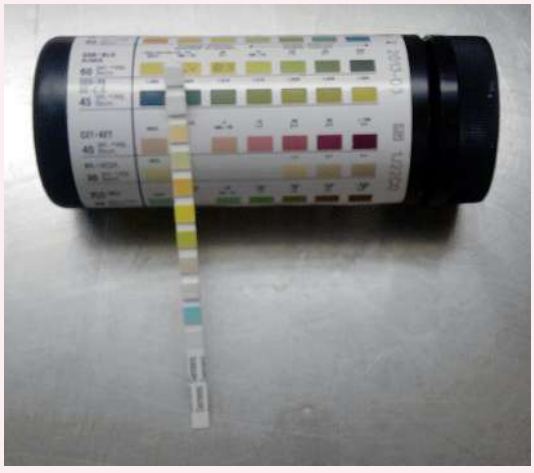


Figure 9.3. *Check-up. Medical report and urine test strips.*

Source: By J3D3 – Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=18675760.

Ø **Urine Osmolarity:** It is a way to assess the concentration of the urine and may vary between

50 and 1,200 mOsmol/kg. on average, urinary solute comes to about 1,000 mOsmol/ day, with approximately 1.4 liters of urine being secreted per day. The amount and concentration of urine vary with the level of exertion, the environment, the level of hydration, and the intake of salt and protein. The solute concentration is higher in meat-eaters, because of the large amount of urea obtained from meat, whereas lower solutes are formed in vegetarians who get most of their energy from carbohydrates.

Ø **Urinary Physical Characteristics:**

- The pH of urine is normally around 6.2 with a range of 5.5–7.0. A high dietary protein and alcohol intake leads to a lower pH, while vegetables and fruit bring about a more alkaline pH.
- The specific gravity of urine may range from 1.002 to 1.037.
- The mean calorific content of urine may be approximately 100 kcal/day.

Ø **Urine Composition:** Over 99% of urinary solutes are composed of only 68 chemicals which have a concentration of 10 mg/L or more. 42 compounds are involved. They may be classified as follows:

- Electrolytes such as sodium, potassium, calcium, magnesium, and chloride.
- Nitrogenous chemicals such as urea and creatinine.
- Vitamins.
- Hormones.
- Organic acids such as uric acid.
- Other organic compounds.

Ø **Total Dissolved Solids:** These in urine constitute between 24.8 to 37.1 g/kg. Urinary solids are primarily made up of organic matter, largely volatile solids. Urine has large amounts of nitrogen, phosphorus, and potassium. Nitrogen content in urine is high, mostly in urea, which makes up more than 50% of the total organic acids. This includes urea from protein metabolism, sodium and potassium both of which come from food. Dry solids thus comprise 14–18% nitrogen, 13% carbon, and 3.7% each of potassium and phosphorus. The largest excretion of these substances from the body is through urine.

Ø **Nitrogen Excretion:** Nitrogen in urine is excreted mostly as urea, with about 11 g per day being the average excretion of nitrogen. It is most significantly affected by dietary protein intake, with a correlation of 0.91 existing between protein in the diet and urinary nitrogenous components. About 80% of the dietary intake of nitrogen is balanced by the urinary excretion of nitrogenous compounds. Urinary urea concentration ranges from 9 to 23 g/L.

Creatinine is another important nitrogenous compound in urine, and its level depends on the body mass and muscle mass, as well as age. Gender differences may be correlated with these. On average, creatinine production in the body is about 1.6 g/day. The third nitrogenous compound in urine is nitrate, which is present

in higher concentrations in those who consume a high-protein diet. Dietary protein influences not only the concentrations of urine nitrogen but also the levels of other minerals like potassium and phosphorus. Furthermore, a very low protein diet may have an impact on calcium levels.

- **Calcium in Urine:** Calcium excretion is affected by protein intake, as above, and is heavily influenced by sodium excretion. A low sodium diet, therefore, will decrease calcium excretion and vice versa.

  A normal urinary sample from an adult collected over 24 hours should receive a calcium level of 100 to 250 mg.
- **Other Ions:** Other less common ionic groups in urine include ammonium, sulfates from amino acids, and phosphates depending on parathyroid hormone levels.
- **Overall Solute Concentrations:** The concentration of the following constituents in urine may be regarded as a careful approximation:
  - **Urea:** 9.3 g/dL.
  - **Creatinine:** 0.670 g/ L.
  - **Sodium:** 1.17 g/L.
  - **Potassium:** 0.750 g/L.
  - **Chloride:** 1.87 g/L.

9.2.1. Regulation of Urine Concentration and Volume

The pituitary gland secretes antidiuretic hormone (ADH) to regulate the volume of water reabsorbed in the collecting ducts. Urine is produced to regulate the body's water balance and to eliminate numerous waste products from cells. Since more urine will result in less water in the blood, urine volume regulation is in a sense a component of homeostasis since it directly controls blood volume. Several intricate systems, including the relatively simple antidiuretic hormone (ADH) feedback system and the more complex renin–angiotensin system, are involved in controlling blood volume and urine production.

9.2.1.1. Anti-Diuretic Hormone Feedback

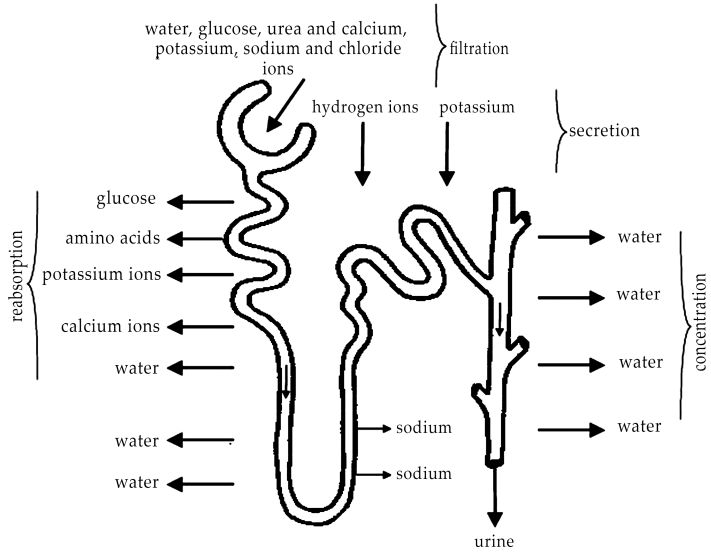
ADH is the main example of an anti-diuretic—a chemical that reduces the volume of urine produced by the body. The posterior pituitary gland secretes the hormone ADH in response to elevated plasma osmolarity (i.e., elevated ion concentration in the blood), which is typically brought on by either a decrease in plasma volume or an increase in ion concentration relative to plasma volume. Osmoreceptors in the hypothalamus detect the elevated plasma osmolarity, which triggers the posterior pituitary gland to release ADH. Following this, ADH interacts with the kidney nephrons to raise the osmolarity of urine and decrease plasma.

The distal convoluted tubule and collecting duct, which are normally impermeable to water, become more permeable to water when ADH is present. Urine production is reduced in comparison to its ion content due to this effect, which also increases water reabsorption and retention. The hypothalamus's osmoreceptors will inactivate and ADH secretion will stop when ADH acts on the nephron to raise urine osmolarity and decrease plasma osmolarity, which increases blood volume. ADH secretion is regarded as a type of negative feedback as a result of this reaction.

9.2.1.2. Diuretics

Any substance that acts in the opposite way to ADH by increasing urine volume, decreasing urine osmolarity, increasing plasma osmolarity, and frequently reducing blood volume, is called a diuretic. Various substances possess diuretic

properties through distinct mechanisms. For example, water can directly prevent the pituitary gland from secreting ADH. On the other hand, caffeine functions as a diuretic by interfering with sodium reabsorption, which lowers the quantity of water reabsorbed by sodium cotransport, and by momentarily raising blood pressure, which raises the glomerular filtration rate. Due to their inhibition of ATPase pumps, which further slows down water reabsorption, many medications are diuretics.



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9.2.2. Urinalysis

One of the most widely used techniques for medical diagnosis is a urinalysis (UA), also referred to as routine and microscopy (R&M), which is a series of tests conducted on urine. Urinalysis, which is the analysis of urine, is a diagnostic tool for a number of illnesses. In a urinalysis, a variety of substances and cells are measured or quantified in addition to other attributes like specific gravity. Urine test strips can be used to perform a portion of a urinalysis; the test results are read as the color of the strip changes. Urine sample light microscopy is an additional technique. Doctors will request either a routine or a routine and microscopy (R&M) urinalysis when they order one; the distinction being that a routine urinalysis excludes microscopy and culture. R&M is a valuable diagnostic tool for certain urinary tract infections because it is specifically used to culture bacteria found in urine.

9.2.2.1. Test Strip Urinalysis

Test strip urinalysis exposes urine to strips that react if the urine contains certain cells or molecules. Test strip urinalysis is the most common technique used in routine urinalysis. A urine test strip can identify:

- **Leukocytes:** Their presence in urine is known as leukocyturia.
- **Nitrites:** Their presence in urine is known as nitrituria.
- **Proteins:** Their presence in urine is known as proteinuria, albuminuria, or microalbuminuria.
- **Blood:** Its presence in urine is known as hematuria.
- **pH:** The acidity of urine is easily quantified by test strips, which can identify cases of metabolic acidosis or alkalosis.

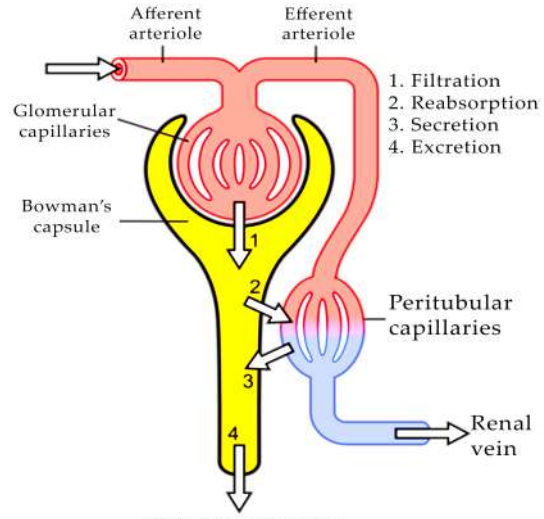
9.2.2.2. Urine Microscopy

The quantity and kinds of cells and/or material (urinary casts, for example) can provide a wealth of information and point toward a particular diagnosis. Any tiny structure found in urine that is made up of several molecules or cells bound together is called a urinary cast. When aberrant cells and molecules are removed from blood and expelled as the bound structures in urine, casts form inside the nephron. Microscopy can identify casts in urine and use them to diagnose kidney diseases, by characterizing symptoms such as:

- Red blood cell casts are associated with glomerulonephritis, vasculitis, or malignant hypertension.
- White blood cell casts are associated with acute interstitial nephritis, exudative glomerulonephritis, or severe pyelonephritis.
- Epithelial cell casts are associated with toxin-induced, acute tubular necrosis, hepatitis, and cytomegalovirus.
- (Heme) granular casts are associated with acute tubular necrosis and are often composed of proteins, especially antibodies.
- Hyaline casts are associated with dehydration; it is the most common type of cast.
- Bacterial casts are associated with urinary tract infections; the cast may be cultured to identify the causative organism of the cast.

9.2.3. Renal Clearance

A measure of the renal excretion capacity is called clearance. In renal physiology, clearance is a measurement of the renal excretion ability, specifically the volume of plasma that is cleared of a substance over a given period of time. Every substance has a distinct clearance that is determined by its own filtration properties. Clearance involves three processes: glomerular filtration, secretion from the peritubular capillaries to the nephron, and reabsorption from the nephron back to the peritubular capillaries. Depending on the substance, clearance can be a variable or constant component over time.



Source: https://upload.wikimedia.org/wikipedia/commons/thumb/2/2b/Physiology_of_Nephron.png/450px-Physiology_of_Nephron.png.

9.2.3.1. Clearance Mechanisms

Renal clearance primarily depends on glomerular filtration rate (GFR), tubular reabsorption, and tubular secretion. If any of those variables change, the renal clearance rate of a substance will change as well. These variables affect clearance through the following rules:

- Increased GFR will increase clearance, while decreased GFR will decrease clearance.
- Increased tubular secretion will increase clearance, while decreased tubular secretion will decrease clearance. This variable is sometimes altered through changes in the expression of ATPase pumps involved in active transport.
- Increased tubular reabsorption will decrease clearance, while increased tubular reabsorption will increase clearance.

Certain aspects of clearance are also determined by the properties of the substance. Various medications, for instance, either bind to plasma proteins or remain unbound in plasma. The body will filter and expel only those that are unbound. The clearance rate also changes depending on the size and molecular structure. It is also important to remember that there are other ways for the chemicals in the body's plasma to be cleared besides renal clearance.

The other types of clearance are:

- Biliary (through bile);
- Salivary;
- Pulmonary clearance (removed during alveolar gas exchange).

These types of clearance may also excrete certain molecules from the bloodstream based on their size and molecular structure; however, these forms of clearance are generally relatively minor compared to renal clearance.

These types of clearance all add up to a summation known as total body clearance, which refers to the removal of a substance from the plasma over time, incorporating all routes of removal in the body.

A Closer Look

Urinary System Work

The urinary system's function is to filter blood and create urine as a waste by-product. The organs of the urinary system include the kidneys, renal pelvis, ureters, bladder and urethra.

The body takes nutrients from food and converts them into energy. After the body has taken the food components that it needs, waste products are left behind in the bowel and in the blood. The kidney and urinary systems help the body to eliminate liquid waste called urea and maintain the balance of chemicals such as potassium and sodium, as well as water. Urea is produced when foods containing protein, such as meat, poultry, and certain vegetables, are broken down in the body. Urea is carried in the bloodstream to the kidneys, where it is removed along with water and other wastes in the form of urine.

Other important functions of the kidneys include blood pressure regulation and the production of erythropoietin, which controls red blood cell production in the bone marrow. Kidneys also regulate the acid-base balance and conserve fluids.

Summary

- The urinary system serves several purposes, including blood purification and waste removal from the body. Additionally, the system performs other equally significant tasks. Consider pH regulation, which is regulated by both the lungs and the blood's buffers.
- The formation of kidneys, also known as nephrogenesis, is a carefully orchestrated process that begins in the embryonic stage and continues into postnatal development.
- The epithelium is surrounded by a significant number of muscle fibers, and the adventitia lies beyond this.
- The urethra, which has thin walls, is the final channel through which urine exits the bladder. This tube connects the exterior of the body to the base of the bladder.
- Urination is the process by which the kidneys produce and expel urine, a liquid byproduct of the body, through the urethra.

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Chapter

10

SKELETAL SYSTEM

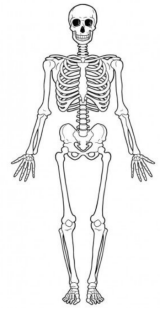
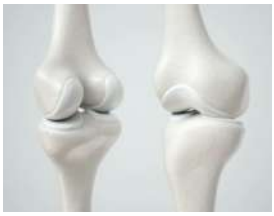
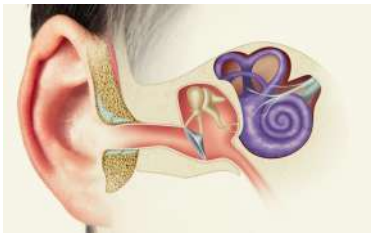
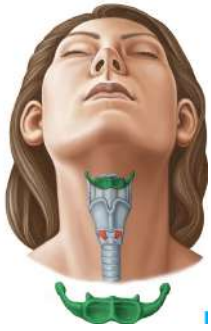
Contents

Unit Introduction

The skeletal system is the body's structural framework, giving it mobility, protection, and support. The skeletal system, composed of bones, cartilage, ligaments, and tendons, is essential for movement, hematopoiesis, mineral storage, and metabolic control. The skeletal system is primarily made up of bones, which provide the hard framework that supports and shields soft tissues and organs. There are four primary categories: long bones (e.g., humerus, femur), short bones (e.g., tarsals, carpals), flat bones (e.g., sternum, skull), and irregular bones (e.g., pelvic bones, vertebrae). Every bone is made up of dynamic, living tissue encased in a mineralized extracellular matrix primarily made up of collagen fibers and calcium phosphate. The strength, flexibility, and resilience of bones are attributed to their distinct composition. A strong, flexible connective tissue, cartilage is vital to the skeletal system. It provides cushioning and facilitates smooth movement by covering the ends of the bones within joints. Furthermore, cartilage contributes to longitudinal bone growth at the epiphyseal plates by acting as the precursor for bone formation during embryonic development and growth. Fibrous connective tissues called ligaments and tendons link bones to other bones and muscles to bones, respectively, enhancing joint stability and transferring forces during motion. Tendons transfer the contractile forces produced by muscles to facilitate movement. Ligaments aid in preventing excessive movement or dislocation of bones within joints.

The bone marrow, a soft, spongy substance found inside the cavities of bones, is also housed within the skeletal system. Hematopoiesis, the process that produces red blood cells, white blood cells, and platelets, takes place in the bone marrow. In addition, bone marrow maintains the body's mineral homeostasis by storing adipose tissue and acting as a reservoir for minerals like calcium and phosphate. In general, the skeletal system is a dynamic and intricate network of tissues that supports the body structure, shields important organs, permits mobility, and keeps the body in a state of homeostasis. Its integrity and functionality underscore the importance of appropriate skeletal development, maintenance, and care throughout life, as they are critical to general health and mobility.

Orientation and Directional Terms

Terms	Definition	Illustration
Skeletal system	The skeletal system is your body's support structure. It gives your body its shape, allows movement, makes blood cells, provides protection for your organs and stores minerals.	
Cartilage	Cartilage is a strong, flexible connective tissue that protects your joints and bones.	
Malleus	The malleus, or hammer, is a hammer-shaped small bone or ossicle of the middle ear. It connects with the incus, and is attached to the inner surface of the eardrum.	
Hyoid	Hyoid bone, U-shaped bone situated at the root of the tongue in the front of the neck and between the lower jaw and the largest cartilage of the larynx, or voice box.	
Musculoskeletal system	The musculoskeletal system provides form, support, stability, and movement to the body. It is made up of the bones of the skeleton, muscles, cartilage, tendons, ligaments, joints, and other connective tissue that supports and binds tissues and organs together.	

10.1. Overview of Skeletal System

The skeletal system maintains the position of your organs and gives it shape, functioning as primary structural support system. However, it encompasses more than the skeleton and bones. Connective tissue is another component of the skeletal system that keeps the body safe and supports both movement and standing. It produces new blood cells that maintain health and supports muscles that aid in movement. Another name for the skeletal system is the musculoskeletal system.

10.1.1. Axial Skeleton Anatomy

The adult axial skeleton consists of 80 bones. It's made up of the bones that form the vertical axis of the body, such as the bones of the head, neck, chest, and spine.

10.1.1.1. Skull Bones

The adult skull comprises 22 bones. These bones can be further classified by location:

- **Cranial Bones:** The eight cranial bones form the bulk of your skull. They help to protect your brain.
- **Facial Bones:** There are 14 facial bones. They're found on the front of the skull and make up the face.

10.1.1.2. Auditory Ossicles

The auditory ossicles are six small bones found within the inner ear canal in the skull. There are three auditory ossicles on each side of the head, known as the:

- Malleus (hammer);
- Incus (anvil);
- Stapes (stirrup).

They work together to transmit sound waves from the surrounding environment to the structures of the inner ear.

10.1.1.3. Hyoid

The hyoid is a U-shaped bone found at the base of the jaw. It serves as a point of attachment for muscles and ligaments in the neck.

10.1.1.4. Vertebral Column

The vertebral column is made up of 26 bones. The first 24 are all vertebrae, followed by the sacrum and coccyx (tailbone).

The 24 vertebrae can be further divided into the:

- **Cervical Vertebrae:** These seven bones are found in the head and neck.
- **Thoracic Vertebrae:** These 12 bones are found in the upper back.
- **Lumbar Vertebrae:** These five bones are found in the lower back.

The sacrum and coccyx are both made up of several fused vertebrae. They help support the weight of the body while sitting. They also serve as attachment points for various ligaments.

10.1.1.5. Thoracic Cage

Twelve pairs of ribs and the sternum, or breastbone, make up the thoracic cage. These bones encircle the heart and lungs, among other upper torso organs, like a protective cage. There are ribs that join the sternum directly and others that join it via cartilage. Some are called "floating ribs" because they lack an attachment point."

10.1.2. Appendicular Skeleton Anatomy

There are a total of 126 bones in the appendicular skeleton. It consists of the bones that make up

the arms and legs, as well as the bones that attach them to the axial skeleton.

10.1.2.1. Pectoral Girdle

The pectoral girdle is where the arms attach to the axial skeleton. It's made up of the clavicle (collarbone) and scapula (shoulder blade). There are two of each of these — one for each arm.

10.1.2.2. Upper Limbs

Each arm contains 30 bones, known as the:

- **Humerus:** The humerus is the long bone of the upper arm.
- **Radius:** The radius is one of two long bones of the forearm, found on the thumb side.
- **Ulna:** The ulna is the second long bone of the forearm, found on the pinky finger side.
- **Carpals:** The carpals are a group of eight bones found in the wrist area.
- **Metacarpals:** The metacarpals are five bones found in the middle area of the hand.
- **Phalanges:** The phalanges are 14 bones that make up the fingers.

10.1.2.3. Pelvic Girdle

The pelvic girdle, commonly known as the hips, is where the legs attach to the axial skeleton. It's made up of two hip bones — one for each leg.

Each hip bone consists of three parts, known as the:

- **Ilium:** The ilium is the top portion of each hip bone.
- **Ischium:** The ischium is a curved bone that makes up the base of each hip bone.
- **Pubis:** The pubis is located in the front part of the hip bone.

10.1.2.4. Lower Limbs

Each leg is composed of 30 bones, known as the:

- **Femur:** The femur is the large bone of the upper leg.
- **Tibia:** The tibia is the main bone of the lower leg. It forms the shin.
- **Fibula:** The fibula is the second bone in the lower leg, found in the outer leg.
- **Patella:** The patella is also called the kneecap.
- **Tarsals:** The tarsals are the seven bones that make up the ankle.
- **Metatarsal:** The metatarsals are the five bones that make up the middle area of the foot.
- **Phalanges:** The phalanges are 14 bones that comprise the toes.

10.2. Functions of the Skeletal System

The skeletal system is made up of bones, cartilage, ligaments, and other tissues that are essential for the human body. Bone tissue, also known as osseous tissue, is a tough and dense connective tissue that forms the majority of the adult skeleton, providing internal support. Cartilages, a semi-rigid type of connective tissue, are found in areas where bones move against each other, such as joints, providing flexibility and smooth surfaces for movement. Ligaments, made of dense connective tissue, surround joints and connect skeletal elements, ensuring stability and strength.

Together, they perform the following functions (Figure 10.1):

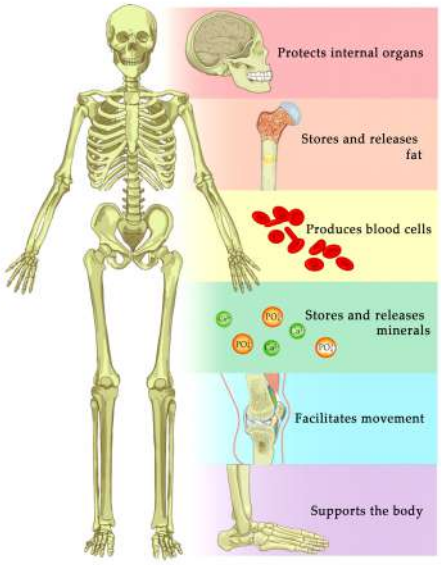


Figure 10.1. *Functions of the skeletal system.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2019/07/mineral_storage_revised-768x938.png.

10.2.1. Support, Movement, and Protection

The skeletal system's bones and cartilages make up the scaffold that supports the rest of the body, much like a building's steel beams do to support its weight. If not for the skeletal system, the body would be a lifeless mass of muscle, skin, and organs. Because they are points of attachment for the muscles, bones help with movement. Additionally, by encircling or covering internal organs, bones prevent damage to them. For instance, the bones of the cranium (skull) shield the brain, the bones of the vertebral column (spine) the spinal cord, and the ribs, the lungs and the heart (Figure 10.1).

10.2.2. Mineral and Fat Storage, Blood Cell Formation

Bone tissue carries out numerous vital metabolic processes. One benefit of bone tissue is that it serves as a storehouse for several minerals, particularly phosphorus and calcium, which are vital to the body's operation. Once assimilated into bone tissue, these minerals can be released back into the bloodstream to sustain the necessary concentrations to support bodily functions. For instance, calcium ions are necessary for both nerve impulse transmission and muscle contractions. Additionally, fat is stored and blood cells are produced in the bones.

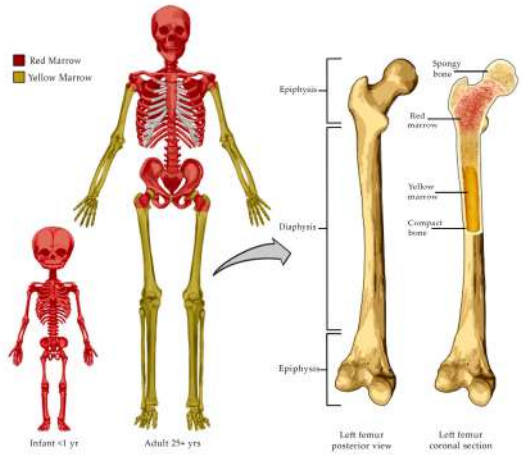


Figure 10.2. *Bone marrow: Bones contain variable amounts of yellow and/or red bone marrow. Yellow bone marrow stores fat and red bone marrow is responsible for producing blood cells (hematopoiesis).*

Source: https://open.oregonstate.education/app/uploads/sites/157/2021/02/marrow_skele-768x690.png.

Bone marrow is the special connective tissue that lines the inside of most bones. Red and yellow bone marrow are the two different varieties of bone marrow. Adipose tissue, or yellow bone marrow, can release its stored triglycerides into the adipocytes, which can then supply energy to other body tissues. Red bone marrow is where the production of blood cells (named hematopoiesis, hemato- = "blood,"

-poiesis = "to make") takes place. Red blood cells, white blood cells, and platelets are all produced in the red bone marrow. As we age, the distribution of red and yellow bone marrow changes as seen in Figure 10.2.

10.2.3. Growth and Development

Early in fetal development, the skeleton begins to form in the form of a flexible structure composed of dense, irregular fibrous connective tissue and hyaline cartilage. These tissues serve as a scaffold for the developing bony skeleton that will eventually replace them. Blood vessels start to grow into the soft fetal skeleton during development, supplying nutrients and stem cells to support the growth of bones. In a process known as calcification, osseous tissue gradually replaces fibrous and cartilage tissue. Up until they approach the edge of another bony region, the calcified regions extend from their blood vessels, replacing the old tissues. A newborn's skeleton contains over 300 bones at birth; as they grow older, these bones fuse together to form larger ones, leaving adults with only 206 bones. The process of intramembranous ossification, in which young bones develop from a primary ossification center in fibrous membranes and leave a small area of fibrous tissue between each other, is followed by the formation of flat bones. These soft areas of the skull, called fontanels, allow the bones to grow and provide the skull with flexibility. The fontanels gradually ossify, and the individual skull bones eventually unite to form an adult, inflexible skull.

The process of endochondral ossification, which produces long bones, is characterized by the diaphysis growing inside cartilage from a primary ossification center until it forms the majority of the bone. Next, from secondary ossification centers on the ends of the bones, the epiphyses develop. As a growth plate, a tiny strip of hyaline cartilage still exists between the bones. Growth and sex hormones cause the growth plates to expand during childhood, gradually separating the bones. The bones enlarge at the same time because they grow back into the growth plates. Up until the end of puberty, when the growth plate stops expanding and the bones irreversibly fuse into one, this process is ongoing. The primary cause of the significant variation in height and limb length observed between birth and adulthood is endochondral ossification of the long bones.

10.3. Bone Structure

Osseous tissue, or bone tissue, is very different from other body tissues. Due to its inherent hardness, bone is essential for many bodily processes. As we shall see in later sections of this chapter, bone is also dynamic in that it changes shape in response to stresses. This section will first examine the gross anatomy of bone. Then, it will explore its histology.

10.3.1. Gross Anatomy of Bones

A long bone consists of two primary regions: the diaphysis and the epiphysis (Figure 10.3). The hollow, tubular shaft that connects the proximal and distal ends of the bone is called the diaphysis. The medullary cavity, which houses the adult's yellow bone marrow, is located inside the diaphysis. Compact bone, a type of osseous tissue, is dense and hard, making up the outer walls of the diaphysis (cortex, cortical bone).

The term epiphysis (plural: epiphyses) refers to the wider section at each end of the bone that is internally filled with spongy bone, another kind of osseous tissue. In certain long bones, the spaces between the spongy bones are filled with red bone marrow. At the metaphysis, each epiphysis and diaphysis converge. The epiphyseal plate, the location of long bone elongation discussed later in the chapter, is located in the metaphysis during growth. In early adulthood (roughly 18–21 years), the bone stops growing, and the epiphyseal plate transforms into an epiphyseal line. The endosteum (endo- =

"inside"; osteo- = "bone") is a layer of bone cells that lines the inside of the bone next to the medullary cavity. The bone grows, repairs, and remodels throughout life because of these bone cells (explained later).

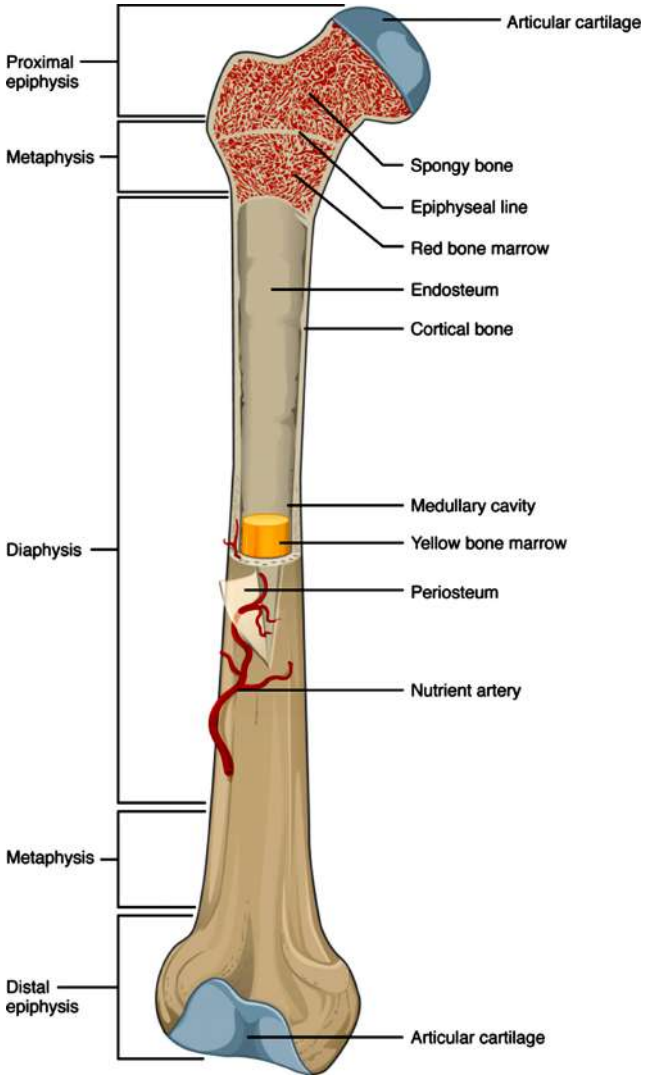


Figure 10.3. *A typical long bone showing gross anatomical features.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2019/07/603_Anatomy_of_a_Long_Bone_revised-606x1024.png.

There is an additional layer of cells that grow, repair, and remodel bone on the outside of bones. These cells are a component of the periosteum, an outer double-layered structure (peri– meaning "around" or "surrounding"). The outer fibrous layer of dense, irregular connective tissue covers the cellular layer, which is located next to the cortical bone (*see* Figure 10.4). In addition, the periosteum is home to lymphatic, neuron, and blood vessels that support compact bone. The periosteum is where ligaments and tendon attach to bones. The entire exterior is covered in

periosteum, except joints formed by the junctions of epiphyses and other bones (Figure 10.4). Articular cartilage, a thin coating of hyaline cartilage that serves as a shock absorber and reduces friction, covers the epiphyses in this area.

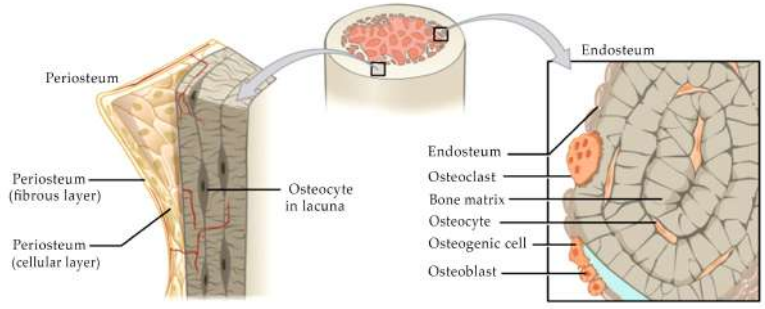


Figure 10.4. *Periosteum and endosteum: The periosteum forms the outer surface of bone, and the endosteum lines the medullary cavity.*

Source: https://encrypted-https://open.oregonstate.education/app/uploads/sites/157/2021/02/607_Periosteum_and_Endosteum_revised-e1568324483343-768x343.png.

Similar to the cranium, flat bones are made up of two layers: one layer of spongy bone, and one layer of compact bone on either side (Figure 10.5). Together, the interior spongy bone and the two layers of compact bone shield the internal organs. The intact inner layer of a cranial bone continues to protect the brain even in the event of an outer layer fracture.

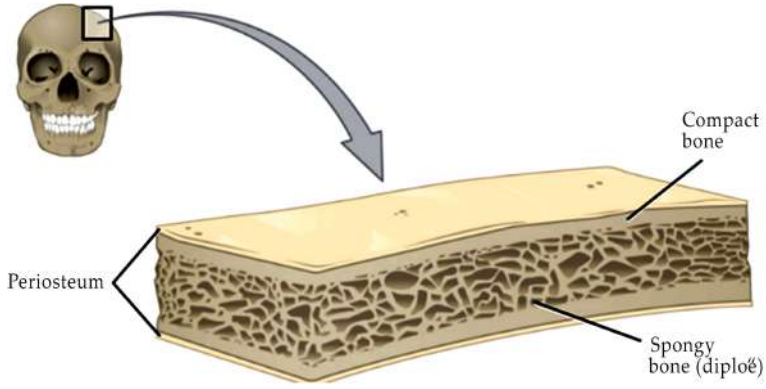


Figure 10.5. *Anatomy of a flat bone: This cross-section of a flat bone shows the spongy bone (diploë) covered on either side by a layer of compact bone.*

Source: https://upload.wikimedia.org/wikipedia/commons/1/1f/621_Anatomy_of_a_Flat_Bone.jpg.

10.3.2. Osseous Tissue: Bone Matrix and Cells

10.3.2.1. Bone Matrix

Osseous tissue, like all connective tissues, like all connective tissues, is primarily composed

of extracellular matrix and has comparatively few cells. Osseous tissue matrix is made up of two-thirds calcium phosphate salt and one-third collagen fibers by mass. Inorganic salt crystals attach to the collagen scaffold (see Figure 10.6). Salt crystals form when calcium carbonate and calcium phosphate combine to create hydroxyapatite. As hydroxyapatite crystallizes, or calcifies, on the collagen fibers, it also absorbs other inorganic salts such as magnesium hydroxide, fluoride, and sulfate. While collagen fibers provide a framework for calcification and give the bone flexibility so that it can bend without becoming brittle, hydroxyapatite crystals give bones their strength and hardness. For example, a bone would easily crumble and break if the organic matrix (collagen) were completely removed. On the other hand, if you take out all of the collagen and inorganic matrix (minerals) from the bone, the bone becomes too flexible to support weight.

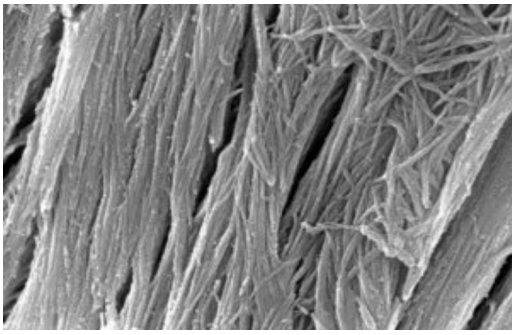


Figure 10.6. *Calcified collagen fibers from bone.*

Source: https://upload.wikimedia.org/wikipedia/commons/thumb/0/03/Bertazzo_S_-_SEM_deproteined_bone_-_wistar_rat_-_x10k.tif/lossy-page1-1200px-Bertazzo_S_-_SEM_deproteined_bone_-_wistar_rat_-_x10k.tif.jpg.

10.3.2.2. Bone Cells

Although bone cells compose less than 2% of the bone mass, they are crucial to the function of bones. Four types of cells are found within bone tissue: osteoblasts, osteocytes, osteogenic cells, and osteoclasts (Figure 10.7).

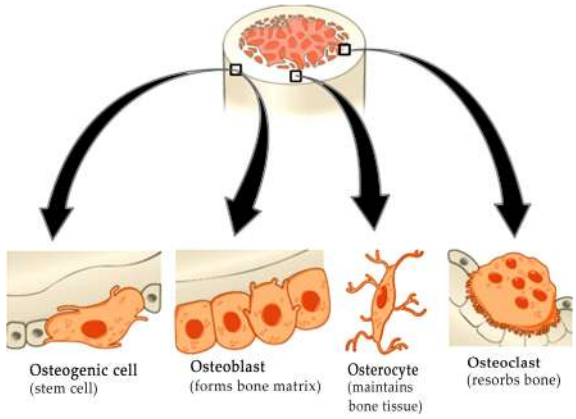


Figure 10.7. *Bone cells: Four types of cells are found within bone tissue. Osteogenic cells are undifferentiated and develop into osteoblasts. Osteoblasts deposit bone matrix. When osteoblasts get trapped within the calcified matrix, they become osteocytes. Osteoclasts develop from a different cell lineage and act to resorb bone.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2021/02/604_Bone_cells_revised-768x552.png.

The bone cell called an osteoblast is found in the growing portions of bone, such as the cellular layer of the periosteum and the endosteum. It is responsible for forming new bone. Collagen matrix and other proteins are synthesized and secreted by osteoblasts, which are non-dividing cells. The osteoblast becomes trapped in the calcified matrix, changing into an osteocyte, the main mature bone cell and the most prevalent type. Every osteocyte is found in a tiny space in the bone tissue known as a lacuna, or lacunae in plural. Osteocytes secrete enzymes to keep the matrix's mineral concentration constant. Osteocytes do not undergo mitosis, much like osteoblasts do. Through long cytoplasmic processes that stretch through channels within the bone matrix called canaliculi (plural: canaliculus), they can

communicate with one another and receive nutrients. Gap junctions allow the osteocytes within the canaliculi to communicate with one another.

The ability of a third type of bone cell called the osteogenic (osteoprogenitor) cell to undergo mitosis explains how osteoblasts and osteocytes are replaced when their progenitors pass away. Osteogenic cells are the only bone cells that divide; they are undifferentiated and highly mitotic. The periosteum and endosteum contain immature osteogenic cells in their cellular layer. They undergo differentiation and become osteoblasts. Because bone is dynamic, it constantly forms new tissue and dissolves old, damaged, or unnecessary bone to make room for repair or the release of calcium.

Osteoclasts are the cells that cause bone resorption, or disintegration. Rather than originating from osteogenic cells, these multinucleated cells are derived from two subtypes of white blood cells: monocytes and macrophages. While osteoblasts are constantly creating new bone, osteoclasts are constantly disintegrating existing bone. The continuous, subtle reshaping of bone is caused by the balance between osteoblasts and osteoclasts.

The table reviews the bone cells, their functions, and locations.

Bone Cells (Table)

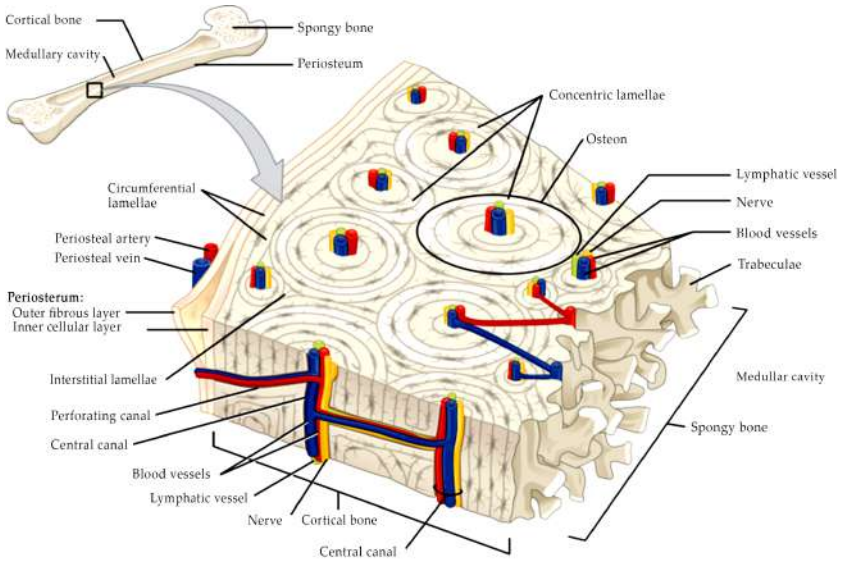
Cell Type	Function	Location
Osteogenic cells	Develop into osteoblasts	Endosteum, cellular layer of the periosteum.
Osteoblasts	Bone formation	Endosteum, cellular layer of the periosteum, growing portions of bone.
Osteocytes	Maintain mineral concentration of matrix	Entrapped in matrix
Osteoclasts	Bone resorption	Endosteum, cellular layer of the periosteum, at sites of old, injured, or unneeded bone.

10.3.3. Compact and Spongy Bone

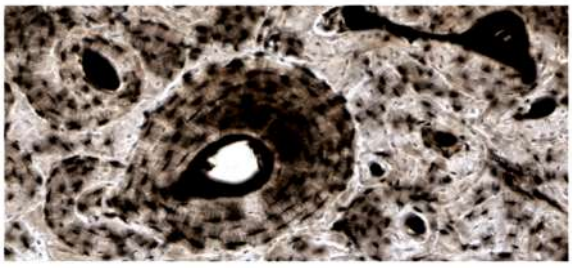
Compact and spongy osseous tissues make up most bones, but their distribution and concentration vary with the bone's function. While both compact and spongy bone consist of the same cells and matrix materials, their anatomical configurations differ. While spongy bone, also known as cancellous bone, is lightweight, supportive, and easily remodeled to meet changing body needs, compact bone is dense and able to withstand compressive forces.

10.3.4. Compact Bone

Compact bone is the denser, stronger of the two types of osseous tissue (Figure 10.8). It makes up the outer cortex of all bones and is in immediate contact with the periosteum. In long bones, as you move from the outer cortical compact bone to the inner medullary cavity, the bone transitions to spongy bone (Figure 10.9).



(a)



(b)

Figure 10.8. *Diagram of compact bone: (a) This cross-sectional view of compact bone shows several osteons, the basic structural unit of compact bone; and (b) a micrograph of the osteon.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2021/02/624_Diagram_of_Compact_Bone_revised-768x910.png.

Under a microscope, a compact bone exhibits a very well-organized pattern of tree-trunk-like concentric circles. An osteon, also known as a Haversian system, is the microscopic structural unit of compact bone composed of each group of concentric circles, or each "tree." Each ring of the osteon is referred to as a lamella (plural: lamellae) and is composed of collagen and calcified matrix. Osteons can withstand twisting forces in multiple directions because the collagen fibers in adjacent lamellae run at perpendicular angles to one another (*see* Figure 10.8(a)). The Haversian canal, or central canal, is located in the middle of each osteon and is home to lymphatic, nerve, and blood vessels. To reach the periosteum and endosteum, these vessels and nerves split off at right angles via perforating canals, also referred to as Volkmann's canals.

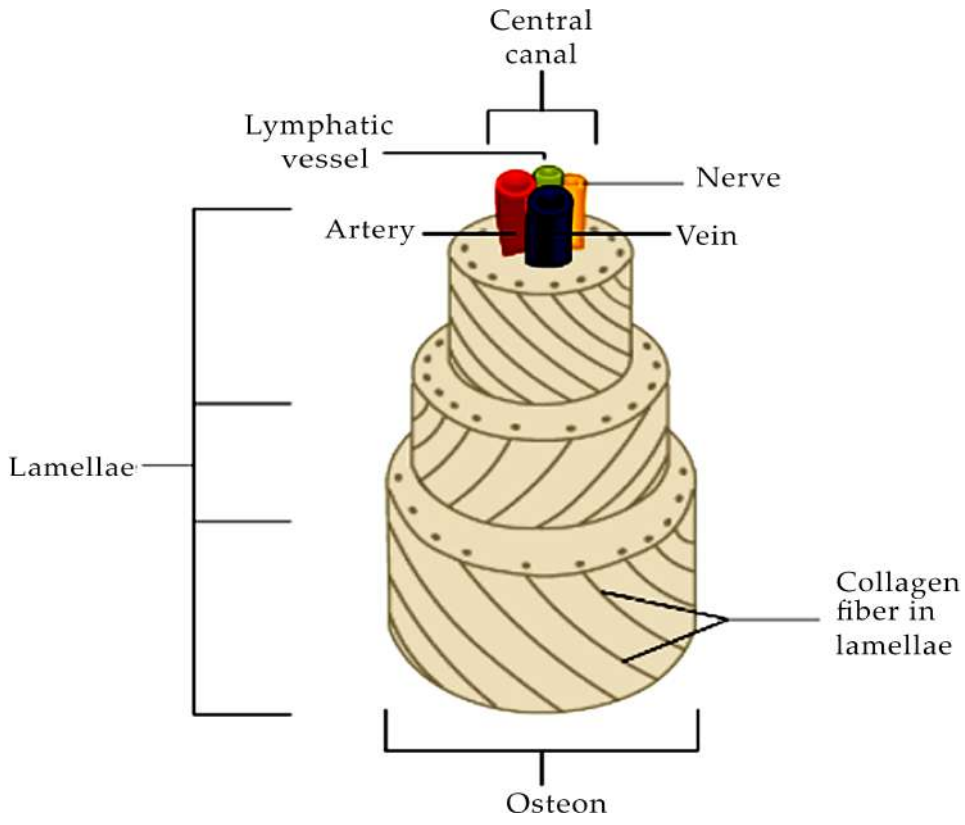


Figure 10.9. *Osteon.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2021/02/624_Diagram_of_Compact_Bone_revised_modified-350x341.png.

Additionally, the endosteum lines each central canal, facilitating the gradual removal, remodeling, and rebuilding of osteons. The lacuane, which is present at the boundaries of neighboring lamellae, contains the trapped osteocytes. Canaliculi link to the canaliculi of other lacunae and ultimately to the central canal, as was previously mentioned. Despite the impermeable calcified matrix, this system enables wastes to be removed from the osteocytes and nutrients to be delivered to them.

10.3.5. Spongy (Cancellous) Bone

Osteocytes in both compact and spongy bone (also called cancellous bone) reside in lacunae, but in spongy bone, they are not arranged in concentric circles. Rather, the osteocytes and lacunae are located within a network of matrix spikes that resembles a lattice, known as trabeculae (singular: trabecula) (Figure 10.10). The endosteum covering the trabeculae can easily remodel them. Although the trabeculae may seem to be a random network, each one forms along stress lines to direct forces outward to the more compact, solid bone, which gives the bone strength. Spongy bone makes bones lighter so that muscles can move them more easily, balancing the dense and heavy compact bone. Furthermore, hematopoiesis takes place in red bone marrow that is housed in the spaces between certain spongy bones and is shielded by trabeculae.

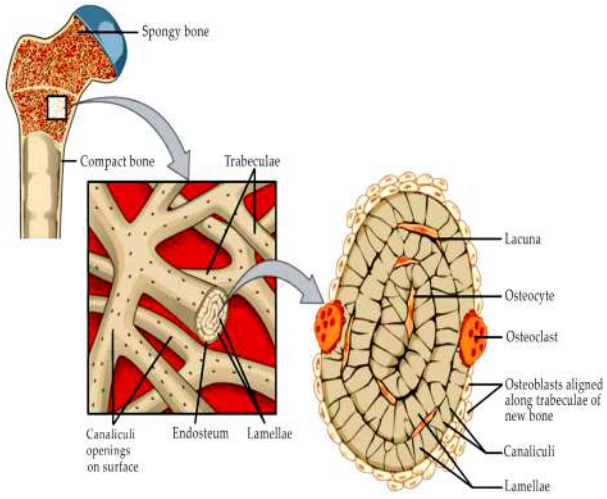


Figure 10.10. *Diagram of spongy bone: Spongy bone is composed of trabeculae that contain the osteocytes. Red marrow fills the spaces in some bones.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2021/02/606_Spongy_Bone-768x510.jpg.

10.3.6. Blood and Nerve Supply

Nutrient flow through the compact bone supplies the medullary cavity and spongy bone. The arteries enter the body through tiny apertures in the diaphysis called nutrient foramina (singular: foramen) (Figure 10.11). Blood that circulates in the marrow cavities and periosteum blood vessels that permeate spongy bone nourish the osteocytes within. Veins gather the blood as it travels through the marrow cavities and exit the bone through the foramina. Nerves enter the bone via the same pathways as blood vessels, with the tendency to concentrate in the areas of the bone that are more metabolically active. In addition to sensing pain, nerves appear to have an impact on bone formation and blood flow, which explains why they are concentrated in areas of the bone that are metabolically active.

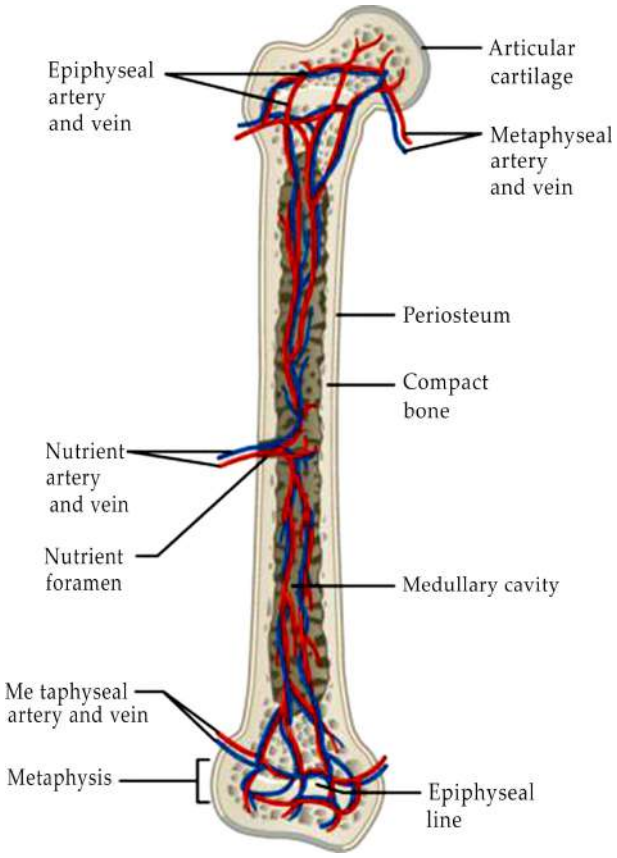


Figure 10.11. *Diagram of blood and nerve supply to bone: blood vessels and nerves enter the bone through the nutrient foramen.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2021/02/609_Body_Supply_to_the_Bone-350x487.jpg.

10.4. Types of Bones

Bone, or osseous tissue, is a type of connective tissue that makes up the endoskeleton. It is made up of specialized cells and a collagen-fiber and mineral-salt matrix. Hydroxyapatite, made of calcium phosphate, is the main component of mineral salts. The process of mineral salts depositing on the collagen fiber matrix to cause the tissue to crystallize and harden is known as calcification.

Calcification is a process that can only take place when collagen fibers are present. The human skeleton's bones are categorized according to their shapes: sesamoid, long, short, flat, sutural, and irregular bones (Figure 10.12).

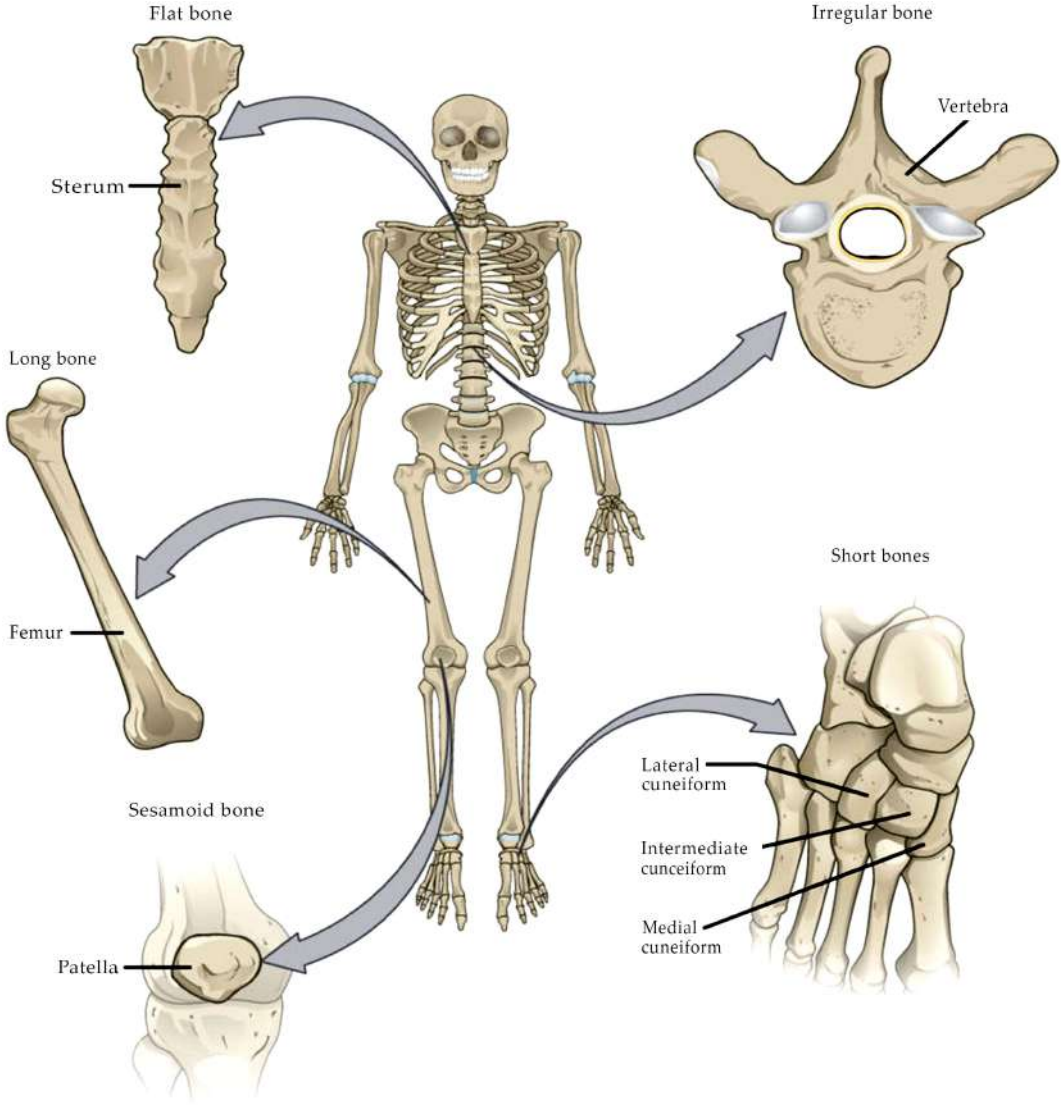


Figure 10.12. *Shown are different types of bones: flat, irregular, long, short, and sesamoid.*

Source: https://s3-us-west-2.amazonaws.com/courses-images/wp-content/uploads/sites/1223/2017/02/07235350/Figure_38_02_01-956x1024.jpg.

Long bones have a shaft and two ends and are longer than they are wide. There is bone marrow in a marrow cavity located in the diaphysis, or central shaft. The epiphyses, or rounded ends, are filled with red bone marrow that produces blood cells and is covered in articular cartilage (Figure 10.13). Most limb bones, such as the radius, ulna, tibia, and femur, are long bones. The patella and the bones in the wrist and ankle are examples of exceptions to this rule.

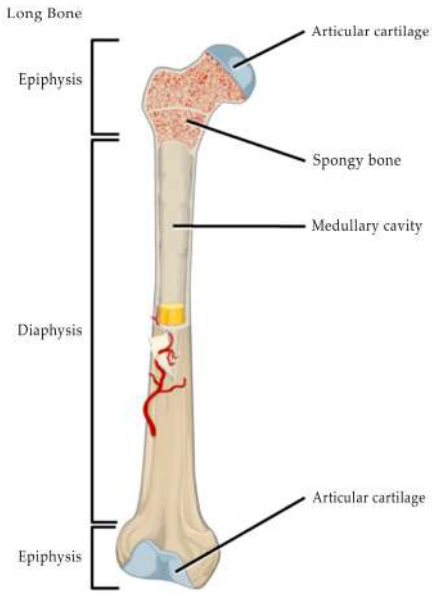


Figure 10.13. *The long bone is covered by articular cartilage at either end or contains bone marrow (shown in yellow in this illustration) in the marrow cavity.*

Source: https://s3-us-west-2.amazonaws.com/courses-images/wp-content/uploads/sites/1223/2017/02/07235425/Figure_38_02_02-350x482.jpg.

1. **Short Bones:** Also known as cuboidal bones, are roughly equal in length and width, giving them a cube-like shape. For example, the bones of the wrist (carpals) and ankle (tarsals) are short bones (Figure 10.12).
2. **Flat Bones:** These are thin and relatively broad bones that are found where extensive protection of organs is required or where broad surfaces of muscle attachment are required. Examples of flat bones are the sternum (breastbone), ribs, scapulae (shoulder blades), and the roof of the skull.
3. **Irregular Bones:** These are bones with complex shapes. These bones may have short, flat, notched, or ridged surfaces. Examples of irregular bones are the vertebrae, hip bones, and several skull bones.
4. **Sesamoid Bones:** These are small, flat bones and are shaped similarly to a sesame seed. The patellae are sesamoid bones. Sesamoid bones develop inside tendons and may be found near joints at the knees, hands, and feet (*see* Figure 10.14).
5. **Sutural Bones:** These are small, flat, irregularly shaped bones. They may be found between the flat bones of the skull. They vary in number, shape, size, and position.

Figure 10.14. *The patella of the knee is an example of a sesamoid bone.*

Source: https://s3-us-west-2.amazonaws.com/courses-images/wp-content/uploads/sites/3206/2018/05/04133413/Figure_38_02_03.jpg.

10.5. Bone Development and Growth

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

- Explain the function of cartilage.
- List the steps of intramembranous ossification.

- List the steps of endochondral ossification
- Explain the growth activity at the epiphyseal plate.
- Compare and contrast the processes of modeling and remodeling.

Hyaline cartilage and fibrous membranes make up the embryo's skeleton in the early phases of embryonic development. Osteogenesis, or the actual process of developing bones, starts during the sixth or seventh week of embryonic life. Intramembranous ossification and endochondral ossification are the two osteogenic pathways; however, bone is the same regardless of the pathway that produces it.

10.5.1. Cartilage Templates

As a replacement tissue, bone builds its mineral matrix by adhering to a model tissue. Cartilage is the most frequently used template for skeletal development. Where bones will form is determined by the framework that is laid down during fetal development. This framework is made of hyaluronic acid, chondroitin sulfate, collagen fibers, and water. Chondroblasts produce this flexible, semi-solid matrix. Chondroblasts are referred to as chondrocytes because of the matrix that envelops and separates them. In contrast to the majority of connective tissues, cartilage lacks blood vessels that would otherwise carry nutrients and eliminate waste products from the body. Diffusion through the matrix carries out each of these tasks. For this reason, compared to most tissues, damaged cartilage does not heal itself as quickly. On the cartilaginous matrix, bone forms during fetal development and continues to grow and develop throughout childhood. Most of the cartilage has been replaced with bone by the time a fetus is born. Throughout childhood, some cartilage will grow back, and in the adult skeleton, some cartilage will still be present.

10.5.2. Intramembranous Ossification

Compact and spongy bone forms during intramembranous ossification directly from sheets of mesenchymal (undifferentiated) connective tissue. Intramembranous ossification is the process by which the clavicles (collarbones), the majority of the cranial bones, and the flat bones of the face form. When mesenchymal cells in the embryonic skeleton congregate and start to differentiate into specialized cells, the process starts (Figure 10.15(a)). While some of these cells will differentiate into osteogenic cells and eventually osteoblasts, others will become capillaries. Early osteoblasts appear in a cluster known as an ossification center, but they will eventually be dispersed by the formation of bone tissue. The uncalcified, osteoid matrix secreted by the osteoblasts calcifies (hardens) in a matter of days upon the deposition of mineral salts, trapping the osteoblasts inside. The osteoblasts become osteocytes once they are trapped (Figure 10.15(b)). Osteogenic cells in the surrounding connective tissue differentiate into new osteoblasts, while osteoblasts trapped in the matrix become osteocytes. A trabecular matrix is produced by osteoid (unmineralized bone matrix) secreted around capillaries, and the periosteum is formed by osteoblasts on the surface of spongy bones (Figure 10.15(c)). Subsequently, a compact bone layer that is superficial to the trabecular bone is formed by the periosteum. Neighboring blood vessels become crowded by the trabecular bone and eventually condense into red marrow (Figure 10.15(d)). During fetal development, intramembranous ossification starts in the womb and lasts until adolescence. The clavicles, skull, and sutures are not closed at birth, nor are they completely ossified. This permits the shoulders and skull to sag as they pass through the birth canal. The face's flat bones, which mature to adult size at the conclusion of the adolescent growth spurt, are the last bones to ossify through intramembranous ossification.

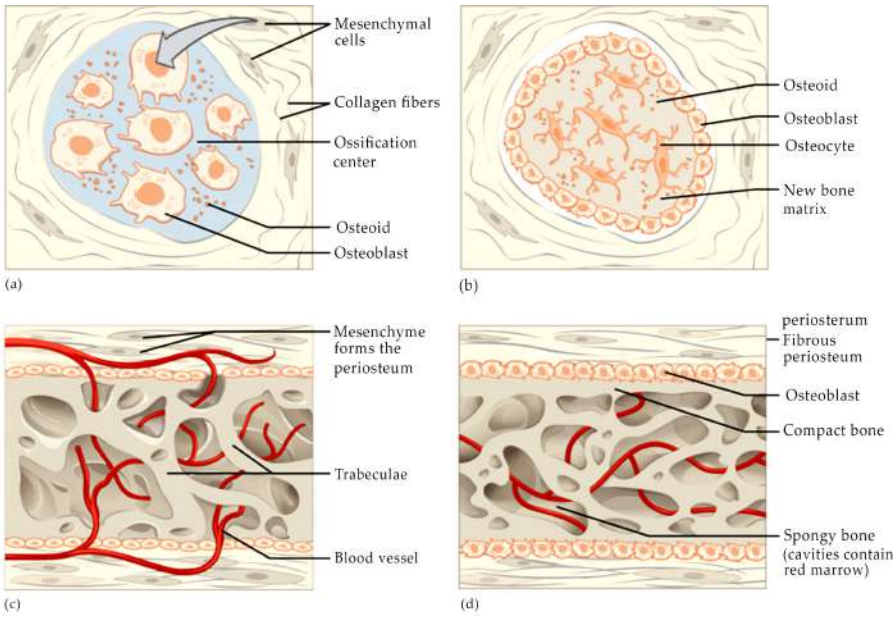


Figure 10.15. *Intramembranous ossification follows four steps. (a) Mesenchymal cells group into clusters, and ossification centers form. (b) Secreted osteoid traps osteoblasts, which then become osteocytes. (c) Trabecular matrix and periosteum form. (d) Compact bone develops superficial to the trabecular bone, and crowded blood vessels condense into red marrow.*

Source: https://open.oregonstate.education/app/uploads/sites/157/2019/07/611_Intramembraneous_Ossification_revised-768x524.png.

10.5.3. Endochondral Ossification

Endochondral ossification is the process by which hyaline cartilage is replaced with bone. Bone does not grow from cartilage. Rather, cartilage acts as a template for new bone to grow in its place. Compared to intramembranous ossification, endochondral ossification occurs much more slowly. Endochondral ossification is the process by which long bones and the base of the skull form. For instance, in a long bone, some of the mesenchymal cells differentiate into chondrocytes, or cartilage cells, about 6 to 8 weeks after conception, forming the cartilaginous skeletal precursor of the bones (Figure 10.16). Subsequently, the cartilage-covering membrane known as the perichondrium emerges (Figure 10.16).

As the amount of matrix increases, the chondrocytes located in the center of the cartilaginous model begin to grow larger. Once the matrix hardens, nutrients are unable to reach the chondrocytes, leading to their death and the breakdown of the surrounding cartilage. Blood vessels then move into the empty spaces, expanding the cavities and bringing osteogenic cells that will eventually turn into osteoblasts. These growing spaces eventually merge to form the medullary cavity. In the meantime, as the cartilage expands, capillaries infiltrate it, causing the perichondrium to transform into the bone-forming periosteum. Osteoblasts create a collar of compact bone around the cartilage of the diaphysis. By the second or third month of fetal development, bone cell creation and ossification accelerate, establishing the primary ossification center within the periosteal collar.

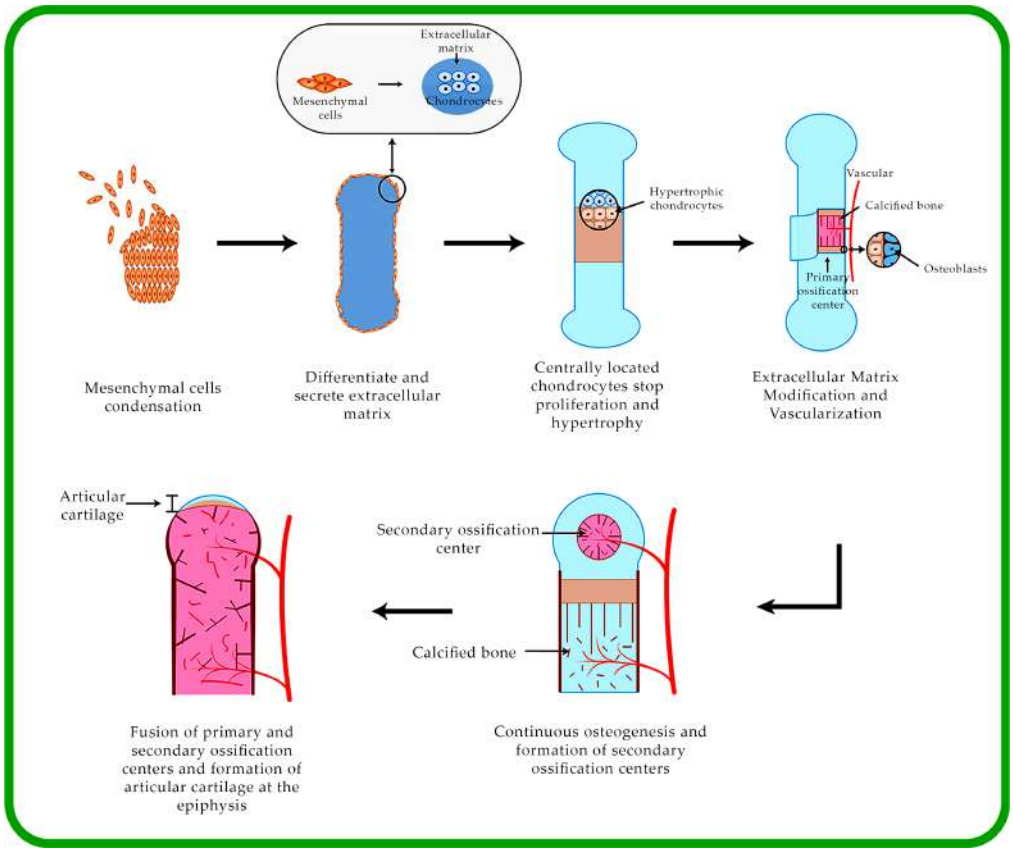


Figure 10.16. *Endochondral ossification follows five steps.*

Source: Su, Z., Zong, Z., Deng, J., et al., (2022). Lipid metabolism in cartilage development, degeneration, and regeneration. Nutrients, 14(19), 3984. Published 2022 Sep 25. doi: 10.3390/nu14193984.

While these internal changes are happening, chondrocytes and cartilage continue to grow at the ends of the bone (the future epiphyses), lengthening the bone as cartilage is replaced by bone at the diaphyses. Once the fetal skeleton is fully developed, cartilage remains at the joint surfaces as articular cartilage and between the diaphysis and epiphysis as the epiphyseal plate, which is responsible for the longitudinal growth of bones. After birth, a similar process of matrix mineralization, chondrocyte death, blood vessel invasion, and osteoblast seeding occurs in the epiphyseal regions, each known as a secondary ossification center.

10.5.4. Grow in Length

The epiphyseal plate is where growth takes place in a long bone. It consists of hyaline cartilage where ossification occurs in immature bones. Cartilage is formed on the epiphyseal side, while ossification takes place on the diaphyseal side, leading to lengthening of the diaphysis. The plate is made up of four zones of cells and activity. The reserve zone is the area closest to the epiphyseal end and contains small chondrocytes that help secure the plate to the epiphysis. These chondrocytes do not play a role in bone growth (Figure 10.17).

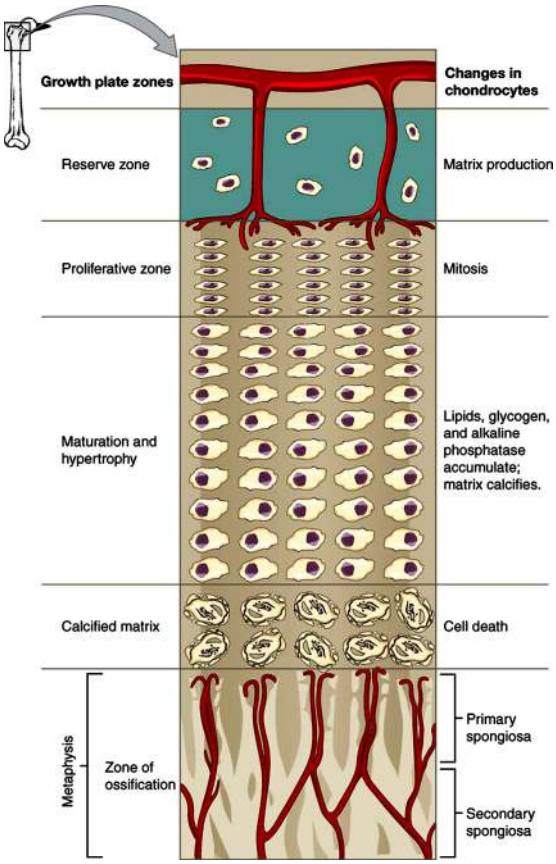


Figure 10.17. *The epiphyseal plate is responsible for longitudinal bone growth.*

Source: https://bio.libretexts.org/@api/deki/files/78113/2-longitudinal-bone-growth.jpefixme?revision=1.

The layer next to the diaphysis is called the proliferative zone, composed of stacks of slightly larger chondrocytes. At the diaphyseal end of the plate, chondrocytes undergo mitosis to produce new cells that replace those that perish. The chondrocytes found in the proliferative zone are younger and smaller than those found in the zone of maturation and hypertrophy, which is the next layer. The more developed cells are located in closer proximity to the plate's diaphyseal end. Cell division in the proliferative zone and cell maturation in the maturation and hypertrophy zone are what lead to the longitudinal growth of bone. Because the matrix surrounding them has hardened, most of the chondrocytes in the zone of the calcified matrix—the zone nearest to the diaphysis—are dead. This area is penetrated by capillaries and diaphysis-derived osteoblasts, which secrete bone tissue onto the residual calcified cartilage. Therefore, the diaphysis and epiphyseal plate are connected by the zone of the calcified matrix. When osseous tissue is added to the diaphysis, a bone grows longer. The length of bones stretches until early adulthood. Hormones are responsible for controlling the rate of growth; they will be covered later. Longitudinal growth ceases when the chondrocytes in the epiphyseal plate stop proliferating and bone takes the place of the cartilage. The epiphyseal line is all that is left of the epiphyseal plate (Figure. 10.18).

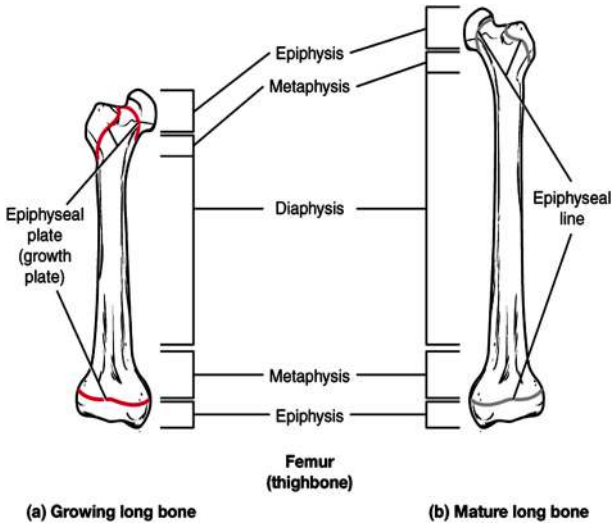


Figure 10.18. *Progression from epiphyseal plate to epiphyseal line as a bone matures, the epiphyseal plate progresses to an epiphyseal line. (a) Epiphyseal plates are visible in a growing bone. (b) Epiphyseal lines are the remnants of epiphyseal plates in a mature bone.*

Source: https://bio.libretexts.org/@api/deki/files/78114/623-epiphyseal-plate-line.jpefixme?revision=1.

10.5.5. Bones Grow in Diameter

As bones grow longer, they also grow wider through a process known as appositional growth. While osteoclasts break down old bone in the medullary cavity, osteoblasts create new bone tissue beneath the periosteum. This cycle of resorption and deposition not only increases the diameter of the bone but also the medullary cavity. This process is called modeling.

10.5.6. Bone Remodeling

Bone modeling is the process of resorbing matrix from one surface of a bone and depositing it on another. Most modeling occurs when a bone is growing. During adulthood, remodeling involves resorbing old or damaged bone on the same surface where osteoblasts form new bone to replace it. Remodeling is caused by injuries, exercise, and other activities. These factors are covered later in the chapter, but even in the absence of trauma or exercise, the annual remodeling of 5–10% of the skeleton occurs from the simple removal of old bone and replacement of it with new bone.

A Closer Look

Skeletal System

The skeletal system, comprised of bones, cartilage, joints, ligaments, and tendons, forms the structural foundation of the human body, serving vital functions essential for movement, protection, and support. The adult human skeleton consists of 206 bones, each uniquely shaped and positioned to fulfill its specific role. Bones are classified into four main types: long, short, flat, and irregular, each adapted to specific functions such as providing support (long bones), enabling movement (short bones), protecting vital organs (flat bones), or offering structural stability (irregular bones). Joints, the connections between bones, facilitate movement and flexibility. Joints vary in structure and function, such as hinge joints (e.g., elbow) that allow movement in one direction, and ball-and-socket joints (e.g., shoulder and hip) that provide a wide range of motion. Cartilage, a resilient connective tissue, covers the ends of bones within joints, acting as a shock absorber and reducing friction during movement. Ligaments, strong bands of fibrous tissue, anchor bones to one another at joints, providing stability and preventing excessive movement or dislocation. Meanwhile, tendons attach muscles to bones, transmitting the force generated by muscle contraction to produce movement.

Besides facilitating movement, the skeletal system protects vital organs, such as the skull safeguarding the brain and the rib cage shielding the heart and lungs. Bones also serve as a reservoir for minerals, particularly calcium and phosphorus, essential for numerous bodily functions such as muscle contraction and nerve transmission. The bone marrow, found within certain bones, serves as the site of hematopoiesis, where red and white blood cells and platelets are produced.

However, the skeletal system is susceptible to various disorders, including osteoporosis, arthritis, scoliosis, fractures, and osteoarthritis, which can significantly impact an individual's mobility, quality of life, and overall health. Understanding the complexities of the skeletal system is crucial for comprehending human anatomy and physiology and addressing issues related to bone health and mobility throughout the lifespan.

Summary

- The skeletal system is the body's structural framework, giving it mobility, protection, and support. The skeletal system, composed of bones, cartilage, ligaments, and tendons, is essential for movement, hematopoiesis, mineral storage, and metabolic control.
- Osseous tissue, or bone tissue, is very different from other body tissues. Due to its inherent hardness, bone is essential for many bodily processes.
- Bone, or osseous tissue, is a type of connective tissue that makes up the endoskeleton. It is made up of specialized cells and a collagen-fiber and mineral-salt matrix. Hydroxyapatite, made of calcium phosphate, is the main component of mineral salts.
- Compact and spongy bone forms during intramembranous ossification directly from sheets of mesenchymal (undifferentiated) connective tissue. Intramembranous ossification is the process by which the clavicles (collarbones), the majority of the cranial bones, and the flat bones of the face form.
- Endochondral ossification is the process by which hyaline cartilage is replaced with bone.

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Chapter

MUSCULAR SYSTEM

11

Contents

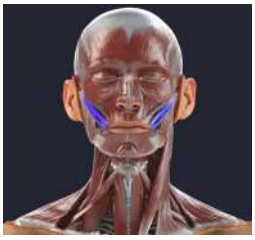
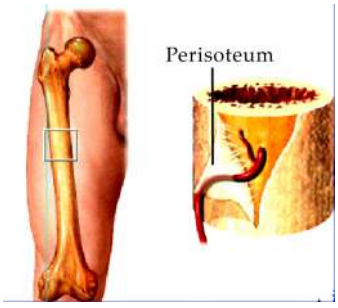
Unit Introduction

Muscle fibers are specialized cells that make up the muscular system, with their primary feature being the ability to contract. Movement is facilitated by muscles attached to bones, internal organs, and blood vessels.

Although muscle contraction underlies most bodily movement, exceptions include cilia movement, sperm cell flagella, and the amoeboid movement of some white blood cells. Movements as simple as walking and running are the result of the coordinated action of joints, bones, and skeletal muscles. More delicate skeletal muscle movements also result in different facial expressions, eye movements, and breathing patterns.

Muscle contraction serves the body's needs for posture, joint stability, and heat production in addition to facilitating movement. Muscle contraction is responsible for maintaining posture, including sitting and standing. The skeletal muscles maintain the body's stationary postures by continuously making minute adjustments. Many tendons of muscles cover joints, which helps to maintain joint stability. Muscle tendons play a significant role in stabilizing the knee and shoulder joints, where this is especially noticeable. A crucial byproduct of muscle metabolism is the generation of heat, which is necessary to maintain body temperature. Nearly 85% of the heat produced in the body is the result of muscle contraction.

Orientation and Directional Terms

Terms	Definition	Illustration
Bones	Bones is an American police procedural drama television series created by Hart Hanson for Fox.	
Zygomaticus	The zygomaticus major muscle raises the upper lip to bare the upper teeth. It additionally deepens and raises the nasolabial furrow.	
Diaphragm	The diaphragm is a muscle that helps you inhale and exhale (breathe in and out). This thin, dome-shaped muscle sits below your lungs and heart.	
Detoxification	Detoxification or detoxication is the physiological or medicinal removal of toxic substances from a living organism, including the human body, which is mainly carried out by the liver.	
Periosteum	The periosteum is a membrane that covers the outer surface of all bones, except at the articular surfaces of long bones.	

11.1. Overview of Muscular System

The human muscle system consists of voluntary muscles that support the skeletal system and are involved in posture, movement, and balance. In general, skeletal muscle, smooth muscle, and cardiac muscle are the three types of muscle found in humans and all other vertebrates. Smooth muscle, which is found in the walls of blood vessels and organs like the stomach, intestines, and bladder, is controlled involuntarily. The heart is composed of involuntary cardiac muscle, responsible for regular contractions. The human heart and smooth muscle are arranged in the same way as those of other vertebrate animals, with very few exceptions.

The human body's skeletal muscles, with a focus on muscle function and the alterations brought about by the protracted evolutionary process that included the adoption of an erect posture.

11.1.1. Functions of Muscles

Muscles play a role in nearly every system and function of the body. Different kinds of muscles help with:

- Breathing, speaking, and swallowing;
- Digesting food and getting rid of waste;
- Moving, sitting still, and standing up straight;
- Pumping blood through the heart and blood vessels;
- Pushing a baby through the birth canal as muscles in the uterus contract and relax;
- Seeing and hearing.

11.1.2. Properties of Muscle

1. **Irritability (Electrical Excitability):** The muscle responds to electrical stimulation from nerve impulses.
2. **Contractility:** Muscle responds to stimuli by contracting lengthwise, or shortening.
3. Extensibility:
   - Once the stimulus has subsided and the muscle fiber is relaxed it is capable of being stretched beyond its resting length by the contraction of an opposing muscle.
   - Muscles can be stretched up to 30% beyond their resting length, preparing the fibers for subsequent contractions.
4. **Elasticity:** Muscle fibers, after being stretched, tend to recoil to their original resting length.

11.1.3. Disorders Affecting Muscles

A wide range of disorders, diseases, drugs, and injuries can cause problems with how the muscles work. They include:

- **Cancer and Other Diseases:** Several types of cancer (such as sarcoma) and other diseases can lead to muscle problems. Other diseases include neuromuscular diseases such as amyotrophic lateral sclerosis (ALS), autoimmune disorders such as myasthenia gravis (MG), and many types of myopathies (muscle disease). A disease called polymyositis causes inflammation in the muscles, leading to muscle weakness.
- **Cardiovascular Disease:** Several kinds of venous disease and

cardiovascular disease, including coronary artery disease, can cause problems with the heart and blood vessels. A heart attack can result when muscles in the blood vessels weaken.

- **Chronic Pain Disorders:** Fibromyalgia and other disorders cause chronic pain in the muscles all over the body.
- **Genetic Disorders:** Muscular dystrophy is an inherited disorder (passed down through families). There are more than 30 types of muscular dystrophy. The disorder causes permanent muscle weakness.
- **Infections:** Bacterial and viral infections can damage muscle fibers. These infections include Lyme disease, malaria and Rocky Mountain spotted fever.
- **Injuries:** Many different injuries can cause muscles to tear or stretch too far (muscle strain). Back strains are a very common injury. Accidents, trauma and overuse injuries can cause muscle cramps or muscle spasms. In severe cases, these injuries can lead to paralysis.
- **Medications:** Certain drugs, such as chemotherapy medications, can cause muscle pain. Sore muscles can also result from medications that treat high blood pressure. Some people develop muscle weakness after having a severe allergic reaction to a medication or a toxic substance.

11.1.4. Muscle Groups

There are more than 600 muscles in the body, which together account for about 40% of a person's weight. The majority of skeletal muscles have names that indicate a characteristic of the muscle. Frequently, a name will combine multiple criteria. You will learn and retain the characteristics of the muscle more easily if you associate its name with it. The terms listed below refer to characteristics of muscles that are used in muscle naming:

- **Size:** Vastus (huge); maximus (large); longus (long); minimus (small); brevis (short).
- **Shape:** Deltoid (triangular); rhomboid (like a rhombus with equal and parallel sides); latissimus (wide); teres (round); trapezius (like a trapezoid, a four-sided figure with two sides parallel).
- **Direction of Fibers:** Rectus (straight); transverse (across); oblique (diagonally); orbicularis (circular).
- **Location:** Pectoralis (chest); gluteus (buttock or rump); brachii (arm); supra- (above); infra- (below); sub- (under or beneath); lateralis (lateral).
- **Number of Origins:** Biceps (two heads); triceps (three heads); quadriceps (four heads).
- **Origin and Insertion:** Sternocleidomastoideus (origin on the sternum and clavicle, insertion on the mastoid process); brachioradialis (origin on the brachium or arm, insertion on the radius).
- **Action:** Abductor (to abduct a structure); adductor (to adduct a structure); flexor (to flex a structure); extensor (to extend a structure); levator (to lift or elevate a structure); masseter (a chewer).

11.1.4.1. Muscles of the Head and Neck

Humans are capable of a wide range of facial expressions due to their highly developed facial muscles. The muscles play a crucial role in nonverbal communication because they can convey a variety of emotions, including surprise, disgust, anger, fear, and others. The frontalis, orbicularis oris, orbicularis oculi, buccinator, and zygomaticus are the muscles involved in facial expression (Figure 11.1).

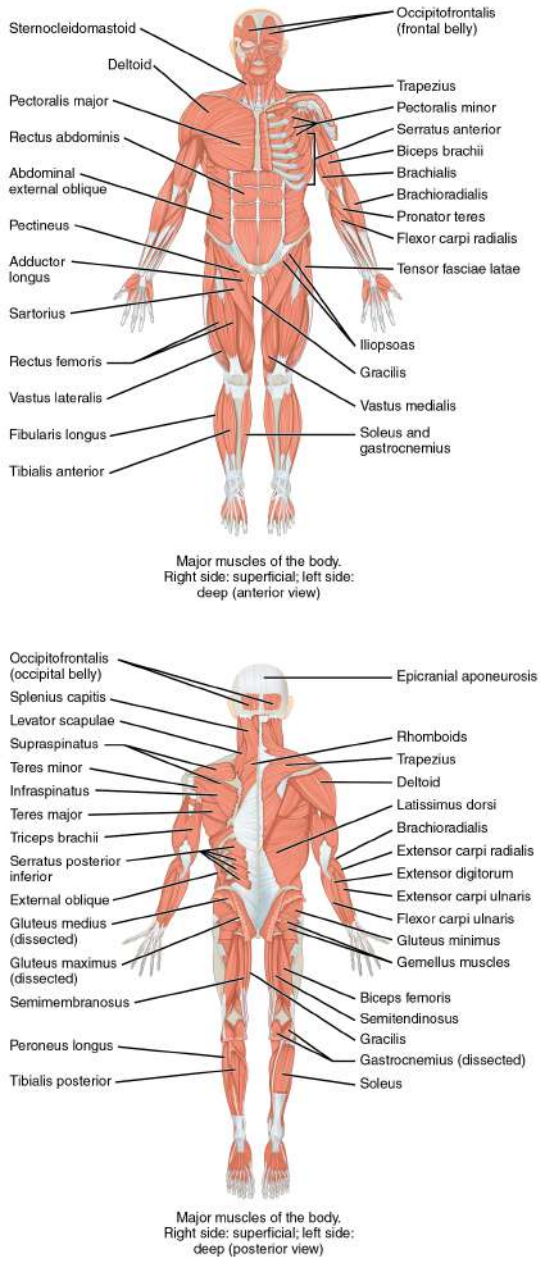


Figure 11.1. *The muscular system.*

Source: https://courses.lumenlearning.com/suny-hccc-fitness-2/chapter/naming-skeletal-muscles/.

The process of mastication, or chewing, is carried out by four pairs of muscles. These muscles, which are among the strongest in the body, are all attached to the mandible. The masseter and temporalis are two of the muscles. The hyoid bone, the spinal column, and the throat are all connected by a multitude of muscles.

11.1.4.2. Muscles of the Trunk

The muscles of the trunk include those that move the vertebral column, the muscles that form the thoracic and abdominal walls, and those that cover the pelvic outlet.

Stretching from the sacrum to the skull, the erector spinae group of muscles is a substantial muscle mass on both sides of the vertebral column. These muscles primarily function to extend the vertebral column, helping to maintain an upright posture. The area between the transverse and spinous processes of neighboring vertebrae is occupied by the deep back muscles. The main function of the thoracic wall muscles is to facilitate breathing. The spaces between the ribs are home to the intercostal muscles. During forced expiration, they contract. During the inspiration phase of breathing, the muscles that are external to the rib cage contract, raising the ribs. The diaphragm is a dome-shaped muscle that separates the thorax from the abdomen. For structures that need to go from the thorax to the abdomen, it has three openings. Unlike the thorax and pelvis, the abdomen is not protected or reinforced by bones. The wall is made up of four muscle pairs that are layered together along with the fascia covering them. The abdominal wall muscles are identified in the illustration below.

The pelvic outlet is formed by two muscular sheets and their associated fascia.

1. **Muscles of the Upper Extremity:** The muscles that attach the scapula to the thorax and move the scapula, the muscles that attach the humerus to the scapula and move the arm, and the muscles that are located in the arm or forearm and move the hand, wrist, and forearm are the muscles of the upper extremity.

   The serratus anterior and trapezius muscles are responsible for the movement of the arm and shoulder. The humerus is connected to the pectoralis major, latissimus dorsi, deltoid, and rotator cuff muscles, which are responsible for arm movement. The biceps brachii, brachialis, brachioradialis, and triceps brachii are the muscles that move the forearm and are situated along the humerus. The forearm contains at least 20 muscles that are responsible for the majority of wrist, hand, and finger movements.

2. **Muscles of the Lower Extremity:** The thigh-moving muscles originate from various parts of the pelvic girdle and insert into the femur. The gluteal muscles, which collectively adduct the thigh, are the largest group of muscles in the posterior region. The anterior muscle that flexes the thigh is the iliopsoas. The thigh is adducted by the muscles in the medial compartment.

   The thigh contains the muscles that move the leg. The muscle group responsible for knee straightening is the quadriceps femoris. The quadriceps femoris group extends the leg at the knee and is antagonistic to the hamstrings, which flex the leg. There are anterior, posterior, and lateral

compartments in the leg muscles that control the ankle and foot. The gastrocnemius and soleus muscles, which plantar flex the foot, are antagonistic to the tibialis anterior, which dorsiflexes the foot.

11.2. Types of Muscles

In the body, there are three types of muscle:

- Skeletal (striated) muscles;
- Smooth muscles;
- Cardiac muscles.

11.2.1. Skeletal Muscle

Of the three types of muscle in the body, skeletal muscle also referred to as voluntary muscle, is the most prevalent in vertebrates. Tendons connect skeletal muscles to bones, enabling all body parts to move in relation to one another. Unlike cardiac and smooth muscle, skeletal muscle is under voluntarily control. Skeletal muscle, on the other hand, is striated, much like cardiac muscle. It has a characteristic appearance due to the regular crossing of its long, thin, multinucleated fibers with fine red and white lines. Connective tissue holds skeletal muscle fibers together, allowing them to communicate with blood vessels and nerves.

11.2.2. Smooth Muscle

Smooth muscle is distributed throughout the body and performs a multitude of tasks. It aids in digestion and nutrient absorption in the stomach and intestines. It is present throughout the urinary system and aids in the body's detoxification as well as electrolyte balance. It is present in all veins and arteries, where it is essential for controlling tissue oxygenation and blood pressure. The body could not sustain even the most basic functions in the absence of these essential functions. There are several ways in which smooth muscle differs from skeletal muscle, but its capacity for involuntary contraction and control may be the most significant. The nervous system can regulate many of the body's subsystems using smooth muscle without conscious effort. When an individual engages in exercise, their blood pressure adjusts to the increased oxygen demands without their conscious awareness. Instead, the nervous system uses other receptors, hormones, and neurotransmitters to naturally regulate smooth muscle.

A significant part of the disease process in the body is also played by smooth muscle. For asthmatics, bronchodilators are a crucial and potentially life-saving treatment because they relax the smooth muscle of the airways. Metoclopramide is one example of a medication that increases smooth muscle signaling to stimulate and promote gastric emptying. When combined with ACEI, nitrates are used to treat ischemic heart disease, which is one of the most well-known uses of smooth muscle and medical therapy. This combination has been shown to reduce patient mortality. Understanding smooth muscle is crucial for medical professionals due to its unique influence on various parts of the body. Since the fundamental mechanism of many treatments is altering the signaling pathways that impact smooth muscle (Figure 11.2).

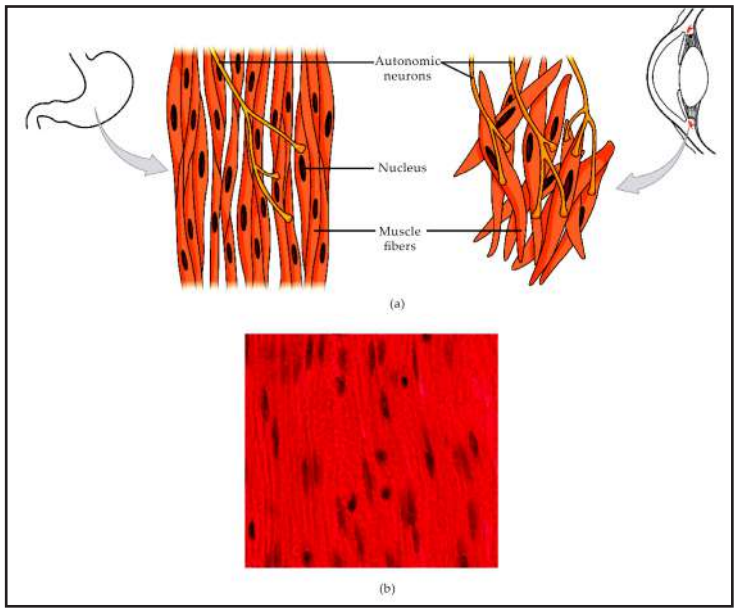


Figure 11.2. *Smooth muscle.*

Source: https://courses.lumenlearning.com/suny-ap1/chapter/smooth-muscle/.

11.2.3. Cardiac Muscle

One of the three main muscle types exclusively present in the heart of vertebrates is cardiac muscle, also known as the myocardium. The fact that cardiac muscle has sarcomeres, which are contractile units, sets it apart from smooth muscle, the third major muscle type, but it also makes cardiac muscle similar to skeletal muscle, another major muscle type. Unlike skeletal muscle, cardiac muscle is not controlled voluntarily and exhibits rhythmic contractions. As the heart's pacemaker, the sinoatrial node controls the heart's rhythmic contraction of cardiac muscle. The myocardium, or cardiac muscle cells, make up the majority of the heart. The heart's contractility, which underpins its pumping action, and the rhythmicity of its contractions are what make its action so remarkable.

To meet the metabolic needs of peripheral tissues, especially the skeletal muscles, kidneys, brain, skin, liver, heart, and gastrointestinal tract, the cardiac output, or amount of blood pumped by the heart per minute, varies. The contractile force produced by the cardiac muscle cells and their frequency of activation (rhythmicity) determine the cardiac output. The heart's ability to pump blood normally and adapt to variations in demand are largely dependent on the parameters influencing the frequency and force of heart muscle contraction.

11.3. Muscle Structure and Function

Thousands of muscle fibers encased in connective tissue sheaths make up each skeletal muscle. Fascicles are the discrete bundles of muscle fibers that make up a skeletal muscle. The term "epimysium" refers to the outermost connective tissue sheath that envelops the entire muscle.

11.3.1. Structure and Function of Skeletal Muscle

Every skeletal muscle is an organ made up of different tissues that are integrated together. These tissues include connective tissue, blood vessels, nerve fibers, and skeletal muscle fibers. The three layers of connective tissue, or mysia, that envelop and give structure to each skeletal muscle also serve to compartmentalize the muscle fibers within the muscle. The epimysium, a sheath of dense, asymmetric connective tissue, envelops every muscle and permits it to contract and move forcefully while preserving its structural integrity. Moreover, the epimysium permits muscle to move independently by dividing it from nearby tissues and organs.

Muscle fibers within skeletal muscles are arranged into bundles called fascicles, which are encircled by the perimysium, a middle layer of connective tissue. This fascicular organization, which is typical of limb muscles, enables the nervous system to initiate a particular muscle movement by stimulating a subset of muscle fibers within a muscle fascicle. A thin layer of collagen and reticular fibers, known as the endomysium, encases each muscle fiber inside each fascicle. The endomysium, which envelops the cells' extracellular matrix, aids in the force transmission from the muscle fibers to the tendons. The collagen in the three layers of connective tissue intertwines with the collagen of a tendon in skeletal muscles that pull on bones in concert with tendons.

The tendon merges with the periosteum that covers the bone at the opposite end. To pull on the bone to allow the skeleton to move, the tension produced by the contraction of the muscle fibers is subsequently transmitted through the layers of connective tissue, to the tendon, and finally to the periosteum. In other locations, the mysia may unite with fascia, the connective tissue that lies between the skin and bones, or with an aponeurosis, a broad sheet resembling a tendon. An example of an aponeurosis is the broad sheet of connective tissue in the lower back into which the latissimus dorsi muscles, also known as the "lats," fuse.

Additionally, blood vessels supply every skeletal muscle with an abundance of nutrients, oxygen, and waste removal agents. Additionally, the axon branch of a somatic motor neuron supplies each muscle fiber in skeletal muscle, signaling the fiber to contract. Skeletal muscle can only contract functionally through nerve system signals, unlike cardiac and smooth muscle.

11.3.1.1. Skeletal Muscle Fibers

Skeletal muscle cells are often referred to as muscle fibers (or myofibers) because they are long and cylindrical. In the Sartorius of the upper leg, skeletal muscle fibers can reach lengths of up to 30 cm (11.8 in) and diameters of up to 100 μm, making them relatively large in comparison to other cells. These large, protein-dense cells can produce the necessary proteins and enzymes to sustain their functions due to their numerous nuclei. Skeletal muscle fibers include cellular organelles like mitochondria and endoplasmic reticulum in addition to nuclei, which are present in other cells. Some of these structures, though, are specific to muscle fibers. Sarcoplasmic reticulum (SR), a specialized smooth endoplasmic reticulum, is responsible for storing, releasing, and retrieving calcium ions (Ca^{++}).

The cytoplasm of muscle fibers is referred to as sarcoplasm, and the plasma membrane is known as sarcolemma (from the Greek sarco, which means "flesh"). Proteins are arranged into organelles called myofibrils, which run the length of the cell and contain sarcomeres connected in series. One muscle fiber can contain hundreds to thousands of myofibrils, each with thousands of sarcomeres, because myofibrils are only about 1.2 μm in diameter.

The sarcomere is a highly ordered arrangement of contractile, regulatory, and structural proteins that makes up the smallest functional unit of a skeletal muscle fiber. The contraction of individual skeletal muscle fibers (and eventually the entire muscle) is caused by the shortening of these individual sarcomeres.

11.3.2. Structure and Function of Smooth Muscle

11.3.2.1. Structure

Unlike skeletal or cardiac tissues, smooth muscle tissue lacks visible, well-defined striations on its cells. This is a result of the distinct organization of smooth muscle cells compared to other muscle cells. The actin and myosin filaments in smooth muscle are stacked throughout the cell, as seen in the illustration below. The structure of skeletal and cardiac muscle differs greatly from this "staircase" arrangement of actin and myosin. Smooth muscle's actin filaments, which are represented by red lines, connect at the cell membrane and dense bodies as they travel throughout the cell. Actin filaments in skeletal and cardiac muscle are attached to Z plates, which aggregate a large number of actin filaments and appear as dark bands under a microscope. The actin and myosin fibers in smooth muscle are oriented at right angles to one another as they pass through the cell (Figure 11.3).

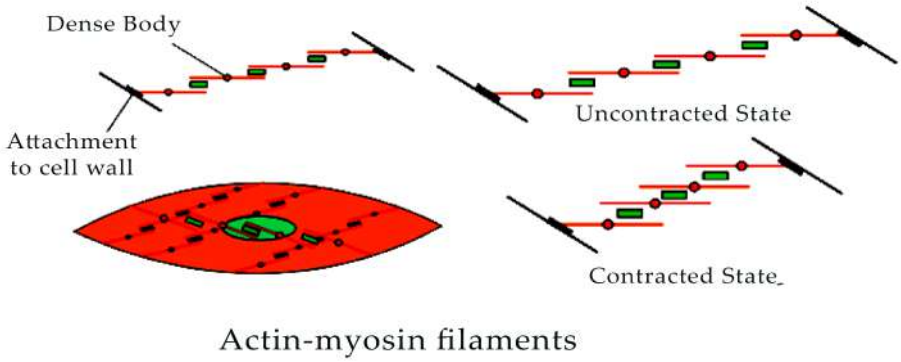


Figure 11.3. *Actin-myosin filaments.*

Source: https://upload.wikimedia.org/wikipedia/commons/b/bc/Actin_myosin_filaments.png.

11.3.2.2. Function

Smooth muscle has the same ability to contract as any other type of muscle tissue. The actin and myosin fibers shorten in the image above, causing the cell to effectively shrink. When compared to other muscle types, the smooth muscle contracts in a few significant ways differently. A signal travels from the somatic nervous system to the skeletal muscle, where it activates the muscle cell's organelles to release calcium. Myosin rapidly binds to actin after a protein moves due to the action of calcium. The myosin uses the constant supply of ATP to rapidly contract the cell. In smooth muscle tissue, this is not the case. Nerve impulses, hormones, and other chemicals released by specialized organs are examples of signals from the autonomous nervous system that control smooth muscle contraction instead of the somatic nervous system.

Unlike skeletal muscle, which must contract and release rapidly, smooth muscle is designed to contract continuously. Smooth muscle functions more like a car's throttle than a calcium trigger that initiates a contraction reaction. The cell receives a signal from an external stimulus or nerve impulse telling it to release calcium. Actin does not have a unique protein on smooth muscle cells that stops myosin from binding. Actin and myosin, on the other hand, bind continuously. However, myosin can only cling to and advance in response to energy. A sophisticated mechanism found inside smooth muscle cells enables calcium levels to regulate the quantity of ATP that myosin can use. Therefore, the cells do not immediately relax after the stimulus is removed. Myosin keeps attaching to actin and moving along the filaments until the calcium level drops.

11.3.2.3. Location

Smooth muscle has been adapted to many different parts of the body because of its unique ability to contract for extended periods and maintain that force. In addition to lining many sections of the digestive and circulatory systems, smooth muscle is also in charge of raising the hairs on your arms. Smooth muscle is essential to the circulatory system because it regulates and maintains blood pressure and oxygen flow throughout the body.

All veins and arteries are lined with smooth muscle, even though the heart exerts the majority of the pressure. These tiny muscles can contract to put pressure on the system or to relax and let blood flow more freely. Experiments have demonstrated that these smooth muscles respond to oxygen availability or deficiency by contracting the veins to deliver sufficient oxygen.

For similar reasons, smooth muscle lines most of the digestive tract. The stimuli that affect the cells in the digestive system differ from those in the circulatory system, though. For example, when you swallow, your gut's smooth muscle sheets contract. Tension is put on one side of the sheet when you swallow. In response, the cells on that side contract, causing a wave to start moving down your digestive tract. Food is moved through the numerous twists and turns of the stomach by a process called peristalsis.

Smooth muscle performs a wide range of functions due to its ability to contract and maintain tension. In addition to the functions mentioned above, smooth muscle is also in charge of contracting your irises, lifting the tiny hairs on your arm, sphincter contraction, and even the movement of fluids through your organs through pressure. Smooth muscle is much better at producing steady, elastic tension even though it doesn't contract or release as quickly as skeletal or cardiac muscle.

11.3.3. Structure and Function of Cardiac Muscle

11.3.3.1. Structure

It is a specific type of muscle that has evolved to contract repeatedly and continuously, allowing blood to circulate throughout the body. The heart is a complex organ with three main visible layers despite its intricate structure of chambers. The cardiac muscle is encircled on the outside by the epicardium, also referred to as the visceral pericardium. This keeps it safe from harm from other organs. By adhering to this outer layer, the parietal pericardium forms a fluid-filled layer that aids in lubricating the heart. The muscle and the blood it pumps through the heart's chambers are separated by the inner layer, or endocardium. The heart muscle lies between these two sheets. Myocardium is another term for cardiac muscle.

Heart muscle is made up of layers of cells that are connected to one another like a lattice when we take a closer look at it. An intercalated

disc is a type of specialized junction that locks two cells together at their meeting point. Under a microscope, this area appears as a dark disc, but it is the interlocking of hundreds of projections that resemble fingers from individual cells. Gap junctions, which are tiny holes in these projections, allow connected cells to receive the impulse to contract. Neural and vascular networks are entwined within and surrounding these cells, transmitting signals and oxygen to the heart muscle. The structure of cardiac muscle is similar to that of skeletal muscle at the microscopic level. Both muscle tissues are striated, which means that, when examined under a microscope, they display bands of light and dark (Figure 11.4).

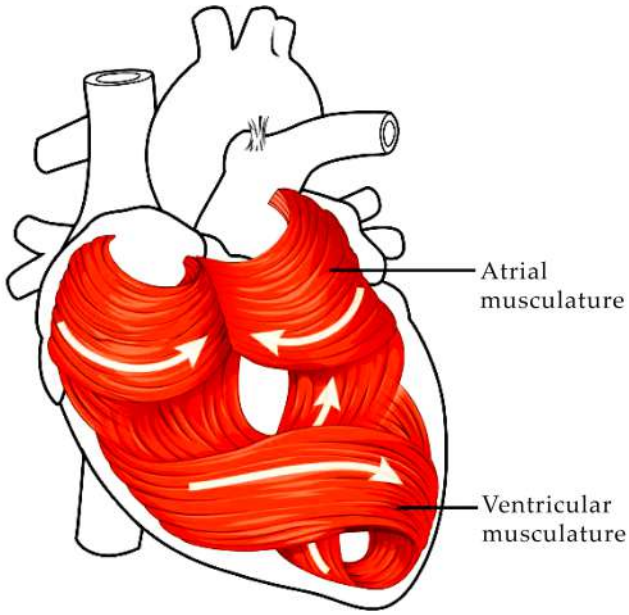


Figure 11.4. *Heart muscle.*

Source: https://courses.lumenlearning.com/suny-ap2/chapter/heart-anatomy/.

The incredibly well-organized sarcomeres are what form these bands. A sarcomere is a collection of protein fibers that contract in response to a signal. These sarcomeres are supported by the same proteins and consist of actin and myosin in both cardiac and skeletal muscle. Actin is wrapped by a protein called tropomyosin, which prevents myosin from attaching to it. Tropomyosin is held in place by the protein troponin until a signal to contract is received. The skeletal and cardiac muscles share the same proteins.

11.3.3.2. Function

An action potential is used as the contracting signal, just like in skeletal muscle. But in the case of skeletal muscle, the somatic, or voluntary, nervous system is typically the source of this signal. The autonomic nervous system regulates cardiac muscle. Your brain and heart cells work together to release precisely timed nerve impulses that instruct your heart's cells to contract in the proper sequence. The signal's source may differ, but the signal's reception and the remainder of the contraction are remarkably similar.

A specialized organelle is stimulated by the action potential, also known as the nerve impulse, on the cell surface to release calcium ions (Ca^{2+}). Derived from the endoplasmic reticulum present in a general cell, this organelle is known as the sarcoplasmic reticulum. Troponin is a protein that is affected by the release of Ca^{2+} ions into the cytoplasm, which causes it to release tropomyosin. Myosin is permitted to attach to actin when tropomyosin changes positions. Subsequently, myosin reduced the length of each sarcomere by walking along the actin filaments using the energy contained in ATP molecules. The Ca^{2+} is swiftly reabsorbed into the sarcoplasmic reticulum after the impulse has passed. When troponin and tropomyosin reattach, the heart muscle cells relax. Your heart goes through this general process each time it beats.

A force can be applied to the heart's chambers as a result of the coordinated action of muscle cells. The cardiac muscle sheets are arranged such that they are perpendicular to one another. This has the effect of causing the heart to contract in various directions. The contraction of these multiple layers of muscle fibers causes the ventricles and atria of the heart to contract from top to bottom and from side to side. This causes the ventricles to pump and twist vigorously, pushing blood throughout the body.

11.4. Muscle Contraction

The tightening, shortening, or lengthening of muscles during an activity is known as muscle contraction. It can occur during weightlifting, stretching, or holding or picking up objects. Muscle relaxation, the return of contracted muscles to their normal state, often follows muscle contraction. Myosin is one of the key proteins in muscle fibers responsible for contraction. Myosin fibers either tighten and shorten or loosen and stretch out depending on how your muscles must be used. Muscle contractions that occur at regular intervals, such as your heartbeat, are also caused by myosin.

11.4.1. Reasons for Muscle Contraction

Muscles serve several purposes in the body. The muscles contract for several reasons, primarily to:

- Offer stability to your joints and connective tissues – Your muscles lengthen and shorten, sometimes involuntarily, as your body needs them.
- Produce heat to maintain your body temperature – Around 40% of your body's temperature converts into muscle work. Shivering is your body's response to feeling cold, and your skeletal muscles activate to warm your body.
- Maintain posture – Muscles help you maintain a position like sitting or standing.

11.4.2. Types of Muscle Contraction

There are three types of Muscle Contraction are:

1. **Concentric Contractions:** Your muscle contracts in this way when it is actively shortened. Tension is created when you activate your muscle to lift something heavier than usual, causing it to tighten. Remember that this kind of muscle contraction occurs when the load is less than the maximal strength of your muscle. Without physically shortening the fibers to move the object, your muscle is unable to lift the load. Taking up a heavy box is an example of a concentric muscle contraction. Your leg muscles tighten as you stand up with the extra weight after squatting down to lift a

box, even though your arm muscles may have contracted to support the weight.

2. **Eccentric Contractions:** This type of contraction happens when your muscle is actively lengthened during normal activity. An example of this is walking because your quadriceps muscles are active when your heel touches the ground and your knee is bending or straightening out in stride. Eccentric muscle contractions also happen when you lower something heavy. Your muscle has to remain tight to manage the weight, but it lengthens to shift the weight into a different position.
3. **Isometric Contraction:** When your muscle remains at a specific length without lengthening or shortening, it undergoes this type of contraction. When you hold it in a position that demands a specific length once activated, it does not lengthen and shorten as it would during certain activities. Holding something in front of you in your arms is an illustration of this kind of contraction. Instead of attempting to raise or lower the object, your goal is to maintain its position.

11.4.3. Uses of Muscle Contraction

11.4.3.1. Isometric Muscle Contractions

When your muscle remains in one position and the joint to which it is attached remains motionless, you use this kind of contraction. It does not generally strengthen the entire muscle group. Rather, it fortifies your muscles for that one, particular motion. It is beneficial to practice using a muscle in a specific way after an injury by performing an isometric muscle contraction.

11.4.3.2. Concentric and Eccentric Muscle Contractions

Combinations of these two contraction types are common. When lifting something heavy, a concentric muscle contraction comes in handy. Concentric muscle contractions are often referred to as positive work, while eccentric muscle contractions are referred to as negative work. To assist you in lowering something heavy, your muscle contracts eccentrically. During an exercise routine, lifting a dumbbell is an example of these two contractions. Your bicep muscle contracts and tightens as you pick up the dumbbell to lift the weight. Your bicep muscle stays contracted when you reduce the weight; instead, it lengthens.

11.4.3.3. Passive Stretching

It's beneficial to use this kind of muscle contraction to gradually extend your muscles. Passive stretching involves extending your muscles to their maximum length, which activates them without forceful contraction. Your muscles become longer as a result, activating them without the need for force.

11.5. Muscle Energy Metabolism

Muscle tissue is characterized by its ability to contract, typically in response to a nervous system stimulus. Skeletal and cardiac muscles are the highest energy consumers among the three main types of muscle. The circulatory system pumps blood through the heart, a muscular pump. Heart muscle is relatively small in relation to other muscle types, but it has a remarkable blood supply share and a vibrant energy metabolism. The respiratory, urinary, and gastrointestinal tracts, as well as the reproductive system and blood vessels,

are the primary locations for smooth muscle. The contraction and tone of smooth muscle in these tissues and organs regulate many essential processes, including blood pressure and flow regulation, respiratory tract air flow direction, and the transmission of contents in the intestines and urinary tract. Smooth muscle has a high workload, but it consumes very little energy. Approximately two-thirds of the body's mass is made up of the skeletal muscle that makes up the locomotor system. At rest, skeletal muscle receives about one-sixth of the cardiac output, similar to the brain's share. Muscle consumes the most oxygen during maximal activation in aerobic work, and its blood circulation accounts for four-fifths of the cardiac output.

The metabolism of energy is distinct in skeletal muscle. Its adaptation for brief anaerobic exercise, in addition to its aerobic capacity, enables both prolonged lower-intensity endurance exercise and brief high-energy output. For skeletal muscle, the dynamic range of the change in the rate of ATP utilization is greater than a hundredfold. Circulatory, cardiac, and respiratory functions must be adjusted to compensate for changes in ATP utilization. Skeletal muscle in humans at rest receives approximately 5 milliliters of blood per 100 grams of tissue. The percentage of muscle tissue's cardiac output that comes from heavy exercise can reach up to four-fifths or higher in trained subjects. The extraction of oxygen also increases during heavy exercise, as shown by the rising arterio-venous difference, which goes from 25% at rest to 80% or higher during maximal exercise. As a result, when human muscle is worked, the amount of oxygen used can increase by approximately 100 times. This is quite a small increase when compared to some animals, where the increase can reach a 1,000 times. Muscle metabolism can be understood from a set of basic statements about the biochemical energy balance:

- Chemical energy is stored in muscle cells as ATP and creatine phosphate, which are biochemical capacitors;
- ATP provides the energy for all forms of muscle work;
- ATPases, the enzymes that break down ATP and release the energy for muscle work and metabolism, are the demand side of the balance and define energetic states; and
- This demand is supplied mainly by continuous aerobic metabolism.

The fundamental component of every muscle is the myofibril, a tiny, thread-like structure made up of intricate protein structures. Numerous myofibrils, which are made up of thin and thick myofilaments arranged in a regular pattern, are found inside each muscle cell, or fiber. When skeletal muscle contracts, the plasma membrane typically depolarizes, causing the sarcoplasmic reticulum's intracellular calcium ion stores to release calcium ions. The conformation changes of a protein when calcium ions attach to troponin C, a regulatory protein connected to thin filaments. The actin subunits of the thin filaments can interact with the nearby myosin molecules, which are made up of thick filaments, as a result of this shape change that is transferred to the other thin filament components (troponin T, troponin I, tropomyosin, and actin). When calcium ions are absorbed by the sarcoplasmic reticulum via the action of an ATP-driven pump, also referred to as Ca2+ ATPase, the contraction stops.

11.5.1. Anaerobic Energy Metabolism

The cytosolic pathway for the catabolism of glucose is called glycolysis. Glycolysis can operate without oxygen, converting pyruvate to lactate, or with oxygen, converting pyruvate to acetyl-CoA. Different tissues use glycolysis

differently as a source of energy; the heart uses it less than other tissues, while the brain and red blood cells use it more. Glycolysis allows skeletal muscle to function at a high level when aerobic metabolism is insufficient. Glycolysis produces almost half of the acetyl-CoA required for the citric acid cycle in skeletal muscle at rest. Six-carbon glucose is catabolized into three-carbon pyruvate and then acetyl-CoA during this process, producing two NADH and two ATP net. With a net yield of two ATP per NADH, NADH produced by glycolysis is moved into the mitochondria by the malate shuttle and oxidized in the respiratory chain. So, during the aerobic full oxidation of one mole of glucose, the citric acid cycle produces 30 ATP and glycolysis produces eight ATP. Anaerobiosis can also easily occur in skeletal muscle. This characteristic enables short-term performance that is significantly higher than what is possible to sustain aerobically. Two of the three ways that ATP is resynthesized involve anaerobic metabolism or metabolism that does not require oxygen. Anaerobic energy metabolism, also referred to as anaerobic glycolysis, is the process by which carbohydrates are partially broken down into lactic acid through anaerobic metabolic pathways. When aerobic metabolism is insufficient to meet the energy needs of muscle activity, which can occur in as little as a few minutes, anaerobic glycolysis is triggered.

Even though ATP is produced quickly during this cytoplasmic process, anaerobic glycolysis is not as efficient as aerobic glycolysis. The amount and duration of exercise are directly correlated with the lactic acid byproduct of anaerobic energy metabolism. Lactic acid buildup lowers intracellular pH, which stops phosphofructokinase—the enzyme that limits the rate of glycolysis—from working. Additionally, during low-intensity exercise, muscle NADH decreases, but during high-intensity exercise, it increases above resting values. Limited O2 availability in the contracting muscle may be the cause of the increase in muscle NADH. Intense exercise causes an increase in cytosolic NADH, which inhibits pyruvate dehydrogenase and increases the extraction of hydrogen atoms from NADH to reduce pyruvate to lactate. To facilitate the process of glycolysis and supply energy for the reconstitution of the energy-rich phosphates, oxidized NAD can function as a hydrogen acceptor. However, the cost of producing ATP anaerobically is high. Just two moles of ATP are produced net when one mole of glucose is oxidized. Increased lactic acid production can impair the function of vessels, neuromuscular junctions, muscle fibers, and connective tissue cells. However, it can also trigger adaptive changes in metabolism, which are crucial for training, particularly in sports. Excessive oxygen consumption also leads to the profound production of various forms of oxygen, such as reactive oxygen species (ROS) in fibroblasts, endothelium, neutrophils, and erythrocytes in (C) skeletal muscle fiber and (D) endothelium. ROS cause tissue damage and muscular exhaustion. Numerous aqueous and lipid phase antioxidant defense systems exist in muscle tissue, shielding the tissue from the damaging effects of excessively produced ROS. The synthesis of glutathione (GSH), which is essential for the upkeep of the antioxidant defense, is a function of skeletal muscle. It supports the preservation of the reduced forms of the vitamins C (in the soluble phase) and E (in the lipid phase) as an oxidizable substrate in and of itself. In the metabolism of peroxides, glutathione system enzymes such as glutathione-S-transferases and glutathione peroxidase work in tandem with catalase.

11.5.2. Aerobic Metabolism

The respiratory cascade carries oxygen to the site of oxidation in living tissues. Since over 90% of energy is used by muscle cells during intense exercise, the aerobic demand is

ultimately determined by active skeletal muscle cells. Substances are transported in plasma, whereas oxygen is carried in the bloodstream attached to erythrocyte hemoglobin. Because most mammalian species have very small oxygen stores in their bodies and large amounts of substrates stored in tissue substrate stores as well as within muscle cells, the oxygen supply needs to be constant.

11.5.2.1. Mitochondrial Oxidative Phosphorylation

The mitochondria are the site of aerobic energy metabolism, which releases the most energy. However, as the name suggests, it needs oxygen. For the production of energy, aerobic glycolysis is the most efficient process. In the absence of oxygen, a single mole of glycogen can produce only two moles of ATP anaerobically, but in the presence of oxygen, the same amount of glycogen can produce 38 moles of ATP.

After deducting the 2 moles of ATP consumption, the net yield amounts to 36 moles of ATP (with 38 molecules in the heart muscle, liver, and kidney). Oxidative phosphorylation is the process by which hydrogen atoms are taken out of the reducing equivalents created during the citric acid cycle in the mitochondria of muscle cells. As a result, unique electron transport proteins take electrons from hydrogen atoms and ultimately move them to molecules of oxygen. ATP is a form of energy conservation that is produced during the transfer of electrons to oxygen. In the respiratory chain, electrons move from more electronegative to more electropositive oxygen molecules in an order that increases redox potential.

The rate of mitochondrial respiration in cells under high oxygen pressure is determined by energy demand, while the cellular energy level at which that rate is reached is determined by substrate supply. When compared to the energy needed by contracting muscle cells, the pool of ATP and CP is considerably smaller. For very brief intervals of time, the rate of ATP utilization can be higher or lower than the rate of ATP synthesis due to the small size of the high-energy phosphate pool. Therefore, the rate at which ATP is synthesized needs to be, on average, equal to the rate at which it is hydrolyzed by cellular processes. As a result, mitochondrial oxidative phosphorylation is closely linked to numerous metabolic processes and reacts fast to variations in the ATP requirements of tissues. But the respiratory chain's coupling isn't flawless. Superoxide is thought to escape from the respiratory chain at rest in an amount of 1-3%. Reactive oxygen species production like this could have effects during exercise and while at rest.

11.5.2.2. Citric Acid Cycle

The majority of oxygen in skeletal muscle is used by the mitochondria, which also provide the main metabolic energy source for prolonged activity. The citric acid cycle sometimes referred to as the Krebs or tricarboxylic acid cycle, is a set of events that occur in the mitochondria that catabolize acetyl-CoA and release hydrogen equivalents, which are then utilized in oxidative phosphorylation to produce ATP from ADP. An essential component of aerobic metabolism is the citric acid cycle.

The common final pathway for the catabolism of proteins, lipids (fatty acid beta-oxidation), and glucose (glycolysis) is the citric acid cycle. Fatty acid beta-oxidation and glycolysis contribute more than 95% of the acetyl-CoA that enters the citric acid cycle, both at rest and during exercise. Acetyl-CoA condenses with oxaloacetate to form citrate in the citric acid cycle. Oxaloacetate is once more created in the reactions that follow. Three NADH, one FADH2, one GTP, and two CO2 are produced during the process. After that, the hydrogen equivalents go through oxidative phosphorylation. In the

process, 11 ATP is produced by the 3 NADH and 1 FADH2. Consequently, 12 ATP are produced by one citric acid cycle turn.

11.5.3. Metabolism of Glucose and Glycogen in Muscle Fibers

Glycogen is obtained by skeletal muscle through either transport from the blood or glycogenolysis. Glycogen can be stored in muscle tissue up to a maximum of 4–5% of the tissue's wet weight. The primary source of glucose during moderate to intense exercise is glycogen, which also poses a constraint on endurance events like marathons. The best way to characterize the glycogen and glucose catabolic rates is as exponential functions of exercise intensity, with the glycogen response having a higher gain in slope than the glucose response. Muscle takes up glucose from the blood using insulin-dependent processes. Insulin sensitivity in skeletal muscle is increased by exercise. Muscle increases its uptake of glucose during exercise by an increased metabolic rate and an increase in membrane permeability to glucose brought on by contraction. It has been demonstrated that glucose uptake is inhibited by additional regulatory mechanisms, such as elevated glycogenolysis or higher resting glycogen concentration. Increased concentrations of free fatty acids may also reduce the uptake of glucose during exercise, though this is a contentious claim. Exercise training causes an increase in muscle glucose transporter levels, including GLUT4, an essential limiting factor of glucose utilization, and glycogen synthase activity. However, elevated GLUT4 levels may not always correlate with increased uptake of glucose. Furthermore, the balance of substrate utilization during intense muscle work is influenced by both phenotypic adaptations to short- and long-term physical activity and genotypic adaptation for aerobic capacity.

A Closer Look

Muscle

Every skeletal muscle in your body is made up of hundreds of thousands of tiny muscle fibers (or muscle cells). Each muscle fiber is wrapped in a connective tissue sheath, called an endomysium. Several muscle fibers gathered into a bundle are called muscle fascicle. Each fascicle is wrapped in a collagen sheath, called a perimysium.

Many muscle fascicles together make up the whole muscle, which is wrapped in a connective tissue sheath, called the epimysium. Each skeletal muscle fiber has a nerve ending that controls its activity, an artery and one or more veins. The muscles are wrapped in a connective tissue deep fascia sheet that binds them into functional groups. The muscle connects to the bone via a tendon.

Summary

- Muscle fibers are specialized cells that make up the muscular system, with their primary feature being the ability to contract. Movement is facilitated by muscles attached to bones, internal organs, and blood vessels.
- Smooth muscle is distributed throughout the body and performs a multitude of tasks. It aids in digestion and nutrient absorption in the stomach and intestines.
- Every skeletal muscle is an organ made up of different tissues that are integrated together. These tissues include connective tissue, blood vessels, nerve fibers, and skeletal muscle fibers.
- It is a specific type of muscle that has evolved to contract repeatedly and continuously, allowing blood to circulate throughout the body.
- The tightening, shortening, or lengthening of muscles during an activity is known as muscle contraction. It can occur during weightlifting, stretching, or holding or picking up objects.
- The cytosolic pathway for the catabolism of glucose is called glycolysis. Glycolysis can operate without oxygen, converting pyruvate to lactate, or with oxygen, converting pyruvate to acetyl-CoA.

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Medical Embryology

Clinical embryology is an advanced field that intersects the study of embryology with assisted reproductive technologies (ART). This discipline primarily focuses on the intricacies of human development from conception to the early stages of pregnancy, specifically within the context of fertility treatments. The scope of clinical embryology encompasses a broad range of techniques and processes designed to assist in the conception and ensure the healthiest possible start for human embryos. At the core of clinical embryology are sperm preparation and analysis procedures. These are critical steps in assessing the viability and quality of sperm for use in assisted reproductive techniques such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). These procedures are fundamental in selecting the best possible sperm for fertilization, aiming to increase the chances of successful pregnancy. Another crucial aspect of clinical embryology is the insemination process used in IVF and ICSI treatments. This involves carefully introducing sperm to the oocyte (egg) to facilitate fertilization. Following fertilization, embryologists undertake the evaluation of the embryos. This evaluation can be performed using traditional morphological assessment techniques or with the aid of more advanced processes. Among these, time-lapse imaging stands out as a technique that allows continuous monitoring of embryo development, providing invaluable data on the embryo's growth patterns and viability. Metabolomics, the study of chemical processes involving metabolites, and the measurement of microRNAs (miRNAs) using computational methods, offer deep insights into the health and development potential of embryos, beyond what can be discerned through visual assessment alone.

The field also involves the vitrification (fast freezing) and thawing of gametes (sperm and eggs) and embryos. This process is essential for preserving these cells for future use, without compromising their viability. The techniques and protocols for freezing and thawing are continuously refined to ensure the highest possible survival rates and maintain the integrity of the gametes and embryos. Quality control and assurance within embryology laboratories are paramount. These protocols ensure that all procedures are conducted under optimal conditions to maximize the chances of success. This includes maintaining sterile environments, ensuring equipment is functioning correctly, and adhering to strict protocols for handling gametes and embryos. In recent years, there has been a significant emphasis on the need to assess the quality of embryos before transfer. This is crucial for improving the success rates of ART procedures. Additionally, the stimulation protocols used to induce the production of oocytes have been finely tuned to match the specific needs of each patient. This personalized approach to fertility treatment has significantly improved the quality of oocytes and subsequent embryos, tailoring the process to the individual's physiological response to stimulate medications. Beyond the technical and procedural aspects, clinical embryology and reproductive medicine also navigate complex bioethical issues. Since the field involves the manipulation of gametes and pre-implantation stage embryos, there are profound ethical considerations to be addressed. These include the moral implications of embryo selection, the disposal of unused embryos, and the potential for genetic modifications. The field constantly grapples with these issues, striving to balance the incredible potential of assisted reproductive technologies with ethical principles and societal values. This book provides an in-depth exploration of human development from conception through to birth, focusing on the fundamental concepts and latest advancements in the field of embryology. It is designed to bridge the gap between basic embryological knowledge and its clinical applications, thereby enhancing the understanding of human developmental processes and congenital anomalies. The text details the stages of human development, the cellular and molecular mechanisms involved, and the embryological basis of various medical conditions, aiming to equip medical students, healthcare professionals, and researchers with a comprehensive understanding of the subject. The book will serve medical students, residents in pediatrics, obstetrics, and gynecology, as well as professionals in reproductive medicine and developmental biology as both an educational resource and a reference guide. Through clear illustrations, up-to-date text, and clinical correlates, it endeavors to enrich the reader's knowledge, aiding in diagnostic and therapeutic applications related to embryology. This book is particularly valuable for those seeking to grasp the complexities of human development, understand the origins of congenital anomalies, and apply embryological knowledge in clinical practice to improve patient care.

Donikë Demelezi is a dedicated medical doctor with a diverse background in pathology, general practice, and research. Currently serving as a Resident of Pathology and Cytodiagnostics at the University Clinical Center of Kosovo in Pristina, she meticulously analyzes bodily fluids and tissue specimens, compiles pathology reports, and engages in research. Previously, Donikë honed her clinical skills as a General Practitioner, where she assessed and treated patients during COVID-19 pandemic. Donikë's academic journey includes earning her MD degree from the University "Hasan Prishtina", Faculty of Medicine in Pristina. She furthered her knowledge through research summer school at the University of Angers in France. Committed to continuous learning, Donikë actively participates in extracurricular activities. Alongside her professional endeavors, she dedicates her time to volunteering with organizations like the Red Cross of Kosovo. Donikë's passion for medicine, coupled with her diverse experiences, shapes her into a compassionate and skilled healthcare professional.

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