Essentials of Human Anatomy and Pathology

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PREFACE

Anatomy is the branch of biology concerned with the study of the structure of organisms and their parts. Pathology is a branch of medical science primarily concerning the cause, origin, and nature of disease. It involves the examination of tissues, organs, bodily fluids and autopsies in order to study and diagnose disease. This book offers a balanced presentation of content. Through years of collaboration with students and instructors alike, this text brings together deep experience and modern innovation to provide solutions for students' greatest challenges. The organization and flow of content of the book within the pages provide students with an accurate, clearly written, and expertly illustrated presentation of the structure and function of the human body.This book meets the changing standards and offers dynamic and engaging choices to make this course more rewarding and fruitful. Students can start here, and armed with the knowledge they gain through a professor's guidance using these materials, be ready to go anywhere with their careers. Scientists and students of this field will find this book valuable.

The author would like to express his sincere thanks to his friends and family for their support in the completion of this book. He wants to thank Springer MedPress Corporation to recognise the intensity of the subject and help me publish this masterpiece which will educate well the newcomers. Also thanks the staff and the editorial team for their kind support and encouragement. This book has all the relevant details with the new concepts.

-Author

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Gross Anatomy: An Introduction

Anatomy is the identification and description of the structures of living things. It is a branch of biology and medicine. The study of anatomy goes back over 2,000 years, to the Ancient Greeks. It can be divided into three broad areas: Human anatomy, zootomy, or animal anatomy, and phytotomy, which is plant anatomy. Human anatomy is the study of the structures of the human body. An understanding of anatomy is key to the practice of health and medicine.

Anatomy The word 'anatomy' derives from the Greek *ana* (up) and *tome* (a cutting)—hence 'dissection'—and it can be defined as the science of the structure of a body learned by dissection. The word can thus be applied to any structure, and we can talk about the anatomy of a plant, an insect, or even a machine, but here the term will be restricted to the structure of the human being.

Since earliest times, man may have been curious about the inner structure and workings of his body. Certainly the ancient Egyptians, in performing mummification, which involved preliminary removal of the viscera, would have gained considerable information about the organs of the chest and abdomen. However, the practitioners of this art were not medical, and there is little evidence that the doctors of those times derived any knowledge from this potentially rich source of anatomical material. The first recorded school of anatomy, where dissection of the human body was performed, was in Alexandria, and it flourished between the first century BC and the second century AD. Here two Greeks, Herophilus and Erasistratus, were celebrated for their experience of anatomy acquired by the dissection of condemned criminals, and they described many structures of the human body. Herophilus recognized the brain as the central organ of the nervous system and the seat of intelligence, thus reversing the view of Aristotle, the Greek philosopher, of the primacy of the heart. Erasistratus observed the convolutions of the brain, noted that they were more marked in man than in lower animals, and associated this complexity with the higher intelligence of man. He also described the main parts of the brain, its coverings, and its cavities, the ventricles.

The most celebrated anatomist of the ancient world was undoubtedly Galen (129–216 ad). Born in Pergamon in Asia Minor, he studied in Smyrna and Alexandria before settling in Rome. He studied the human skeleton in Alexandria, but by then human dissection had virtually ceased, and much of his anatomy was based on animal studies.

Although Galen made many contributions to the subject, his work on bones and muscles being particularly good, and although many of the anatomical terms still in use today have their roots in his work, he also made errors and misinterpretations in his findings. In spite of this, his writings were regarded as definitive and beyond criticism over the next 1300 years. As a simple example, he described the kidneys as being lobulated, as they are in cattle, when the most casual glance would have shown that they are smooth in man. His statement that blood passed through pores between the left and right side of the heart again could have been refuted by simple observation. To make matters worse, continued copying of his writings and translations from one language to another led to further mistakes and faults creeping into his texts.

During the Middle Ages, human dissection was frowned upon by the Church. In the late fifteenth and early sixteenth centuries, a revival of learning and, with it, of anatomical observation took place, especially in Italy and more particularly in the University of Padua. It was there that a revolution in anatomy took place with the publication, in 1543, by Andreas Vesalius, then aged only 28, of his book De Fabrica Corporis Humani (The Structure of the Human Body). This was based on his personal observations of his own human dissections, and of studies of the human skeleton. It contained magnificent illustrations, taken directly from his dissections, which could be used today in any modern textbook of anatomy.

Over the next centuries dissection of the human body became a standard part of the training of medical students. Indeed, it provided more or less the only scientific subject in the curriculum. However, because of religious and social attitudes surrounding the acquisition of bodies, and because of the unpleasant nature of dissection on unpreserved and often decomposing material, both anatomy and practitioners followed a somewhat chequered course. Anatomies were usually made in winter months, when the process of putrefaction was delayed, and the timing in England was also made to correspond with the assizes, when the bodies of executed criminals would be available. The legitimate sources of bodies—executed criminals and unclaimed corpses of paupers—were often inadequate for the increasing numbers of medical schools and of medical students.

In Britain in particular, there was the scandal of the grave robbers (or 'resurrectionists' as they were called), who would dig up a body shortly after burial and sell it to an anatomy school. Relatives would sit up, armed, at night to protect the grave, or secure the graves with iron cages known as 'mort-safes'. Sometimes, indeed, because of the chronic shortage of bodies, criminals would resort to murder to obtain their material, as in the infamous case of Burke and Hare in Edinburgh, who committed no less than 16 murders. Hare turned King's evidence, but Burke was hanged and afterwards publicly dissected. The scandal of this case undoubtedly led to the Anatomy Act of 1832, which licensed premises for dissection and made legal the provision of bodies from workhouses or elsewhere which were unclaimed. The anatomy school was responsible for the subsequent burial or cremation of the body according to the religion of the deceased. These regulations have gradually been replaced by the bequests of individuals of their bodies for anatomical purposes after death so that today, in the UK, virtually all bodies are received at anatomy departments by these means.

The techniques of anatomical studies were improved by the injection of coloured materials into blood vessels and lymphatics, and by methods of embalming and preserving the body. Formalin, discovered in 1868 by Von Hoffman, rapidly replaced other preservative agents, and remains the basis of modern preservation methods.

The development of simple microscopes in the seventeenth century founded the important science of *microscopic anatomy*. A pioneer in this field was Malpighi, whose extensive studies demonstrated the blood capillaries, thus finally establishing the anatomical basis of the circulation of the blood. He also described red blood corpuscles, and the structure of the skin and of many other tissues. The modern achromatic compound microscope was invented in 1878, and it was this instrument that added the extra dimension of the microscopic study of tissues to anatomical teaching.

With the advent of anaesthesia in 1846, and the introduction of antiseptic surgery as a result of the work of Lister in 1867, the vistas of surgery were greatly increased and, with them, the importance of a detailed knowledge of anatomy to the surgeon. To most students, however, anatomical teaching was something of a sterile test of memory, with emphasis on exact topographical details of the finer ramifications of nerves and blood vessels. In the twentieth century, particularly in its second half, the subject of anatomy became much wider and of a more practical nature. It is true to say that there is little interest today in 'pure' topographical anatomy. The detailed mapping of the human body is now fully documented and is to be found in the major textbooks. Indeed, the name of Gray's Anatomy, the standard text, has passed into popular parlance. However, in its various sub-divisions, the subject is thriving and the most important of these need some separate descriptions.

COMBINATION OF THE ANATOMY STUDY OF MEDICINE AND BIOLOGY

Anatomy is a combination of the study of medicine and biology, since its main concern is the studying of the structure of all living things, it can be with regards to animals, human and plants. Anatomy is divided into sub categories, which are the gross and microscopic anatomy. Gross anatomy is the study of all structures that is visible to the eye. It can be seen clearly and does not need an aid of a microscope. Microscopic anatomy on the other hand is the complete opposite of gross anatomy. A person would need the use of a microscope; an example would be the study of cells.

Anatomy can be categorized in two, which are the human anatomy and the comparative anatomy. Human anatomy is the study of human body and its structure. It can be divided into two, which are the regional and systematic approach. In regional approach, most studies are simultaneous and are to the external parts of the body like legs, knees, hands, arms *etc.* Systematic approach on the other hand is a study mostly on the inside part of the body, like the skeletal system, digestive system and the nervous system, which are being studied altogether.

Most students who are taking medical studies are familiarized with the real meaning of what is anatomy through books, pictures, skeletal model, diagrams, lectures and anatomical models. Microscopic anatomy can be learned with the help of not just by microscope itself but also with the slide, especially in studying cells. Using dead bodies or cadavers are another instruments that can help professionals and student alike to learn more about human anatomy. In relation to human anatomy, embryology can also be traced through the skeleton. A person can distinguish the roots of the evolution through looking at the similarities present in ones skeletal system such as the ribcage and vertebrate.

Comparative anatomy on the other hand is the study of the resemblance and diversity of living organisms. Mostly related to animals, comparative anatomy traces similarities of present living organisms to historical living creatures. It is best describes Darwin's theory of evolution. Comparative anatomy also distinguishes each body part of an animal for their functions. Although most animals would have the same bone structure as the other animals, even compared to human, each would have different functions. The similarities can be found and the differences can be distinguished through comparative anatomy. Their function would still depend on the environment that they are in. It will also depend on the animals' everyday task and living, also on their habitat.

Presently, comparative anatomy is mostly being used through the study of paleontology, since it deals with the bone structures that can be traced way back through pre-historic era. With the comparative anatomy, scientist would be able to determine from what animal kingdom they used to belong, or that they would be able to tell the ancestors of each animal by just studying their bones or fossils. There are two major perceptions in comparative anatomy; these are homologous structures and analogous structures.

Homologous structures are body parts that can be the same on different species but serve different functions or use. Like for example, a similarity in the bone structure of a whale and a cat does not mean that they can do the same purpose, it may just be the same but of different use. While analogous structure on the other hand are body parts that can be the same but not because they have the same origin or species, but because they have the same environment or habitat, that is why they are functioning as the same. Like for example, creatures living in water can have similar structure not because they have the same ancestor but because they both live in water. With this information, one can have a better understanding of what is anatomy.

GROSS ANATOMY

In medicine, gross anatomy, macro anatomy, or topographical anatomy refers to the study of the biological structures that are visible to the naked eye. The study of gross anatomy may involve dissection or non-invasive methods. The aim is to collect data about the larger structures of organs and organ systems.

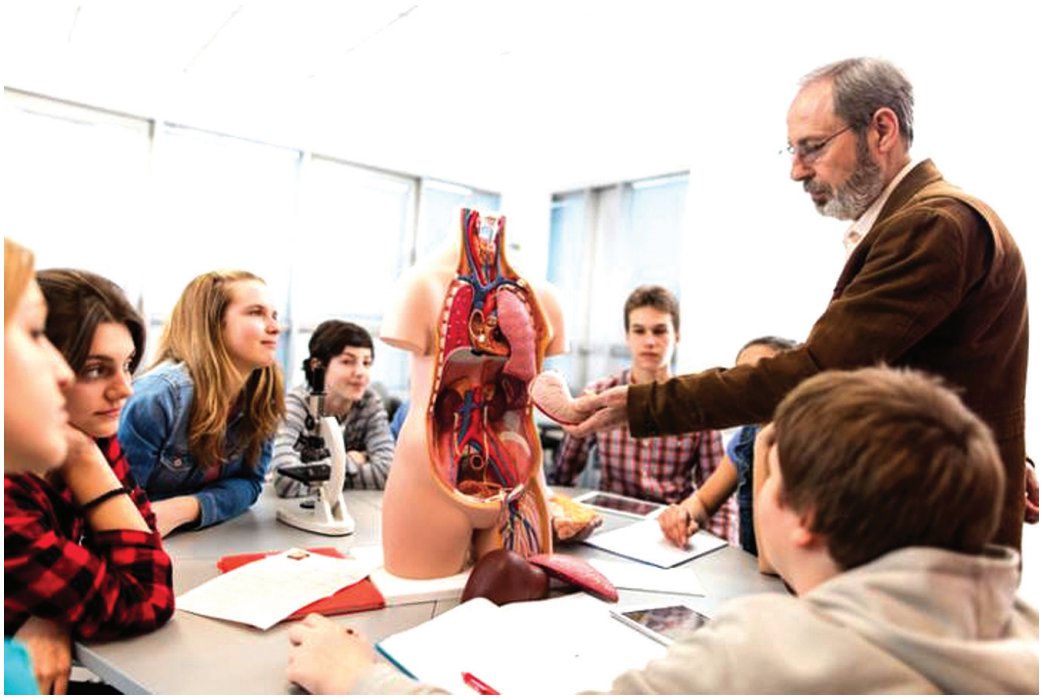


Fig. Knowing about Anatomy is Key to Understanding Health care.

In dissection, the scientist cuts open the human or animal cadaver is cut open and examines its organs. Endoscopy, inserting a tube with a camera at the end, might be used to study structures within living animals. Endoscopy is performed either through the mouth or through the rectum, so the gastrointestinal tract is often the primary organ of interest. There are also less invasive methods. For example, to study the blood vessels of living animals or humans, the scientist may insert an opaque dye into the animal that will highlight the circulatory system when imaging technology, such as angiography. Techniques such as magnetic resonance imaging (MRI), computed tomography (CT), or X-ray also reveal information about the inside of a living body. Medical and dental students perform dissection as part of their practical work in gross human anatomy during their studies. They may dissect a human corpse. Students of gross anatomy will need to learn about the major body systems.

HUMAN BODY SYSTEMS

There are 11 organ systems in the human body:

- The integumentary system, meaning skin, hair, nails, and so on,
- Skeletal System,
- Muscular System,
- Lymphatic System,
- Respiratory System,
- Digestive System,
- Nervous System,
- Endocrine System, which regulates hormone production,
- Cardiovascular System,
- Urinary System,
- Reproductive Systems.

Although these systems have different names, they all work interdependently, meaning they work together and depend on each other.

TOPOGRAPHIC ANATOMY

In this, the body is studied by regions rather than by organs. This is of importance to the surgeon who exposes different planes after the skin incision and who, of course, must be perfectly familiar with structures as he explores the limbs and body cavities. Once the sole preserve of the surgeon, this field has acquired immense significance today for the radiologist. In this respect cross-sectional topographic anatomy has come into its own.

ENDOSCOPIC ANATOMY

With the development of fibreoptic instruments, the body's tubes and cavities are now being explored in life. The detailed anatomy, for example, of the bronchial tree as seen through the bronchoscope is now of great importance. The introduction of laparoscopic and thoracoscopic instruments to explore and operate in the abdomen and thorax respectively has also opened new vistas as surgeons require to learn their anatomical landmarks through these approaches.

SURFACE (LIVING) ANATOMY

From the practical point of view, every medical practitioner needs to know the detailed structure of the tissues beneath the skin of his patient. This forms an important part of the teaching of medical students, who can practise on themselves the identification of bones, landmarks, muscles, and arterial pulses; the palpation of normal structures through the intact skin; and the range of movement of the joints.

RADIOLOGICAL AND IMAGING ANATOMY

The discovery by Röntgen of X-rays a century ago opened new vistas of anatomical study. This was enhanced by the development of radiological techniques to outline viscera, for example by injecting radio-opaque solutions into blood vessels (*angiography*) or by swallowing barium paste in order to demonstrate the oesophagus and stomach. More recently, other imaging techniques, which include ultrasonography, computerized tomography, and, in particular, magnetic resonance imaging, have provided unrivalled information of three-dimensional anatomy in the living body. Indeed, today, the radiologist must possess a detailed knowledge of anatomy that certainly rivals that of his surgical colleagues.

EMBRYOLOGICAL ANATOMY

The complex changes in the growing fetus are studied because much of adult anatomy can only be understood by appreciating its prenatal development. More and more has been learned about the underlying causes of the numerous congenital abnormalities that may arise as aberrations of normal development.

MICROSCOPIC ANATOMY

Is of fundamental importance in the understanding of pathological changes, and has advanced with the introduction of electron microscopy, which enables the finest details of the cells to be studied at an *ultramicroscopic* magnification of several thousands.

Kinesiology

The study of joint and limb movement, has developed into a subject of immense importance, together with biomechanics and *orthotics* (the study and use of artificial limbs). Here, research has an immediate application

in orthopaedic practice, for the study of joint prostheses, the measurement of forces acting on the skeleton, and choosing the strength of materials utilized in reconstructive surgery; also for the analysis of the causes of failures of artificial joint implants, or of the materials used in internal fixation of fractures.

Neuroanatomy

The study of the brain, spinal cord, and nerves, forms an important part of the battery of approaches needed for neurobiological exploration, which today is complemented by physiology, pharmacology, molecular biology, and dynamic whole brain imaging. All these topics are of obvious importance in the various expanding fields of medicine, but anatomy also impinges on other sciences. Examples are *comparative anatomy*—the comparison of structures in different animals and species; *palaeoanatomy*—the study of ancient remains—mainly, of course, of bones; and *physical anthropology*—the study of the different human races.

A recent development has been the appearance of a complete, sectioned human body appearing on the World Wide Web. The Visible Human Project presents transverse CT, MRI and cryosection images of two complete human cadavers, one male and one female, at an average of 1 mm intervals. These allow three-dimensional constructions to be 'visualized' from any angle on the computer screen.

Anatomy is thus a subject which encompasses a great variety of endeavours characterized by the study of the organization of the human body, and which impinges on many other sciences. In teaching anatomy to medical students, dissection of the cadaver remains fundamental, but the student also studies living, imaging, microscopic, and embryological anatomy. Anatomy forms an essential part of the scientific basis of medicine. All those concerned with disorders of the human body must start from a background of knowledge of its normal macroscopic and microscopic structure.

MICROSCOPIC ANATOMY

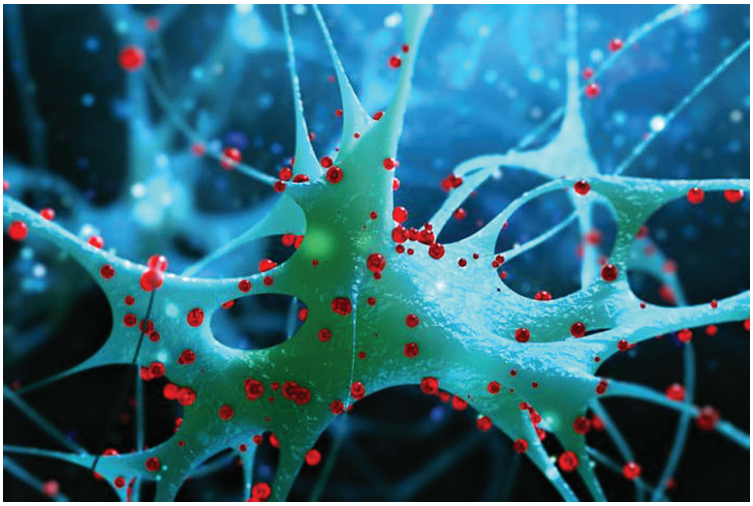


Fig. On a Microscopic level, Anatomy looks at Cell Structure and Function.

Microscopic anatomy, also known as histology, is the study of cells and tissues of animals, humans and plants that are too small to been seen with the naked eye. By looking at tissue under the microscope, we can learn about the architecture of the cells, how they are put together, and how they relate to each other. For example, if a person has cancer, examining the tissue under the microscope will reveal how the cancer cells are acting and how they affect normal human tissue. This commonly involves studying tissues and cells using histological techniques such as sectioning and staining, and then looking at them under an electron or light microscope.

Sectioning involves cutting tissue into very thin slices so they can be examined. Histological stains are added to biological structures, such as tissues, to add colours or to enhance colours so they can be more easily distinguished when they are examined, especially if different structures are next to each other. Histology is vital for the understanding and advancement of medicine, veterinary medicine, biology, and other aspects of life science.

Histology is used for:

Teaching: Histology slides are used in teaching labs to help students who are learning about the microstructures of biological tissues.

Diagnosis: Tissue samples, or biopsies, are taken from patients and sent to the lab for analysis by a histologist.

Forensic Investigations: The microscopic study of biological tissues can help explain why, for example, somebody unexpectedly died.

Autopsies: As in forensic investigations, biological tissues from deceased people and animals can be analyzed, so that investigators may better understand the causes of death.

Archeology: Biological samples from archeological sites can provide useful data about what was going on in history or ancient history.

HISTOPATHOLOGY

Histotechnicians, also known as histology technicians, histology technologists, biomedical scientists, medical scientists, or medical laboratory technicians, work in histology laboratories. These specialists use special skills to process samples of biological tissues that may come from patients, from suspects if it is a forensic lab, or from corpses. Using a series of techniques, they prepare tiny slices of tissue, known as sections. They mount the slices on slides and add histology stains. The slides are then examined by a histopathologist, or pathologist, for analysis.

The skills of a histologist must be meticulous and precise to deliver top-quality samples for examination under a microscope by histopathologist. A pathologist is a medical doctor who has graduated from medical school and then goes on to specialize in pathology through their residency. Residency programmes are required for all specialties, and for pathology, the training is an additional four years. They examine cells and tissues and interpret what they see, so that they or others can use the data to decide on treatment for an illness, determine how somebody was injured or died, and so on. Histopathology is a sub-discipline of pathology. It is the microscopic study of disease tissues and cells.

STUDYING ANATOMY

Most health-care related studies need training in gross anatomy and histology. Paramedics, physical therapists, occupational therapists, medical doctors, orthotists and prosthetists, and biological scientists all need a knowledge of anatomy. Some web sites offer a "tour" of the human body which explains the different organs and how they are made up. The National Institutes of Health offer a range of resources about the different parts of the body.

MODERN ANATOMY

Anatomy today makes use of knowledge from many fields of science to explore and understand how the structure of an organism's cells, tissues, and organs relates to their function. Human anatomy, a crucial element in the medical school curriculum, divides the body into separate functional systems. These consist of the skin, the muscles, the skeleton, the circulatory system (blood, blood vessels, and heart), the digestive system, the urinary system, the respiratory system (lungs and breathing), the nervous system (brain, spinal cord, and nerves), the endocrine system (glands and hormones), and the reproductive system.

2

Osteology

Make no bones about it, there are a lot of very specific scientific fields. There is physics, chemistry, and biology. There are subfields of each one, like biomedical sciences. There are even subfields of subfields, like human medicine and veterinary medicine. There are even nuanced variations of the latter two. And just like all of that, osteology, the study (*-ology*) of the structure and function of bones (*osteo-*), is very specific and refined as well. It's not just about bones in general, it's about specific bones, unique notches and grooves of each bone, and nuanced variations that may be normal or not of those notches and grooves.

THE SKULL

Let's go over a couple examples of how this is true and learn some osteology-related terms along the way. The skull is the skeleton of your head. It includes all of the bones of the head, including the lower jaw. You'd think that the skull is this one thing. But it's not. It's actually a collection of over 20 bones! The skull can be divided numerous ways. For example, we can divide it in two general ways. One part of the skull consists of the facial bones, the ones that make up the face, and the other part consists of bones that make up the neurocranium, which holds the brain.

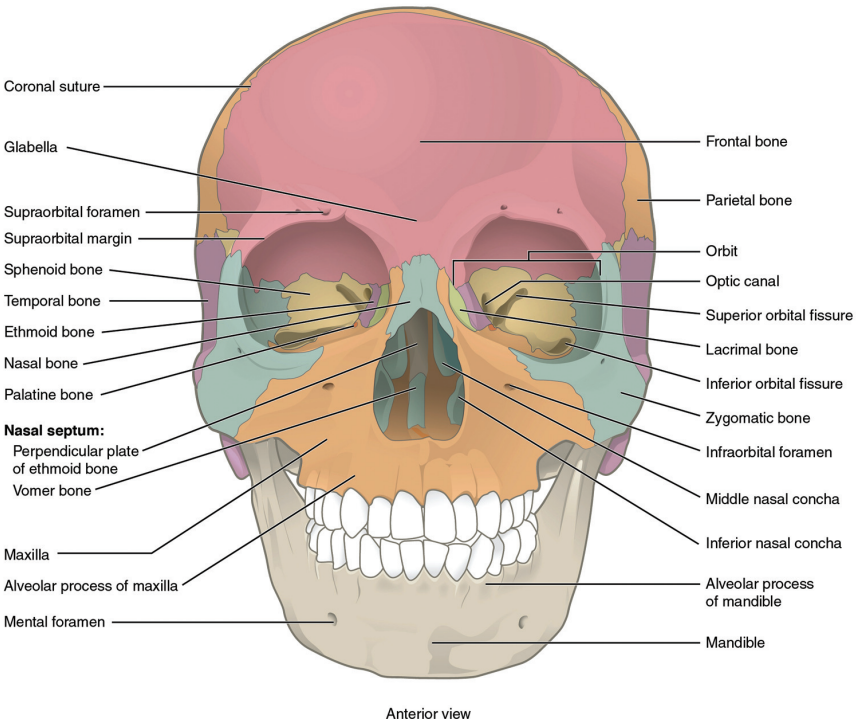


Fig. The skull is Composed of many Different bones, Some of which are Pictured and Labeled here.

Yet there are hiccups even with this simple delineation of the skull. For instance, the cranium is partly composed of the frontal bone. This is the bone of the forehead. You'd think that because we associate the forehead with our face, it would be a part of the facial bones. Alas, while the frontal bone is also part of the facial skeleton in some sense, it's developmentally considered to be a cranial bone.

THE RIBS AND STERNUM

Then there's the ribs and sternum, the breastbone. These bony structures help to protect vital structures like our lungs and heart from damage. They also help us breathe. Just put your hands on your ribcage as you take in a breath and exhale to see and feel why.

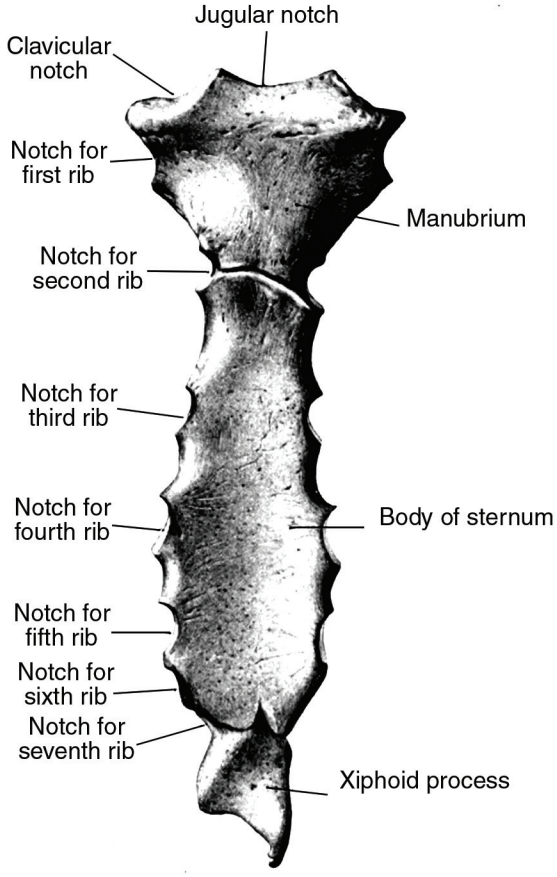


Fig. The breastbone is Divided into Three parts. From top to bottom They are Labeled: Manubrium, Body, and Xyphoid Process.

The ribs and sternum are just as nuanced as the skull in some ways. For example, the sternum can be divided into three distinct sections. Nearest the head is the manubrium, then comes the body, and nearest the feet is the smallest portion, called the xiphoid process.

TYPES OF BONES

Bones are Divisible into Four Classes: Long, Short, Flat, and Irregular. Long Bones are found in the limbs and function as levers, they are longer than they are wide. Short Bones transfer forces of movement and are cube shaped as in the carpus and tarsus. Flat Bones are used for either extensive protection or the provision of broad surfaces for muscular attachment. The bones expand into broad, flat plates, as in the skull and the scapula. Irregular Bones have peculiar forms, cannot be grouped under the preceding heads, and are used for muscle attachement and articulation. Some irregular bones include the vertebræ, sacrum and coccyx.

LONG BONE

Long bones consists of a body or shaft and two extremities. The body, or diaphysis is cylindrical, with a central cavity termed the medullary cavity. The wall consists of dense, compact tissue of considerable thickness in the middle part of the body, but becoming thinner towards the extremities. Within the medullary cavity is adipose tissue or "yellow bone marrow".

The extremities are refered to as the epiphysis. Within the epiphysis is the "spongy bone" also known as "red bone marrow". It is within this marrow that red blood cells are produced at an average rate of 2.5 million per second. Running horizontally across the spongy bone of this region is the Epiphyseal line which is a region of cell growth responsible for lateral bone growth during youth, when growth is complete this line calcifies and becomes known as the epiphyseal plate.

Nutrient foramen run through the compact bone and allow the passage of nutrients in and out of the bone. There is a thin outer layer of connective tissue called the PERIOSTEUM which is highly vascular and allows for muscle and tendon attachment, it is bound to the bone itself by PERFORATING FIBRES which are composed of collagen. This layer does not cover the articulating regions of the bone. The bones belonging to this class include: the clavicle, humerus, radius, ulna, femur, tibia, fibula, metacarpals, metatarsals, and phalanges. it is strongest largest of all body bones.

SHORT BONE

Short bones are generally equal in length, width, and thickness. They are found in the wrists and ankles. Aside from points of insertion and vascular areas, short bones are almost completely covered by articular surfaces.

FLAT BONE

These bones are composed of two thin layers of compact tissue enclosing between them a variable quantity of spongy bone. They generally offer protection, as is the case with the bones of the cranium and with the ribs and sternum.

BONES OF THE LOWER LIMB

Like the upper limb, the lower limb is divided into three regions. The thigh is that portion of the lower limb located between the hip joint and knee joint. The leg is specifically the region between the knee joint and the ankle joint. Distal to the ankle is the foot. The lower limb contains 30 bones. These are the femur, patella, tibia, fibula, tarsal bones, metatarsal bones, and phalanges. The femur is the single bone of the thigh. The patella is the kneecap and articulates with the distal femur. The tibia is the larger, weight-bearing bone located on the medial side of the leg, and the fibula is the thin bone of the lateral leg. The bones of the foot are divided into three groups. The posterior portion of the foot is formed by a group of seven bones, each of which is known as a tarsal bone, whereas the mid-foot contains five elongated bones, each of which is a metatarsal bone. The toes contain 14 small bones, each of which is a phalanx bone of the foot.

FEMUR

The femur, or thigh bone, is the single bone of the thigh region. It is the longest and strongest bone of the body, and accounts for approximately one-quarter of a person's total height. The rounded, proximal end is the head of the femur, which articulates with the acetabulum of the hip bone to form the hip joint. The fovea capitis is a minor indentation on the medial side of the femoral head that serves as the site of attachment for the

ligament of the head of the femur. This ligament spans the femur and acetabulum, but is weak and provides little support for the hip joint. It does, however, carry an important artery that supplies the head of the femur.

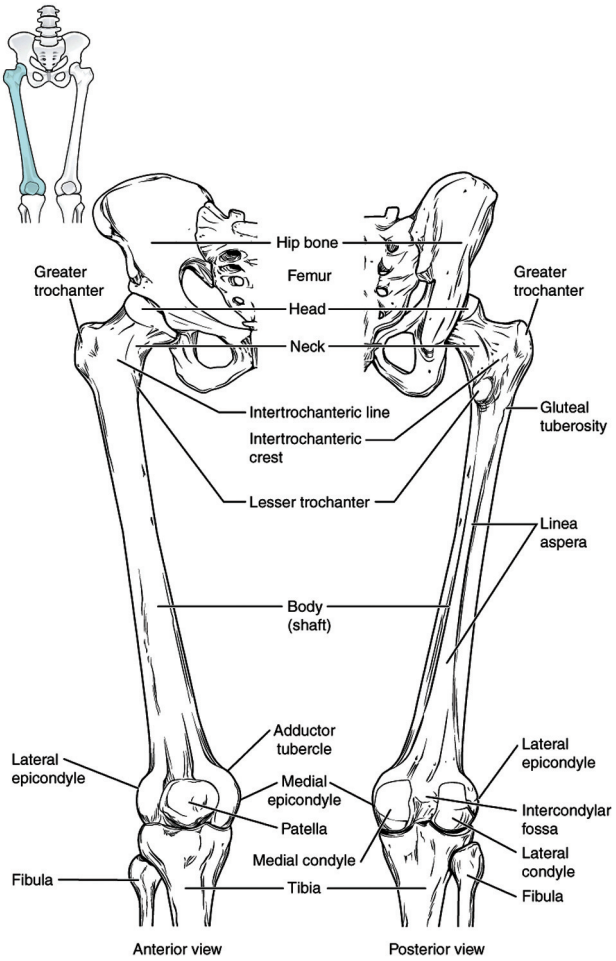


Fig. Femur and Patella. The femur is the single bone of the thigh region. It articulates superiorly with the hip bone at the hip joint, and inferiorly with the tibia at the knee joint. The patella only articulates with the distal end of the femur.

The narrowed region below the head is the neck of the femur. This is a common area for fractures of the femur. The greater trochanter is the large, upward, bony projection located above the base of the neck. Multiple muscles that act across the hip joint attach to the greater trochanter, which, because of its projection from the femur, gives additional leverage to these muscles. The greater trochanter can be felt just under the skin on the lateral side of your upper thigh. The lesser trochanter is a small, bony prominence that lies on the medial aspect of the femur, just below the neck. A single, powerful muscle attaches to the lesser trochanter. Running between the greater and lesser trochanters on the anterior side of the femur is the roughened intertrochanteric line. The trochanters are also connected on the posterior side of the femur by the larger intertrochanteric crest.

The elongated shaft of the femur has a slight anterior bowing or curvature. At its proximal end, the posterior shaft has the gluteal tuberosity, a roughened area extending inferiorly from the greater trochanter. More inferiorly, the gluteal tuberosity becomes continuous with the linea aspera ("rough line"). This is the roughened ridge that passes distally along the posterior side of the mid-femur. Multiple muscles of the hip and thigh regions make long, thin attachments to the femur along the linea aspera.

The distal end of the femur has medial and lateral bony expansions. On the lateral side, the smooth portion that covers the distal and posterior aspects of the lateral expansion is the lateral condyle of the femur. The roughened area on the outer, lateral side of the condyle is the lateral epicondyle of the femur.

Similarly, the smooth region of the distal and posterior medial femur is the medial condyle of the femur, and the irregular outer, medial side of this is the medial epicondyle of the femur. The lateral and medial condyles articulate with the tibia to form the knee joint. The epicondyles provide attachment for muscles and supporting ligaments of the knee. The adductor tubercle is a small bump located at the superior margin of the medial epicondyle. Posteriorly, the medial and lateral condyles are separated by a deep depression called the intercondylar fossa. Anteriorly, the smooth surfaces of the condyles join together to form a wide groove called the patellar surface, which provides for articulation with the patella bone. The combination of the medial and lateral condyles with the patellar surface gives the distal end of the femur a horseshoe (U) shape.

Watch this video to view how a fracture of the mid-femur is surgically repaired. How are the two portions of the broken femur stabilized during surgical repair of a fractured femur?

PATELLA

The patella (kneecap) is largest sesamoid bone of the body. A sesamoid bone is a bone that is incorporated into the tendon of a muscle where that tendon crosses a joint. The sesamoid bone articulates with the underlying bones to prevent damage to the muscle tendon due to rubbing against the bones during movements of the joint. The patella is found in the tendon of the quadriceps femoris muscle, the large muscle of the anterior thigh that passes across the anterior knee to attach to the tibia. The patella articulates with the patellar surface of the femur and thus prevents rubbing of the muscle tendon against the distal femur. The patella also lifts the tendon away from the knee joint, which increases the leverage power of the quadriceps femoris muscle as it acts across the knee. The patella does not articulate with the tibia.

HOMEOSTATIC IMBALANCES

Runner's Knee

Runner's knee, also known as patellofemoral syndrome, is the most common overuse injury among runners. It is most frequent in adolescents and young adults, and is more common in females. It often results from excessive running, particularly downhill, but may also occur in athletes who do a lot of knee bending, such as jumpers, skiers, cyclists, weight lifters, and soccer players. It is felt as a dull, aching pain around the front of the knee and deep to the patella. The pain may be felt when walking or running, going up or down stairs, kneeling or squatting, or after sitting with the knee bent for an extended period.

Patellofemoral syndrome may be initiated by a variety of causes, including individual variations in the shape and movement of the patella, a direct blow to the patella, or flat feet or improper shoes that cause excessive turning in or out of the feet or leg. These factors may cause in an imbalance in the muscle pull that acts on the patella, resulting in an abnormal tracking of the patella that allows it to deviate too far towards the lateral side of the patellar surface on the distal femur.

Because the hips are wider than the knee region, the femur has a diagonal orientation within the thigh, in contrast to the vertically oriented tibia of the leg. The Q-angle is a measure of how far the femur is angled laterally away from vertical. The Q-angle is normally 10–15 degrees, with females typically having a larger Q-angle due to their wider pelvis. During extension of the knee, the quadriceps femoris muscle pulls the patella both superiorly and laterally, with the lateral pull greater in women due to their large Q-angle. This makes women more vulnerable to developing patellofemoral syndrome than men. Normally, the large lip on the lateral side of the patellar surface of the femur compensates for the lateral pull on the patella, and thus helps to maintain its proper tracking.

However, if the pull produced by the medial and lateral sides of the quadriceps femoris muscle is not properly balanced, abnormal tracking of the patella towards the lateral side may occur. With continued use, this produces pain and could result in damage to the articulating surfaces of the patella and femur, and the possible future development of arthritis. Treatment generally involves stopping the activity that produces knee pain for a period of time, followed by a gradual resumption of activity. Proper strengthening of the quadriceps femoris muscle to correct for imbalances is also important to help prevent reoccurrence.

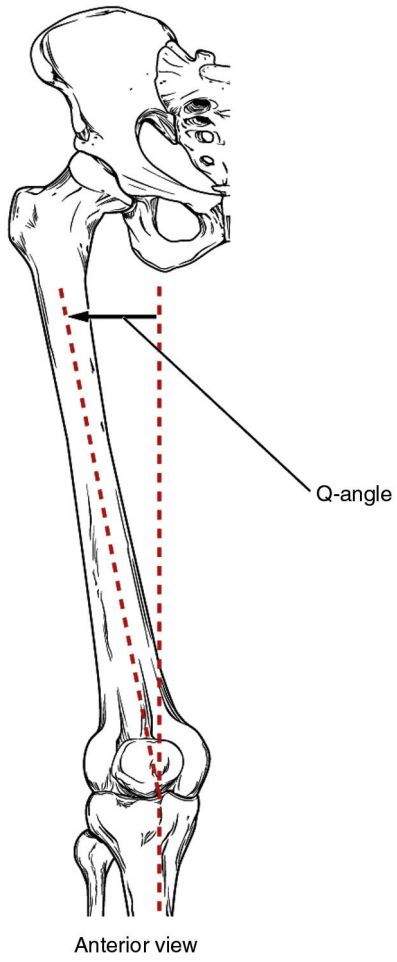


Fig. The Q-Angle. The Q-angle is a measure of the amount of lateral deviation of the femur from the vertical line of the tibia. Adult females have a larger Q-angle due to their wider pelvis than adult males.

Tibia

The tibia (shin bone) is the medial bone of the leg and is larger than the fibula, with which it is paired. The tibia is the main weight-bearing bone of the lower leg and the second longest bone of the body, after the femur. The medial side of the tibia is located immediately under the skin, allowing it to be easily palpated down the entire length of the medial leg.

The proximal end of the tibia is greatly expanded. The two sides of this expansion form the medial condyle of the tibia and the lateral condyle of the tibia. The tibia does not have epicondyles. The top surface of each condyle is smooth and flattened. These areas articulate with the medial and lateral condyles of the femur to form the knee joint. Between the articulating surfaces of the tibial condyles is the intercondylar eminence, an irregular, elevated area that serves as the inferior attachment point for two supporting ligaments of the knee.

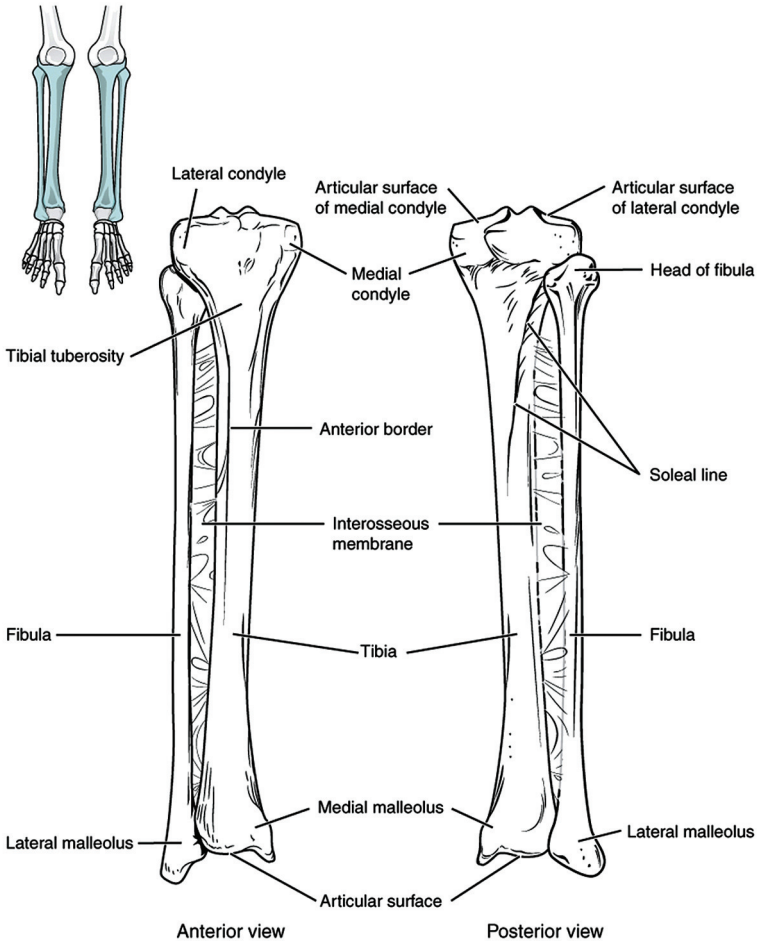


Fig. Tibia and Fibula. The tibia is the larger, weight-bearing bone located on the medial side of the leg. The fibula is the slender bone of the lateral side of the leg and does not bear weight.

The tibial tuberosity is an elevated area on the anterior side of the tibia, near its proximal end. It is the final site of attachment for the muscle tendon associated with the patella. More inferiorly, the shaft of the tibia becomes triangular in shape. The anterior apex of MH this triangle forms the anterior border of the tibia, which begins at the tibial tuberosity and runs inferiorly along the length of the tibia. Both the anterior border and the medial side of the triangular shaft are located immediately under the skin and can be easily palpated along the entire length of the tibia. A small ridge running down the lateral side of the tibial shaft is the interosseous border of the tibia. This is for the attachment of the interosseous membrane of the leg, the sheet of dense connective tissue that unites the tibia and fibula bones. Located on the posterior side of the tibia is the soleal line, a diagonally running, roughened ridge that begins below the base of the lateral condyle, and runs down and medially across the proximal third of the posterior tibia. Muscles of the posterior leg attach to this line.

The large expansion found on the medial side of the distal tibia is the medial malleolus (“little hammer”). This forms the large bony bump found on the medial side of the ankle region. Both the smooth surface on the inside of the medial malleolus and the smooth area at the distal end of the tibia articulate with the talus bone of the foot as part of the ankle joint. On the lateral side of the distal tibia is a wide groove called the fibular notch. This area articulates with the distal end of the fibula, forming the distal tibiofibular joint.

FIBULA

The fibula is the slender bone located on the lateral side of the leg. The fibula does not bear weight. It serves primarily for muscle attachments and thus is largely surrounded by muscles. Only the proximal and distal ends

of the fibula can be palpated. The head of the fibula is the small, knob-like, proximal end of the fibula. It articulates with the inferior aspect of the lateral tibial condyle, forming the proximal tibiofibular joint. The thin shaft of the fibula has the interosseous border of the fibula, a narrow ridge running down its medial side for the attachment of the interosseous membrane that spans the fibula and tibia. The distal end of the fibula forms the lateral malleolus, which forms the easily palpated bony bump on the lateral side of the ankle. The deep (medial) side of the lateral malleolus articulates with the talus bone of the foot as part of the ankle joint. The distal fibula also articulates with the fibular notch of the tibia.

TARSAL BONES

The posterior half of the foot is formed by seven tarsal bones. The most superior bone is the talus. This has a relatively square-shaped, upper surface that articulates with the tibia and fibula to form the ankle joint. Three areas of articulation form the ankle joint: The superomedial surface of the talus bone articulates with the medial malleolus of the tibia, the top of the talus articulates with the distal end of the tibia, and the lateral side of the talus articulates with the lateral malleolus of the fibula. Inferiorly, the talus articulates with the calcaneus (heel bone), the largest bone of the foot, which forms the heel. Body weight is transferred from the tibia to the talus to the calcaneus, which rests on the ground. The medial calcaneus has a prominent bony extension called the sustentaculum tali ("support for the talus") that supports the medial side of the talus bone.

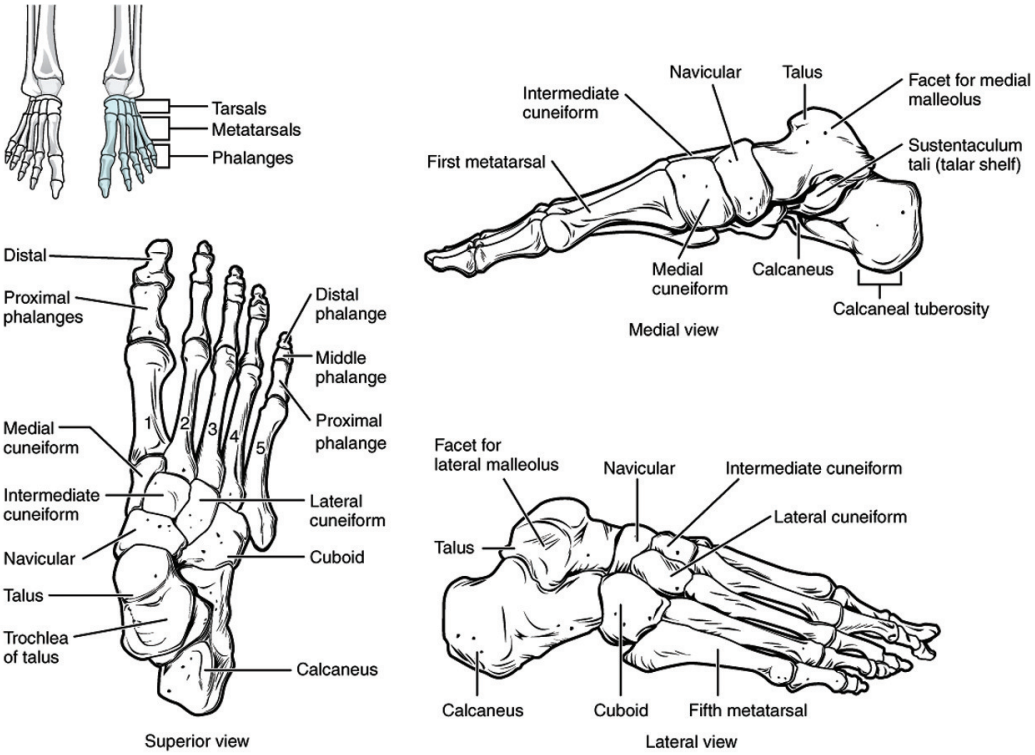


Fig. Bones of the Foot. The bones of the foot are divided into three groups. The posterior foot is formed by the seven tarsal bones. The mid-foot has the five metatarsal bones. The toes contain the phalanges.

The cuboid bone articulates with the anterior end of the calcaneus bone. The cuboid has a deep groove running across its inferior surface, which provides passage for a muscle tendon. The talus bone articulates anteriorly with the navicular bone, which in turn articulates anteriorly with the three cuneiform ("wedge-shaped") bones. These bones are the medial cuneiform, the intermediate cuneiform, and the lateral cuneiform. Each of these bones has a broad superior surface and a narrow inferior surface, which together produce the transverse (medial-lateral) curvature of the foot. The navicular and lateral cuneiform bones also articulate with the medial side of the cuboid bone.

METATARSAL BONES

The anterior half of the foot is formed by the five metatarsal bones, which are located between the tarsal bones of the posterior foot and the phalanges of the toes. These elongated bones are numbered 1–5, starting with the medial side of the foot. The first metatarsal bone is shorter and thicker than the others. The second metatarsal is the longest. The base of the metatarsal bone is the proximal end of each metatarsal bone. These articulate with the cuboid or cuneiform bones. The base of the fifth metatarsal has a large, lateral expansion that provides for muscle attachments. This expanded base of the fifth metatarsal can be felt as a bony bump at the midpoint along the lateral border of the foot. The expanded distal end of each metatarsal is the head of the metatarsal bone. Each metatarsal bone articulates with the proximal phalanx of a toe to form a metatarsophalangeal joint. The heads of the metatarsal bones also rest on the ground and form the ball (anterior end) of the foot.

PHALANGES

The toes contain a total of 14 phalanx bones (phalanges), arranged in a similar manner as the phalanges of the fingers. The toes are numbered 1–5, starting with the big toe (hallux). The big toe has two phalanx bones, the proximal and distal phalanges. The remaining toes all have proximal, middle, and distal phalanges. A joint between adjacent phalanx bones is called an interphalangeal joint.

ARCHES OF THE FOOT

When the foot comes into contact with the ground during walking, running, or jumping activities, the impact of the body weight puts a tremendous amount of pressure and force on the foot. During running, the force applied to each foot as it contacts the ground can be up to 2.5 times your body weight. The bones, joints, ligaments, and muscles of the foot absorb this force, thus greatly reducing the amount of shock that is passed superiorly into the lower limb and body. The arches of the foot play an important role in this shock-absorbing ability. When weight is applied to the foot, these arches will flatten somewhat, thus absorbing energy. When the weight is removed, the arch rebounds, giving "spring" to the step. The arches also serve to distribute body weight side to side and to either end of the foot.

The foot has a transverse arch, a medial longitudinal arch, and a lateral longitudinal arch. The transverse arch forms the medial-lateral curvature of the mid-foot. It is formed by the wedge shapes of the cuneiform bones and bases (proximal ends) of the first to fourth metatarsal bones. This arch helps to distribute body weight from side to side within the foot, thus allowing the foot to accommodate uneven terrain.

The longitudinal arches run down the length of the foot. The lateral longitudinal arch is relatively flat, whereas the medial longitudinal arch is larger (taller). The longitudinal arches are formed by the tarsal bones posteriorly and the metatarsal bones anteriorly. These arches are supported at either end, where they contact the ground. Posteriorly, this support is provided by the calcaneus bone and anteriorly by the heads (distal ends) of the metatarsal bones. The talus bone, which receives the weight of the body, is located at the top of the longitudinal arches. Body weight is then conveyed from the talus to the ground by the anterior and posterior ends of these arches. Strong ligaments unite the adjacent foot bones to prevent disruption of the arches during weight bearing. On the bottom of the foot, additional ligaments tie together the anterior and posterior ends of the arches. These ligaments have elasticity, which allows them to stretch somewhat during weight bearing, thus allowing the longitudinal arches to spread. The stretching of these ligaments stores energy within the foot, rather than passing these forces into the leg. Contraction of the foot muscles also plays an important role in this energy absorption. When the weight is removed, the elastic ligaments recoil and pull the ends of the arches closer together. This recovery of the arches releases the stored energy and improves the energy efficiency of walking.

Stretching of the ligaments that support the longitudinal arches can lead to pain. This can occur in overweight individuals, with people who have jobs that involve standing for long periods of time (such as a waitress), or walking or running long distances. If stretching of the ligaments is prolonged, excessive, or repeated, it can result in a gradual lengthening of the supporting ligaments, with subsequent depression or collapse of the longitudinal arches, particularly on the medial side of the foot. This condition is called pes planus ("flat foot" or "fallen arches").

BONES OF THE UPPER LIMB

The upper limb is divided into three regions. These consist of the arm, located between the shoulder and elbow joints; the forearm, which is between the elbow and wrist joints; and the hand, which is located distal to the wrist. There are 30 bones in each upper limb. The humerus is the single bone of the upper arm, and the ulna (medially) and the radius (laterally) are the paired bones of the forearm. The base of the hand contains eight bones, each called a carpal bone, and the palm of the hand is formed by five bones, each called a metacarpal bone. The fingers and thumb contain a total of 14 bones, each of which is a phalanx bone of the hand.

HUMERUS

The humerus is the single bone of the upper arm region. At its proximal end is the head of the humerus. This is the large, round, smooth region that faces medially. The head articulates with the glenoid cavity of the scapula to form the glenohumeral (shoulder) joint. The margin of the smooth area of the head is the anatomical neck of the humerus.

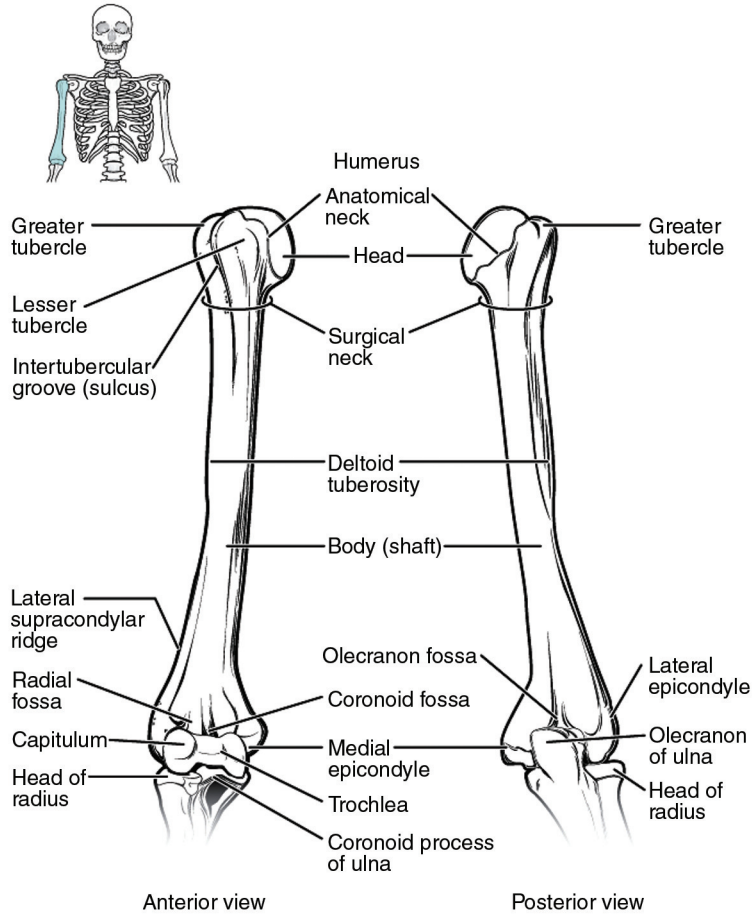


Fig. Humerus and Elbow Joint. The humerus is the single bone of the upper arm region. It articulates with the radius and ulna bones of the forearm to form the elbow joint.

Located on the lateral side of the proximal humerus is an expanded bony area called the greater tubercle. The smaller lesser tubercle of the humerus is found on the anterior aspect of the humerus. Both the greater and lesser tubercles serve as attachment sites for muscles that act across the shoulder joint. Passing between the greater and lesser tubercles is the narrow intertubercular groove (sulcus), which is also known as the bicipital groove because it provides passage for a tendon of the biceps brachii muscle. The surgical neck is located at the base of the expanded, proximal end of the humerus, where it joins the narrow shaft of the humerus. The surgical neck is a common site of arm fractures. The deltoid tuberosity is a roughened, V-shaped region located on the lateral side in the middle of the humerus shaft. As its name indicates, it is the site of attachment for the deltoid muscle.

Distally, the humerus becomes flattened. The prominent bony projection on the medial side is the medial epicondyle of the humerus. The much smaller lateral epicondyle of the humerusis found on the lateral side of the distal humerus. The roughened ridge of bone above the lateral epicondyle is the lateral supracondylar ridge. All of these areas are attachment points for muscles that act on the forearm, wrist, and hand. The powerful grasping muscles of the anterior forearm arise from the medial epicondyle, which is thus larger and more robust than the lateral epicondyle that gives rise to the weaker posterior forearm muscles.

The distal end of the humerus has two articulation areas, which join the ulna and radius bones of the forearm to form the elbow joint. The more medial of these areas is the trochlea, a spindle- or pulley-shaped region (trochlea = "pulley"), which articulates with the ulna bone. Immediately lateral to the trochlea is the capitulum ("small head"), a knob-like structure located on the anterior surface of the distal humerus. The capitulum articulates with the radius bone of the forearm. Just above these bony areas are two small depressions. These spaces accommodate the forearm bones when the elbow is fully bent (flexed). Superior to the trochlea is the coronoid fossa, which receives the coronoid process of the ulna, and above the capitulum is the radial fossa, which receives the head of the radius when the elbow is flexed. Similarly, the posterior humerus has the olecranon fossa, a larger depression that receives the olecranon process of the ulna when the forearm is fully extended.

ULNA

The ulna is the medial bone of the forearm. It runs parallel to the radius, which is the lateral bone of the forearm. The proximal end of the ulna resembles a crescent wrench with its large, C-shaped trochlear notch. This region articulates with the trochlea of the humerus as part of the elbow joint. The inferior margin of the trochlear notch is formed by a prominent lip of bone called the coronoid process of the ulna. Just below this on the anterior ulna is a roughened area called the ulnar tuberosity. To the lateral side and slightly inferior to the trochlear notch is a small, smooth area called the radial notch of the ulna. This area is the site of articulation between the proximal radius and the ulna, forming the proximal radioulnar joint. The posterior and superior portions of the proximal ulna make up the olecranon process, which forms the bony tip of the elbow.

More distal is the shaft of the ulna. The lateral side of the shaft forms a ridge called the interosseous border of the ulna. This is the line of attachment for the interosseous membrane of the forearm, a sheet of dense connective tissue that unites the ulna and radius bones. The small, rounded area that forms the distal end is the head of the ulna. Projecting from the posterior side of the ulnar head is the styloid process of the ulna, a short bony projection. This serves as an attachment point for a connective tissue structure that unites the distal ends of the ulna and radius.

In the anatomical position, with the elbow fully extended and the palms facing forward, the arm and forearm do not form a straight line. Instead, the forearm deviates laterally by 5–15 degrees from the line of the arm. This deviation is called the carrying angle. It allows the forearm and hand to swing freely or to carry an object without hitting the hip. The carrying angle is larger in females to accommodate their wider pelvis.

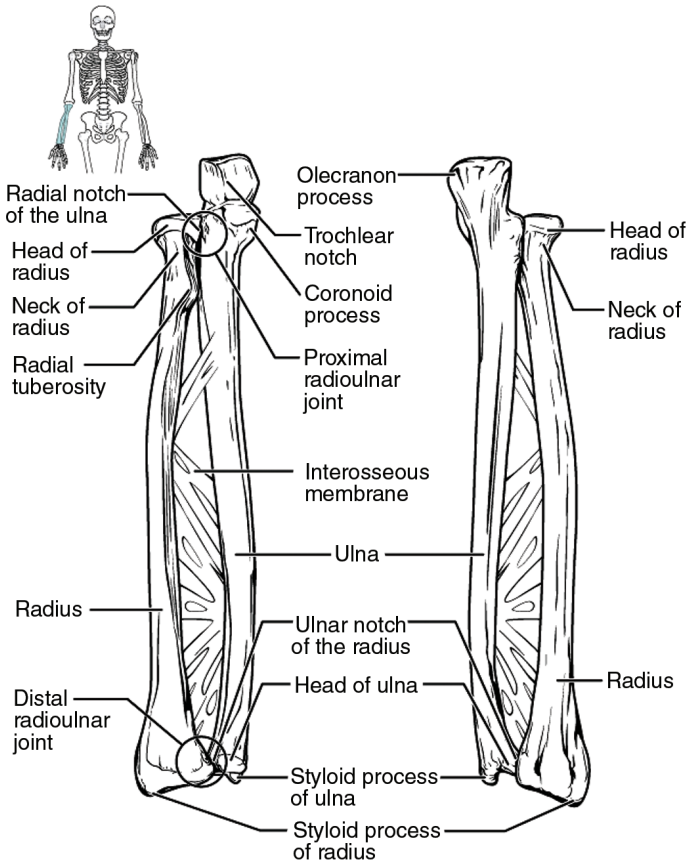


Fig. Ulna and Radius. The ulna is located on the medial side of the forearm, and the radius is on the lateral side. These bones are attached to each other by an interosseous membrane.

RADIUS

The radius runs parallel to the ulna, on the lateral (thumb) side of the forearm. The head of the radius is a disc-shaped structure that forms the proximal end. The small depression on the surface of the head articulates with the capitulum of the humerus as part of the elbow joint, whereas the smooth, outer margin of the head articulates with the radial notch of the ulna at the proximal radioulnar joint. The neck of the radius is the narrowed region immediately below the expanded head. Inferior to this point on the medial side is the radial tuberosity, an oval-shaped, bony protuberance that serves as a muscle attachment point. The shaft of the radius is slightly curved and has a small ridge along its medial side. This ridge forms the interosseous border of the radius, which, like the similar border of the ulna, is the line of attachment for the interosseous membrane that unites the two forearm bones. The distal end of the radius has a smooth surface for articulation with two carpal bones to form the radiocarpal joint or wrist joint. On the medial side of the distal radius is the ulnar notch of the radius. This shallow depression articulates with the head of the ulna, which together form the distal radioulnar joint. The lateral end of the radius has a pointed projection called the styloid process of the radius. This provides attachment for ligaments that support the lateral side of the wrist joint. Compared to the styloid process of the ulna, the styloid process of the radius projects more distally, thereby limiting the range of movement for lateral deviations of the hand at the wrist joint.

CARPAL BONES

The wrist and base of the hand are formed by a series of eight small carpal bones. The carpal bones are arranged in two rows, forming a proximal row of four carpal bones and a distal row of four carpal bones. The

bones in the proximal row, running from the lateral (thumb) side to the medial side, are the scaphoid ("boat-shaped"), lunate ("moon-shaped"), triquetrum ("three-cornered"), and pisiform ("pea-shaped") bones. The small, rounded pisiform bone articulates with the anterior surface of the triquetrum bone. The pisiform thus projects anteriorly, where it forms the bony bump that can be felt at the medial base of your hand. The distal bones (lateral to medial) are the trapezium ("table"), trapezoid ("resembles a table"), capitate ("head-shaped"), and hamate ("hooked bone") bones. The hamate bone is characterized by a prominent bony extension on its anterior side called the hook of the hamate bone.

A helpful mnemonic for remembering the arrangement of the carpal bones is "So Long To Pinky, Here Comes The Thumb." This mnemonic starts on the lateral side and names the proximal bones from lateral to medial (scaphoid, lunate, triquetrum, pisiform), then makes a U-turn to name the distal bones from medial to lateral (hamate, capitate, trapezoid, trapezium). Thus, it starts and finishes on the lateral side.

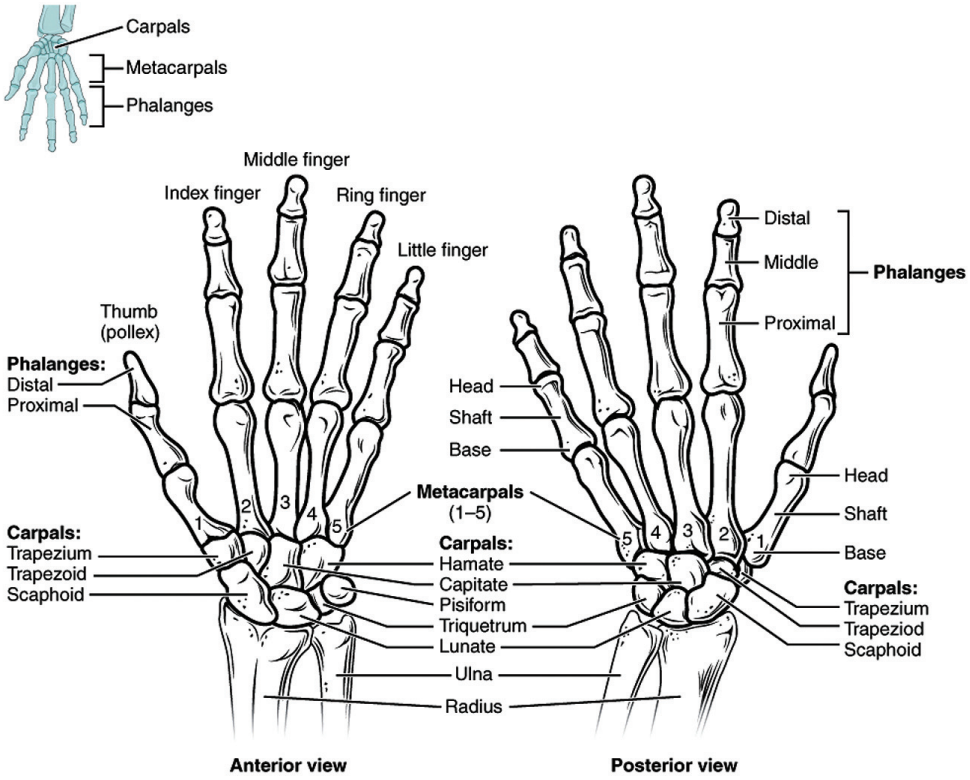


Fig. Bones of the Wrist and Hand. The eight carpal bones form the base of the hand. These are arranged into proximal and distal rows of four bones each. The metacarpal bones form the palm of the hand. The thumb and fingers consist of the phalanx bones.

The carpal bones form the base of the hand. This can be seen in the radiograph (X-ray image) of the hand that shows the relationships of the hand bones to the skin creases of the hand. Within the carpal bones, the four proximal bones are united to each other by ligaments to form a unit. Only three of these bones, the scaphoid, lunate, and triquetrum, contribute to the radiocarpal joint. The scaphoid and lunate bones articulate directly with the distal end of the radius, whereas the triquetrum bone articulates with a fibrocartilaginous pad that spans the radius and styloid process of the ulna. The distal end of the ulna thus does not directly articulate with any of the carpal bones.

The four distal carpal bones are also held together as a group by ligaments. The proximal and distal rows of carpal bones articulate with each other to form the midcarpal joint. Together, the radiocarpal and midcarpal joints are responsible for all movements of the hand at the wrist. The distal carpal bones also articulate with the metacarpal bones of the hand.

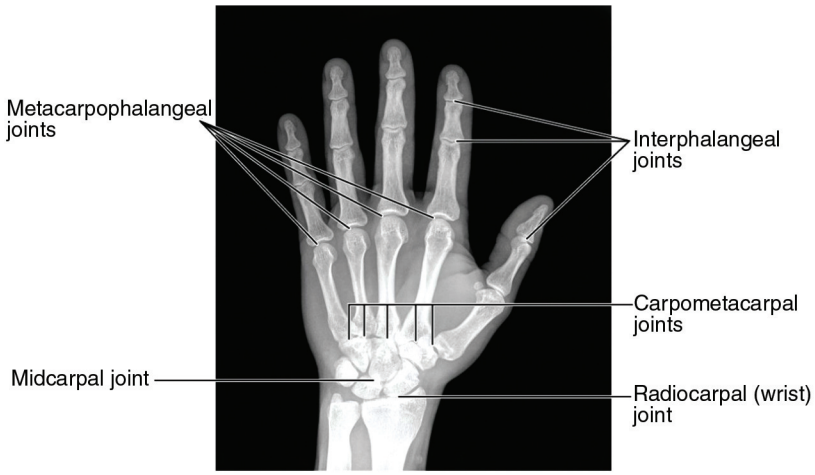


Fig. Bones of the Hand. This radiograph shows the position of the bones within the hand. Note the carpal bones that form the base of the hand.

In the articulated hand, the carpal bones form a U-shaped grouping. A strong ligament called the flexor retinaculum spans the top of this U-shaped area to maintain this grouping of the carpal bones. The flexor retinaculum is attached laterally to the trapezium and scaphoid bones, and medially to the hamate and pisiform bones. Together, the carpal bones and the flexor retinaculum form a passageway called the carpal tunnel, with the carpal bones forming the walls and floor, and the flexor retinaculum forming the roof of this space. The tendons of nine muscles of the anterior forearm and an important nerve pass through this narrow tunnel to enter the hand. Overuse of the muscle tendons or wrist injury can produce inflammation and swelling within this space. This produces compression of the nerve, resulting in carpal tunnel syndrome, which is characterized by pain or numbness, and muscle weakness in those areas of the hand supplied by this nerve.

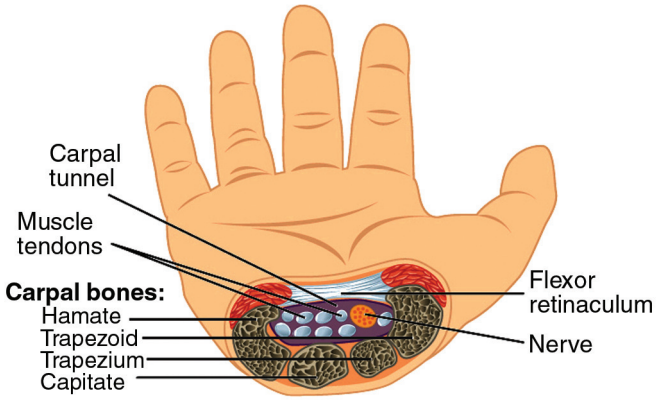


Fig. Carpal Tunnel. The carpal tunnel is the passageway by which nine muscle tendons and a major nerve enter the hand from the anterior forearm. The walls and floor of the carpal tunnel are formed by the U-shaped grouping of the carpal bones, and the roof is formed by the flexor retinaculum, a strong ligament that anteriorly unites the bones.

METACARPAL BONES

The palm of the hand contains five elongated metacarpal bones. These bones lie between the carpal bones of the wrist and the bones of the fingers and thumb. The proximal end of each metacarpal bone articulates with one of the distal carpal bones. Each of these articulations is a carpometacarpal joint. The expanded distal end of each metacarpal bone articulates at the metacarpophalangeal joint with the proximal phalanx bone of the thumb or one of the fingers. The distal end also forms the knuckles of the hand, at the base of the fingers. The metacarpal bones are numbered 1–5, beginning at the thumb.

The first metacarpal bone, at the base of the thumb, is separated from the other metacarpal bones. This allows it a freedom of motion that is independent of the other metacarpal bones, which is very important for thumb mobility. The remaining metacarpal bones are united together to form the palm of the hand. The second and third metacarpal bones are firmly anchored in place and are immobile. However, the fourth and fifth metacarpal bones have limited anterior-posterior mobility, a motion that is greater for the fifth bone. This mobility is important during power gripping with the hand. The anterior movement of these bones, particularly the fifth metacarpal bone, increases the strength of contact for the medial hand during gripping actions.

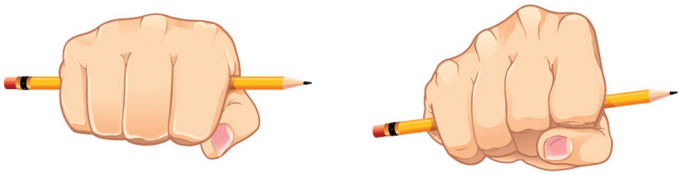


Fig. Hand During Gripping. During tight gripping—compare (b) to (a)—the fourth and, particularly, the fifth metatarsal bones are pulled anteriorly. This increases the contact between the object and the medial side of the hand, thus improving the firmness of the grip.

PHALANX BONES

The fingers and thumb contain 14 bones, each of which is called a phalanx bone (plural = phalanges), named after the ancient Greek phalanx (A rectangular block of soldiers). The thumb (pollex) is digit number 1 and has two phalanges, a proximal phalanx, and a distal phalanx bone. Digits 2 (index finger) through 5 (little finger) have three phalanges each, called the proximal, middle, and distal phalanx bones. An interphalangeal joint is one of the articulations between adjacent phalanges of the digits.

APPENDICULAR SYSTEM: FRACTURES OF UPPER LIMB BONES

Due to our constant use of the hands and the rest of our upper limbs, an injury to any of these areas will cause a significant loss of functional ability. Many fractures result from a hard fall onto an outstretched hand. The resulting transmission of force up the limb may result in a fracture of the humerus, radius, or scaphoid bones. These injuries are especially common in elderly people whose bones are weakened due to osteoporosis.

Falls onto the hand or elbow, or direct blows to the arm, can result in fractures of the humerus. Following a fall, fractures at the surgical neck, the region at which the expanded proximal end of the humerus joins with the shaft, can result in an impacted fracture, in which the distal portion of the humerus is driven into the proximal portion. Falls or blows to the arm can also produce transverse or spiral fractures of the humeral shaft.

In children, a fall onto the tip of the elbow frequently results in a distal humerus fracture. In these, the olecranon of the ulna is driven upward, resulting in a fracture across the distal humerus, above both epicondyles (supracondylar fracture), or a fracture between the epicondyles, thus separating one or both of the epicondyles from the body of the humerus (intercondylar fracture). With these injuries, the immediate concern is possible compression of the artery to the forearm due to swelling of the surrounding tissues. If compression occurs, the resulting ischemia (lack of oxygen) due to reduced blood flow can quickly produce irreparable damage to the forearm muscles. In addition, four major nerves for shoulder and upper limb muscles are closely associated with different regions of the humerus, and thus, humeral fractures may also damage these nerves.

Another frequent injury following a fall onto an outstretched hand is a Colles fracture (“col-lees”) of the distal radius. This involves a complete transverse fracture across the distal radius that drives the separated distal fragment of the radius posteriorly and superiorly. This injury results in a characteristic “dinner fork” bend of the forearm just above the wrist due to the posterior displacement of the hand. This is the most frequent forearm fracture and

is a common injury in persons over the age of 50, particularly in older women with osteoporosis. It also commonly occurs following a high-speed fall onto the hand during activities such as snowboarding or skating. The most commonly fractured carpal bone is the scaphoid, often resulting from a fall onto the hand. Deep pain at the lateral wrist may yield an initial diagnosis of a wrist sprain, but a radiograph taken several weeks after the injury, after tissue swelling has subsided, will reveal the fracture. Due to the poor blood supply to the scaphoid bone, healing will be slow and there is the danger of bone necrosis and subsequent degenerative joint disease of the wrist.

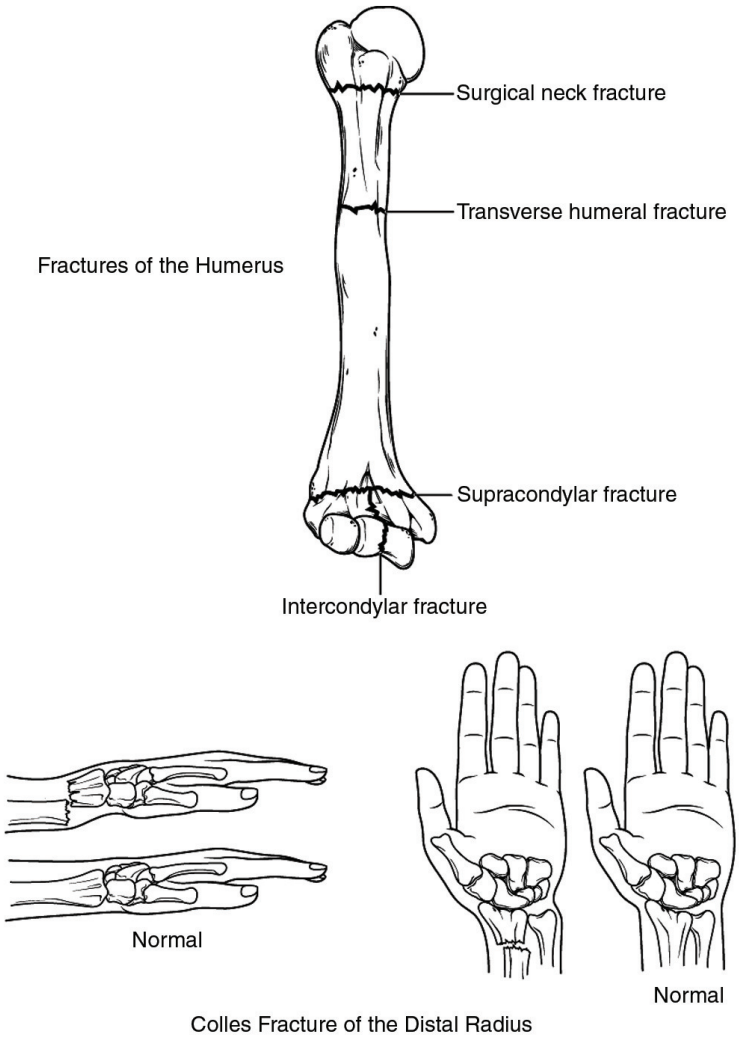


Fig. Fractures of the Humerus and Radius. Falls or direct blows can result in fractures of the surgical neck or shaft of the humerus. Falls onto the elbow can fracture the distal humerus. A Colles fracture of the distal radius is the most common forearm fracture.

HUMAN SKELETON

The human skeleton is the internal framework of the body. It is composed of around 270 bones at birth – this total decreases to around 206 bones by adulthood after some bones get fused together. The bone mass in the skeleton reaches maximum density around age 21. The human skeleton can be divided into the axial skeleton and the appendicular skeleton. The axial skeleton is formed by the vertebral column, the rib cage, the skull and other associated bones. The appendicular skeleton, which is attached to the axial skeleton, is formed by the shoulder girdle, the pelvic girdle and the bones of the upper and lower limbs.

The human skeleton performs six major functions; support, movement, protection, production of blood cells, storage of minerals, and endocrine regulation. The human skeleton is not as sexually dimorphic as that of

many other primate species, but subtle differences between sexes in the morphology of the skull, dentition, long bones, and pelvis exist. In general, female skeletal elements tend to be smaller and less robust than corresponding male elements within a given population. The human female pelvis is also different from that of males in order to facilitate childbirth. Unlike most primates, human males do not have penile bones.

SKELETAL DIVISIONS

Axial Skeleton

The axial skeleton (80 bones) is formed by the vertebral column (32–34 bones; the number of the vertebrae differs from human to human as the lower 2 parts, sacral and coccygeal bone may vary in length), a part of the rib cage (12 pairs of ribs and the sternum), and the skull (22 bones and 7 associated bones). The upright posture of humans is maintained by the axial skeleton, which transmits the weight from the head, the trunk, and the upper extremities down to the lower extremities at the hip joints. The bones of the spine are supported by many ligaments. The erector spinae muscles are also supporting and are useful for balance.

Appendicular Skeleton

The appendicular skeleton (126 bones) is formed by the pectoral girdles, the upper limbs, the pelvic girdle or pelvis, and the lower limbs. Their functions are to make locomotion possible and to protect the major organs of digestion, excretion and reproduction.

FUNCTIONS

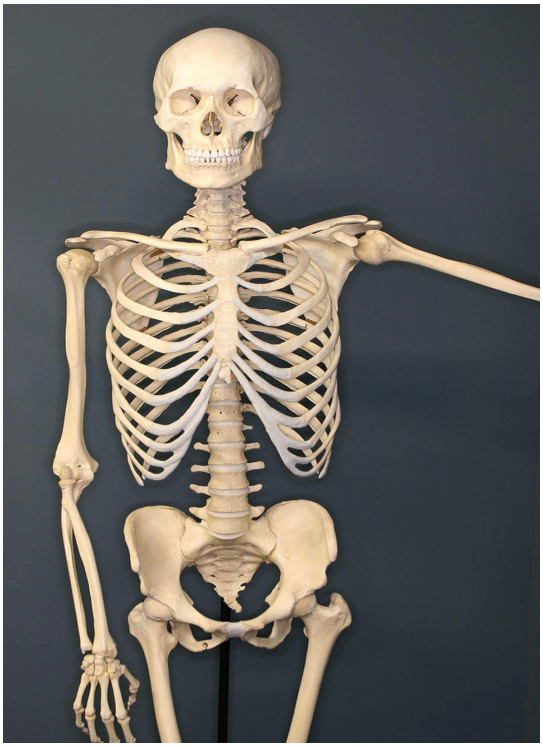


Fig. A human skeleton on exhibit at the Museum of Osteology, Oklahoma City, Oklahoma

The Skeleton Serves Six Major Functions: Support, movement, protection, production of blood cells, storage of minerals and endocrine regulation.

SUPPORT

The skeleton provides the framework which supports the body and maintains its shape. The pelvis, associated ligaments and muscles provide a floor for the pelvic structures. Without the rib cages, costal cartilages, and intercostal muscles, the lungs would collapse.

MOVEMENT

The joints between bones allow movement, some allowing a wider range of movement than others, *e.g.* the ball and socket joint allows a greater range of movement than the pivot joint at the neck. Movement is powered by skeletal muscles, which are attached to the skeleton at various sites on bones. Muscles, bones, and joints provide the principal mechanics for movement, all coordinated by the nervous system.

It is believed that the reduction of human bone density in prehistoric times reduced the agility and dexterity of human movement. Shifting from hunting to agriculture has caused human bone density to reduce significantly.

PROTECTION

The skeleton helps to protect our many vital internal organs from being damaged:

- The skull protects the brain,
- The vertebrae protect the spinal cord,
- The rib cage, spine, and sternum protect the lungs, heart and major blood vessels.

BLOOD CELL PRODUCTION

The skeleton is the site of haematopoiesis, the development of blood cells that takes place in the bone marrow. In children, haematopoiesis occurs primarily in the marrow of the long bones such as the femur and tibia. In adults, it occurs mainly in the pelvis, cranium, vertebrae, and sternum.

STORAGE

The bone matrix can store calcium and is involved in calcium metabolism, and bone marrow can store iron in ferritin and is involved in iron metabolism. However, bones are not entirely made of calcium, but a mixture of chondroitin sulfate and hydroxyapatite, the latter making up 70% of a bone. Hydroxyapatite is in turn composed of 39.8% of calcium, 41.4% of oxygen, 18.5% of phosphorus, and 0.2% of hydrogen by mass. Chondroitin sulfate is a sugar made up primarily of oxygen and carbon.

ENDOCRINE REGULATION

Bone cells release a hormone called osteocalcin, which contributes to the regulation of blood sugar (glucose) and fat deposition. Osteocalcin increases both the insulin secretion and sensitivity, in addition to boosting the number of insulin-producing cells and reducing stores of fat.

SEX DIFFERENCES

Anatomical differences between human males and females are highly pronounced in some soft tissue areas, but tend to be limited in the skeleton. The human skeleton is not as sexually dimorphic as that of many other primate species, but subtle differences between sexes in the morphology of the skull, dentition, long bones, and pelvis are exhibited across human populations. In general, female skeletal elements tend to be smaller and less robust than corresponding male elements within a given population. It is not known whether or to what extent those differences are genetic or environmental.

Fig. During construction of the York to Scarborough Railway Bridge in 1901, workmen discovered a large stone coffin, close to the River Ouse. Inside was a skeleton, accompanied by an array of unusual and expensive objects. This chance find represents one of the most significant discoveries ever made from Roman York. Study of the skeleton has revealed that it belonged to a woman.

SKULL

A variety of gross morphological traits of the human skull demonstrate sexual dimorphism, such as the median nuchal line, mastoid processes, supraorbital margin, supraorbital ridge, and the chin.

DENTITION

Human inter-sex dental dimorphism centers on the canine teeth, but it is not nearly as pronounced as in the other great apes.

LONG BONES

Long bones are generally larger in males than in females within a given population. Muscle attachment sites on long bones are often more robust in males than in females, reflecting a difference in overall muscle mass and development between sexes. Sexual dimorphism in the long bones is commonly characterized by morphometric or gross morphological analyses.

PELVIS

The human pelvis exhibits greater sexual dimorphism than other bones, specifically in the size and shape of the pelvic cavity, ilia, greater sciatic notches, and the sub-pubic angle. The Phenice method is commonly used to determine the sex of an unidentified human skeleton by anthropologists with 96% to 100% accuracy in some populations. Women's pelvises are wider in the pelvic inlet and are wider throughout the pelvis to allow for child birth. The sacrum in the women's pelvis is curved inwards to allow the child to have a "funnel" to assist in the child's pathway from the uterus to the birth canal.

CLINICAL SIGNIFICANCE

There are many classified skeletal disorders. One of the most common is osteoporosis. Also common is scoliosis, a side-to-side curve in the back or spine, often creating a pronounced "C" or "S" shape when viewed on an x-ray of the spine. This condition is most apparent during adolescence, and is most common with females.

ARTHRITIS

Arthritis is a disorder of the joints. It involves inflammation of one or more joints. When affected by arthritis, the joint or joints affected may be painful to move, may move in unusual directions or may be immobile completely. The symptoms of arthritis will vary differently between types of arthritis. The most common form of arthritis: Osteoarthritis can affect both the larger and smaller joints of the human skeleton. The cartilage in the affected joints will degrade, soften and wear away. This decreases the mobility of the joints and decreases the space between bones where cartilage should be.

OSTEOPOROSIS

Osteoporosis is a disease of bone where there is reduced bone mineral density, increasing the likelihood of fractures. Osteoporosis is defined by the World Health Organization in women as a bone mineral density 2.5 standard deviations below peak bone mass, relative to the age and sex-matched average, as measured by Dual energy X-ray absorptiometry, with the term "established osteoporosis" including the presence of a fragility fracture. Osteoporosis is most common in women after menopause, when it is called "postmenopausal osteoporosis", but may develop in men and premenopausal women in the presence of particular hormonal disorders and other chronic diseases or as a result of smoking and medications, specifically glucocorticoids. Osteoporosis usually has no symptoms until a fracture occurs. For this reason, DEXA scans are often done in people with one or more risk factors, who have developed osteoporosis and be at risk of fracture.

Osteoporosis treatment includes advice to stop smoking, decrease alcohol consumption, exercise regularly, and have a healthy diet. Calcium supplements may also be advised, as may Vitamin D. When medication is used, it may include bisphosphonates, Strontium ranelate, and osteoporosis may be one factor considered when commencing Hormone replacement therapy.

HISTORY

The study of human bones probably started in ancient Greece under Ptolemaic kings due to their link to Egypt. Herophilos, through his work by studying dissected human corpses in Alexandria is credited to be the pioneer of the field. His works are lost but are often cited by notable persons in the field such as Galen and Rufus of Ephesus. Galen himself did little dissection though and relied on the work of others like Marinus of Alexandria, as well as his own observations of gladiator cadavers and animals. According to Katherine Park, in medieval Europe dissection continued to be practiced, contrary to the popular understanding that such practices are taboo and thus completely banned. The practice of *holy autopsy*, such as in the case of Clare of Montefalco further supports the claim. Alexandria continued as a center of anatomy under Islamic rule, with Ibn Zuhr a notable figure. Chinese understandings are divergent, as the closest corresponding concept in the medicinal system seem to be the meridians, although given that Hua Tuo regularly performs surgery, there must be some distance between medical theory and actual understanding.

THE RENAISSANCE

Leonardo Da Vinci, among his many talents also contributed to the study of the skeleton, albeit unpublished in his time. Many artists, Antonio Pollaiuolo being the first, performed dissections for better understanding of the body, although they concentrated mostly on the muscles. Vesalius, regarded as the founder of modern anatomy authored the book *De humani corporis fabrica*, which contained many illustrations of the skeleton and other body parts, correcting some theories dating from Galen, such as the lower jaw being a single bone instead of two. Various other figures like Alessandro Achillini also contributed to the further understanding of the skeleton.

THE STRUCTURE OF BONES

Bones are Composed of Two Types of Tissue:

1. Compact (cortical) bone: A hard outer layer that is dense, strong, and durable. It makes up around 80 percent of adult bone mass.
2. Cancellous (trabecular or spongy) bone: This consists of a network of trabeculae or rod-like structures. It is lighter, less dense, and more flexible than compact bone.

Also Found in Bones:

- Osteoblasts and osteocytes, responsible for creating bone
- Osteoclasts or bone resorbing cells
- Osteoid, a mix of collagen and other proteins
- Inorganic mineral salts within the matrix
- Nerves and blood vessels
- Bone marrow
- Cartilage
- Membranes, including the endosteum and periosteum.

BONE CELLS

Bones are not a static tissue but need to be constantly maintained and remodeled. There are three main cell types involved in this process.

Osteoblasts: These are responsible for making new bone and repairing older bone. Osteoblasts produce a protein mixture called osteoid, which is mineralized and becomes bone. They also manufacture hormones, including prostaglandins.

Osteocytes: These are inactive osteoblasts that have become trapped in the bone that they have created. They maintain connections to other osteocytes and osteoblasts. They are important for communication within bone tissue.

Osteoclasts: These are large cells with more than one nucleus. Their job is to break down bone. They release enzymes and acids to dissolve minerals in bone and digest them. This process is called resorption. Osteoclasts help remodel injured bones and create pathways for nerves and blood vessels to travel through.

BONE MARROW

Bone marrow is found in almost all bones where cancellous bone is present. The marrow is responsible for making around 2 million red blood cells every second. It also produces lymphocytes or the white blood cells involved in the immune response.

EXTRACELLULAR MATRIX

Bones are essentially living cells embedded in a mineral-based organic matrix. This extracellular matrix is made of:

Organic Components: Being mostly type 1 collagen.

Inorganic Components: Including hydroxyapatite and other salts, such as calcium and phosphate.

Collagen gives bone its Tensile Strength: namely the resistance to being pulled apart. Hydroxyapatite gives the bones compressive strength or resistance to being compressed.

BONES SERVE SEVERAL VITAL FUNCTIONS

Mechanical

Bones Provide a Frame to Support the Body: Muscles, tendons, and ligaments attach to bones. Without anchoring to bones, muscles could not move the body.

Some bones Protect the Body's Internal Organs: For instance, the skull protects the brain, and the ribs protect the heart and lungs.

Synthesizing

Cancellous bone produces red blood cells, Platelets, and white blood cells. Also, defective and old red blood cells are destroyed in bone marrow.

Metabolic

Storing Minerals: Bones act as a reserve for minerals, particularly calcium and phosphorous.

They also store some growth factors, such as insulin-like growth factor:

Fat Storage: Fatty acids can be stored in the bone marrow adipose tissue.

pH balance: Bones can release or absorb alkaline salts, helping blood to stay at the right pH level.

Detoxification: Bones can absorb heavy metals and other toxic elements from the blood.

Endocrine Function: Bones release hormones that act on the kidneys and influence blood sugar regulation and fat deposition.

Calcium Balance: Bones can raise or reduce calcium in the blood by forming bone, or breaking it down in a process called resorption.

TYPES OF BONE

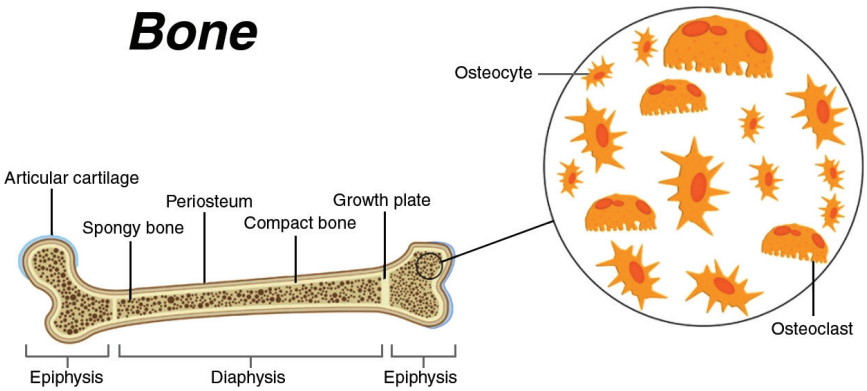


Fig. Bone Anatomy.

There are five types of bones in the human body:

Long Bones: These are mostly compacted bone with little marrow and include most of the bones in the limbs. These bones tend to support weight and help movement.

Short Bones: Only a thin layer of compact bone, these include bones of the wrist and ankle.

Flat Bones: Usually bones that are thin and curved. They consist of two outer layers of compact bone and an inner layer of spongy bone. Flat bones include most of the bones of the skull and the sternum or breastbone. They tend to have a protective role.

Sesamoid Bones: These are embedded in tendons, such as the patella or kneecap. They protect tendons from wear and stress.

Irregular Bones: As their name implies, these are bones that do not fit into the first four categories and are an unusual shape. They include the bones of the spine and pelvis. They are often protecting organs or tissues.

Bones of the Skeleton are Split into two Groups:

Appendicular Skeleton: Bones of the limbs, shoulders, and pelvic girdle.

Axial Skeleton: Bones of the skull, vertebral column, thoracic cage.

BONE REMODELING

Fig. Bone is Constantly Under Construction.

Bone is always being remodeled. This is a two-part process:

1. Resorption when osteoclasts break down and remove bone.
2. Formation when new bone tissue is laid down.

An estimated 10 percent of an adult's skeleton is replaced each year. Remodeling allows the body to fix damaged sections, reshape the skeleton during growth, and regulate calcium levels. If one part of the skeleton is put under increased stress over time, for instance, during sport or exercise, the sections of bone under most pressure will become thicker in response. Remodeling is under the control of several hormones, including parathyroid hormone, calcitonin, vitamin D, estrogen in women, and testosterone in men.

OSTEOPOROSIS

Osteoporosis is a bone disease where there is a reduction in bone mineral density. This increases the risk of fractures occurring. Osteoporosis is most common in women after the menopause. However, it can happen in premenopausal women and men.

Osteoporosis occurs either when removal or resorption of bone happens too quickly, new bone is formed too slowly, or for both reasons. It can be caused by having inadequate calcium, a vitamin D deficiency, consuming excessive alcohol, or smoking tobacco.

In a Nutshell

Although they get less attention than other body parts, bones are more than just a protective scaffold on which the human body is built. Bones also maintain appropriate levels of many compounds and regulate hormonal pathways. Bones are the unsung heroes of anatomy.

OSTEOGENESIS: THE DEVELOPMENT OF BONES

Some of the most obvious structures derived from the paraxial mesoderm are bones. There are three distinct lineages that generate the skeleton. The somites generate the axial skeleton, the lateral plate mesoderm generates the limb skeleton, and the cranial neural crest gives rise to the branchial arch and craniofacial bones and cartilage. There are two major modes of bone formation, or osteogenesis, and both involve the transformation of a preexisting mesenchymal tissue into bone tissue. The direct conversion of mesenchymal tissue into bone is called intramembranous ossification. This process occurs primarily in the bones of the skull. In other cases, the mesenchymal cells differentiate into cartilage, and this cartilage is later replaced by bone. The process by which a cartilage intermediate is formed and replaced by bone cells is called endochondral ossification.

INTRAMEMBRANOUS OSSIFICATION

Intramembranous ossification is the characteristic way in which the flat bones of the skull and the turtle shell are formed. During intramembranous ossification in the skull, neural crest-derived mesenchymal cells proliferate and condense into compact nodules. (Thus, intramembranous ossification is not occurring from sclerotome-derived cells.) Some of these cells develop into capillaries; others change their shape to become osteoblasts, committed bone precursor cells. The osteoblasts secrete a collagen-proteoglycan matrix that is able to bind calcium salts. Through this binding, the prebone (osteoid) matrix becomes calcified. In most cases, osteoblasts are separated from the region of calcification by a layer of the osteoid matrix they secrete. Occasionally, though, osteoblasts become trapped in the calcified matrix and become osteocytes—bone cells. As calcification proceeds, bony spicules radiate out from the region where ossification began. Furthermore, the entire region of calcified spicules becomes surrounded by compact mesenchymal cells that form the periosteum (a membrane that surrounds the bone). The cells on the inner surface of the periosteum also become osteoblasts and deposit osteoid matrix parallel to that of the existing spicules. In this manner, many layers of bone are formed.

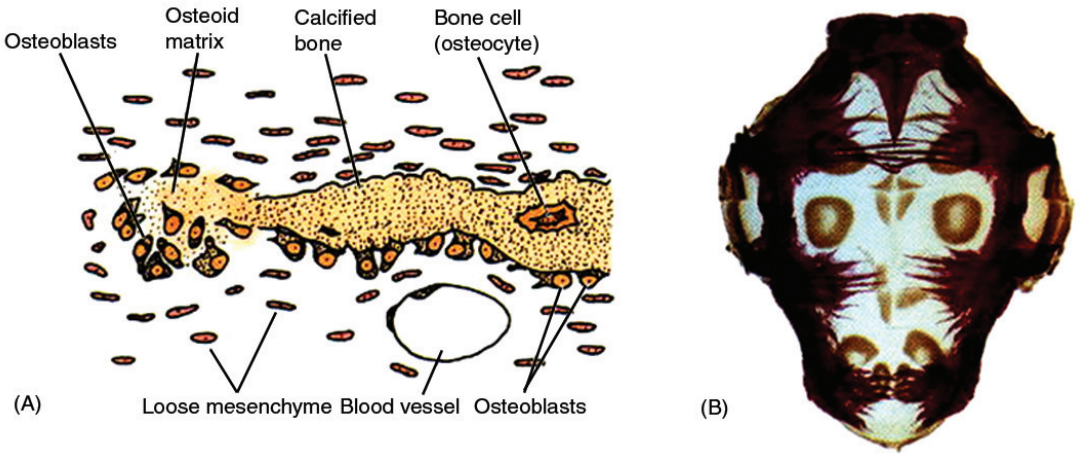


Fig. Schematic diagram of intramembranous ossification. (A) Mesenchymal cells condense to produce osteoblasts, which deposit osteoid matrix. These osteoblasts become arrayed along the calcified region of the matrix. Osteoblasts that are trapped within the bone matrix become osteocytes. (B) Intramembranous ossification in the plastron (ventral shell) of the red-ear slider turtle *Trachemys scripta.* The plastron of a one-month-old hatchling was stained with alcian blue (for cartilage) and alizarin red (for bone). No cartilage was seen to precede the formation of bone.

The mechanism of intramembranous ossification involves bone morphogenetic proteins and the activation of a transcription factor called CBFA1. Bone morphogenetic proteins (probably BMP2, BMP4, and BMP7) from the head epidermis are thought to instruct the neural crest-derived mesenchymal cells to become bone cells directly (Hall 1988). The BMPs activate the *Cbfa1* gene in the mesenchymal cells. Just as the myogenic bHLH family of transcription factors is competent to transform primitive mesenchyme cells (or just about any other cell) into muscle-forming myoblasts, the CBFA1 transcription factor appears to be able to transform mesenchyme cells into osteoblasts. Ducy and her colleagues (1997) found that the mRNA for mouse CBFA1 is severely restricted to the mesenchymal condensations that form bone, and is limited to the osteoblast lineage. The protein appears to activate the genes for osteocalcin, osteopontin, and other bone-specific extracellular matrix proteins.

Confirmation and extension of this conclusion was obtained from gene targeting experiments wherein the mouse *Cbfa1* gene was knocked out. Mice homozygous for this deletion died shortly after birth without taking a breath, and their skeletons completely lacked bone. The mutants had only the cartilaginous skeletal model. In these mice, both endochondral and intramembranous ossification had been eliminated. The osteoblasts were in an arrested state of development, expressing neither osteocalcin nor osteopontin. Mice that were heterozygous for *Cbfa1* showed skeletal defects similar to those of a human syndrome called cleidocranial dysplasia (CCD). In this syndrome, the skull sutures fail to close (adults retain the fontanel associated with young infants), growth is stunted, and the clavicle (collarbone) is often absent or deformed. When DNA from patients with CCD was analyzed, each patient had either deletions or point mutations in the *CBFA1* gene. Control individuals did not have such mutations. Therefore, it appears that cleidocranial dysplasia is caused by heterozygosity of the *CBFA1* gene.

ENDOCHONDRAL OSSIFICATION

Endochondral ossification involves the formation of cartilage tissue from aggregated mesenchymal cells, and the subsequent replacement of cartilage tissue by bone. The process of endochondral ossification can be divided into five stages. First, the mesenchymal cells are commited to become cartilage cells. This committment is caused by paracrine factors that induce the nearby mesodermal cells to express two transcription factors, Pax1 and Scleraxis. These transcription factors are thought to activate cartilage-specific genes. Thus, Scleraxis is expressed in the mesenchyme from the sclerotome, in the facial mesenchyme that forms cartilaginous precursors to bone, and in the limb mesenchyme.

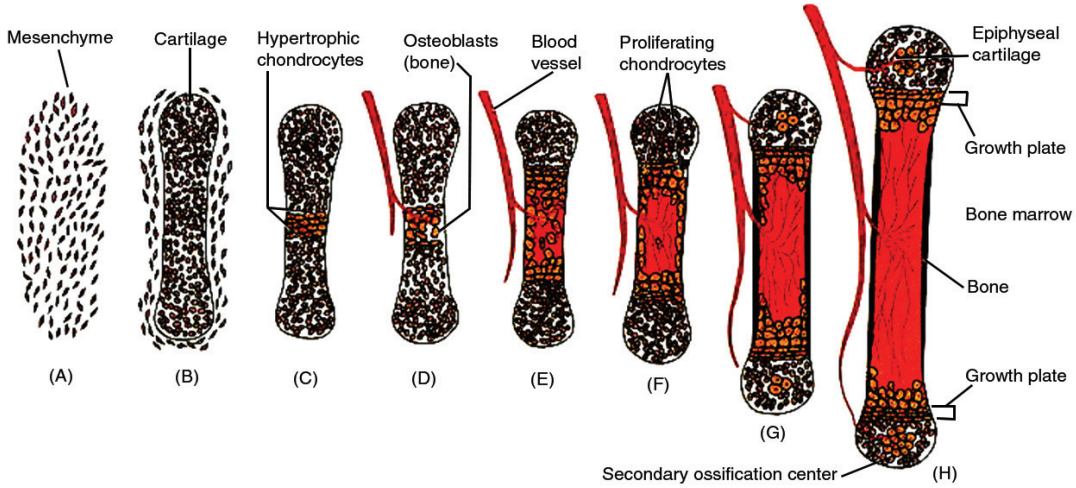


Fig. Schematic diagram of endochondral ossification. (A, B) Mesenchymal cells condense and differentiate into chondrocytes to form the cartilaginous model of the bone. (C) Chondrocytes in the center of the shaft undergo hypertrophy and apoptosis while they change and mineralize their extracellular matrix. Their deaths allow blood vessels to enter. (D, E) Blood vessels bring in osteoblasts, which bind to the degenerating cartilaginous matrix and deposit bone matrix. (F-H) Bone formation and growth consist of ordered arrays of proliferating, hypertrophic, and mineralizing chondrocytes. Secondary ossification centers also form as blood vessels enter near the tips of the bone.

During the second phase of endochondral ossification, the committed mesenchyme cells condense into compact nodules and differentiate into chondrocytes, the cartilage cells. N-cadherin appears to be important in the initiation of these condensations, and N-CAM seems to be critical for maintaining them. In humans, the *SOX9* gene, which encodes a DNA-binding protein, is expressed in the precartilaginous condensations. Mutations of the *SOX9* gene cause camptomelic dysplasia, a rare disorder of skeletal developmentthat results in deformities of most of the bones of the body. Most affected babies die from respiratory failure due to poorly formed tracheal and rib cartilage.

During the third phase of endochondral ossification, the chondrocytes proliferate rapidly to form the model for the bone. As they divide, the chondrocytes secrete a cartilage-specific extracellular matrix. In the fourth phase, the chondrocytes stop dividing and increase their volume dramatically, becoming hypertrophic chondrocytes. These large chondrocytes alter the matrix they produce (by adding collagen X and more fibronectin) to enable it to become mineralized by calcium carbonate. The fifth phase involves the invasion of the cartilage model by blood vessels. The hypertrophic chondrocytes die by apoptosis. This space will become bone marrow. As the cartilage cells die, a group of cells that have surrounded the cartilage model differentiate into osteoblasts. The ostoblasts begin forming bone matrix on the partially degraded cartilage. Eventually, all the cartilage is replaced by bone. Thus, the cartilage tissue serves as a model for the bone that follows. The skeletal components of the vertebral column, the pelvis, and the limbs are first formed of cartilage and later become bone.

The replacement of chondrocytes by bone cells is dependent on the mineralization of the extracellular matrix. This is clearly illustrated in the developing skeleton of the chick embryo, which utilizes the calcium carbonate of the eggshell as its calcium source. During development, the circulatory system of the chick embryo translocates about 120 mg of calcium from the shell to the skeleton. When chick embryos are removed from their shells at day 3 and grown in shell-less cultures (in plastic wrap) for the duration of their development, much of the cartilaginous skeleton fails to mature into bony tissue. A number of events lead to the hypertrophy and mineralization of the chondrocytes, including an initial switch from aerobic to anaerobic respiration, which alters their cell metabolism and mitochondrial energy potential. Hypertrophic chondrocytes secrete numerous small membrane-bound vesicles into the extracellular matrix. These vesicles contain enzymes that are active in the generation of calcium and phosphate ions and initiate the mineralization process within the cartilaginous matrix. The hypertrophic chondrocytes, their metabolism and mitochondrial membranes altered, then die by apoptosis.

In the long bones of many mammals (including humans), endochondral ossification spreads outward in both directions from the center of the bone. If all of our cartilage were turned into bone before birth, we would not grow any larger, and our bones would be only as large as the original cartilaginous model. However, as the ossification front nears the ends of the cartilage model, the chondrocytes near the ossification front proliferate prior to undergoing hypertrophy, pushing out the cartilaginous ends of the bone. These cartilaginous areas at the ends of the long bones are called epiphyseal growth plates. These plates contain three regions: a region of chondrocyte proliferation, a region of mature chondrocytes, and a region of hypertrophic chondrocytes. As the inner cartilage hypertrophies and the ossification front extends farther outward, the remaining cartilage in the epiphyseal growth plate proliferates. As long as the epiphyseal growth plates are able to produce chondrocytes, the bone continues to grow.

SUPPLY OF BLOOD AND NERVES TO BONE

The blood and nerve supply to bones are carried in Haversian canals that run along the long axis of bones. Blood is supplied to mature compact bone through the Haversian canal. Haversian canals are formed when individual lamellae form concentric rings around larger longitudinal canals (approx. 50 μm in diameter) within the bone tissue.

Haversian canals typically run parallel to the surface and along the long axis of the bone. The canals and the surrounding lamellae (8–15) are called a Haversian system or an osteon. A Haversian canal generally contains one or two capillaries and nerve fibres. The Haversian canals also surround nerve cells throughout the bone and communicate with osteocytes in lacunae (spaces within the dense bone matrix that contain the living bone cells) through canaliculi. This unique arrangement is conducive to the storage of mineral salt deposits that give bone tissue its strength.

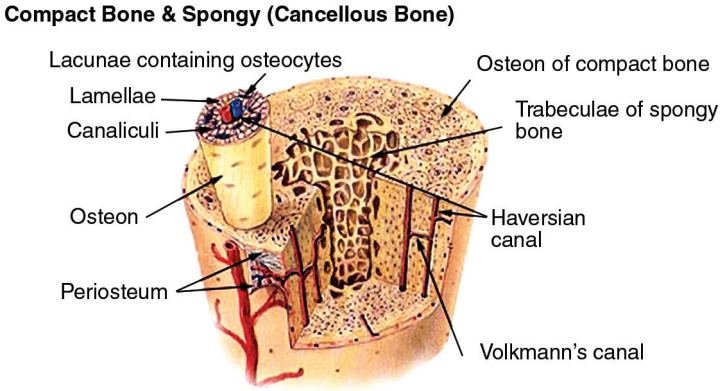


Fig. Haversian canal: The Haversian canals surround blood vessels and nerve cells throughout the bone.

The vascular supply of long bones depends on several points of inflow, which feed complex sinusoidal networks within the bone. These in turn drain to various channels through all surfaces of the bone except that covered by articular cartilage.

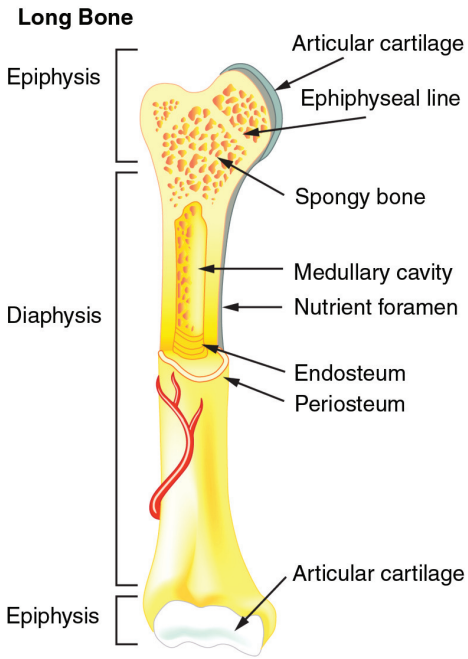


Fig. Epiphyseal Plate: Image shows the location of the epiphyseal plates (or lines) and the articular surfaces of long bones.

Volkmann's canals are channels that assist with blood and nerve supply from the periosteum to the Haversian canal. One or two main diaphyseal nutrient arteries enter the shaft obliquely through one or two nutrient foramina leading to nutrient canals. Their sites of entry and angulation are almost constant and characteristically directed away from the growing epiphysis.

Except for a few with double or no foramina, 90% of long bones have a single nutrient foramen in the middle third of the shaft. The nutrient arteries divide into ascending and descending branches in the medullary cavity. These approach the epiphysis dividing into smaller rami. Near the epiphysis, they anastomose with the metaphyseal and epiphyseal arteries. The blood supply of the immature bones is similar, but the epiphysis is a discrete vascular zone separated from the metaphysis by the growth plate. Epiphyseal and metaphyseal arteries enter on both sides of the growth cartilage, with anastamoses between them being few or absent. Growth cartilage receives its blood supply from both sources and also from an anastamotic collar in the adjoining perichondrium. Young periosteum is more vascular, has more metaphyseal branches, and its vessels communicate more freely with those of the shaft than adult periosteum.

MICROSCOPIC ANATOMY OF BONE

The basic microscopic unit of bone is an osteon, which can be arranged into woven bone or lamellar bone. Bones are composed of bone matrix, which has both organic and inorganic components. Bone matrix is laid down by osteoblasts as collagen, also known as osteoid. Osteoid is hardened with inorganic salts, such as calcium and phosphate, and by the chemicals released from the osteoblasts through a process known as mineralization. The basic microscopic unit of bone is an osteon (or Haversian system). Osteons are roughly cylindrical structures that can measure several millimeters long and around 0.2 mm in diameter. Each osteon consists of a lamellae of compact bone tissue that surround a central canal (Haversian canal). The Haversian canal contains the bone's blood supplies. The boundary of an osteon is called the cement line. Osteons can be arranged into woven bone or lamellar bone.

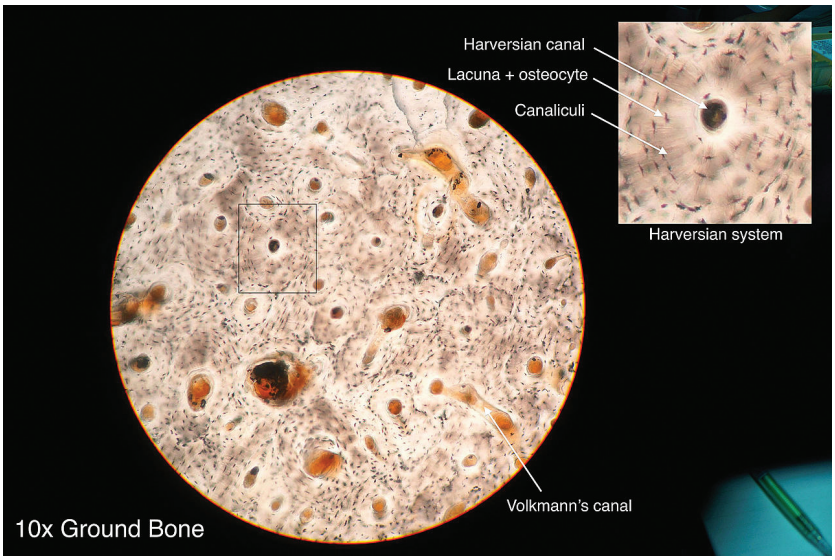


Fig. *Osteon:* A photo taken through a microscope that shows the anatomy of compact bone with a detailed view of an osteon.

WOVEN BONE

Woven bone is found on the growing ends of an immature skeleton or, in adults, at the site of a healing fracture. Woven bone is characterized by the irregular organization of collagen fibres and is mechanically weak, but forms quickly. The criss-cross appearance of the fibrous matrix is why it is referred to as woven. It has a high proportion of osteocytes to hard inorganic salts that leads to its mechanical weakness. Woven bone is replaced by lamellar bone during development. In contrast to woven bone, lamellar bone is highly organized in concentric sheets with a much lower proportion of osteocytes to surrounding tissue. The regular parallel alignment of collagen into sheets, or, lamellae, causes lamellar bone to be mechanically strong.

LAMELLAR BONE

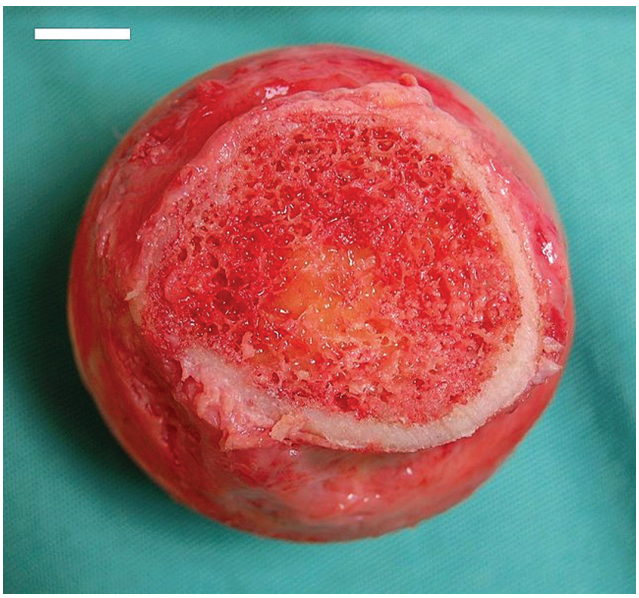


Fig. Femur head showing trabecular bone: A cross-section of the head of the femur showing lamellar bone on the borders and trabecular bone in the center.

Lamellar bone makes up the compact or cortical bone in the skeleton, such as the long bones of the legs and arms. In a cross-section, the fibres of lamellar bone can be seen to run in opposite directions in alternating layers, much like in plywood, assisting in the bone's ability to resist torsion forces.

When the same lamellar bone is loosely arranged, it is referred to as trabecular bone. Trabecular bone gets its name because of the spongy pattern it displays in an x-ray. The spaces within trabecular bone are filled with active bone marrow. After a fracture, woven bone forms initially, but it is gradually replaced by lamellar bone during a process known as bony substitution.

CHEMICAL COMPOSITION OF BONE

Acid-base imbalances, including metabolic acidosis and alkalosis, can produce severe, even life-threatening medical conditions. Traveling to a high altitude can cause an acid-base imbalance due to reduced levels of oxygen in the atmosphere, and, therefore, in the blood. To compensate for this, the traveler begins to hyperventilate, trying to expel excess carbon dioxide and bring pH back to normal. However, if the traveler stays at high altitude, it may take several days for their pH to fully return to normal.

ACID-BASE DISORDERS

Acid-base imbalance is an abnormality of the human body's normal balance of acids and bases that causes the plasma pH to deviate out of normal range (7.35 to 7.45). In the fetus, the normal range differs based on which umbilical vessel is sampled (umbilical vein pH is normally 7.25 to 7.45; umbilical artery pH is normally 7.18 to 7.38). Acid-base imbalances can exist in varying levels of severity, some life-threatening.

An excess of acid is called acidosis and an excess in bases is called alkalosis. The process that causes the imbalance is classified based on the etiology of the disturbance (respiratory or metabolic) and the direction of change in pH (acidosis or alkalosis). Mixed disorders may feature an acidosis and alkalosis excess at the same time that partially counteract each other, or there can be two different conditions affecting the pH in the same direction. The phrase mixed acidosis, for example, refers to metabolic acidosis in conjunction with respiratory acidosis.

METABOLIC ACIDOSIS

In medicine, metabolic acidosis is a condition that occurs when the body produces too much acid or when the kidneys are not removing enough acid from the body. If unchecked, metabolic acidosis leads to acidemia, that is, blood pH is less than 7.35 due to increased production of hydrogen by the body, or because of the body's inability to form bicarbonate (HCO_3-) in the kidneys.

Acidosis refers to a low pH in tissue. Acidemia refers to a low pH in the blood. Symptoms may include chest pain, palpitations, headache, altered mental status such as severe anxiety due to hypoxia, decreased visual acuity, nausea, vomiting, abdominal pain, altered appetite (either loss of or increased) and weight loss (longer term), muscle weakness, and bone pains. Rapid deep breaths increase the amount of carbon dioxide exhaled, thus lowering the serum carbon dioxide levels, resulting in some degree of compensation. Overcompensation via respiratory alkalosis to form an alkalemia does not occur.

Neurological complications include lethargy, stupor, coma, seizures. Cardiac complications include arrhythmias (ventricular tachycardia) and decreased response to epinephrine; both lead to hypotension (low blood pressure).

METABOLIC ALKALOSIS

Metabolic alkalosis is a metabolic condition in which the pH of tissue is elevated beyond the normal range (7.35 to 7.45). This is the result of decreased hydrogen ion concentration, leading to increased bicarbonate concentration, or as a direct result of increased bicarbonate concentrations. Alkalosis refers to a high pH in tissue.

Alkalemia refers to a high pH in the blood. The causes of metabolic alkalosis can be divided into two categories, depending upon urine chloride levels. Chloride-responsive causes result from the loss of hydrogen ions via vomiting or the kidneys. Vomiting results in the loss of hydrochloric acid (hydrogen and chloride ions) with the stomach contents.

The kidneys compensate for these losses by retaining sodium in the collecting ducts at the expense of hydrogen ions (sparing sodium/potassium pumps to prevent further loss of potassium), and leads to metabolic alkalosis. The excess sodium increases extracellular volume and the loss of hydrogen ions creates a metabolic alkalosis.

Later, the kidneys respond through the aldosterone escape to excrete sodium and chloride in urine. Compensation for metabolic alkalosis occurs mainly in the lungs, which retain carbon dioxide (CO_2) through slower breathing, or hypoventilation (respiratory compensation).

CO_2 is then consumed towards the formation of the carbonic acid intermediate, thus decreasing pH. Renal compensation for metabolic alkalosis, less effective than respiratory compensation, consists of increased excretion of HCO_3– (bicarbonate), as the filtered load of HCO_3– exceeds the ability of the renal tubule to reabsorb it.

RESPIRATORY ACIDOSIS

Respiratory acidosis is a medical condition in which decreased ventilation (hypoventilation) causes an increase in blood carbon dioxide concentration and decreased pH (a condition generally called acidosis). Carbon dioxide is produced constantly as the body's cells respire, and this CO_2 will accumulate rapidly if the lungs do not adequately expel it through alveolar ventilation.

Acute respiratory acidosis occurs when an abrupt failure of ventilation occurs. This failure in ventilation may be caused by depression of the central respiratory center by cerebral disease or drugs, an inability to ventilate adequately due to neuromuscular disease (*e.g.*, myasthenia gravis, amyotrophic lateral sclerosis, Guillain-Barré syndrome, muscular dystrophy), or airway obstructions related to asthma or chronic obstructive pulmonary disease (COPD) exacerbation.

RESPIRATORY ALKALOSIS

Respiratory alkalosis is a medical condition in which increased respiration (hyperventilation) elevates the blood pH (a condition generally called alkalosis). There are two types of respiratory alkalosis: chronic and acute. Acute respiratory alkalosis occurs rapidly. During acute respiratory alkalosis, the person may lose consciousness whereupon the rate of ventilation will resume to normal.

Chronic respiratory alkalosis is a more long-standing condition. Respiratory alkalosis may be produced accidentally (iatrogenically) during excessive mechanical ventilation. Other causes include: psychiatric causes, drug use, fever, and pregnancy.

3

Muscular System

Human muscle system, the muscles of the human body that work the skeletal system, that are under voluntary control, and that are concerned with movement, posture, and balance. Broadly considered, human muscle—like the muscles of all vertebrates—is often divided into striated muscle (or skeletal muscle), smooth muscle, and cardiac muscle. Smooth muscle is under involuntary control and is found in the walls of blood vessels and of structures such as the urinary bladder, the intestines, and the stomach. Cardiac muscle makes up the mass of the heart and is responsible for the rhythmic contractions of that vital pumping organ; it too is under involuntary control. With very few exceptions, the arrangement of smooth muscle and cardiac muscle in humans is identical to the arrangement found in other vertebrate animals.

This chapter is concerned with the skeletal muscles of the human body, with emphasis on muscle movements and the changes that have occurred in human skeletal musculature as a result of the long evolutionary process that involved the assumption of upright posture. Smooth muscle and cardiac muscle and the physiology of muscle contraction are treated at great length in the article muscle. For descriptions of disorders that affect the human muscle system, *see*muscle disease.

MUSCULAR SYSTEM DEFINITION

The muscular system is a set of tissues in the body with the ability to change shape. Muscle cells contain a variety of proteins which help them contract in size. The proteins form fibers, which connect various parts of the cells. The main proteins used are actin and myosin.

Movement

The most obvious function of the muscular system is movement. Organisms have adopted a variety of methods to use the contractile function of the muscular system to move through the environment. The most basic movements of fish include contracting muscles on opposite sides of the body in succession. This action propels them through the water. In organisms with limbs, tendons and other connective tissues are used to secure muscles to the joints and skeleton. Skeletons may be internal like the human skeletons, or they may be external like the exoskeleton of crabs. The nervous system coordinates the contraction of the muscular system to synchronize the movement of the limbs. Animals like the cheetah, swordfish, and bat have obtained speeds above 60 miles per hour or more through the power of their muscles alone.

Circulation

The second and less obvious function of the muscular system is to assist with circulation. Visceral and cardiac muscle tissues surround the blood vessels and lymph vessels that carry crucial nutrients and oxygen to the cells of the body. Cardiac muscle makes up the heartand supplies the main force for blood traveling through the body.

Large arteries and veins have associated muscles which can contract or relax to control blood pressure. The actions of large skeletal muscles also help pump the blood and lymph fluid throughout the body. While you exercise and contract large and small muscles, they push vessels aside, which works like a pump to move fluids around your body.

Much like its ability to move fluids through vessels in the circulatory system, the muscular system also aids in moving food through the digestive system. Most digestive organs are surrounded by smooth muscle tissue. Although the tissue cannot be voluntarily contracted like skeletal muscles, it is controlled subconsciously. When food needs to be moved through the gut, the muscles contract in a synchronized fashion in a wave through the digestive system. These wave-like muscular contractions are called peristalsis.

THE MUSCLE GROUPS AND THEIR ACTIONS

The basic framework for the understanding of gross human muscular anatomy, with descriptions of the large muscle groups and their actions. The various muscle groups work in a coordinated fashion to control the movements of the human body.

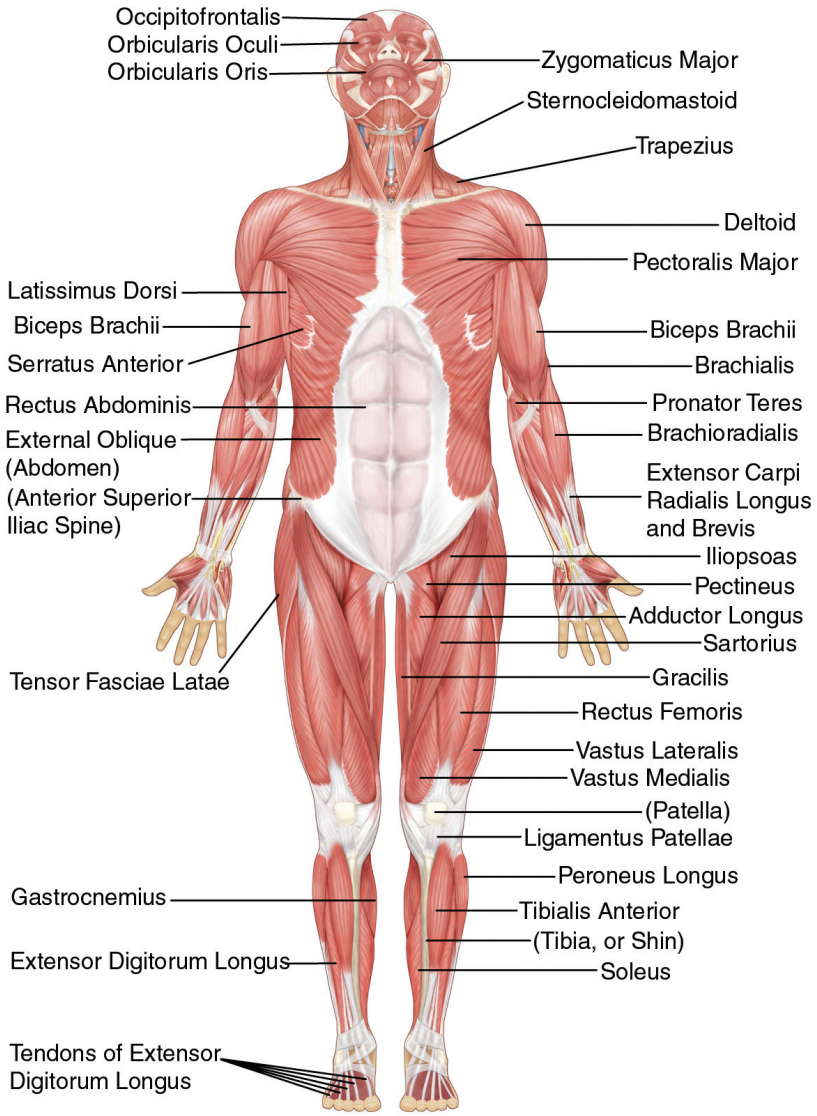


Fig. Anterior view of the human Muscular System.

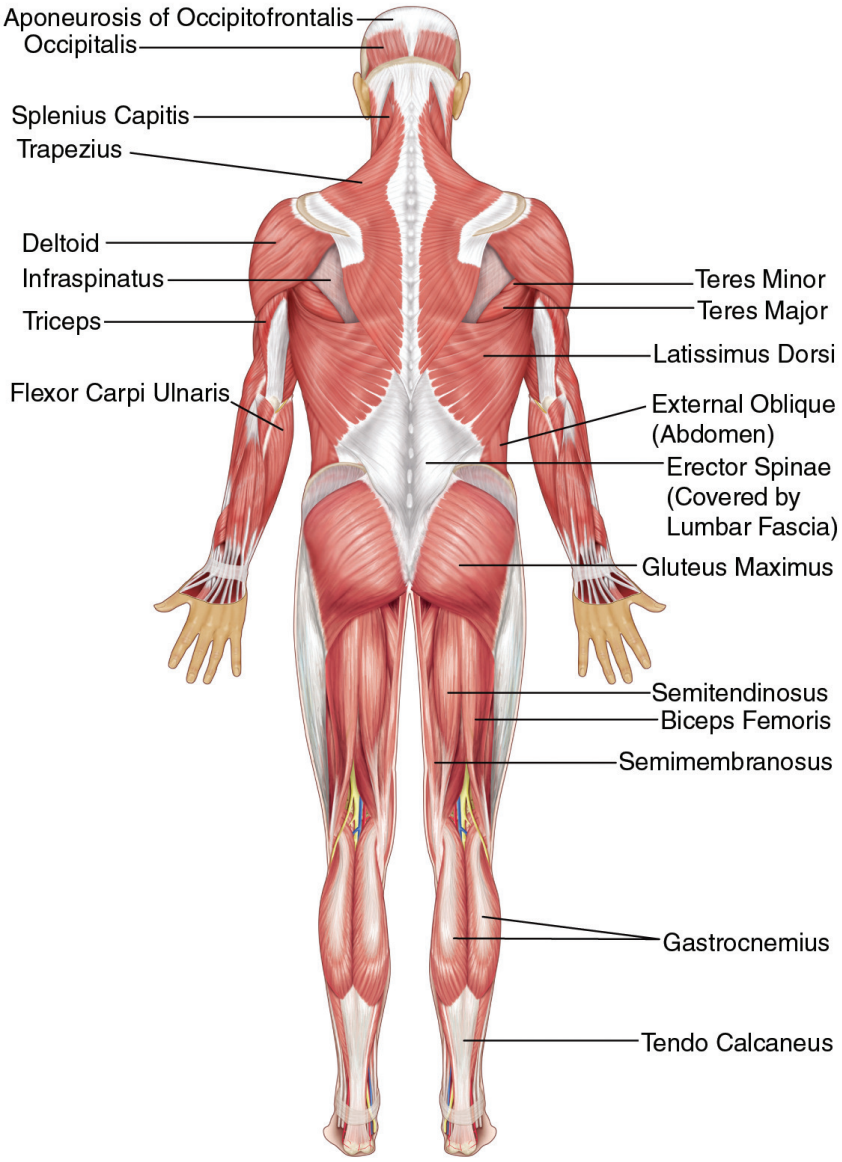


Fig. Posterior view of human Muscular System.

THE NECK

The motion of the neck is described in terms of rotation, flexion, extension, and side bending (*i.e.*, the motion used to touch the ear to the shoulder). The direction of the action can be ipsilateral, which refers to movement in the direction of the contracting muscle, or contralateral, which refers to movement away from the side of the contracting muscle.

Rotation is one of the most-important actions of the cervical (neck) spine. Rotation is accomplished primarily by the sternocleidomastoid muscle, which bends the neck to the ipsilateral side and rotates the neck contralaterally. Together, the sternocleidomastoid muscles on both sides of the neck act to flex the neck and raise the sternum to assist in forced inhalation. The anterior and middle scalene muscles, which also are located at the sides of the neck, act ipsilaterally to rotate the neck, as well as to elevate the first rib. The splenius capitis and splenius cervicis, which are located in the back of the neck, work to rotate the head.

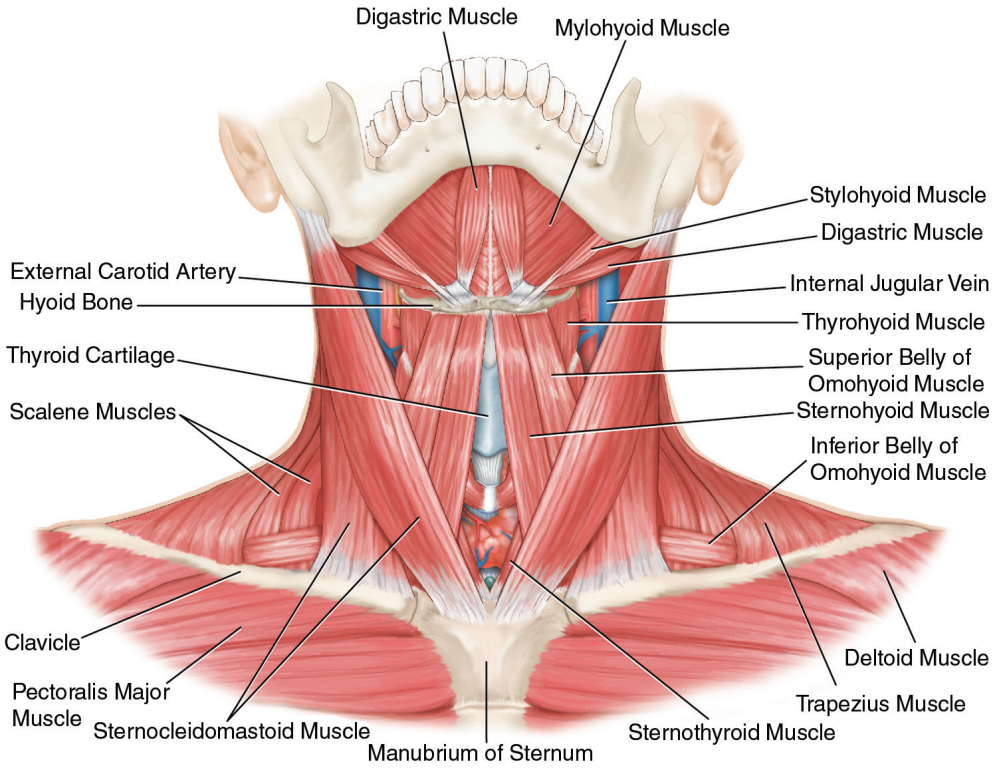


Fig. Muscles of the Neck.

Side bending also is an important action of the cervical spine. The sternocleidomastoid muscles are involved in cervical side bending. The posterior scalene muscles, located on the lower sides of the neck, ipsilaterally bend the neck to the side and elevate the second rib. The splenius capitis and splenius cervicis also assist in neck side bending. The erector spinae muscles (iliocostalis, longissimus, and spinalis) are large, deep muscles that extend the length of the back. All three act to ipsilaterally side bend the neck.

Neck flexion refers to the motion used to touch the chin to the chest. It is accomplished primarily by the sternocleidomastoid muscles, with assistance from the longus colli and the longus capitis, which are found in the front of the neck. Neck extension is the opposite of flexion and is accomplished by many of the same muscles that are used for other neck movements, including the splenius cervicis, splenius capitis, iliocostalis, longissimus, and spinalis muscles.

THE BACK

The back contains the origins of many of the muscles that are involved in the movement of the neck and shoulders. In addition, the axial skeleton that runs vertically through the back protects the spinal cord, which innervates almost all the muscles in the body.

Multiple muscles in the back function specifically in movements of the back. The erector spinae muscles, for example, extend the back (bend it backward) and side bend the back. The semispinalis dorsi and semispinalis capitis muscles also extend the back. The small muscles of the vertebrae (the multifidi and rotators) help rotate, extend, and side bend the back. The quadratus lumborum muscle in the lower back side bends the lumbar spine and aids in the inspiration of air through its stabilizing affects at its insertion at the 12th rib (the last of the floating ribs). The scapula (shoulder blade) is elevated by the trapezius muscle, which runs from the back of the neck to the middle of the back, by the rhomboid major and rhomboid minor muscles in the upper back, and by the levator scapulae muscle, which runs along the side and back of the neck.

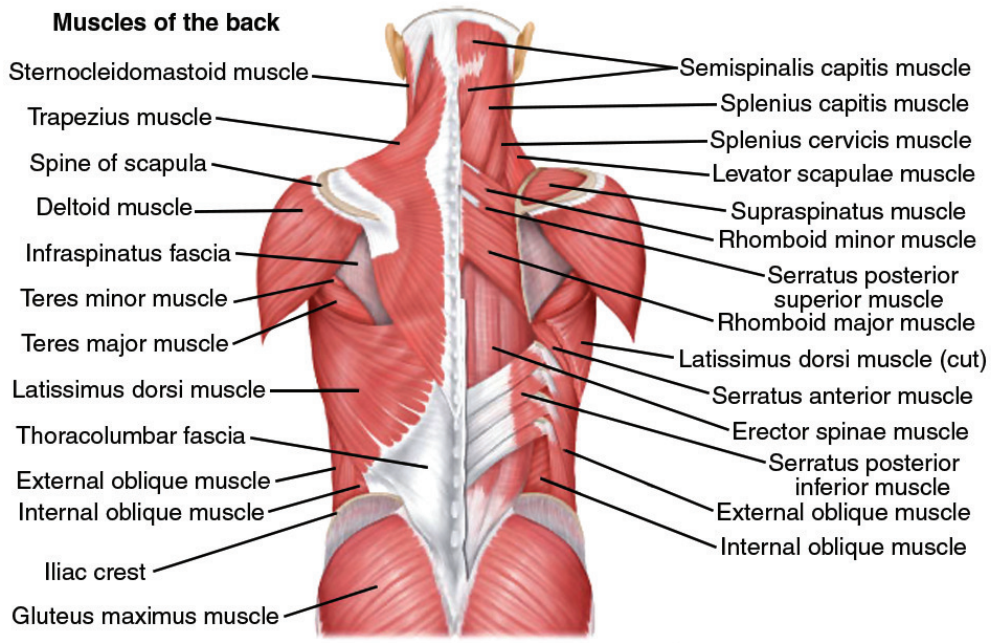


Fig. Muscles of the Back.

THE SHOULDER

The shoulder is a complex ball-and-socket joint comprising the head of the humerus, the clavicle (collarbone), and the scapula. The shoulder's main motions are flexion, extension, abduction, adduction, internal rotation, and external rotation.

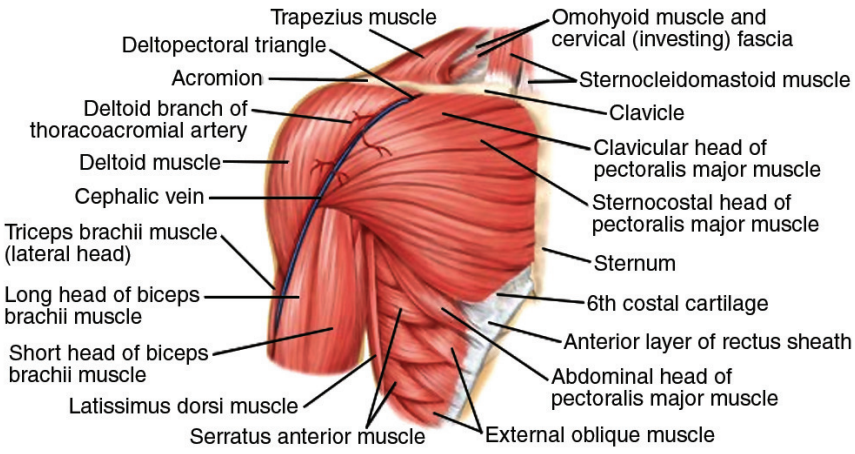


Fig. Muscles of the Shoulder.

Shoulder flexion is movement of the shoulder in a forward motion. An example of shoulder flexion can be seen when reaching forward to grasp an object. That action is accomplished primarily by the combined actions of the deltoid muscle in the uppermost extent of the arm, the pectoralis major muscle in the chest, the coracobrachialis muscle on the inside of the upper arm, and the biceps brachii muscles on the front of the upper arm.

Extension of the shoulder is opposite to flexion. Pure shoulder extension is the movement of the arm directly behind the body, as in receiving a baton in a relay race. That movement is accomplished by the actions of the deltoid muscle, the latissimus dorsi muscle in the back, the teres major muscle in the armpit area, and the triceps

muscle in the back of the upper arm. The triceps, as the name suggests, consists of three heads that originate from different surfaces but share the same insertion at the olecranon process of the ulna (a bone in the forearm); the three heads together act to extend the elbow.

Shoulder adduction and abduction serve to lower the arm towards and lift the arm away from the body, respectively. They can be visualized by picturing someone doing jumping jacks. Adduction is accomplished primarily by the pectoralis major, latissimus dorsi, teres major, triceps, and coracobrachialis. The deltoid and the supraspinatus, a muscle that runs along the scapula in the back, are the two main abductors of the shoulder.

An example of external rotation of the shoulder is seen in a tennisbackhand stroke. External rotation is attributed primarily to the deltoid, the teres minor in the armpit area, and the infraspinatus muscle, which covers the scapula. Internal rotation of the shoulder is the opposite of external rotation. An example is the shoulder movement that occurs when reaching into a back pocket. That movement is achieved through the coordinated action of the pectoralis major, latissimus dorsi, deltoid, teres major, and subscapularis muscles. (The subscapularis is a deep muscle situated on the anterior, or front-facing, surface of the scapula.)

The teres minor, subscapularis, supraspinatus, and infraspinatus muscles together form the rotator cuff, which stabilizes the humeral head (the ball portion of the ball-and-socket shoulder joint). The muscles of the rotator cuff are common sites of injury in adults, particularly among people who perform overhead motions repeatedly (*e.g.*, throwing a baseball or painting a ceiling). Several of the rotator cuff muscles have tendons that run under the acromion, a bony prominence at the distal end of the scapula. (The term *distal* describes a relative position away from the centre of the body; it often is contrasted with the term *proximal*, which describes a relative position near to the centre of the body.) The position of the tendons and of the subacromial bursae (fluid-filled sacs located beneath the acromion) leaves them vulnerable to compression and pinching, which can result in an injury known as shoulder impingement syndrome.

THE ARM

In addition to aiding the movement of the shoulder, the muscles of the upper arm produce various movements of the forearm. For example, the primary muscles involved in forearm flexion, in which the angle formed at the elbow becomes smaller (*i.e.*, the hand moves closer to the shoulder), are the biceps brachii, the brachialis (situated beneath the biceps brachii in the upper arm), and the brachioradialis (the origin of which is on the humerus). Minor contributions to forearm flexion are provided by the coracobrachialis and by flexor muscles situated in the anterior compartment of the forearm (the palm side of the forearm; also known as the flexor compartment), including the pronator teres, the flexor carpi radialis, the flexor digitorum superficialis, the palmaris longus, and the flexor carpi ulnaris.

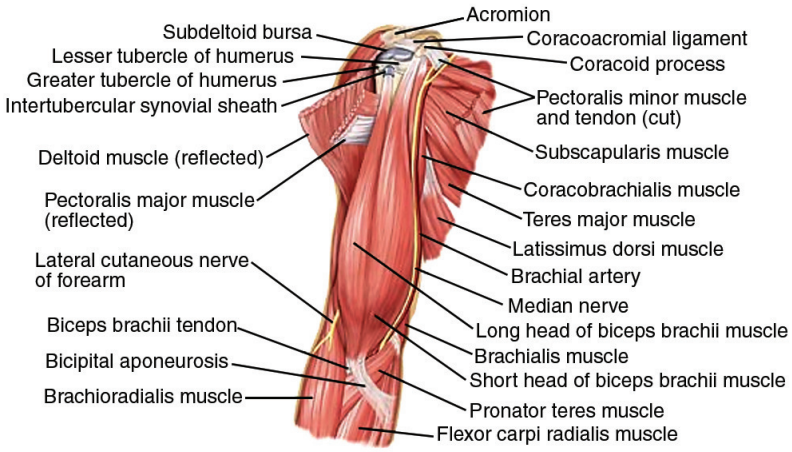


Fig. Muscles of the Upper Arm.

Extension of the forearm increases the angle at the elbow, moving the hand away from the shoulder. That action is accomplished primarily by the triceps brachii. Other muscles that make minor contributions to forearm extension include the extensor muscles of the posterior compartment of the forearm (the side of the forearm that is contiguouswith the back of the hand; also known as the extensor compartment), including the extensor carpi radialis longus, the extensor carpi radialis brevis, the extensor digitorum, the extensor carpi ulnaris, and the anconeus.

THE WRIST

Wrist flexion refers to movement of the wrist that draws the palm of the hand downward. That action is carried out by the flexor carpi radialis, the flexor carpi ulnaris, the flexor digitorum superficialis, the flexor digitorum profundus, and the flexor pollicis longus.

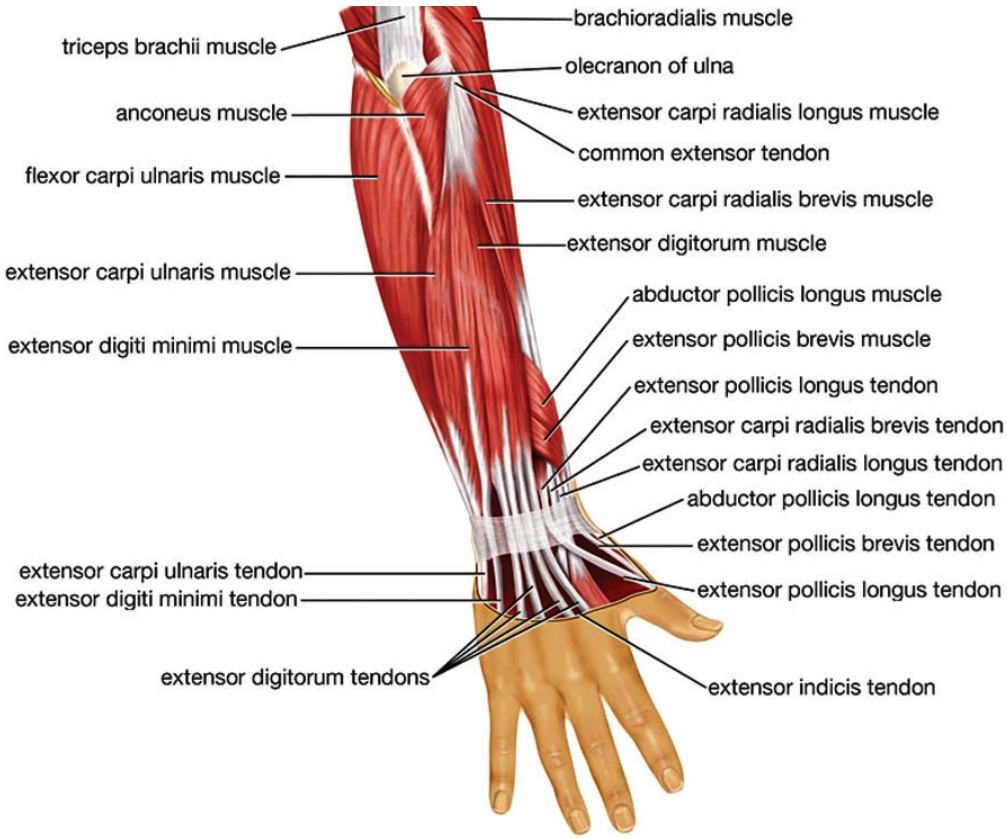


Fig. Muscles of the Forearm.

Wrist extension, by contrast, shortens the angle at the back of the wrist. The muscles responsible for that action are the extensor carpi radialis longus and the extensor carpi radialis brevis, which also abduct the hand at the wrist (move the hand in the direction of the thumb, or first digit); the extensor digitorum, which also extends the index to little finger (the second to fifth digits); the extensor digiti minimi, which also extends the little finger and adducts the hand (moves the hand in the direction of the little finger); and the extensor carpi ulnaris, which also adducts the hand. Other small muscles that cross the wrist joint may add to wrist extension, but they do so to only a small degree.

Wrist supination is the rotation of the wrist that brings the palm facing up. The supinator muscle in the posterior compartment acts to supinate the forearm. The biceps brachii also adds to supination. Pronation is the opposing action, in which the wrist is rotated so that the palm is facing down. The pronator quadratus, a deep muscle in the anterior compartment, along with the pronator teres, pronates the forearm.

THE HAND

The hand is a complex structure that is involved in fine motor coordination and complex task performance. Its muscles generally are small and extensively innervated. Even simple actions, such as typing on a keyboard, require a multitude of precise movements to be carried out by the hand muscles. Because of that complexity, the following paragraphs cover only the primary action of each hand muscle. Several muscles that originate at the posterior surface of the ulna or the radius (the other bone in the forearm) have their actions in the hand. Those include the abductor pollicis longus, which abducts and extends the thumb; the extensor pollicis brevis, which extends the metacarpophalangeal (MCP) joint of the thumb; the extensor pollicis, which extends the distal phalanx (finger bone) of the thumb; and the extensor indicis, which extends the index finger at the MCP joint. (MCP joints are located between the metacarpal bones, which are situated in the hand, and the phalanges, which are the small bones of the fingers.)

Although several of the muscles that move the hand have their origins in the forearm, there are many small muscles of the hand that have both their origin and their insertion within the hand. Those are referred to as the intrinsic muscles of the hand. They include the palmaris brevis, which assists with grip; the umbricals, which flex the MCP joints and extend the interphalangeal joints (IPs; the joints between the phalanges) of the fingers; the palmar interossei, which adduct the fingers towards the middle finger (the third digit); and the dorsal interossei, which abduct the fingers away from the middle finger. All the interossei flex the MCP joints and extend the IP joints. The thenar eminence is located on the palm side of the base of the thumb and is composed of three muscles, the abductor pollicis brevis, the flexor pollicis brevis, and the opponens pollicis, all of which are innervated by the median nerve. The abductor pollicis brevis abducts the thumb; the flexor pollicis brevis flexes the MCP joint of the thumb; and the opponens pollicis acts to oppose the thumb to the other fingers. The adductor pollicis, which is not part of the thenar eminence, acts to adduct the thumb. The hypothenar enimence is located on the palm side of the hand below the little finger. It contains three muscles that are innervated by the deep branch of the ulnar nerve. The abductor digiti minimi abducts the little finger. The flexor digiti minimi flexes the little finger. The opponens digiti minimi opposes the little finger with the thumb.

THE ABDOMEN

There are three muscular layers of the abdominal wall, with a fourth layer in the middle anterior region. The fourth layer in the midregion is the rectus abdominis, which has vertically running muscle fibres that flex the trunk and stabilize the pelvis.

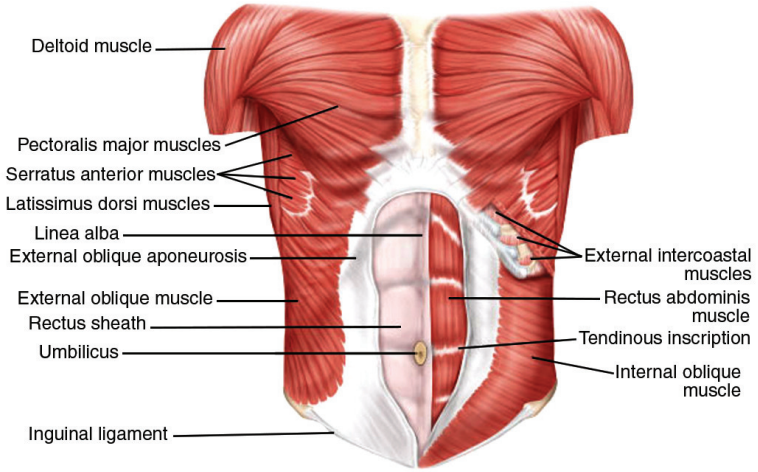


Fig. Muscles of the Abdominal Wall.

To either side of the rectus abdominis are the other three layers of abdominal muscles. The deepest of those layers is the transversus abdominis, which has fibres that run perpendicular to the rectus abdominus; the transversus abdominis acts to compress and support the abdomen and provides static core stabilization. The internal oblique layers run upward and forward from the sides of the abdomen, and the external oblique layers, which form the outermost muscle layers of the abdomen, run downward and forward. The internal oblique layers act in conjunction with the external oblique on the opposite side of the body to flex and rotate the trunk towards the side of the contracting internal oblique ("same-side rotator").

THE HIP

The hip joint is a complex weight-bearing ball-and-socket joint that can sustain considerable load. The socket of the joint is relatively deep, allowing for stability but sacrificing some degree in range of motion. The movements described in this chapter include flexion, extension, abduction, and adduction.

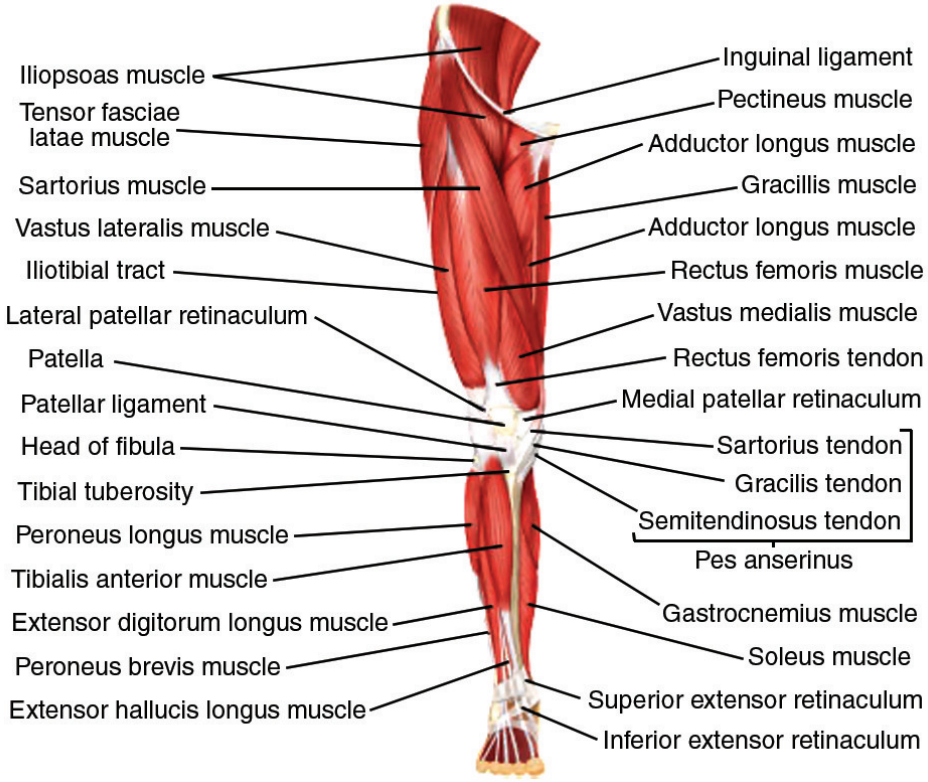


Fig. Anterior view of the Muscles of the Human Leg.

Hip flexion is the hip motion that brings the knee towards the chest. The major muscles of hip flexion include the iliopsoas, which is made up of the psoas major, psoas minor, and iliacus. Together, those muscles act mainly to flex the hip, but they also contribute to abdominal flexion and hip stabilization. Other hip flexors include the sartorius, the rectus femoris, the pectineus, and the gracilis. The sartorius also contributes to external hip rotation and knee extension and abduction, and the rectus femoris also acts in knee extension. The pectineus is also involved in hip adduction and internal rotation.

Hip extension is accomplished primarily by the muscles of the posterior thigh and buttocks, which when contracted serve to move the thigh from a flexed position towards the midline of the body or the trunk of the body from a bent position towards a more-erect posture. Hip extension is accomplished mostly by the gluteus maximus, the biceps femoris (which is divided into two heads, the long head and the short head), the semitendinosus, and the semimembranosus. A minor contribution is also provided by the adductor magnus and other small pelvic muscles.

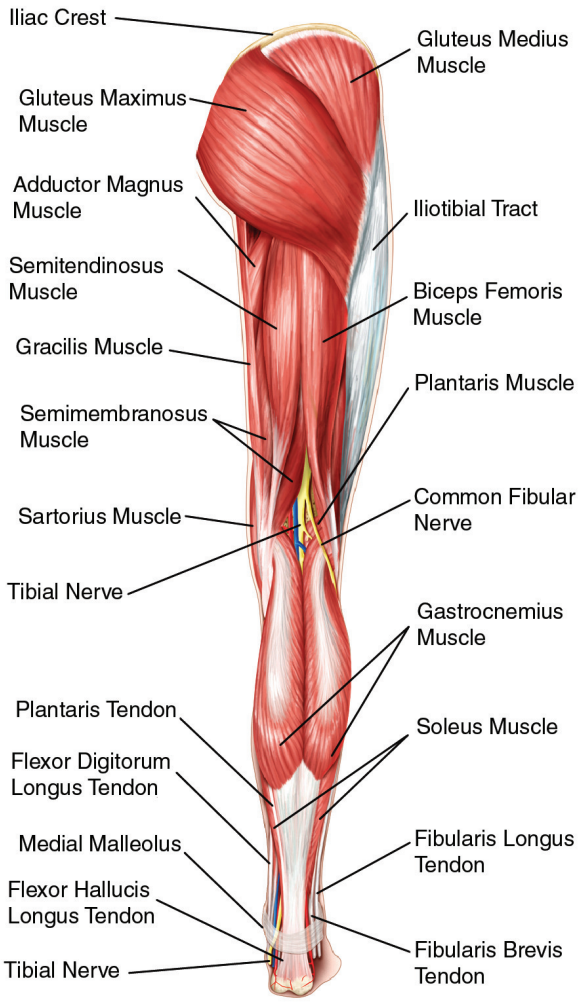


Fig. Posterior view of the Right Leg, Showing the muscles of the hip, thigh, and Lower Leg.

The movement of adduction is used to describe a direction of limb motion that serves to take the limb from a lateral position to its more-axial alignment. During a jumping-jack exercise, for example, abduction of the leg occurs when it is moved away from the midline and adduction when it is moved back towards the midline. The main abductors of the hip are the gluteus medius, gluteus minimus, and tensor fascia lata. Those three muscles also serve to internally rotate the thigh in an extended position and externally rotate the thigh in the flexed position. Another minor contributor is the piriformis. The main hip adductors are the adductor magnus, the adductor brevis, and the adductor longus. A minor contribution to hip adduction is performed by the pectineus and the gracilis.

THE UPPER LEG AND KNEE

Extension of the knee is accomplished by a group of muscles collectively referred to as the quadriceps femoris, which increases the angle of the knee, bringing the lower leg into a straight position. Knee extension is used in the forward, swing phase of the gait and is integral in movements such as kicking. The quadriceps femoris group includes the vastus medius, vastus lateralis, vastus intermedius, and rectus femoris. A minor contribution to knee extension is provided by the sartorius. Knee flexion refers to bending of the knee from the straight position. The muscles that perform that action oppose those of knee extension and are generally referred to as the hamstring muscles. The hamstring muscles are situated in the back of the thigh and include the biceps femoris, the semitendinosus, and the semimembranosus. Small contributions to knee flexion are made by the gastrocnemius muscle in the back of the calf and by several small muscles that cross the knee joint posteriorly.

THE LOWER LEG AND FOOT

The muscles of the lower leg and foot are complex and work in many planes. Their actions depend on whether the person is bearing weight, as well as on the position of the foot. The following paragraphs provide a brief overview of the actions of the muscles of the lower leg and foot.

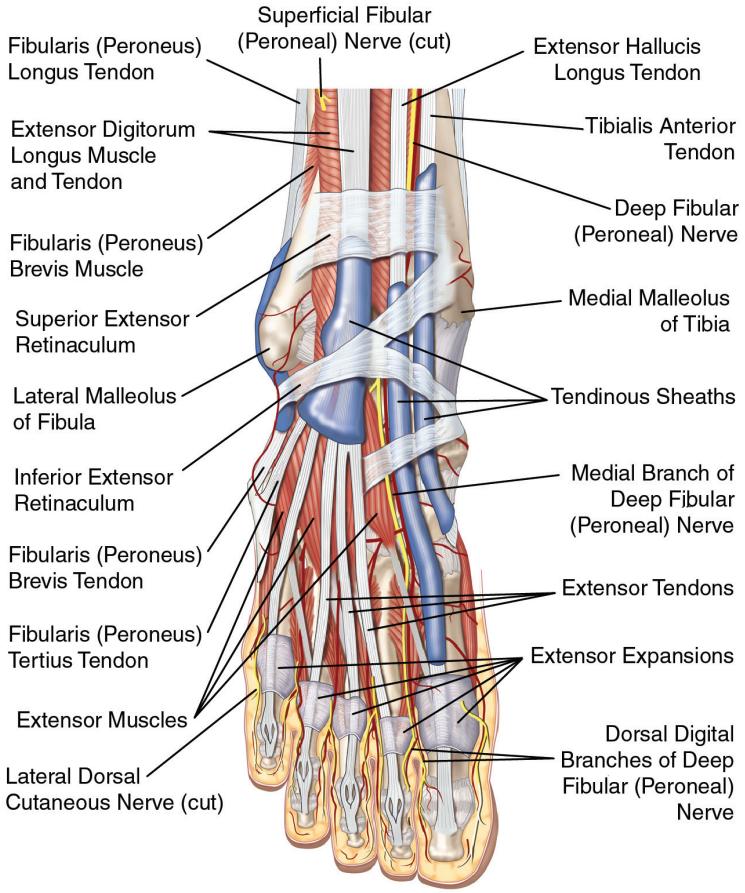


Fig. Dorsal view of the Right Foot, Showing Major Muscles, Tendons, and Nerves.

Dorsiflexion refers to ankle flexion in the direction of the dorsum, or anterior surface of the foot (the surface of the foot viewed from above). Dorsiflexion is accomplished by several muscles, including the tibialis anterior, which in addition to dorsiflexion also inverts the foot (tilts the foot towards the midline), stabilizes the foot when striking the ground, and locks the ankle when kicking. The extensor digitorum longus (EDL) also acts in dorsiflexion and functions to extend the last four toes. In addition to the EDL, some individuals also have a muscle called the peroneus tertius (fibularis tertius), which participates to a limited extent in dorsiflexion and eversion of the foot (tilting of the foot away from the midline). The extensor hallucis longus primarily acts in big toe (hallux) dorsiflexion, but it also acts to dorsiflex, as well as weakly invert, the ankle.

Plantarflexion refers to flexion of the ankle in the direction of the sole of the foot. That is most easily demonstrated by having a person stand on his or her toes. The majority of ankle plantarflexion is performed by the large calf musculature, including the gastrocnemius and the soleus, which lies just behind the gastrocnemius. It is generally accepted that those are two distinct muscles; however, there is some debate as to whether the gastrocnemius and the soleus are two parts of the same muscle.

Other muscles of the lower leg and foot include the plantaris, which runs obliquely between the gastrocnemius and the soleus; the flexor hallucis longus, which contributes to ankle flexion but is involved primarily in big toe flexion; the flexor digitorum longus, which also flexes the second to fifth toes; the peroneus longus, which flexes the ankle and everts the foot; and the peroneus brevis, which is involved in plantarflexion and eversion of the foot.

Intrinsic muscles of the foot arise in the foot and do not cross the ankle joint. Hence, their action is confined to the foot. The intrinsic muscles of the foot include the abductor hallucis, which abducts the big toe; the flexor digitorum brevis, which flexes the second to fifth toes; the abductor digiti minimi, which abducts and flexes the fifth toe; the quadratus plantae, which assists in toe flexion; the lumbricals, which flex the metatarsophalangeal (MTP) joints and extend the distal IP and proximal IP joints of the toes; the flexor hallucis brevis, which flexes the big toe; and the adductor hallucis, which flexes and contracts the big toe. The adductor hallucis has two heads, the oblique head and the transverse head, which share an insertion on the lateral (outer) side of the base of the proximal phalanx of the big toe. The oblique head arises from the base of the second to fourth metatarsal bones, and the transverse head arises from the ligaments of the MTP joints of the third to fifth toes. The flexor digiti minimi brevis extends and adducts the fifth toe. The dorsal interossei abduct the toes, and the plantar interossei adduct the toes.

EVOLUTIONARY CONTEXT

The arrangement of striated muscle in modern humans conforms to the basic plan seen in all pronograde quadrupedal vertebrates and mammals (that is, all vertebrates and mammals that assume a horizontal and four-legged posture).

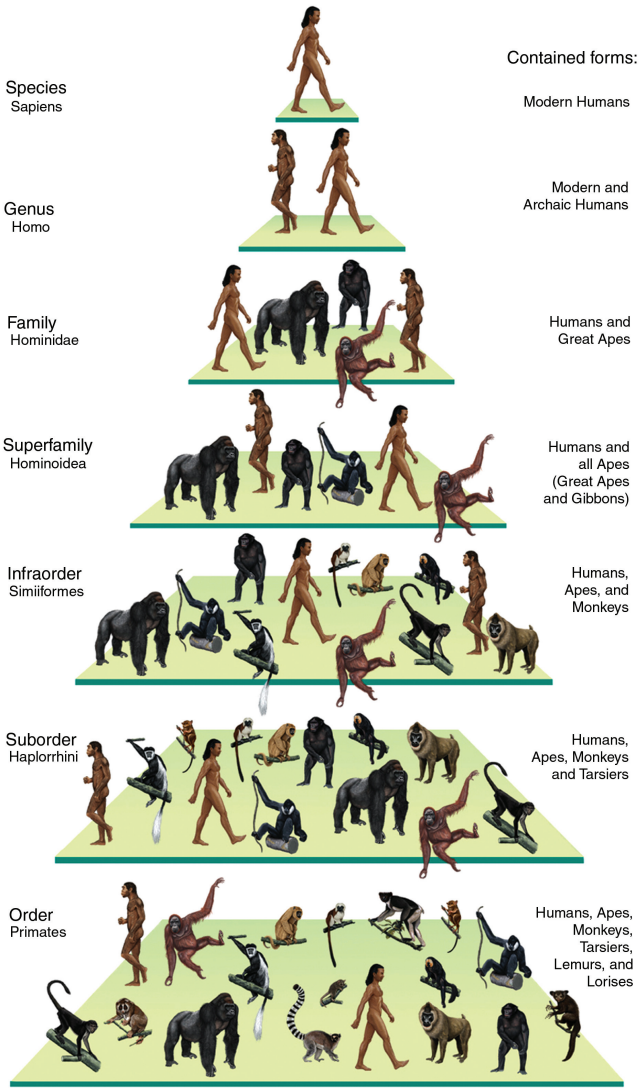


Fig. Classification of Homo Sapiens within the order Primates.

The primates (the order of mammals to which humans belong) inherited the primitive quadrupedal stance and locomotion, but since their appearance in the Late Cretaceous Period some 65 million years ago, several groups have modified their locomotor system to concentrate on the use of the arms for propulsion through the trees. The most-extreme expression of that skeletal adaptation in living primates is seen in the modern gibbonfamily. Their forelimbs are relatively elongated; they hold their trunk erect; and, for the short periods that they spend on the ground, they walk only on their hind limbs (in a bipedal fashion).

Modern humans are most closely related to the living great apes: the chimpanzee, the gorilla, and the orangutan. The human's most-distant relative in the group, the orangutan, has a locomotor system that is adapted for moving among the vertical tree trunks of the Asian rainforests. It grips the trunks equally well with both fore and hind limbs and was at one time aptly called quadrumanal, or "four-handed."

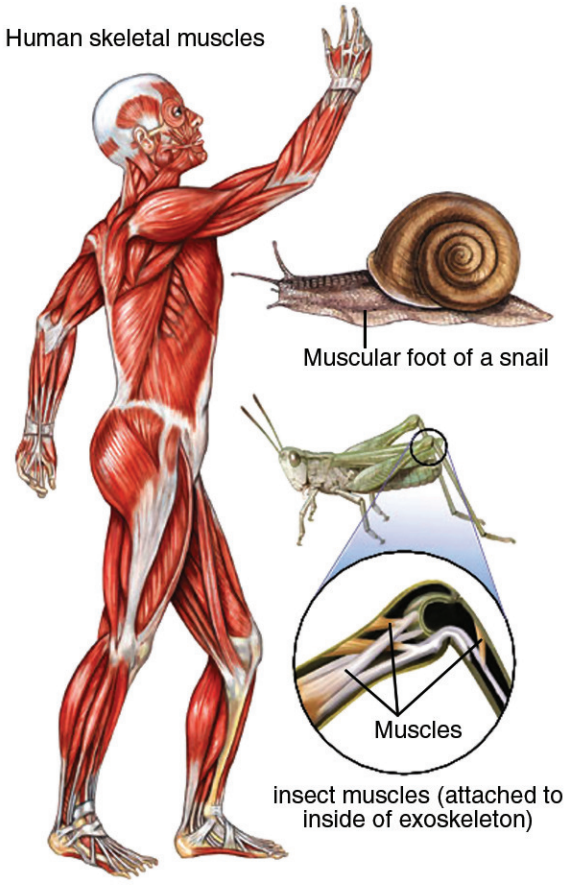


Fig. Lateral view of human muscle system, with insect and mollusk for comparison.

There is little direct fossil evidence about the common ancestor of modern humans, chimpanzees, and gorillas, so inferences about its habitat and locomotion must be made. The ancestor was most likely a relatively generalized tree-dwelling animal that could walk quadrupedally along branches as well as climb between them. From such an ancestor, two locomotor trends were apparently derived. In one, which led to the gorillas and the chimpanzees, the forelimbs became elongated, so when those modern animals come to the ground, they support their trunks by placing the knuckles of their outstretched forelimbs on the ground. The second trend involved shortening the trunk, relocating the shoulder blades, and, most important, steadily increasing the emphasis on hind-limb support and truncal erectness. In other words, that trend saw the achievement of an upright bipedal, or orthograde, posture instead of a quadrupedal, or pronograde, one. The upright posture probably was quite well established by 3 million to 3.5 million years ago, as evidenced both by the form of the limb bones and by the preserved footprints of early hominins found from that time.

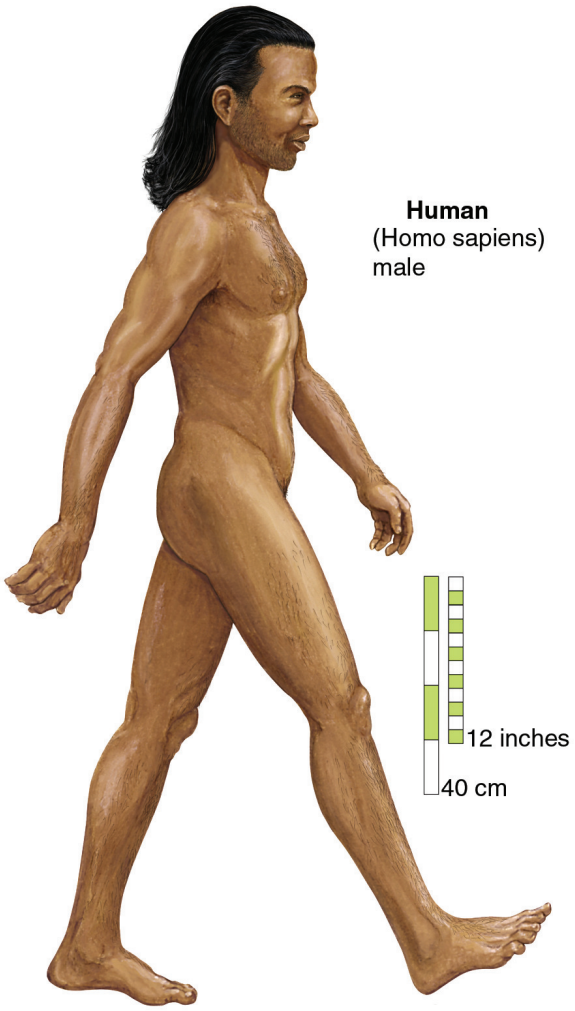


Fig. Human being (*Homo Sapiens*), Male.

CHANGES IN THE MUSCLES OF THE LOWER LIMB

The major muscular changes directly associated with the shift to bipedal locomotion are seen in the lower limb. The obvious skeletal changes are in the length of the hind limb, the development of the heel, and the change in the shape of the knee joint so that its surface is flat and not evenly rounded. The hind limbs of apes are relatively short for their body size compared with modern human proportions.

The changes that occurred in the bones of the pelvis are not all directly related to the shift in locomotion, but they are a consequence of it. Bipedality, by freeing the hands from primary involvement with support and locomotion, enabled the development of manual dexterity and thus the manufacture and use of tools, which has been linked to the development in human ancestors of language and other intellectualcapacities. The result is a substantially enlarged brain. Large brains clearly affect the form of the skull and thus the musculature of the head and neck. A larger brain also has a direct effect on the pelvis because of the need for a wide pelvic inlet and outlet for the birth of relatively large-brained young. A larger pelvic cavity means that the hip joints have to be farther apart. Consequently, the hip joints are subjected to considerable forces when weight is taken on one leg, as it has to be in walking and running.

To counteract that, the muscles (gluteus minimus and gluteus medius) that are used by the chimpanzee to push the leg back (hip extensors) have shifted in modern humans in relation to the hip joint so that they now act as abductors to balance the trunk on the weight-bearing leg during walking.

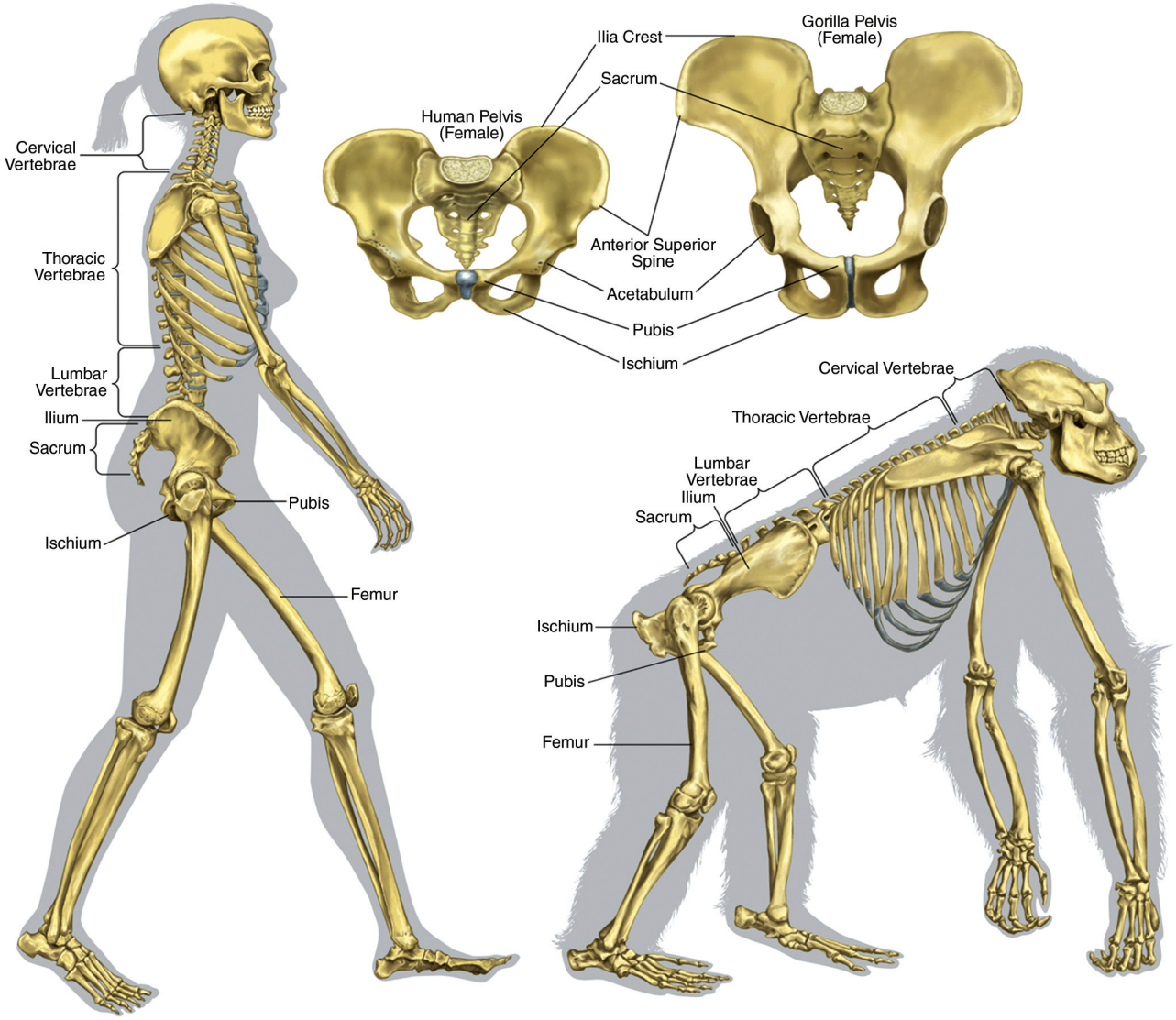


Fig. The skeletal structure of a human being (left) and of a gorilla (right). Several differences allow the human being to walk erect on two legs with a striding gait rather than move in a knuckle-walking fashion like the gorilla. In the pelvis these differences include shorter ischia, a broader sacrum, and broader, curved-in ilia with a lower iliac crest. In the legs the femurs (thighbones) are relatively long and are set farther apart at the hips than they are at the knees.

Part of a third climbing muscle (gluteus maximus) also assists in abduction as well as in maintaining the knee in extension during weight bearing. The gluteal muscles are also responsible for much of the rotation of the hip that has to accompany walking. When the right leg is swung forward and the right foot touches the ground, the hip joint of the same side externally rotates, whereas that of the opposite side undergoes a similar amount of internal rotation. Both of those movements are made possible by rearrangements of the muscles crossing the hip. The bones of the trunk and the lower limb are so arranged in modern humans that standing upright requires a minimum of muscle activity. Some muscles, however, are essential to maintaining balance, and the extensors of the knee have been rearranged and realigned, as have the muscles of the calf. The foot is often but erroneously considered to be a poor relation of the hand. Although the toes in modern humans are normally incapable of useful independent movement, the flexor muscles of the big toe are developed to provide the final push off in the walking cycle. Muscles of all three compartments of the modern human lower leg contribute to making the foot a stable platform, which non-etheless can adapt to walking over rough and sloping ground.

CHANGES IN THE MUSCLES OF THE UPPER LIMB

The human upper limb has retained an overall generalized structure, with its details adapted to upright existence. Among the primitive features that persist are the clavicle, or collarbone, which still functions as part of the shoulder; the ability to twist one of the forearm bones (the radius) around the other (the ulna) so that the palm is turned forward or backward, a process called pronation and supination; and a full complement of five digits in the hand.

Pronation and supination of the forearm, which allows the palm of the hand to rotate 180°, is not peculiar to humans. That movement depends upon the possession of both a small disk in the wrist joint and an arrangement of the muscles such that they can rotate the radius to and fro. Both the disk and the muscle arrangement are present in the great apes.

In quadrupedal animals the thorax (chest) is suspended between the shoulder blades by a muscular hammock formed by the serratus anterior muscle. In upright sitting and standing, however, the shoulder girdle is suspended from the trunk. The scapula, or shoulder blade, floats over the thoracic surface by reason of the arrangement of the fibres of the serratus anterior muscle and the support against gravity that is provided by the trapezius, rhomboid, and levator scapulae muscles. When the arms are required to push forward against an object at shoulder level, their action is reminiscent of quadrupedal support.

The change in shape of the chest to emphasize breadth rather than depth altered the relation of muscles in the shoulder region, with an increase in size of the latissimus dorsi muscle and the pectoralis major muscle. The human pectoralis minor muscle has forsaken its attachment to the humerus, the long bone of the upper arm, and presumably derives some stability from attaching to the coracoid process, a projection from the scapula, instead of gliding over it.

The hand of a chimpanzee is dexterous, but the proportions of the digits and the rearrangement and supplementation of muscles are the major reasons for the greater manipulative ability of the hand of a modern human. Most of those changes are concentrated on the thumb. For example, modern humans are the only living hominids to have a separate long thumb flexor, and the short muscle that swings the thumb over towards the palm is particularly well developed in humans. That contributes to the movement of opposition that is crucial for the so-called precision grip—*i.e.*, the bringing together of the tips of the thumb and forefinger.

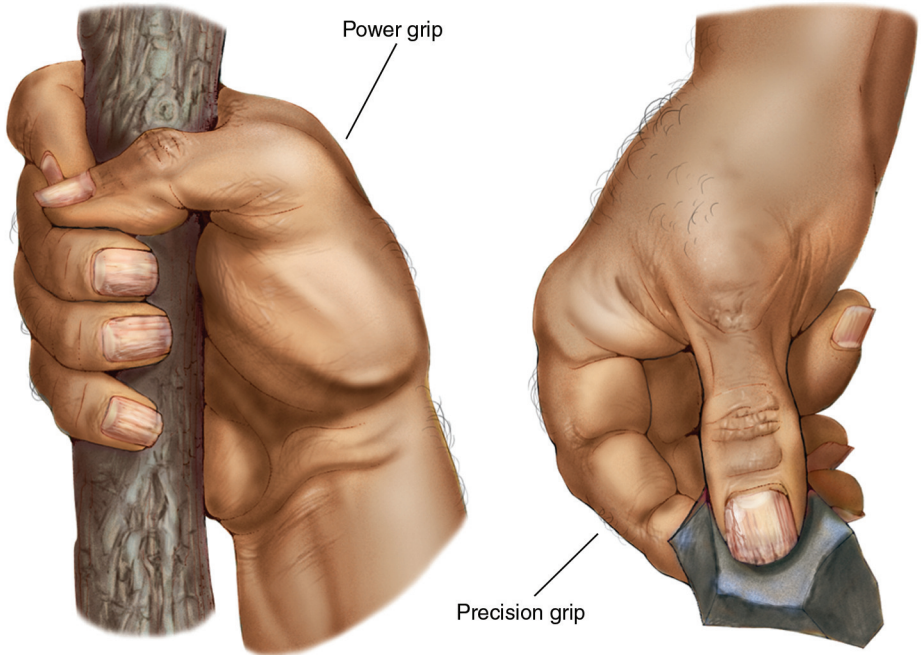


Fig. A Fully Opposable thumb gives the Human hand its Unique Power Grip (left) and Precision Grip (Right).

CHANGES IN THE MUSCLES OF THE HEAD AND NECK

The muscle group of the head and neck is most directly influenced by the change to an upright posture. That group comprises the muscles of the back (nape) and side of the neck. Posture is not the only influence on those muscles, for the reduction in the size of the jaws in modern humans also contributes to the observed muscular differences. Generally, those involve the reduction in bulk of nuchal (nape) muscles. In the upright posture the head is more evenly balanced on the top of the vertebral column, so less muscle force is needed, whereas in a pronograde animal with large jaws the considerable torque developed at the base of the skull must be resisted by muscle force. The poise of the human head does pose other problems, and the detailed attachment and role of some neck muscles (*e.g.*, sternocleidomastoid) are different in humans from those in apes.

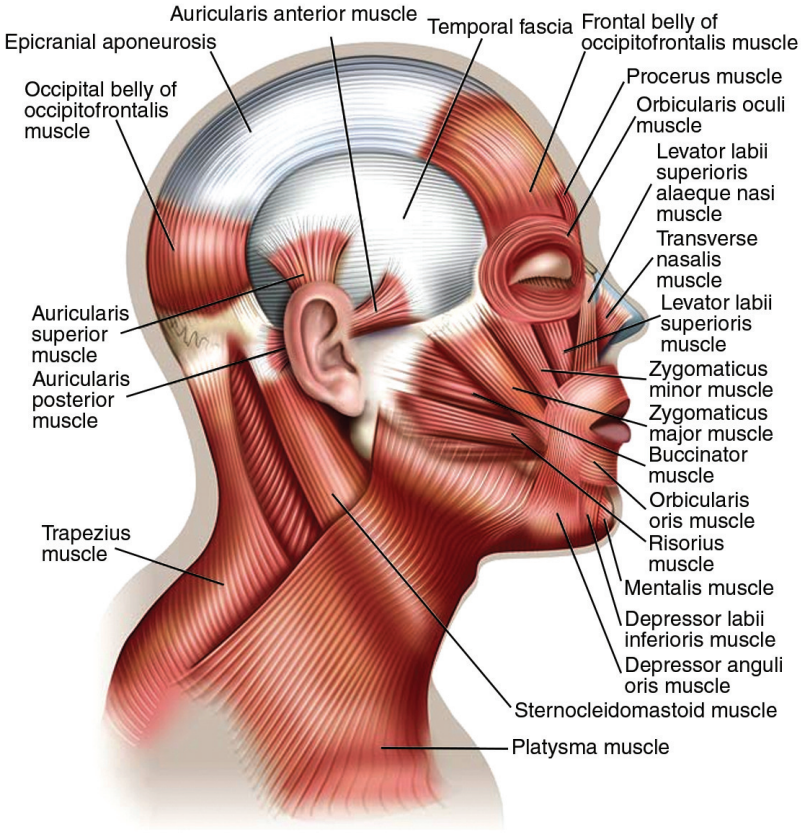


Fig. Muscles of Facial Expression.

CHANGES IN THE MUSCLES OF THE TRUNK

The consequences of an upright posture for the support of both the thoracic and the abdominal viscera are profound, but the muscular modifications in the trunk are few. Whereas in pronograde animals the abdominal viscera are supported by the ventral abdominal wall, in the orthograde posture most support comes from the pelvis. That inevitably places greater strain on the passage through the muscles of the anterior abdominal wall, the inguinal canal, which marks the route taken by the descending testicle in the male. Weakness in the canal can result in herniation.

Differences are also seen in the musculature, the levator ani, that supports the floor of the pelvis and that also controls the passage of feces. The loss of the tail in all apes has led to a major rearrangement of that muscle. There is more overlap and fusion between the various parts of the levator ani in modern humans than in apes, and the muscular sling that comprises the puborectalis in humans is more-substantial than in apes.

The muscular compression of the abdomen and the thorax that accompanies upright posture aids the vertebral column in supporting the body and in providing a firm base for upper-limb action. Anteroposterior (fore-and-aft) stability of the trunk is achieved by balancing the flexing action of gravity against back muscles that act to extend the spine. Lateral stability is enhanced by the augmented leverage provided to the spinal muscles by the broadening of the chest.

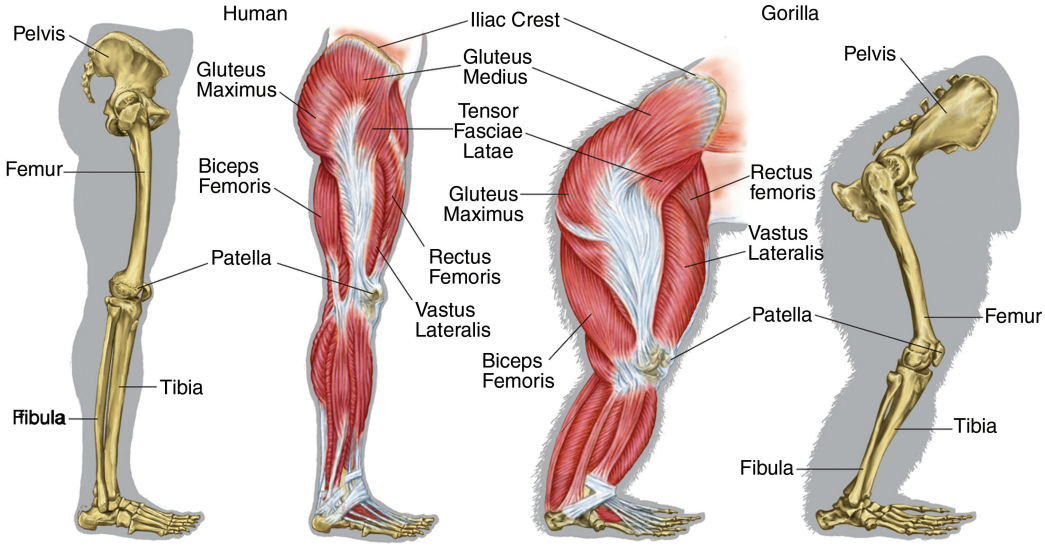


Fig. Skeletal and Muscular Structures of a Human leg (Left) and a Gorilla leg (Right).

MUSCULAR SYSTEM PHYSIOLOGY

FUNCTION OF MUSCLE TISSUE

The main function of the muscular system is movement. Muscles are the only tissue in the body that has the ability to contract and therefore move the other parts of the body. Related to the function of movement is the muscular system's second function: the maintenance of posture and body position. Muscles often contract to hold the body still or in a particular position rather than to cause movement. The muscles responsible for the body's posture have the greatest endurance of all muscles in the body—they hold up the body throughout the day without becoming tired. Another function related to movement is the movement of substances inside the body. The cardiac and visceral muscles are primarily responsible for transporting substances like blood or food from one part of the body to another. The final function of muscle tissue is the generation of body heat. As a result of the high metabolic rate of contracting muscle, our muscular system produces a great deal of waste heat. Many small muscle contractions within the body produce our natural body heat. When we exert ourselves more than normal, the extra muscle contractions lead to a rise in body temperature and eventually to sweating.

SKELETAL MUSCLES AS LEVERS

Skeletal muscles work together with bones and joints to form lever systems. The muscle acts as the effort force; the joint acts as the fulcrum; the bone that the muscle moves acts as the lever; and the object being moved acts as the load. There are three classes of levers, but the vast majority of the levers in the body are third class levers. A third class lever is a system in which the fulcrum is at the end of the lever and the effort is between the fulcrum and the load at the other end of the lever. The third class levers in the body serve to increase the distance moved by the load compared to the distance that the muscle contracts.

The tradeoff for this increase in distance is that the force required to move the load must be greater than the mass of the load. For example, the biceps brachia of the arm pulls on the radius of the forearm, causing flexion at the elbow joint in a third class lever system. A very slight change in the length of the biceps causes a much larger movement of the forearm and hand, but the force applied by the biceps must be higher than the load moved by the muscle.

MOTOR UNITS

Nerve cells called motor neurons control the skeletal muscles. Each motor neuron controls several muscle cells in a group known as a motor unit. When a motor neuron receives a signal from the brain, it stimulates all of the muscles cells in its motor unit at the same time. The size of motor units varies throughout the body, depending on the function of a muscle. Muscles that perform fine movements—like those of the eyes or fingers—have very few muscle fibres in each motor unit to improve the precision of the brain's control over these structures. Muscles that need a lot of strength to perform their function—like leg or arm muscles—have many muscle cells in each motor unit. One of the ways that the body can control the strength of each muscle is by determining how many motor units to activate for a given function. This explains why the same muscles that are used to pick up a pencil are also used to pick up a bowling ball.

CONTRACTION CYCLE

Muscles contract when stimulated by signals from their motor neurons. Motor neurons contact muscle cells at a point called the Neuromuscular Junction (NMJ). Motor neurons release neurotransmitter chemicals at the NMJ that bond to a special part of the sarcolemma known as the motor end plate. The motor end plate contains many ion channels that open in response to neurotransmitters and allow positive ions to enter the muscle fibre. The positive ions form an electrochemical gradient to form inside of the cell, which spreads throughout the sarcolemma and the T-tubules by opening even more ion channels. When the positive ions reach the sarcoplasmic reticulum, Ca^{2+} ions are released and allowed to flow into the myofibrils. Ca^{2+} ions bind to troponin, which causes the troponin molecule to change shape and move nearby molecules of tropomyosin. Tropomyosin is moved away from myosin binding sites on actin molecules, allowing actin and myosin to bind together.

ATP molecules power myosin proteins in the thick filaments to bend and pull on actin molecules in the thin filaments. Myosin proteins act like oars on a boat, pulling the thin filaments closer to the center of a sarcomere. As the thin filaments are pulled together, the sarcomere shortens and contracts. Myofibrils of muscle fibres are made of many sarcomeres in a row, so that when all of the sarcomeres contract, the muscle cells shortens with a great force relative to its size. Muscles continue contraction as long as they are stimulated by a neurotransmitter. When a motor neuron stops the release of the neurotransmitter, the process of contraction reverses itself. Calcium returns to the sarcoplasmic reticulum; troponin and tropomyosin return to their resting positions; and actin and myosin are prevented from binding. Sarcomeres return to their elongated resting state once the force of myosin pulling on actin has stopped.

Certain conditions or disorders, such as myoclonus, can affect the normal contraction of muscles. You can learn about musculoskeletal health problems in our section devoted to diseases and conditions. Also, learn more about advances in DNA health testing that help us understand genetic risk of developing early-onset primary dystonia.

TYPES OF MUSCLE CONTRACTION

The strength of a muscle's contraction can be controlled by two factors: the number of motor units involved in contraction and the amount of stimulus from the nervous system. A single nerve impulse of a motor neuron

will cause a motor unit to contract briefly before relaxing. This small contraction is known as a twitch contraction. If the motor neuron provides several signals within a short period of time, the strength and duration of the muscle contraction increases. This phenomenon is known as temporal summation. If the motor neuron provides many nerve impulses in rapid succession, the muscle may enter the state of tetanus, or complete and lasting contraction. A muscle will remain in tetanus until the nerve signal rate slows or until the muscle becomes too fatigued to maintain the tetanus.

Not all muscle contractions produce movement. Isometric contractions are light contractions that increase the tension in the muscle without exerting enough force to move a body part. When people tense their bodies due to stress, they are performing an isometric contraction. Holding an object still and maintaining posture are also the result of isometric contractions. A contraction that does produce movement is an isotonic contraction. Isotonic contractions are required to develop muscle mass through weight lifting.

Muscle tone is a natural condition in which a skeletal muscle stays partially contracted at all times. Muscle tone provides a slight tension on the muscle to prevent damage to the muscle and joints from sudden movements, and also helps to maintain the body's posture. All muscles maintain some amount of muscle tone at all times, unless the muscle has been disconnected from the central nervous system due to nerve damage.

FUNCTIONAL TYPES OF SKELETAL MUSCLE FIBRES

Skeletal muscle fibres can be divided into two types based on how they produce and use energy: Type I and Type II.

1. *Type I Fibres are very slow and Deliberate in their Contractions*: They are very resistant to fatigue because they use aerobic respiration to produce energy from sugar. We find Type I fibres in muscles throughout the body for stamina and posture. Near the spine and neck regions, very high concentrations of Type I fibres hold the body up throughout the day.
2. *Type II Fibres are Broken down into two Subgroups:* Type II A and Type II B.
   - Type II A fibres are faster and stronger than Type I fibres, but do not have as much endurance. Type II A fibres are found throughout the body, but especially in the legs where they work to support your body throughout a long day of walking and standing.
   - Type II B fibres are even faster and stronger than Type II A, but have even less endurance. Type II B fibres are also much lighter in colour than Type I and Type II A due to their lack of myoglobin, an oxygen-storing pigment. We find Type II B fibres throughout the body, but particularly in the upper body where they give speed and strength to the arms and chest at the expense of stamina.

MUSCLE METABOLISM AND FATIGUE

Muscles get their energy from different sources depending on the situation that the muscle is working in. Muscles use aerobic respiration when we call on them to produce a low to moderate level of force. Aerobic respiration requires oxygen to produce about 36-38 ATP molecules from a molecule of glucose. Aerobic respiration is very efficient, and can continue as long as a muscle receives adequate amounts of oxygen and glucose to keep contracting. When we use muscles to produce a high level of force, they become so tightly contracted that oxygen carrying blood cannot enter the muscle. This condition causes the muscle to create energy using lactic acid fermentation, a form of anaerobic respiration. Anaerobic respiration is much less efficient than aerobic respiration—only 2 ATP are produced for each molecule of glucose. Muscles quickly tire as they burn through their energy reserves under anaerobic respiration.

To keep muscles working for a longer period of time, muscle fibres contain several important energy molecules. Myoglobin, a red pigment found in muscles, contains iron and stores oxygen in a manner similar to hemoglobin

in the blood. The oxygen from myoglobin allows muscles to continue aerobic respiration in the absence of oxygen. Another chemical that helps to keep muscles working is creatine phosphate. Muscles use energy in the form of ATP, converting ATP to ADP to release its energy. Creatine phosphate donates its phosphate group to ADP to turn it back into ATP in order to provide extra energy to the muscle. Finally, muscle fibres contain energy-storing glycogen, a large macromolecule made of many linked glucoses. Active muscles break glucoses off of glycogen molecules to provide an internal fuel supply.

When muscles run out of energy during either aerobic or anaerobic respiration, the muscle quickly tires and loses its ability to contract. This condition is known as muscle fatigue. A fatigued muscle contains very little or no oxygen, glucose or ATP, but instead has many waste products from respiration, like lactic acid and ADP. The body must take in extra oxygen after exertion to replace the oxygen that was stored in myoglobin in the muscle fibre as well as to power the aerobic respiration that will rebuild the energy supplies inside of the cell. Oxygen debt (or recovery oxygen uptake) is the name for the extra oxygen that the body must take in to restore the muscle cells to their resting state. This explains why you feel out of breath for a few minutes after a strenuous activity—your body is trying to restore itself to its normal state.

AXIAL MUSCLES OF THE HEAD NECK AND BACK

MUSCLES OF FACIAL EXPRESSION

The muscles of facial expression originate from the surface of the skull or the fascia (connective tissue) of the face. The insertions of these muscles have fibres intertwined with connective tissue and the dermis of the skin. Because the muscles insert in the skin rather than on bone, when they contract, the skin moves to create facial expression.

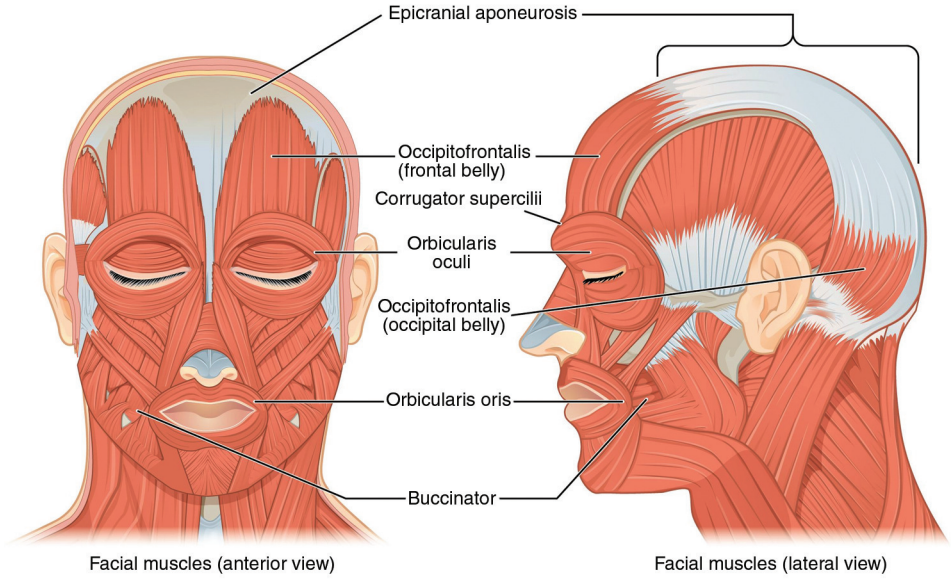


Fig. Muscles of Facial Expression. Many of the muscles of facial expression insert into the skin surrounding the eyelids, nose and mouth, producing facial expressions by moving the skin rather than bones.

The orbicularis oris is a circular muscle that moves the lips, and the orbicularis oculi is a circular muscle that closes the eye. The occipitofrontalis muscle elevates the scalp and eyebrows. The muscle has a frontal belly and an occipital belly (near the occipital bone on the posterior part of the skull). In other words, there is a muscle on the forehead (frontalis) and one on the back of the head (occipitals). The two bellies are connected by a broad tendon called the epicranial aponeurosis, or galea aponeurosis (galea = "apple"). The physicians originally studying human anatomy thought the skull looked like an apple.

The buccinator muscle compresses the cheek. This muscle allows you to whistle, blow, and suck; and it contributes to the action of chewing. There are several small facial muscles, one of which is the corrugator supercilii, which is the prime mover of the eyebrows. Place your finger on your eyebrows at the point of the bridge of the nose. Raise your eyebrows as if you were surprised and lower your eyebrows as if you were frowning. With these movements, you can feel the action of the corrugator supercilli.

Table: Muscles in Facial Expression.

Muscle	Origin	Insertion	Action	Innervation
Brow				
Occipito-frontalis, frontal belly	Epicraneal aponeurosis	Underneath skin of forehead	Furrowing brow	Facial nerve
Occipito-frontalis, occipital belly	Occipital bone; mastoid process (temporal bone)	Epicraneal aponeurosis	Unfurrowing brow	Facial nerve
Corrugator supercilii	Frontal bone eyebrow	Skin underneath medially and downward; frowning	Draws eyebrows	Facial nerve
Nose				
Nasalis	Maxilla	Nasal bone	Widens nostrils	Facial nerve
Mouth				
Levator labii superioris	Maxilla orbicularis oris	Underneath Skin at corners of the mouth;	Elevates upper lip	Facial nerve
Depressor labii Inferioris	Mandible	Underneath skin of lower lip	Draws lower lip downward	Facial nerve
Depressor angulus oris	Mandible	Underneath skin at corners of mouth and right	Opening mouth and sliding lower jaw left	Facial nerve
Zygomaticus major	Zygomatic bone corners of mouth (dimple area); orbicularis oris	Underneath skin at upward and laterally; smiling	Draws angle of mouth	Facial nerve
Orbicularis oris	Tissue surrounding lips	Underneath skin at corners of the mouth	Shaping of lips (as during speech)	Facial nerve
Buccinator	Maxilla, mandible; sphenoid bone (via pterygomandibular raphae)	Orbicularis oris	Lateral movement of cheeks (e.g., sucking on a straw; also used to compress air in mouth while blowing)	Facial nerve
Risorius	Fascia of parotid salivary gland	Underneath skin at corners of the mouth	Draws angle of mouth laterally.	Facial nerve
Mentalis	Mandible	Underneath skin of chin lower lip and skin of the chin	Elevates and protrudes	Facial nerve

MUSCLES THAT MOVE THE EYES

The movement of the eyeball is under the control of the extra ocular (extrinsic) eye muscles, which originate from the bones of the orbit and insert onto the outer surface of the white of the eye. These muscles are located inside the eye socket and cannot be seen on any part of the visible eyeball. If you have ever been to a doctor who held up a finger and asked you to follow it up, down, and to both sides, he or she is checking to make sure your eye muscles are acting in a coordinated pattern.

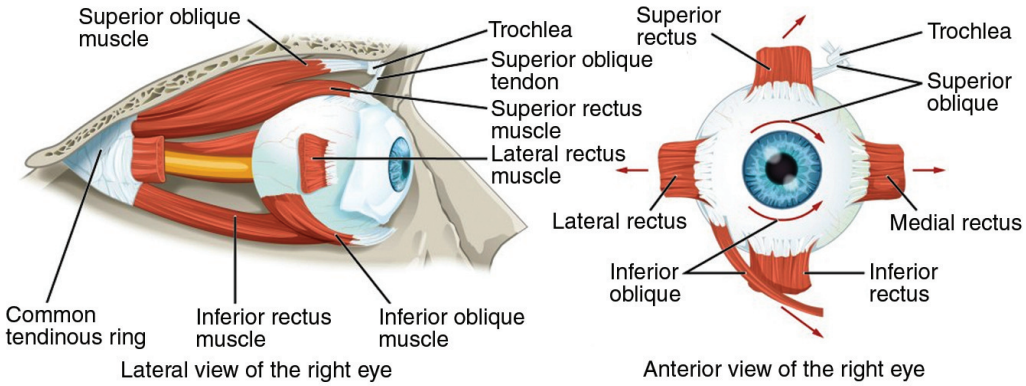


Fig. Muscles of the Eyes. (a) The extraocular eye muscles originate outside of the eye on the skull. (b) Each muscle inserts onto the eyeball.

Table: Muscles of the Eyes

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Moves eyes up and towards nose; rotates eyes from 1 O'clock to 3 o'clock	Eyeballs	Superior (elevates); medial (adducts)	Superior rectus	Common tendinous ring (ring attaches to optic foramen)	Superior surface of eyeball
Moves eyes down and towards nose; rotates eyes from 6 o'clock to 3 o'clock	Eyeballs	Inferior (depresses); medial (adducts)	Inferior rectus	Common tendinous ring (ring attaches to optic foramen)	Inferior surface of eyeball
Moves eyes away from nose	Eyeballs	Lateral (abducts)	Lateral rectus	Common tendinous ring (ring attaches to optic foramen)	Lateral surface of eyeball
Moves eyes towards nose	Eyeballs	Medial (adducts)	Medial rectus	Common tendinous ring (ring attaches to optic foramen) eyeball	Medial surface of eyeballs
Moves eyes up and away from nose; rotates eyeball from 12 o'clock to 9 o'clock	Eyeballs	Superior (elevates); lateral (abducts)	Inferior oblique	Floor of orbit (maxilla)	Surface of eyeball between inferior rectus and lateral rectus
Moves eyes down and away from nose; rotates eyeball from 6 o'clock to 9 o'clock	Eyeballs	Superior (elevates); lateral (abducts)	Superior oblique	Sphenoid bone	Suface of eyeball between superior rectus and lateral rectus
Opens eyes	Upper eyelid	Superior (elevates)	Levator palpabrae superioris	Roof of orbit (sphenoid bone)	Skin of upper eyelids
Closes eyelids	Eyelid skin	Compression along superior-inferior axis	Orbicularis oculi	Medial bones composing the orbit	Circumference of orbit

MUSCLES THAT MOVE THE LOWER JAW

In anatomical terminology, chewing is called mastication. Muscles involved in chewing must be able to exert enough pressure to bite through and then chew food before it is swallowed. The masseter muscle is the prime mover muscle for chewing because it elevates the mandible (lower jaw) to close the mouth, and it is assisted by the temporalis muscle, which retracts the mandible. You can feel the temporalis move by putting your fingers to your temple as you chew. The medial pterygoid and lateral pterygoid muscles provide assistance in chewing and moving food within the mouth by moving the mandible laterally and medially to grind food between the molars.

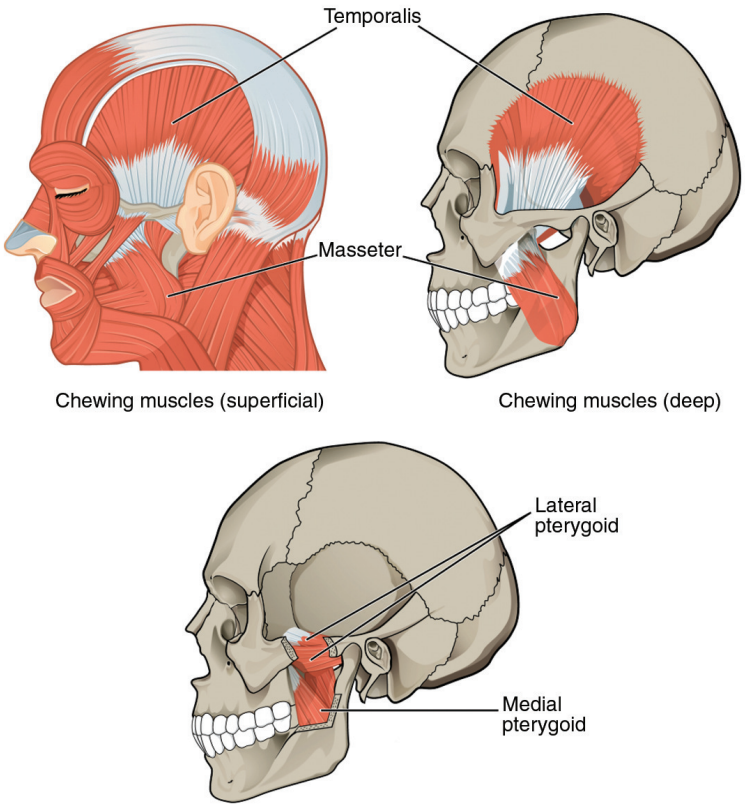


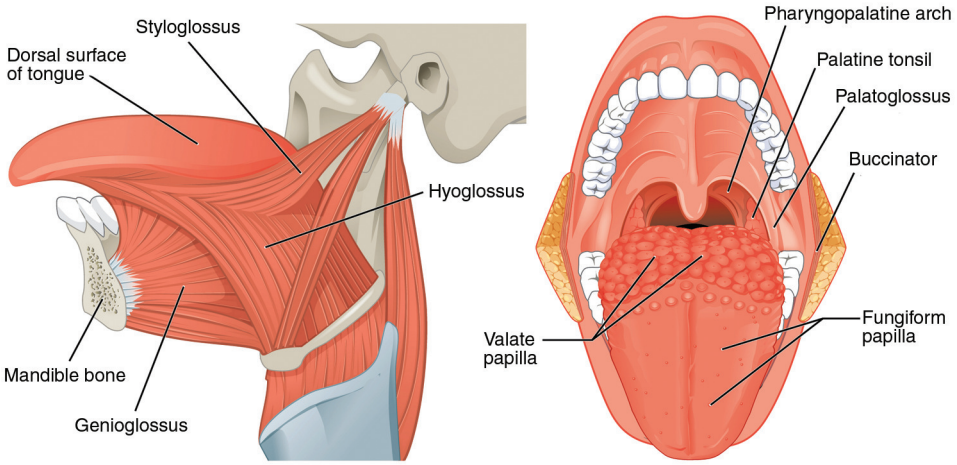
Fig. Muscles That Move the Lower Jaw. The muscles that move the lower jaw are typically located within the cheek and originate from processes in the skull. This provides the jaw muscles with the large amount of leverage needed for chewing.

Table: Muscles of the Lower Jaw.

Movement	Target	Target Motion Direction	Prime mover	Origin	Insertion
Closes mouth; aids chewing	Mandible	Superior (elevates)	Masseter	Maxilla arch; zygomatic arch (for masseter)	Mandible
Closes mouth; pulls lower jaw in under upper jaw	Mandible	Superior (elevates); posterior (retracts)	Temporalis	Temporal bone	Mandible
Opens mouth; pushes lower jaw out under upper jaw; moves lower jaw side-to-side	Mandible	Inferior (depresses); posterior (protracts); lateral (abducts); medial (adducts)	Lateral pterygoid	Pterygoid process of sphenoid bone	Mandible
Closes mouth; pushes lower jaw out under upper jaw; moves lower jaw side-to--side	Mandible	Superior (elevates); posterior (protracts); lateral (abducts); medial (adducts)	Medial pterygoid	Sphenoid bone; maxilla	Mandible; temporo-mandibular joint

MUSCLES THAT MOVE THE TONGUE

Although the tongue is obviously important for tasting food, it is also necessary for mastication, deglutition(swallowing), and speech. Because of its mobility, the tongue facilitates complex speech patterns and sounds.



(a) Extrinsic tongue muscles (b) Palatoglossus and surface of tongue

Fig. Muscles that Move the Tongue.

Table: Muscles for Tongue Movement, Swallowing, and Speech.

Muscle	Origin	Insertion	Movement	Innervation
Tongue				
Genioglossus	Mandible	Tongue undersurface; hyoid bone	Moves tongue down; sticks tongue out of mouth	Hypoglossal nerve
Styloglossus	Temporal bone (styloid process)	Tongue undersurface and sides	Moves tongue up; retracts tongue back into mouth Flattens tongue	Hypoglossal nerve
Hyoglossus	Hyoid bone	Sides of tongue		Hypoglossal nerve
Palatoglossus	Soft palate	Side of tongue	Bulges tongue	Accessory and vagus nerves

Muscle	Origin	Insertion	Movement	Innervation
Swallowing and Speaking				
Digastric	Mandible; temporal bone	Hyoid bone	Raises the hyoid bone in a way that also raises the larynx, allowing the epiglottis to cover the glottis during deglutition; also assists in opening the mouth by depressing the mandible	Posterior belly: facial nerve Anterior belly mylohyoid nerve
Stylohyoid	Temporal bone (styloid process)	Hyoid bone	Raises and retracts the hyoid bone in a way that elongates the oral cavity during deglutition	Facial nerve
Mylohyoid	Mandible	Hyoid bone; median raphe	Raises hyoid bone in a way that presses tongue against the roof of the mouth, pushing food back into the pharynx during deglutition	Mylohyoid nerve
Geniohyoid	Mandible	Hyoid bone	Raises and moves hyoid bone forward, widening pharynx during deglutition	Spinal nerve C1 via hypoglossal nerve
Omohyoid	Scapula	Hyoid bone	Retracts hyoid bone and moves it down during later phases of deglutition	Ansa cervicalis
Sternohyoid	Clavicle	Hyoid bone	Depresses the hyoid bone during swallowing and speaking	Ansa cervicalis
Thyrohyoid	Thyroid cartilage	Hyoid bone	Shrinks distance between thyroid cartilage and hyoid bone, allowing production of high-pitch vocalizations	Spinal nerve C1 via hypoglossal nerve

Sternothyroid	Sternum	Thyroid cartilage	Depresses larynx, thyroid cartilage, and hyoid bone to create different vocal tones	Ansa cervicalis
Sternocleid-omastoid;	Sternum; clavicle	Temporal bone (mastoid process); occipital bone	Rotates and tilts head to he side; tilts head forward	Accessory nerve and spinal nerves C2-C3
Semispinalis capitis	C5-C8; T1-T6	Occiput between the superior and inferior nuchal line	Extends and rotates the head	Posterior rami of middle cervical and thoracic nerves
Splenius capitis;	Nuchal line; spinous process of C7-T3	Superior nuchal line, Mastoid process	Rotates and tilts head to the side; tilts head backwards	Posterior rami of middle cervical nerves
Longissimus capitis	T1-T5; C4-C7	Posterior margin of mastoid process and temporal bone	Extends and hyperextends head; flexes and rotates the head ipsilaterally	Dorsal rami of cervical and thoracic nerves (C6 to T4)

Tongue muscles can be extrinsic or intrinsic. Extrinsic tongue muscles insert into the tongue from outside origins, and the intrinsic tongue muscles insert into the tongue from origins within it. The extrinsic muscles move the whole tongue in different directions, whereas the intrinsic muscles allow the tongue to change its shape (such as, curling the tongue in a loop or flattening it).

The extrinsic muscles all include the word root glossus (glossus = "tongue"), and the muscle names are derived from where the muscle originates. The genioglossus (genio = "chin") originates on the mandible and allows the tongue to move downward and forward. The styloglossus originates on the styloid process of the temporal bone, and allows upward and backward motion. The palatoglossus originates on the soft palate to elevate the back of the tongue, and the hyoglossus originates on the hyoid bone to move the tongue downward and flatten it.

MUSCLES OF THE ANTERIOR NECK

The muscles of the anterior neck assist in deglutition (swallowing) and speech by controlling the positions of the larynx (voice box), and the hyoid bone, a horseshoe-shaped bone that functions as a foundation on which the tongue can move. The muscles of the neck are categorized according to their position relative to the hyoid bone. Suprahyoid muscles are superior to it, and the infrahyoid muscles are located inferiorly.

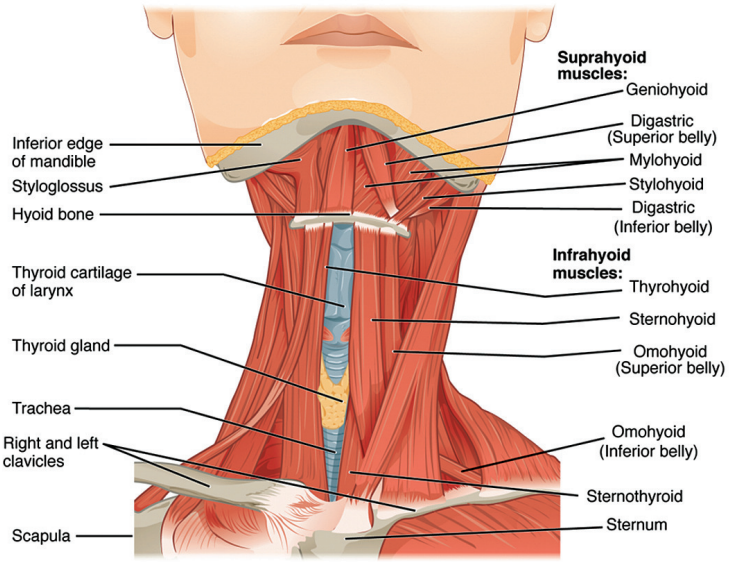


Fig. Muscles of the Anterior Neck. The anterior muscles of the neck facilitate swallowing and speech. The suprahyoid muscles originate from above the hyoid bone in the chin region. The infrahyoid muscles originate below the hyoid bone in the lower neck.

The suprahyoid muscles raise the hyoid bone, the floor of the mouth, and the larynx during deglutition. These include the digastric muscle, which has anterior and posterior bellies that work to elevate the hyoid bone and larynx when one swallows; it also depresses the mandible. The stylohyoid muscle moves the hyoid bone posteriorly, elevating the larynx, and the mylohyoid muscle lifts it and helps press the tongue to the top of the mouth. The geniohyoid depresses the mandible in addition to raising and pulling the hyoid bone anteriorly.

The strap-like infrahyoid muscles generally depress the hyoid bone and control the position of the larynx. The omohyoid muscle, which has superior and inferior bellies, depresses the hyoid bone in conjunction with the sternohyoid and thyrohyoid muscles. The thyrohyoid muscle also elevates the larynx's thyroid cartilage, whereas the sternothyroid depresses it.

MUSCLES THAT MOVE THE HEAD

The head is balanced, moved and rotated by the neck muscles. When these muscles act unilaterally, the head rotates. When they contract bilaterally, the head flexes or extends. The major muscle that laterally flexes and rotates the head is the sternocleidomastoid. In addition, both muscles working together are the flexors of the head. Place your fingers on both sides of the neck and turn your head to the left and to the right. You will feel the movement originate there. This muscle divides the neck into anterior and posterior triangles when viewed from the side.

Table: Muscles that Move the Head.

Movement	Target	Target motion direction	Prime mover	Origin	Insertion
Rotates and tilts head to the side; tilts head forward	Skull; vertebrae	Individually: rotates head to opposite side; bilaterally: flexion	Sternocleidomastoid	Sternum; clavicle	Temporal bone (mastoid process); occipital bone
Rotates and tilts head backward	Skull; vertebrae	Individually: laterally flexes and rotates head to same side; bilaterally: extension	Semispinalis capitis	Transverse and articular processes of cervical and thoracic vertebra	Occipital bone
Rotates and tilts head to the side; tilts head backward	Skull; vertebrae	Individually: laterally flexes and rotates head to same side; bilaterally: extension	Splenius capitis	Spinous processes of cervical and thoracic vertebra	Temporal bone (mastoid process); occipital bone
Rotates and tilts head to the side; tilts head backward	Skull; vertebrae	Individually: laterally flexes and rotates head to same side; bilaterally: extension	Longissimus capitis	Transverse and articular processes of cervical and thoracic vertebra	Temporal bone (mastoid process)

MUSCLES OF THE POSTERIOR NECK AND THE BACK

The posterior muscles of the neck are primarily concerned with head movements, like extension. The back muscles stabilize and move the vertebral column, and are grouped according to the lengths and direction of the fascicles.

The splenius muscles originate at the midline and run laterally and superiorly to their insertions. From the sides and the back of the neck, the splenius capitis inserts onto the head region, and the splenius cervicis extends onto the cervical region. These muscles can extend the head, laterally flex it, and rotate it.

The erector spinae group forms the majority of the muscle mass of the back and it is the primary extensor of the vertebral column. It controls extension, lateral flexion, and rotation of the vertebral column, and maintains the lumbar curve. The erector spinae comprises the iliocostalis (laterally placed) group, the longissimus (intermediately placed) group, and the spinalis (medially placed) group.

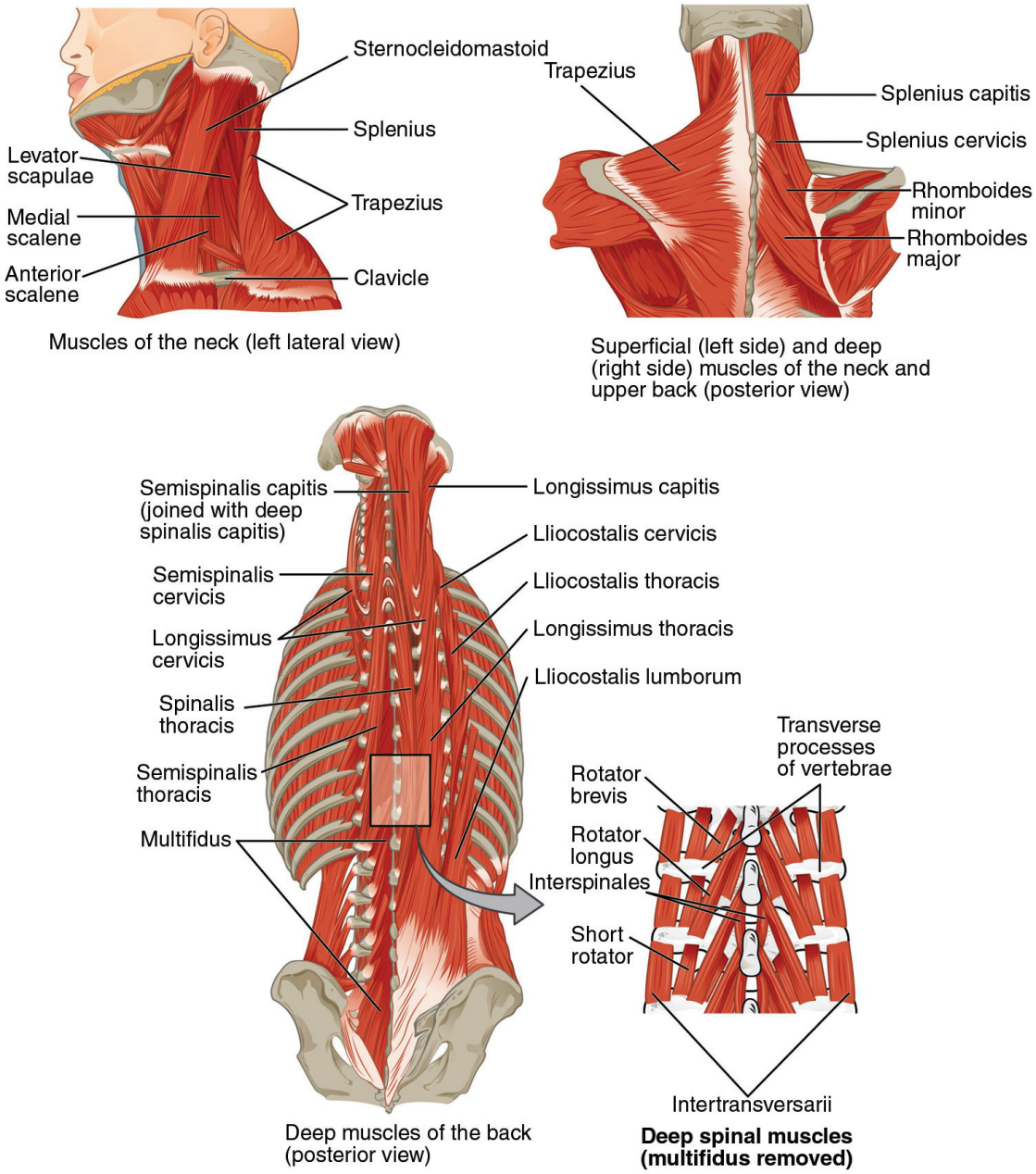


Fig. Muscles of the Neck and Back. The large, complex muscles of the neck and back move the head, shoulders, and vertebral column.

The iliocostalis group includes the iliocostalis cervicis, associated with the cervical region; the iliocostalis thoracis, associated with the thoracic region; and the iliocostalis lumborum, associated with the lumbar region. The three muscles of the longissimus group are the longissimus capitis, associated with the head region; the longissimus cervicis, associated with the cervical region; and the longissimus thoracis, associated with the thoracic region. The third group, the spinalis group, comprises the spinalis capitis (head region), the spinalis cervicis (cervical region), and the spinalis thoracis (thoracic region).

The transversospinales muscles run from the transverse processes to the spinous processes of the vertebrae. Similar to the erector spinae muscles, the semispinalis muscles in this group are named for the areas of the body with which they are associated. The semispinalis muscles include the semispinalis capitis, the semispinalis cervicis, and the semispinalis thoracis. The multifidus muscle of the lumbar region helps extend and laterally flex the vertebral column.

Important in the stabilization of the vertebral column is the segmental muscle group, which includes the interspinales and intertransversarii muscles. These muscles bring together the spinous and transverse processes of each consecutive vertebra. Finally, the scalene muscles work together to flex, laterally flex, and rotate the head. They also contribute to deep inhalation. The scalene muscles include the anterior scalene muscle (anterior to the middle scalene), the middle scalene muscle (the longest, intermediate between the anterior and posterior scalenes), and the posterior scalene muscle (the smallest, posterior to the middle scalene).

4

Cardio Vascular System

THE HEART

The heart is a muscular pumping organ located medial to the lungs along the body's midline in the thoracic region. The bottom tip of the heart, known as its apex, is turned to the left, so that about 2/3 of the heart is located on the body's left side with the other 1/3 on right. The top of the heart, known as the heart's base, connects to the great blood vessels of the body: the aorta, vena cava, pulmonary trunk, and pulmonary veins.

CIRCULATORY LOOPS

There are 2 primary circulatory loops in the human body: the pulmonary circulation loop and the systemic circulation loop:

1. Pulmonary circulation transports deoxygenated blood from the right side of the heart to the lungs, where the blood picks up oxygen and returns to the left side of the heart. The pumping chambers of the heart that support the pulmonary circulation loop are the right atrium and right ventricle.
2. Systemic circulation carries highly oxygenated blood from the left side of the heart to all of the tissues of the body (with the exception of the heart and lungs). Systemic circulation removes wastes from body tissues and returns deoxygenated blood to the right side of the heart. The left atrium and left ventricle of the heart are the pumping chambers for the systemic circulation loop.

BLOOD VESSELS

Blood vessels are the body's highways that allow blood to flow quickly and efficiently from the heart to every region of the body and back again. The size of blood vessels corresponds with the amount of blood that passes through the vessel. All blood vessels contain a hollow area called the lumen through which blood is able to flow. Around the lumen is the wall of the vessel, which may be thin in the case of capillaries or very thick in the case of arteries.

All blood vessels are lined with a thin layer of simple squamous epithelium known as the endothelium that keeps blood cells inside of the blood vessels and prevents clots from forming. The endothelium lines the entire circulatory system, all the way to the interior of the heart, where it is called the endocardium.

There are three major types of blood vessels: arteries, capillaries and veins. Blood vessels are often named after either the region of the body through which they carry blood or for nearby structures. For example, the brachiocephalic artery carries blood into the brachial (arm) and cephalic (head) regions. One of its branches, the subclavian artery, runs under the clavicle; hence the name subclavian. The subclavian artery runs into the axillary region where it becomes known as the axillary artery.

Arteries and Arterioles

Arteries are blood vessels that carry blood away from the heart. Blood carried by arteries is usually highly oxygenated, having just left the lungs on its way to the body's tissues. The pulmonary trunk and arteries of the pulmonary circulation loop provide an exception to this rule—these arteries carry deoxygenated blood from the heart to the lungs to be oxygenated.

Arteries face high levels of blood pressure as they carry blood being pushed from the heart under great force. To withstand this pressure, the walls of the arteries are thicker, more elastic, and more muscular than those of other vessels. The largest arteries of the body contain a high percentage of elastic tissue that allows them to stretch and accommodate the pressure of the heart.

Smaller arteries are more muscular in the structure of their walls. The smooth muscles of the arterial walls of these smaller arteries contract or expand to regulate the flow of blood through their lumen. In this way, the body controls how much blood flows to different parts of the body under varying circumstances. The regulation of blood flow also affects blood pressure, as smaller arteries give blood less area to flow through and therefore increases the pressure of the blood on arterial walls.

Arterioles are narrower arteries that branch off from the ends of arteries and carry blood to capillaries. They face much lower blood pressures than arteries due to their greater number, decreased blood volume, and distance from the direct pressure of the heart. Thus arteriole walls are much thinner than those of arteries. Arterioles, like arteries, are able to use smooth muscle to control their aperture and regulate blood flow and blood pressure.

Capillaries

Capillaries are the smallest and thinnest of the blood vessels in the body and also the most common. They can be found running throughout almost every tissue of the body and border the edges of the body's avascular tissues. Capillaries connect to arterioles on one end and venules on the other.

Capillaries carry blood very close to the cells of the tissues of the body in order to exchange gases, nutrients, and waste products. The walls of capillaries consist of only a thin layer of endothelium so that there is the minimum amount of structure possible between the blood and the tissues. The endothelium acts as a filter to keep blood cells inside of the vessels while allowing liquids, dissolved gases, and other chemicals to diffuse along their concentration gradients into or out of tissues.

Precapillary sphincters are bands of smooth muscle found at the arteriole ends of capillaries. These sphincters regulate blood flow into the capillaries. Since there is a limited supply of blood, and not all tissues have the same energy and oxygen requirements, the precapillary sphincters reduce blood flow to inactive tissues and allow free flow into active tissues.

Veins and Venules

Veins are the large return vessels of the body and act as the blood return counterparts of arteries. Because the arteries, arterioles, and capillaries absorb most of the force of the heart's contractions, veins and venules are subjected to very low blood pressures. This lack of pressure allows the walls of veins to be much thinner, less elastic, and less muscular than the walls of arteries. Veins rely on gravity, inertia, and the force of skeletal muscle contractions to help push blood back to the heart. To facilitate the movement of blood, some veins contain many one-way valves that prevent blood from flowing away from the heart. As skeletal muscles in the body contract, they squeeze nearby veins and push blood through valves closer to the heart. When the muscle relaxes, the valve traps the blood until another contraction pushes the blood closer to the heart. Venules are similar to arterioles as they are small vessels that connect capillaries, but unlike arterioles, venules connect to veins instead of arteries. Venules pick up blood from many capillaries and deposit it into larger veins for transport back to the heart.

CORONARY CIRCULATION

The heart has its own set of blood vessels that provide the myocardium with the oxygen and nutrients necessary to pump blood throughout the body. The left and right coronary arteries branch off from the aorta and provide blood to the left and right sides of the heart. The coronary sinus is a vein on the posterior side of the heart that returns deoxygenated blood from the myocardium to the vena cava.

HEPATIC PORTAL CIRCULATION

The veins of the stomach and intestines perform a unique function: instead of carrying blood directly back to the heart, they carry blood to the liver through the hepatic portal vein. Blood leaving the digestive organs is rich in nutrients and other chemicals absorbed from food. The liver removes toxins, stores sugars, and processes the products of digestion before they reach the other body tissues. Blood from the liver then returns to the heart through the inferior vena cava.

BLOOD

The average human body contains about 4 to 5 litres of blood. As a liquid connective tissue, it transports many substances through the body and helps to maintain homeostasis of nutrients, wastes, and gases. Blood is made up of red blood cells, white blood cells, platelets, and liquid plasma.

Red Blood Cells

Red blood cells, also known as erythrocytes, are by far the most common type of blood cell and make up about 45% of blood volume. Erythrocytes are produced inside of red bone marrow from stem cells at the astonishing rate of about 2 million cells every second. The shape of erythrocytes is biconcave—disks with a concave curve on both sides of the disk so that the center of an erythrocyte is its thinnest part. The unique shape of erythrocytes gives these cells a high surface area to volume ratio and allows them to fold to fit into thin capillaries.

Immature erythrocytes have a nucleus that is ejected from the cell when it reaches maturity to provide it with its unique shape and flexibility. The lack of a nucleus means that red blood cells contain no DNA and are not able to repair themselves once damaged. Erythrocytes transport oxygen in the blood through the red pigment hemoglobin. Hemoglobin contains iron and proteins joined to greatly increase the oxygen carrying capacity of erythrocytes. The high surface area to volume ratio of erythrocytes allows oxygen to be easily transferred into the cell in the lungs and out of the cell in the capillaries of the systemic tissues.

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.

Platelets

Also known as thrombocytes, platelets are small cell fragments responsible for the clotting of blood and the formation of scabs. Platelets form in the red bone marrow from large megakaryocyte cells that periodically rupture and release thousands of pieces of membrane that become the platelets. Platelets do not contain a nucleus and only survive in the body for up to a week before macrophages capture and digest them.

Plasma

Plasma is the non-cellular or liquid portion of the blood that makes up about 55% of the blood's volume. Plasma is a mixture of water, proteins, and dissolved substances. Around 90% of plasma is made of water, although the exact percentage varies depending upon the hydration levels of the individual. The proteins within plasma include antibodies and albumins. Antibodies are part of the immune system and bind to antigens on the surface of pathogens that infect the body. Albumins help maintain the body's osmotic balance by providing an isotonic solution for the cells of the body. Many different substances can be found dissolved in the plasma, including glucose, oxygen, carbon dioxide, electrolytes, nutrients, and cellular waste products. The plasma functions as a transportation medium for these substances as they move throughout the body.

CARDIOVASCULAR SYSTEM PHYSIOLOGY

FUNCTIONS OF THE CARDIOVASCULAR SYSTEM

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 keep 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.

Many serious conditions and diseases can cause our cardiovascular system to stop working properly. Quite often, we don't do enough about them proactively, resulting in emergencies. Browse our content to learn more about cardiovascular health. Also, explore how DNA health testing can allow you to begin important conversations with your doctor about genetic risks for disorders involving clotting, hemophilia, hemochromatosis (a common

hereditary disorder causing iron to accumulate in the heart) and glucose-6-phosphate dehydrogenase (which affects about 1 in 10 African American men).

THE CIRCULATORY PUMP

The heart is a four-chambered "double pump," where each side (left and right) operates as a separate pump. The left and right sides of the heart are separated by a muscular wall of tissue known as the septum of the heart. The right side of the heart receives deoxygenated blood from the systemic veins and pumps it to the lungs for oxygenation. The left side of the heart receives oxygenated blood from the lungs and pumps it through the systemic arteries to the tissues of the body. Each heartbeat results in the simultaneous pumping of both sides of the heart, making the heart a very efficient pump.

REGULATION OF BLOOD PRESSURE

Several functions of the cardiovascular system can control blood pressure. Certain hormones along with autonomic nerve signals from the brain affect the rate and strength of heart contractions. Greater contractile force and heart rate lead to an increase in blood pressure. Blood vessels can also affect blood pressure. Vasoconstriction decreases the diameter of an artery by contracting the smooth muscle in the arterial wall. The sympathetic (fight or flight) division of the autonomic nervous system causes vasoconstriction, which leads to increases in blood pressure and decreases in blood flow in the constricted region. Vasodilation is the expansion of an artery as the smooth muscle in the arterial wall relaxes after the fight-or-flight response wears off or under the effect of certain hormones or chemicals in the blood. The volume of blood in the body also affects blood pressure. A higher volume of blood in the body raises blood pressure by increasing the amount of blood pumped by each heartbeat. Thicker, more viscous blood from clotting disorders can also raise blood pressure.

HEMOSTASIS

Hemostasis, or the clotting of blood and formation of scabs, is managed by the platelets of the blood. Platelets normally remain inactive in the blood until they reach damaged tissue or leak out of the blood vessels through a wound. Once active, platelets change into a spiny ball shape and become very sticky in order to latch on to damaged tissues. Platelets next release chemical clotting factors and begin to produce the protein fibrin to act as structure for the blood clot. Platelets also begin sticking together to form a platelet plug. The platelet plug will serve as a temporary seal to keep blood in the vessel and foreign material out of the vessel until the cells of the blood vessel can repair the damage to the vessel wall.

THE CARDIOVASCULAR SYSTEM (HEART AND BLOOD)

FUNCTIONS OF THE CARDIOVASCULAR SYSTEM

Blood circulates through a network of vessels throughout the body to provide individual cells with oxygen and nutrients and helps dispose of metabolic wastes. The heart pumps the blood around the blood vessels. *Functions of blood and Circulation:*

- Circulates OXYGEN and removes Carbon Dioxide.
- Provides cells with NUTRIENTS.
- Removes the waste products of metabolism to the excretory organs for disposal.
- Protects the body against disease and infection.
- Clotting stops bleeding after injury.
- Transports HORMONES to target cells and organs.
- Helps regulate body temperature.

BLOOD

Blood is made up of about 45% solids (cells) and 55% fluids (plasma). The plasma is largely water, containing proteins, nutrients, hormones, antibodies, and dissolved waste products. General types of blood cells: (each has many different sub-types):

Erythrocytes: (Red cells) are small red disk shaped cells. They contain HAEMOGLOBIN, which combines with oxygen in the lungs and is then transported to the body's cells. The haemoglobin then returns carbon dioxide waste to the lungs. Erythrocytes are formed in the bone marrow in the knobby ends of bones.

Leukocytes: (White cells) help the body fight bacteria and infection. When a tissue is damaged or has an infection the number of leukocytes increases. Leukocytes are formed in the small ends of bones. Leukocytes can be classed as granular or non- granular. There are three types of granular leukocytes (eosinophils, neutrophils, and basophils), and three types of non-granular (monocytes, T-cell lymphocytes, and B-cell lymphocytes).

Thrombocytes: (Platelets) aid the formation of blood CLOTS by releasing various protein substances. When the body is injured thrombocytes disintegrate and cause a chemical reaction with the proteins found in plasma, which eventually create a thread like substance called FIBRIN. The fibrin then "catches" other blood cells which form the clot, preventing further loss of blood and forms the basis of healing.

Blood Vessels

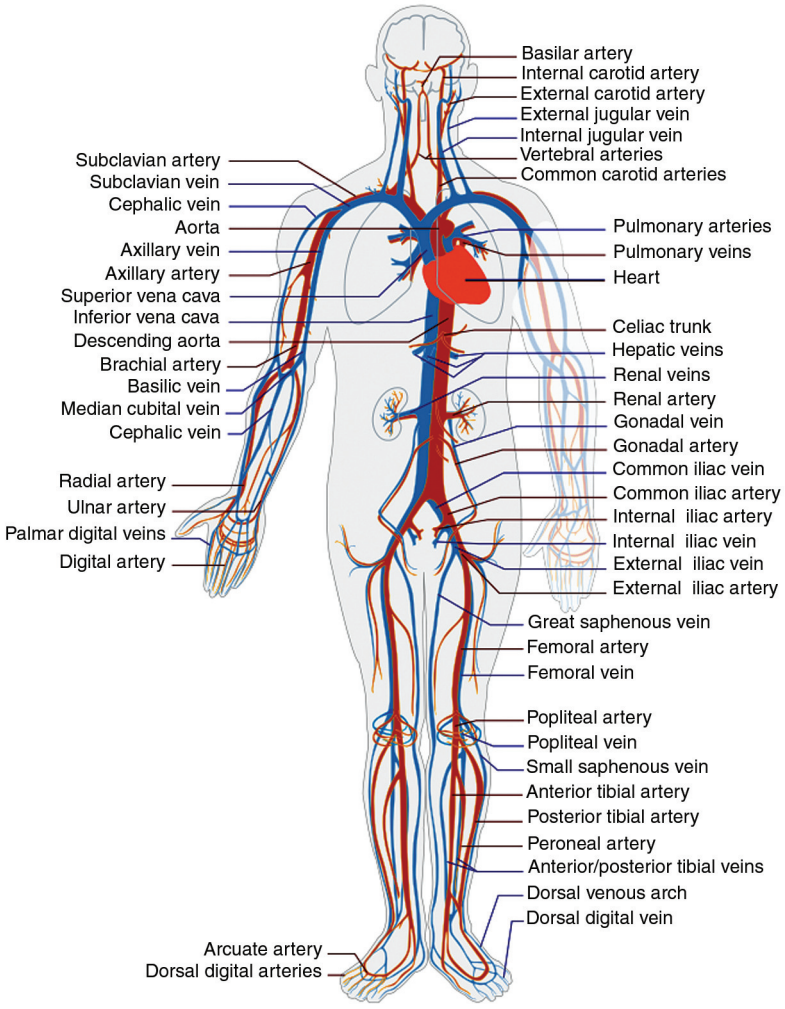


Fig. Simplified Diagram of the Circulatory System.

Arteries: Carry Oxygenated Blood away from the Heart. They are thick hollow tubes which are highly ELASTIC which allows them to DILATE (widen) and constrict (narrow) as blood is forced down them by the heart. Arteries branch and re-branch, becoming smaller until they become small ARTERIOLES which are even more elastic. Arterioles feed oxygenated blood to the capillaries. The AORTA is the largest artery in the body, taking blood from the heart, branching into other arteries that send oxygenated blood to the rest of the body.

Capillaries: Distribute the nutrients and oxygen to the body's tissues and remove deoxygenated blood and waste. They are extremely thin, the walls are only one cell thick and connect the arterioles with the venules (very small veins).

Venules: (Very small veins) merge into VEINS which carry blood back to the heart. The vein walls are similar to arteries but thinner and less elastic. Veins carry deoxygenated blood towards the lungs where oxygen is received via the pulmonary capillaries. The PULMONARY Veins then carries this oxygenated blood back to the heart.

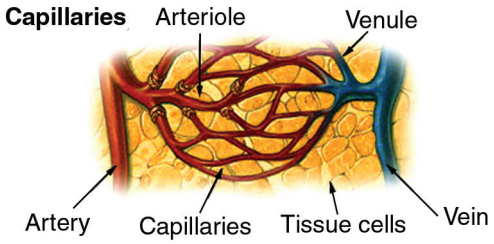


Fig. Blood vessels.

THE HEART

The heart is a hollow muscular organ which beats over 100,000 times a day to pump blood around the body's 60,000 miles of blood vessels. The right side of the heart receives blood and sends it to the lungs to be oxygenated, while the left side receives oxygenated blood from the lungs and sends it out to the tissues of the body. The Heart has three layers; the ENDOCARDIUM (inner layer), the EPICARDIUM (middle layer), and MYOCARDIUM (outer layer). The heart is protected by the PERICARDIUM which is the protective membrane surrounding it.

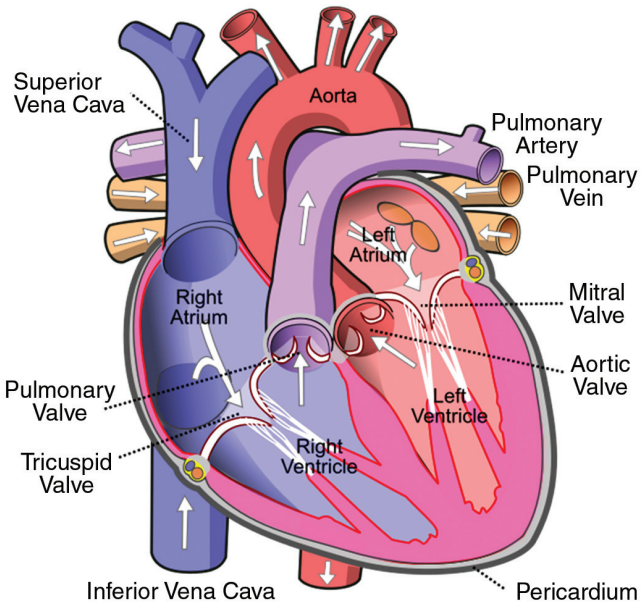


Fig. The Human Heart.

The heart has FOUR CHAMBERS, in the lower heart the right and left Ventricles, and in the upper heart the right and left Atria. In a normal heart beat the atria contract while the ventricles relax, then the ventricles contract while the atria relax. There are VALVES through which blood passes between ventricle and atrium, these close in such a way that blood does not backwash during the pauses between ventricular contractions. The right and left ventricles are divided by a thick wall (the VENTRICULAR SEPTUM), babies born with "hole in the heart" have a small gap here, which is a problem since oxygenated and deoxygenated can blood mix. The walls of the left ventricle are thicker as it has to pump blood to all the tissues, compared to the right ventricle which only pumps blood as far as the lungs.

THE SPLEEN

This is a large flat oval organ located below the diaphragm, it's main function is to STORE BLOOD. The size of the spleen can vary, for example it may enlarge when the body is fighting infection also it's size tends to decrease with age. It is a non-vital organ and it is possible to survive after removal of the spleen.

- *Perinicious Anaemia:* Is a Vitamin B12 deficiency resulting in a reduction in number of erythrocytes.
- *Aplastic Anemia:* Is a failure of the bone marrow to produce the enough red blood cells.
- *Septicaemia:* Bacterial toxins in blood.

ROOTS, SUFFIXES, AND PREFIXES

Most medical terms are comprised of a root word plus a suffix (word ending) and/or a prefix (beginning of the word). Here are some examples related to the Integumentary System.

Component	Meaning	Example
CARDIO-	Heart	Echocardiogram = sound wave image of the heart.
CYTE-	Cell	Thrombocyte = clot forming cell.
HAEM-	Blood	Haematoma - a tumour or swelling filled with blood.
THROMB-	Clot, lump	Thrombocytopenia = deficiency of thrombocytes in the blood
ETHRO-	Red	Ehtrocyte = red blood cell
LEUKO-	White	Leukocyte = white blood cell
SEP, SEPTIV-	Toxicity due to micro-organisms	Septicaemia
VAS-	Vessel/ duct	Cerebrovascular = blood vessels of the cerebrum of the brain.
HYPER-	Excessive	Hyperglycaemia = excessive levels of glucose in blood.
HYPO-	Deficient/ below	Hypoglycaemia = abnormally low glucose blood levels.
-PENIA	Deficiency	Neutropenia = low levels of neutrophilic leukocytes.
-EMIA	Condition of blood	Anaemia = abnormally low levels of red blood cells.

MAJOR FUNCTIONS OF THE CARDIOVASCULAR SYSTEM

The cardiovascular system, also known as the circulatory system, includes the heart, arteries, veins, capillaries and blood. The heart functions as the pump that moves blood through the body. The arterial circulation delivers blood from the heart to the body, and the venous circulation carries it back to the heart. Capillaries are tiny blood vessels at the interface of the arterial and venous circulation where exchange of substances between the blood and body tissues occurs. The cardiovascular system serves several major functions that are necessary for life.

OXYGEN AND CARBON DIOXIDE TRANSPORT

Supplying oxygen to the body is the most essential function of the cardiovascular system. Although all cells require oxygen, brain cells are the most sensitive and begin to die in as little as 3 minutes if deprived of oxygen.

During inhalation, air enters the lungs and oxygen is absorbed through the air sacs into the bloodstream. This oxygen-rich blood is pumped through the heart into the arterial circulation. In the capillaries, oxygen diffuses out of the blood and into the cells of the body's organs and tissues. At the same time, carbon dioxide—a waste product produced by cells—is absorbed into the blood and transported to the lungs through the venous circulation. When this oxygen-poor blood reaches the lungs, carbon dioxide diffuses through the air sacs and is then exhaled. This cycle occurs with every breath.

NUTRIENT AND WASTE PRODUCT TRANSPORT

Delivering nutrients to the body is another critical function of the cardiovascular system. After food is digested in the stomach and intestines, its component nutrients are absorbed into the bloodstream. These nutrients include sugars, fats, vitamins, minerals and protein building blocks called amino acids. Each of these nutrients is vital to healthy body function. For example, the sugar glucose is the body's primary fuel to generate energy, and amino acids enable the body to manufacture new cells. Like oxygen, nutrients diffuse from the bloodstream into body cells via the capillaries. In addition to carbon dioxide, the circulatory system picks up metabolic waste products and toxins and transports them to the liver, kidneys and lungs for eventual elimination from the body.

DISEASE PROTECTION AND HEALING

The circulatory system serves as the highway for disease-fighting cells and proteins, and messengers of the immune system. Immune system cells called white blood cells patrol the body in search of invading germs. If an infection occurs, these cells send chemical alarm signals that travel through the bloodstream, which subsequently transports infection-fighting cells to the site of the infection. The circulatory system also carries chemical messengers that attract cells to heal tissues that have been damaged due to injury or disease.

HORMONE DELIVERY

Hormones are chemical messengers produced by endocrine glands that affect distant organs. The cardiovascular system serves as the transportation connection between the endocrine glands and the organs or tissues they control via hormones. For example, hormones produced in the pituitary gland in the brain control other endocrine glands—such as the thyroid, ovaries and testes—as well as directing childhood growth. Similarly, the blood-sugar-lowering hormone insulin produced in the pancreas affects the uptake and use of blood sugar throughout the body. And thyroid hormones affect the metabolic rate of virtually every body organ and tissue, thanks to their body-wide delivery via the circulatory system.

BODY TEMPERATURE REGULATION

Body temperature regulation is an often overlooked but important function of the cardiovascular system. Optimal function of the human body occurs within a relatively narrow temperature range, which is tightly regulated. If body temperature begins to rise, blood vessels close to the body surface dilate, increasing in size. This allows the body to rid itself excess heat through the skin. Conversely, if body temperature drops, surface blood vessels constrict to conserve body heat. The cardiovascular system works in concert with the body's sweating mechanism as the primary regulators of body temperature.

HEART ANATOMY

The cardiovascular system is a closed system if the heart and blood vessels. The heart pumps blood through a closed system of blood vessels. Blood vessels allow blood to circulate to all parts of the body. Arteries usually

coloured red because oxygen rich, carry blood away from the heart to capillaries within the tissues. Veins usually coloured blue because oxygen poor, carry blood to the heart from the capillaries. Capillaries are the smallest vessels within the tissues where gas exchange take place. The function of the cardiovascular system is to deliver oxygen and nutrients to the body tissues and remove carbon dioxide and wastes products. The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 litres of fluid per minute and approximately 14,000 litres per day. Over one year, that would equal 10,000,000 litres or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

LOCATION OF THE HEART

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

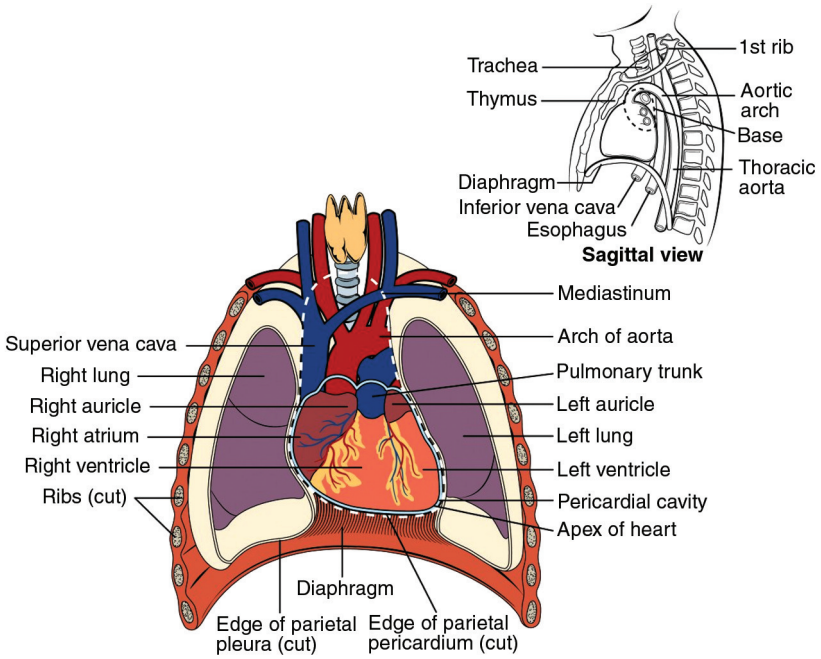


Fig. The heart is located within the thoracic cavity, medially between the lungs in the mediastinum. It is about the size of a fist, is broad at the top, and tapers towards the base.

The position of the heart in the torso between the vertebrae and sternum allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the lines, it is possible to manually compress the blood within the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in "Staying Alive," recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, you can likely find a version of it online. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced health care professional.

When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a consequence that may prove fatal for the patient. Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the American Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.

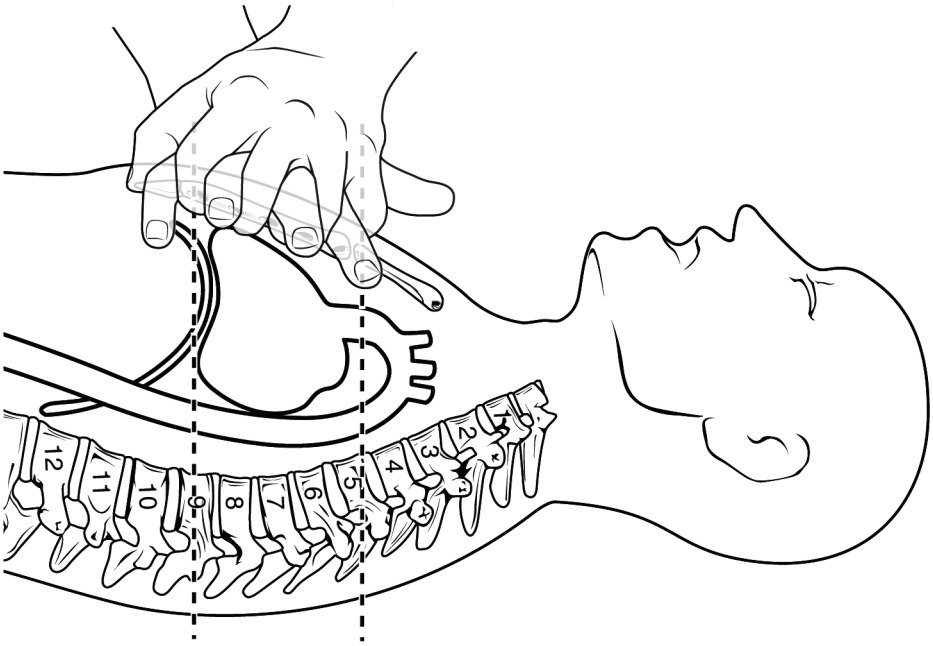


Fig. If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.

SHAPE AND SIZE OF THE HEART

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex. A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle.

That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of non-athletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as hypertrophic cardiomyopathy. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

CHAMBERS AND CIRCULATION THROUGH THE HEART

The human heart consists of four chambers: The left side and the right side each have one atrium and one ventricle. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

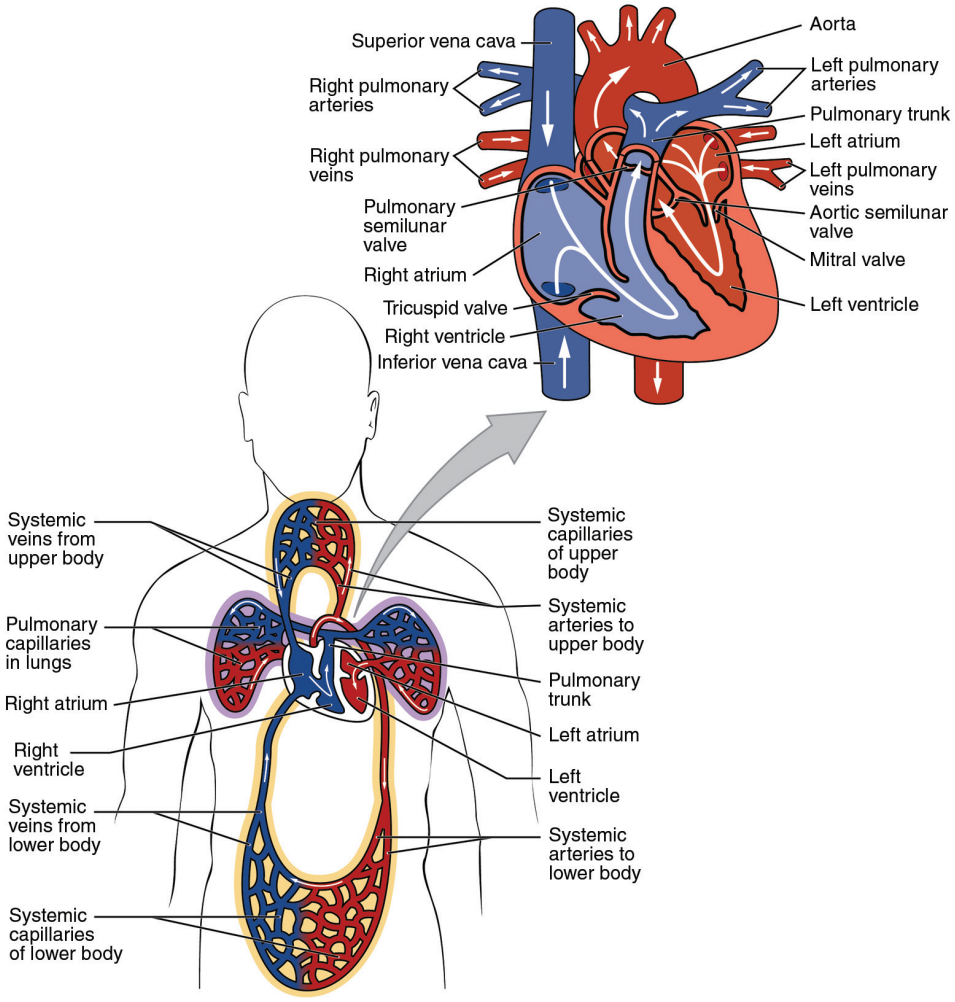


Fig. Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out),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

There are two distinct but linked circuits in the human circulation called the pulmonary and systemic circuits. Although both circuits transport blood and everything it carries, we can initially view the circuits from the point

of view of gases. The pulmonary circuittransports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The systemic circuittransports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

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

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

MEMBRANES, SURFACE FEATURES, AND LAYERS

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

Membranes

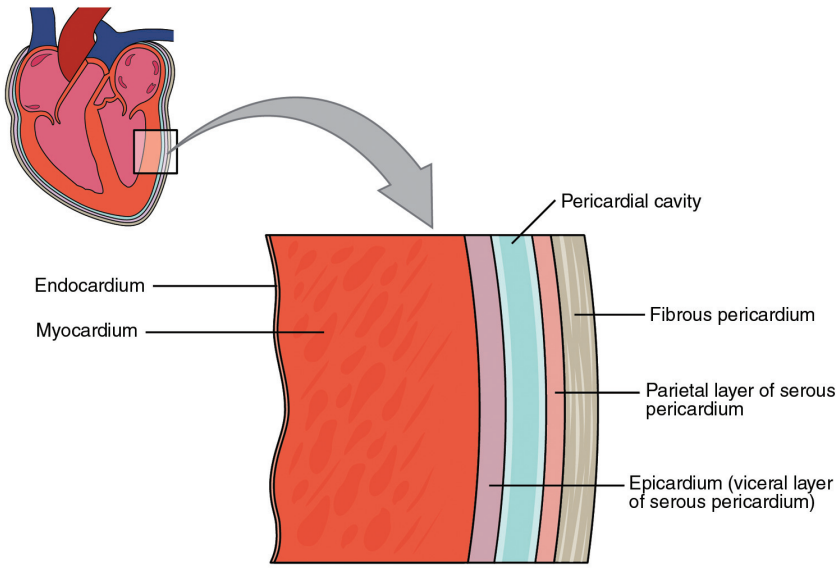


Fig. The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

The membrane that directly surrounds the heart and defines the pericardial cavity is called the pericardium or pericardial sac. It also surrounds the "roots" of the major vessels, or the areas of closest proximity to the heart. The pericardium, which litreally translates as "around the heart," consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium.

The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or epicardium, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

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

DISORDERS OF THE HEART

CARDIAC TAMPONADE

If excess fluid builds within the pericardial space, it can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates within the pericardial cavity. In order to fill with blood for the next contraction, the heart must relax. However, the excess fluid in the pericardial cavity puts pressure on the heart and prevents full relaxation, so the chambers within the heart contain slightly less blood as they begin each heart cycle. Over time, less and less blood is ejected from the heart. If the fluid builds up slowly, as in hypothyroidism, the pericardial cavity may be able to expand gradually to accommodate this extra volume.

Some cases of fluid in excess of one litre within the pericardial cavity have been reported. Rapid accumulation of as little as 100 mL of fluid following trauma may trigger cardiac tamponade. Other common causes include myocardial rupture, pericarditis, cancer, or even cardiac surgery. Removal of this excess fluid requires insertion of drainage tubes into the pericardial cavity. Premature removal of these drainage tubes, for example, following cardiac surgery, or clot formation within these tubes are causes of this condition. Untreated, cardiac tamponade can lead to death.

SURFACE FEATURES OF THE HEART

Inside the pericardium, the surface features of the heart are visible, including the four chambers. There is a superficial leaf-like extension of the atria near the superior surface of the heart, one on each side, called an auricle—a name that means "ear like"—because its shape resembles the external ear of a human. Auricles are relatively thin-walled structures that can fill with blood and empty into the atria or upper chambers of the heart. You may also hear them referred to as atrial appendages.

Also prominent is a series of fat-filled grooves, each of which is known as a sulcus (plural = sulci), along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci. The deep coronary sulcus is located between the atria and ventricles. Located between the left and right ventricles are two additional sulci that are not as deep as the coronary sulcus. The anterior interventricular sulcus is visible on the anterior surface of the heart, whereas the posterior interventricular sulcus is visible on the posterior surface of the heart.

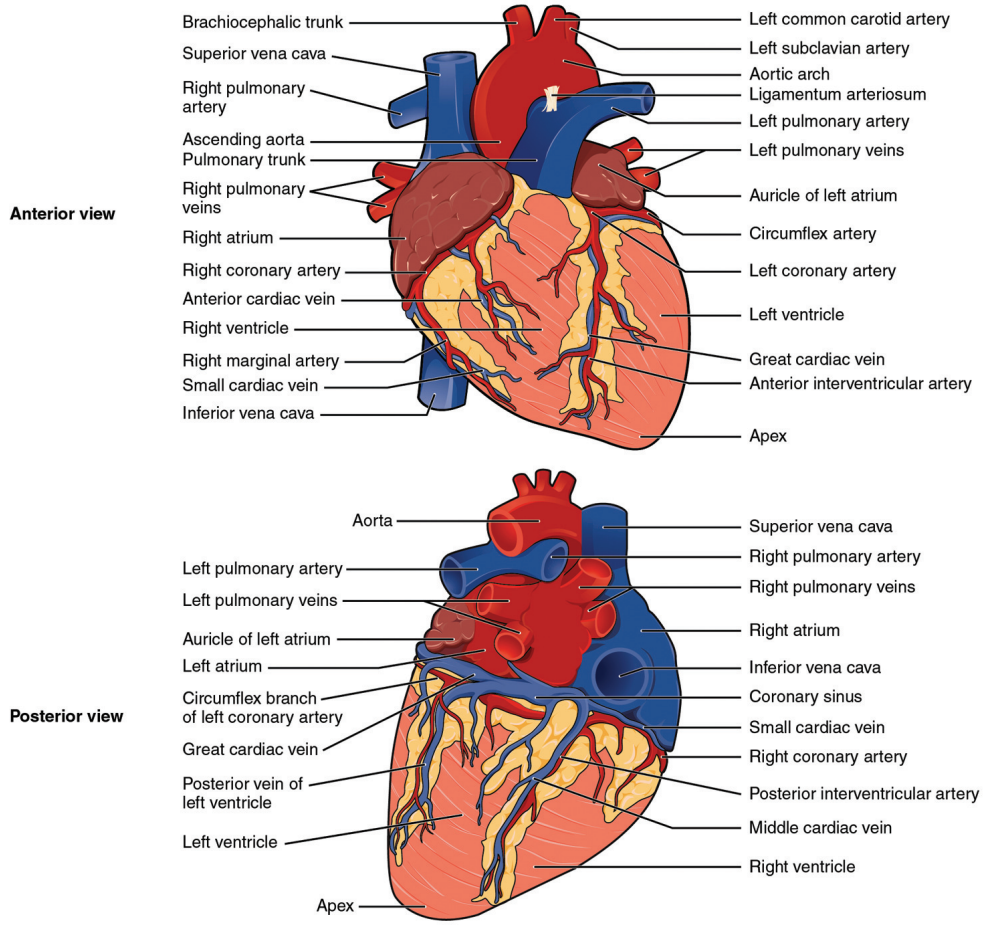


Fig. Inside the pericardium, the surface features of the heart are visible.

LAYERS

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

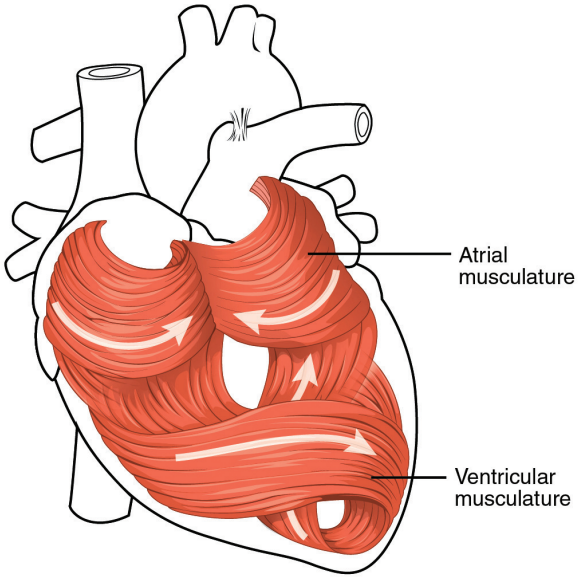


Fig. The swirling pattern of cardiac muscle tissue contributes significantly to the heart's ability to pump blood effectively.

The middle and thickest layer is the myocardium, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibres, plus the blood vessels that supply the myocardium and the nerve fibres that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would.

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

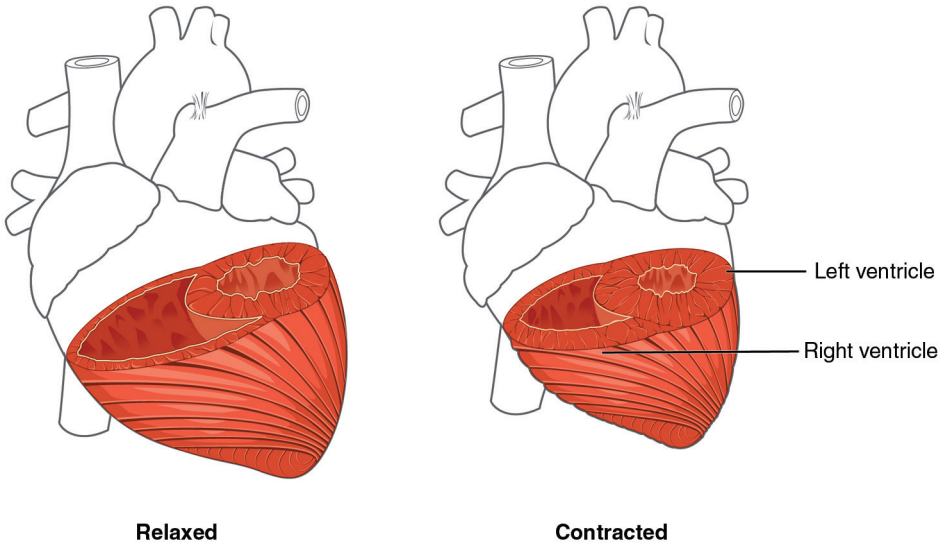


Fig. The myocardium in the left ventricle is significantly thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed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

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

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

INTERNAL STRUCTURE OF THE HEART

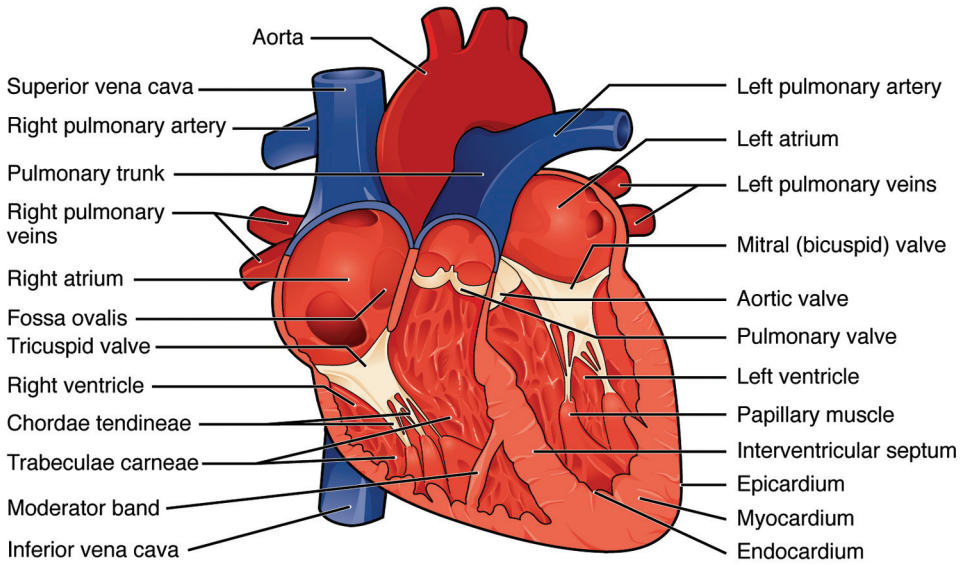
Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal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

Septa of the Heart

The word septum is derived from the Latin for "something that encloses;" in this case, a septum (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the interatrial septum. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the fossa ovalis, a remnant of an opening in the fetal heart known as the foramen ovale. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the septum primum that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

Between the two ventricles is a second septum known as the interventricular septum. Unlike the interatrial septum, the interventricular septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

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



Anterior view

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

DISORDERS OF THE HEART: HEART DEFECTS

One very common form of interatrial septum pathology is patent foramen ovale, which occurs when the septum primum does not close at birth, and the fossa ovalis is unable to fuse. The word patent is from the Latin root patens for "open." It may be benign or asymptomatic, perhaps never being diagnosed, or in extreme cases, it may require surgical repair to close the opening permanently. As much as 20–25 percent of the general population may have a patent foramen ovale, but fortunately, most have the benign, asymptomatic version. Patent foramen ovale is normally detected by auscultation of a heart murmur (an abnormal heart sound) and confirmed by imaging with an echocardiogram. Despite its prevalence in the general population, the causes of patent ovale are unknown, and there are no known risk factors. In non-life-threatening cases, it is better to monitor the condition than to risk heart surgery to repair and seal the opening.

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

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

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

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

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

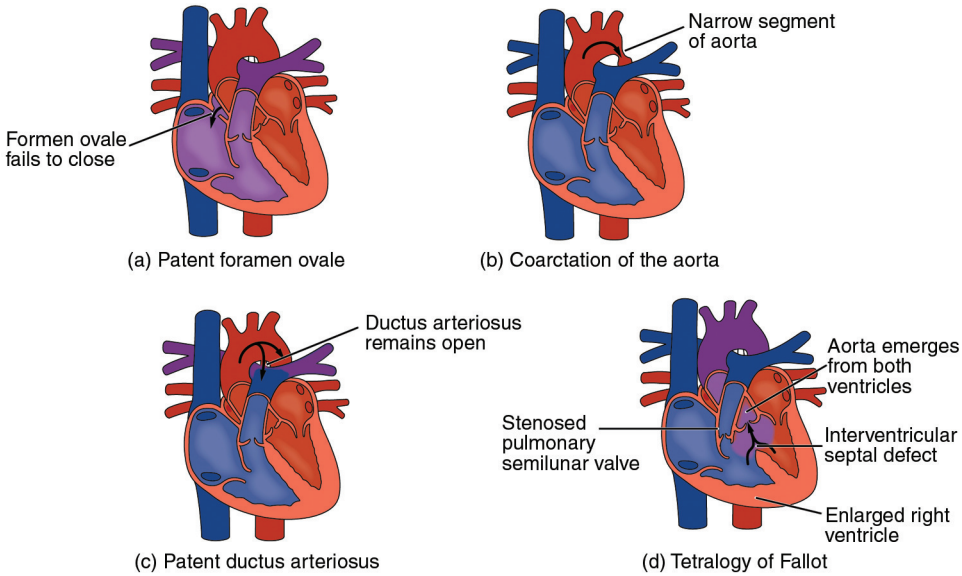


Fig. (a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d)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

RIGHT ATRIUM

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

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

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

RIGHT VENTRICLE

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

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

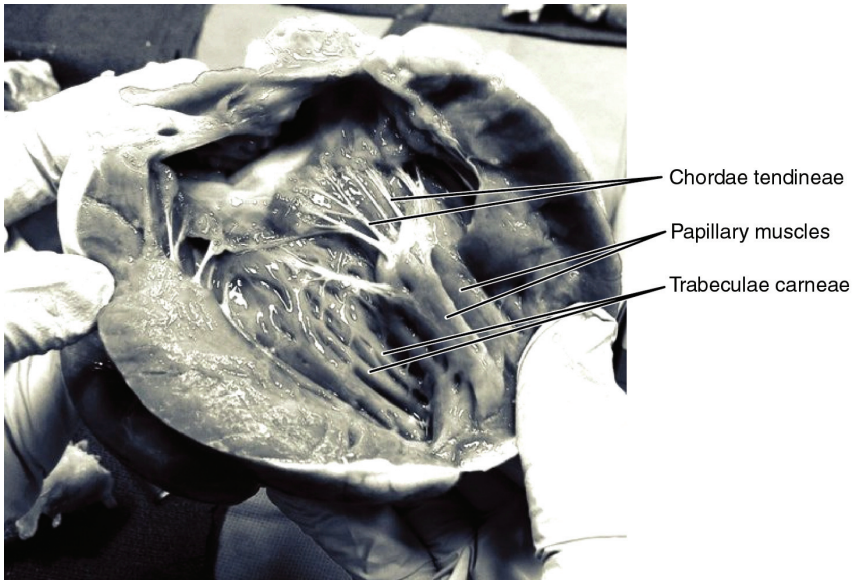


Fig. In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae.

The walls of the ventricle are lined with trabeculae carneae, ridges of cardiac muscle covered by endocardium. In addition to these muscular ridges, a band of cardiac muscle, also covered by endocardium, known as the moderator band reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It arises from the inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

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

LEFT ATRIUM

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle

that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but towards the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve.

LEFT VENTRICLE

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

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

HEART VALVE STRUCTURE AND FUNCTION

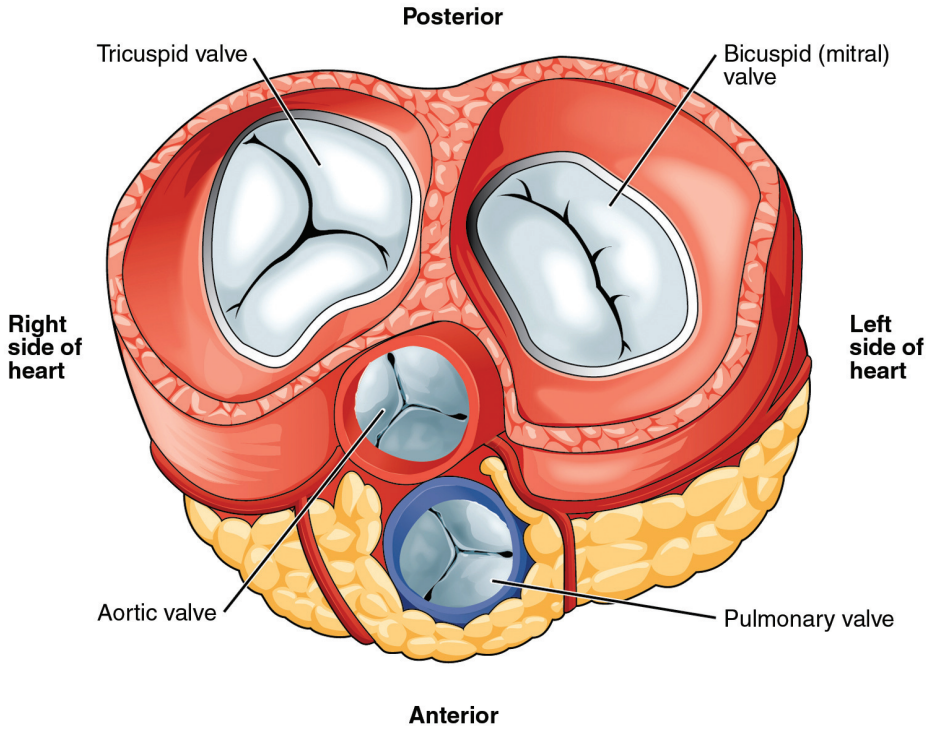


Fig. With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

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

Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or the pulmonary valve; it is also known as the pulmonic valve or the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes,

the pressure differential causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close and producing an audible sound. Unlike the atrioventricular valves, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

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

At the base of the aorta is the aortic semilunar valve, or the aortic valve, which prevents backflow from the aorta. It normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

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

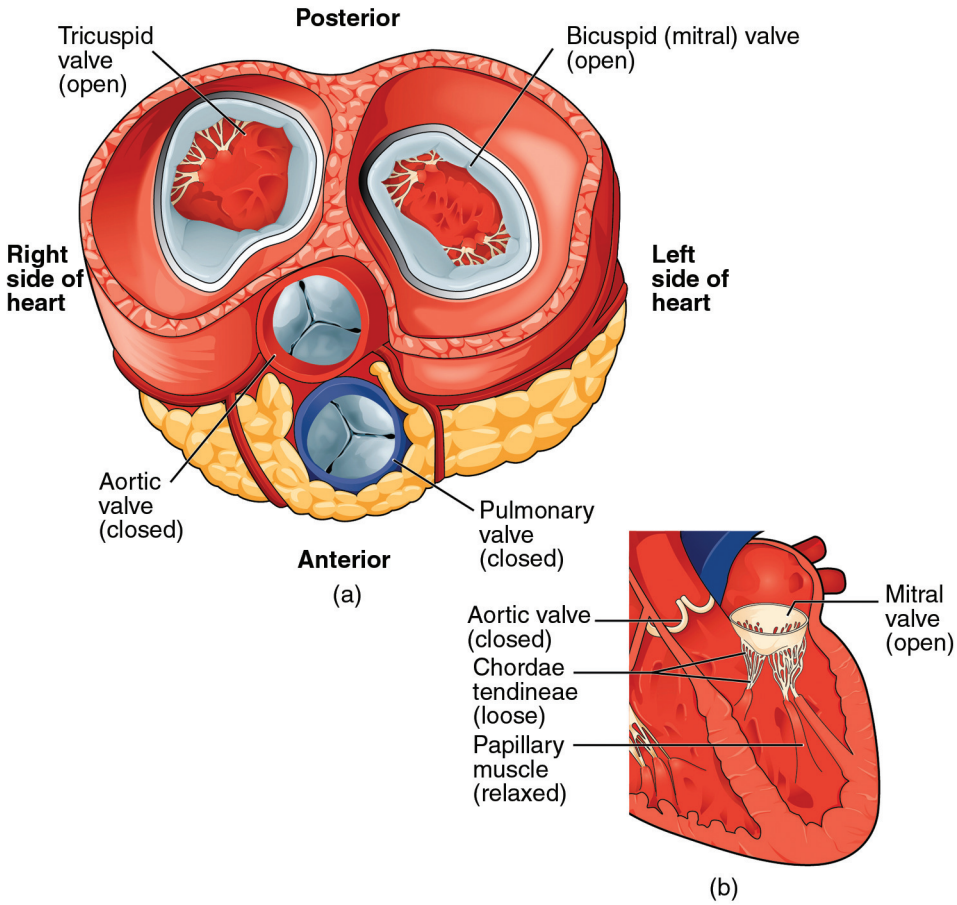


Fig. (a) A transverse section through the heart illustrates the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the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

The atrioventricular valves closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two atrioventricular valves prevents blood from being forced back into the atria.

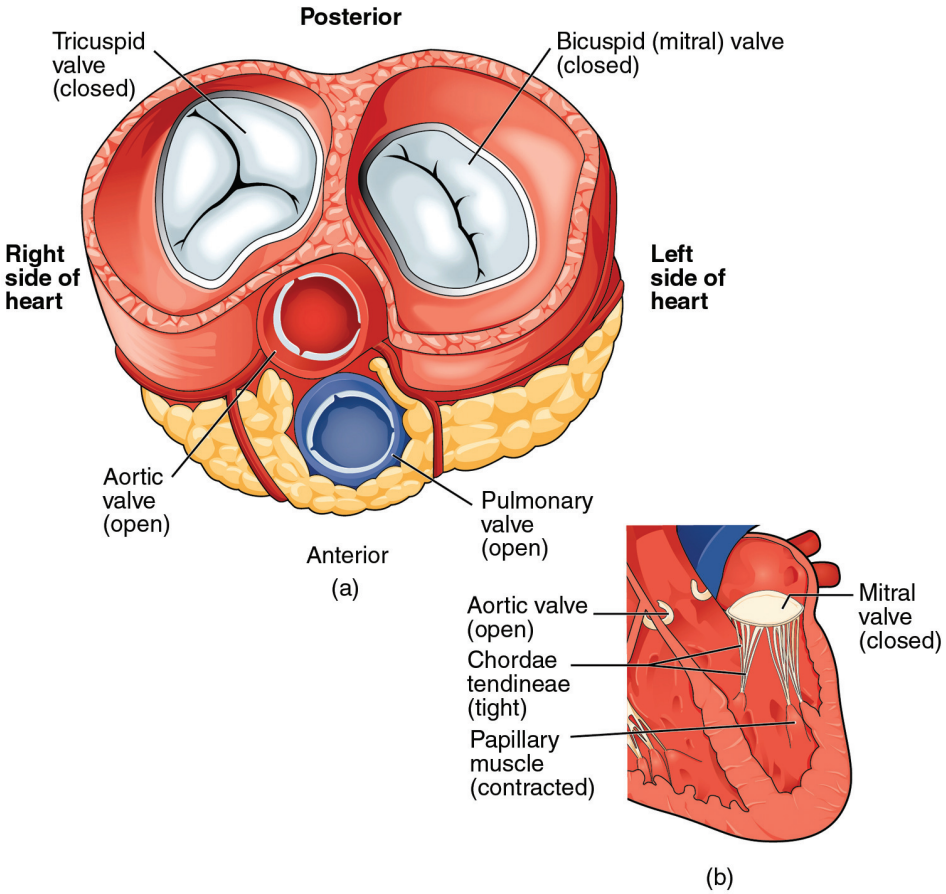


Fig. (a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that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

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

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

DISORDERS OF THE HEART VALVES

When heart valves do not function properly, they are often described as incompetent and result in valvular heart disease, which can range from benign to lethal. Some of these conditions are congenital, that is, the individual was born with the defect, whereas others may be attributed to disease processes or trauma. Some malfunctions are treated with medications, others require surgery, and still others may be mild enough that the condition is merely monitored since treatment might trigger more serious consequences.

Valvular disorders are often caused by carditis, or inflammation of the heart. One common trigger for this inflammation is rheumatic fever, or scarlet fever, an autoimmune response to the presence of a bacterium, *Streptococcus pyogenes*, normally a disease of childhood.

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

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

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

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

CORONARY CIRCULATION

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

Coronary Arteries

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

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The circumflex artery arises from the left coronary artery and follows the coronary

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

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

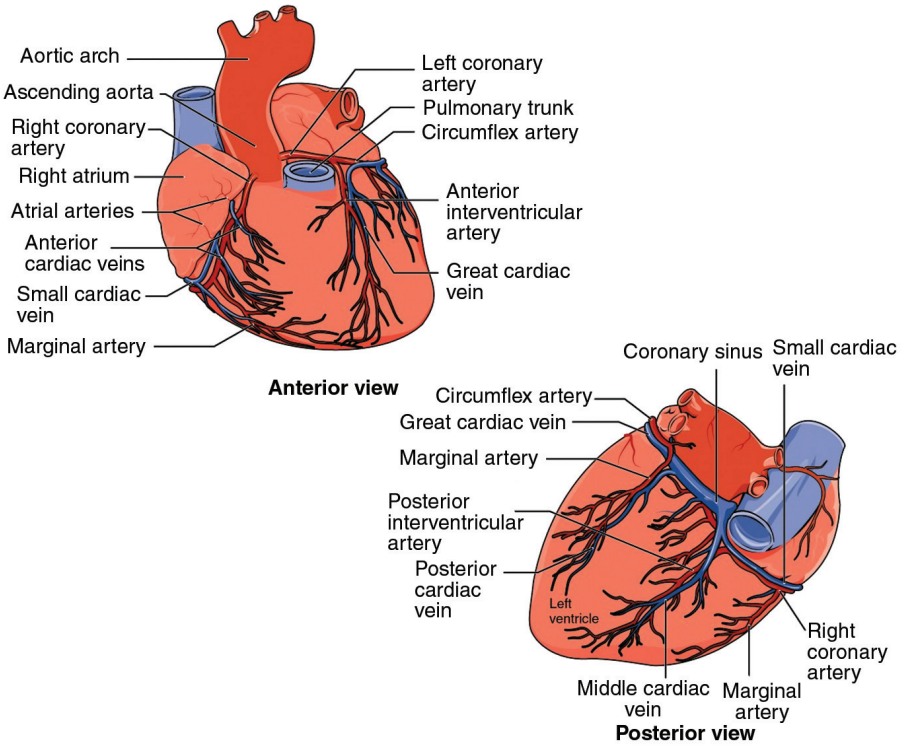


Fig. The anterior view of the heart shows the prominent coronary surface vessels. The posterior view of the heart shows the prominent coronary surface vessels.

5

Respiratory System

The human respiratory system is a series of organs responsible for taking in oxygen and expelling carbon dioxide. The primary organs of the respiratory system are lungs, which carry out this exchange of gases as we breathe.

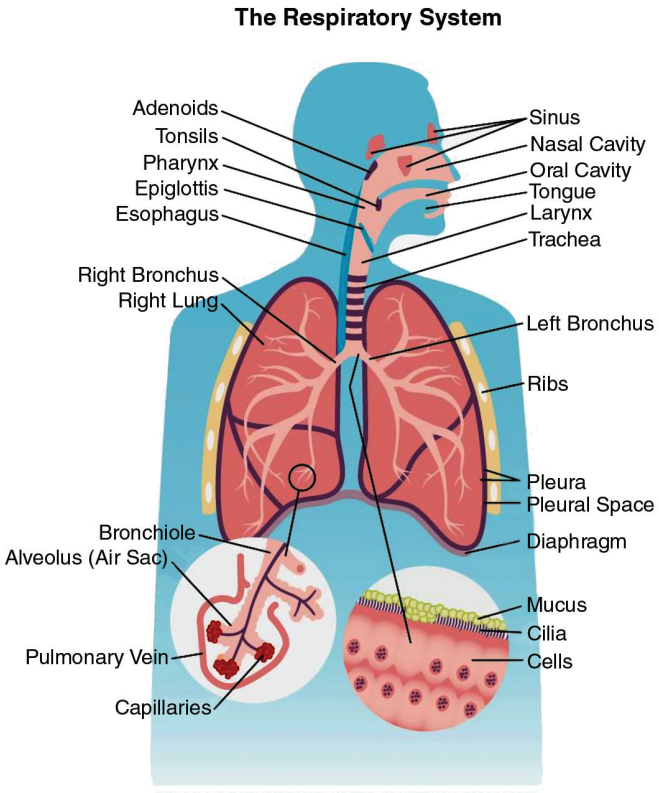


Fig. Respiratory System.

Red blood cells collect the oxygen from the lungs and carry it to the parts of the body where it is needed, according to the American Lung Association. During the process, the red blood cells collect the carbon dioxide and transport it back to the lungs, where it leaves the body when we exhale.

PARTS OF THE RESPIRATORY SYSTEM

As we breathe, oxygen enters the nose or mouth and passes the sinuses, which are hollow spaces in the skull. Sinuses help regulate the temperature and humidity of the air we breathe. The trachea, also called the windpipe, filters the air that is inhaled, according to the American Lung Association. It branches into the bronchi, which are

two tubes that carry air into each lung. (Each one is called a bronchus.) The bronchial tubes are lined with tiny hairs called cilia. Cilia move back and forth, carrying mucus up and out. Mucus, a sticky fluid, collects dust, germs and other matter that has invaded the lungs. We expel mucus when we sneeze, cough, spit or swallow.

The bronchial tubes lead to the lobes of the lungs. The right lung has three lobes; the left lung has two, according to the American Lung Association. The left lung is smaller to allow room for the heart, according to York University. Lobes are filled with small, spongy sacs called alveoli, and this is where the exchange of oxygen and carbon dioxide occurs. The alveolar walls are extremely thin (about 0.2 micrometers). These walls are composed of a single layer of tissues called epithelial cells and tiny blood vessels called pulmonary capillaries. Blood passes through the capillaries. The pulmonary artery carries blood containing carbon dioxide to the air sacs, where the gas moves from the blood to the air. Oxygenated blood goes to the heart through the pulmonary vein, and the heart pumps it throughout the body.

The diaphragm, a dome-shaped muscle at the bottom of the lungs, controls breathing and separates the chest cavity from the abdominal cavity, the American Lung Association noted. When a breath it taken, it flattens out and pulls forward, making more space for the lungs. During exhalation, the diaphragm expands and forces air out.

DISEASES OF THE RESPIRATORY SYSTEM

Diseases and conditions of the respiratory system fall into two categories: viruses, such as influenza, bacterial pneumonia, enterovirus respiratory virus; and chronic diseases, such as asthma and chronic obstructive pulmonary disease (COPD). According to Dr. Neal Chaisson, who practices pulmonary medicine at the Cleveland Clinic, there is not much that can be done for viral infections but to let them run their course. “Antibiotics are not effective in treating viruses and the best thing to do is just rest,” he said.

COPD

COPD is the intersection of three related conditions—chronic bronchitis, chronic asthma and emphysema, Chaisson told Live Science. It is a progressive disease that makes it increasingly difficult for sufferers to breath.

Asthma

Asthma is a chronic inflammation of the lung airways that causes coughing, wheezing, chest tightness or shortness of breath, according to Tonya Winders, president of the Allergy and Asthma Network. These signs and symptoms may be worse when a person is exposed to their triggers, which can include air pollution, tobacco smoke, factory fumes, cleaning solvents, infections, pollens, foods, cold air, exercise, chemicals and medications.

Lung Cancer

Lung cancer is often associated with smoking, but the disease can affect non-smokers as well. Every year, about 16,000 to 24,000 Americans die of lung cancer, even though they have never smoked. In 2018, the American Cancer Society estimates there will be about 234,030 new cases of lung cancer (121,680 in men and 112,350 in women) and around 154,050 deaths from lung cancer (83,550 in men and 70,500 in women).

DIAGNOSING AND TREATING RESPIRATORY AILMENTS

Pulmonologists treat the respiratory system, including the lungs, according to the American College of Physicians. Because of the critical nature of the respiratory system, pulmonologists work in hospitals as well as in private practice. A pulmonologist must first be certified by the American Board of Internal Medicine and then obtain additional training in the subspecialty.

Common diagnostic tools for diagnosing respiratory disease include chest X-rays and a pulmonary function test (PFT), according to Merck Manuals. A PFT measures how well the lungs take in and release air and how well they circulate oxygen. A doctor may also perform a bronchoscopy by inserting a tube with a light and camera into the airways—the trachea and the bronchial tubes—to examine for bleeding, tumors, inflammation or other abnormalities. A similar procedure is a thoracoscopy, in which a doctor uses an optical device to examine the surfaces of the lungs. A physician may order a PFT as part of a routine exam—especially for smokers, according to the University of Pittsburgh Medical Center. A PFT may also be ordered to test lung function before surgery or to help diagnose lung conditions or diseases.

A new nasal swab test measures RNA or protein molecules in human cells and can identify a viral infection, according to a study published Dec. 21, 2017, in the Journal of Infectious Diseases. "It's a simpler test and more cost-effective for looking at viral infection," the author, Dr. Ellen Foxman, assistant professor of laboratory medicine at Yale School of Medicine, told YaleNews. During the test, RNAs predicted viral infection with 97 percent accuracy.

For most healthy individuals, the most common respiratory ailment they may face is an infection, according to Dr. Matthew Exline, a pulmonologist and critical care expert at The Ohio State University Wexner Medical Center. A cough is the first symptom, possibly accompanied by a fever. "However, cough can be a sign of chronic respiratory conditions such as asthma, chronic bronchitis or emphysema," he said. "In chronic lung disease, most respiratory diseases present with shortness of breath, initially with exertion, such as walking a significant distance or climbing several flights of stairs."

The most certain way to diagnose asthma is with a lung function test, a medical history and a physical exam, according to Winders. "However, it's hard to do lung function tests in children younger than 5 years. Thus, doctors must rely on children's medical histories, signs and symptoms, and physical exams to make a diagnosis."

For COPD, many patients benefit from respiratory rehabilitation, according to Dr. Brian Carlin, assistant professor of medicine at Drexel University College of Medicine. "It is much like cardiac rehabilitation for heart patients, and can provide education, exercise and training to reduce the number of respiratory incidents."

LUNGS AND RESPIRATORY SYSTEM

Whether you're wide awake and getting ready for a big date or asleep during your most snooze-worthy afternoon class, you don't have to think about breathing. It's so important to life that it happens automatically. If you didn't breathe, you couldn't live.

LUNGS AND RESPIRATORY SYSTEM BASICS

Each day we breathe about 20,000 times. All of this breathing couldn't happen without help from the respiratory system, which includes the nose, throat, voice box, windpipe, and lungs. With each breath, you take in air through your nostrils and mouth, and your lungs fill up and empty out. As air is inhaled, the mucous membranes of the nose and mouth warm and humidify the air.

Although we can't see it, the air we breathe is made up of several gases. Oxygen is the most important for keeping us alive because body cells need it for energy and growth. Without oxygen, the body's cells would die. Carbon dioxide is the waste gas that is produced when carbon is combined with oxygen as part of the body's energy-making processes. The lungs and respiratory system allow oxygen in the air to be taken into the body, while also enabling the body to get rid of carbon dioxide in the air breathed out.

Respiration is the term for the exchange of oxygen from the environment for carbon dioxide from the body's cells. The process of taking air into the lungs is called inhalation or inspiration, and the process of breathing it out is called exhalation or expiration. Even if the air you breathe is dirty or polluted, your respiratory system filters out foreign matter and organisms that enter through the nose and mouth. Pollutants are breathed or

coughed out, destroyed by digestive juices, or eaten by macrophages, a type of blood cell that patrols the body looking for germs to destroy. Tiny hairs called cilia (pronounced: SIL-ee-uh) protect the nasal passageways and other parts of the respiratory tract, filtering out dust and other particles that enter the nose with the breathed air. As air is inhaled, the cilia move back and forth, pushing any foreign matter (like dust) either towards the nostrils, where it is blown out, or towards the pharynx, where it travels through the digestive system and out with the rest of the body's waste.

The two openings of the airway (the nasal cavity and the mouth) meet at the pharynx(pronounced: FAR-inks), or throat, at the back of the nose and mouth. The pharynx is part of the digestive system as well as the respiratory system because it carries both food and air. At the bottom of the pharynx, the pathway for both food and air divides in two. One passageway is for food (the esophagus, pronounced: ih-SAH-fuh-gus, which leads to the stomach) and the other for air. The epiglottis (pronounced: eh-pih-GLAH-tus), a small flap of tissue, covers the air-only passage when we swallow, keeping food and liquid from going into our lungs.

The larynx (pronounced: LAR-inks), or voice box, is the uppermost part of the air-only passage. This short tube contains a pair of vocal cords, which vibrate to make sounds. The trachea (pronounced: TRAY-kee-uh), or windpipe, extends downward from the base of the larynx. It lies partly in the neck and partly in the chest cavity. The walls of the trachea are strengthened by stiff rings of cartilage to keep it open so air can flow through on its way to the lungs. The trachea is also lined with cilia, which sweep fluids and foreign particles out of the airway so that they stay out of the lungs.

At its bottom end, the trachea divides into left and right air tubes called bronchi(pronounced: BRAHN-kye), which connect to the lungs. Within the lungs, the bronchi branch into smaller bronchi and even smaller tubes called bronchioles (pronounced: BRAHN-kee-olz). Bronchioles, which are as thin as a strand of hair, end in tiny air sacs called alveoli (pronounced: al-VEE-oh-lye). Each of us has hundreds of millions of alveoli in our lungs—enough to cover a tennis court if they were spread out on the ground. The alveoli are where the exchange of oxygen and carbon dioxide takes place. With each inhalation, air fills a large portion of the millions of alveoli. In a process called diffusion (pronounced: dih-FYOO-zhun), oxygen moves from the alveoli to the blood through the capillaries (tiny blood vessels, pronounced: KAP-uh-lair-eez) that line the alveolar walls. Once in the bloodstream, oxygen gets picked up by a molecule called hemoglobin (pronounced: HEE-muh-glo-bun) in the red blood cells. This oxygen-rich blood then flows back to the heart, which pumps it through the arteries to oxygen-hungry tissues throughout the body.

In the tiny capillaries of the body tissues, oxygen is freed from the hemoglobin and moves into the cells. Carbon dioxide, which is made by cells as they do their work, moves out of the cells into the capillaries, where most of it then dissolves into the plasma of the blood. Blood rich in carbon dioxide then returns to the heart via the veins. From the heart, this blood is pumped to the lungs, where carbon dioxide passes into the alveoli to be exhaled.

The lungs also contain elastic tissues that allow them to inflate and deflate without losing shape and are encased by a thin lining called the pleura (pronounced: PLUR-uh). This network of alveoli, bronchioles, and bronchi is known as the bronchial tree. The chest cavity, or thorax (pronounced: THOR-aks), is the airtight box that houses the bronchial tree, lungs, heart, and other structures. The top and sides of the thorax are formed by the ribs and attached muscles, and the bottom by a large muscle called the diaphragm. The chest walls form a protective cage around the lungs and other contents of the chest cavity.

The diaphragm (pronounced: DYE-uh-fram), which separates the chest from the abdomen, plays a lead role in breathing. When we breathe out, the diaphragm moves upward, forcing the chest cavity to get smaller and pushing the gases in the lungs up and out of the nose and mouth.

When we breathe in, the diaphragm moves downward towards the abdomen, and the rib muscles pull the ribs upward and outward, enlarging the chest cavity and pulling air in through the nose or mouth. Air pressure in the chest cavity and lungs is reduced, and because gas flows from high pressure to low, air from the environment flows through the nose or mouth into the lungs.

As we exhale, the diaphragm moves upward and the chest wall muscles relax, causing the chest cavity to contract. Air pressure in the lungs rises, so air flows from the lungs and up and out of respiratory system through the nose or mouth.

THINGS THAT CAN GO WRONG

Many Factors: Including genetics, pollutants and irritants, and infectious diseases—can affect the health of your lungs and respiratory system and cause respiratory problems. Problems of the respiratory system that can affect people during their teen years include:

Asthma: More than 20 million people have asthma in the United States, and it's the #1 reason that kids and teens chronically miss school. Asthma is a long-term, inflammatory lung disease that causes airways to tighten and narrow when a person with the condition comes into contact with irritants such as cigarette smoke, dust, or pet dander.

Bronchitis: Although bronchitis doesn't affect most teens, it can affect those who smoke. In bronchitis, the membranes lining the larger bronchial tubes become inflamed and an excessive amount of mucus is produced. The person with bronchitis develops a bad cough to get rid of the mucus.

Common Cold: Colds are caused by over 200 different viruses that cause inflammation in the upper respiratory tract. The common cold is the most common respiratory infection. Symptoms may include a mild fever, cough, headache, runny nose, sneezing, and sore throat.

Cough: A cough is a symptom of an illness, not an illness itself. There are many different types of cough and many different causes, ranging from not-so-serious to life threatening. Some of the more common causes affecting kids and teens are the common cold, asthma, sinusitis, seasonal allergies, and pneumonia.

Cystic fibrosis (CF): CF is an inherited disease affecting the lungs. CF causes mucus in the body to be abnormally thick and sticky. The mucus can clog the airways in the lungs and make a person more likely to get bacterial infections.

Pneumonia: Pneumonia is an inflammation of the lungs, which usually occurs because of infection with a bacteria or virus. Pneumonia causes fever, inflammation of lung tissue, and makes breathing difficult because the lungs have to work harder to transfer oxygen into the bloodstream and remove carbon dioxide from the blood. Common causes of pneumonia are influenza and infection with the bacterium *Streptococcus pneumoniae*.

ANATOMY OF THE RESPIRATORY SYSTEM

NOSE AND NASAL CAVITY

The nose and nasal cavity form the main external opening for the respiratory system and are the first section of the body's airway—the respiratory tract through which air moves. The nose is a structure of the face made of cartilage, bone, muscle, and skin that supports and protects the anterior portion of the nasal cavity. The nasal cavity is a hollow space within the nose and skull that is lined with hairs and mucus membrane. The function of the nasal cavity is to warm, moisturize, and filter air entering the body before it reaches the lungs. Hairs and mucus lining the nasal cavity help to trap dust, mold, pollen and other environmental contaminants before they can reach the inner portions of the body. Air exiting the body through the nose returns moisture and heat to the nasal cavity before being exhaled into the environment.

MOUTH

The mouth, also known as the oral cavity, is the secondary external opening for the respiratory tract. Most normal breathing takes place through the nasal cavity, but the oral cavity can be used to supplement or replace

the nasal cavity's functions when needed. Because the pathway of air entering the body from the mouth is shorter than the pathway for air entering from the nose, the mouth does not warm and moisturize the air entering the lungs as well as the nose performs this function. The mouth also lacks the hairs and sticky mucus that filter air passing through the nasal cavity. The one advantage of breathing through the mouth is that its shorter distance and larger diameter allows more air to quickly enter the body.

PHARYNX

The pharynx, also known as the throat, is a muscular funnel that extends from the posterior end of the nasal cavity to the superior end of the esophagus and larynx. The pharynx is divided into 3 regions: the nasopharynx, oropharynx, and laryngopharynx. The nasopharynx is the superior region of the pharynx found in the posterior of the nasal cavity. Inhaled air from the nasal cavity passes into the nasopharynx and descends through the oropharynx, located in the posterior of the oral cavity. Air inhaled through the oral cavity enters the pharynx at the oropharynx. The inhaled air then descends into the laryngopharynx, where it is diverted into the opening of the larynx by the epiglottis. The epiglottis is a flap of elastic cartilage that acts as a switch between the trachea and the esophagus. Because the pharynx is also used to swallow food, the epiglottis ensures that air passes into the trachea by covering the opening to the esophagus. During the process of swallowing, the epiglottis moves to cover the trachea to ensure that food enters the esophagus and to prevent choking.

LARYNX

The larynx, also known as the voice box, is a short section of the airway that connects the laryngopharynx and the trachea. The larynx is located in the anterior portion of the neck, just inferior to the hyoid bone and superior to the trachea. Several cartilage structures make up the larynx and give it its structure. The epiglottis is one of the cartilage pieces of the larynx and serves as the cover of the larynx during swallowing. Inferior to the epiglottis is the thyroid cartilage, which is often referred to as the Adam's apple as it is most commonly enlarged and visible in adult males. The thyroid holds open the anterior end of the larynx and protects the vocal folds. Inferior to the thyroid cartilage is the ring-shaped cricoid cartilage which holds the larynx open and supports its posterior end. In addition to cartilage, the larynx contains special structures known as vocal folds, which allow the body to produce the sounds of speech and singing. The vocal folds are folds of mucous membrane that vibrate to produce vocal sounds. The tension and vibration speed of the vocal folds can be changed to change the pitch that they produce.

TRACHEA

The trachea, or windpipe, is a 5-inch long tube made of C-shaped hyaline cartilage rings lined with pseudostratified ciliated columnar epithelium. The trachea connects the larynx to the bronchi and allows air to pass through the neck and into the thorax. The rings of cartilage making up the trachea allow it to remain open to air at all times. The open end of the cartilage rings faces posteriorly towards the esophagus, allowing the esophagus to expand into the space occupied by the trachea to accommodate masses of food moving through the esophagus.

The main function of the trachea is to provide a clear airway for air to enter and exit the lungs. In addition, the epithelium lining the trachea produces mucus that traps dust and other contaminants and prevents it from reaching the lungs. Cilia on the surface of the epithelial cells move the mucus superiorly towards the pharynx where it can be swallowed and digested in the gastrointestinal tract.

BRONCHI AND BRONCHIOLES

At the inferior end of the trachea, the airway splits into left and right branches known as the primary bronchi. The left and right bronchi run into each lung before branching off into smaller secondary bronchi. The secondary bronchi

carry air into the lobes of the lungs—2 in the left lung and 3 in the right lung. The secondary bronchi in turn split into many smaller tertiary bronchi within each lobe. The tertiary bronchi split into many smaller bronchioles that spread throughout the lungs. Each bronchiole further splits into many smaller branches less than a millimeter in diameter called terminal bronchioles. Finally, the millions of tiny terminal bronchioles conduct air to the alveoli of the lungs. As the airway splits into the tree-like branches of the bronchi and bronchioles, the structure of the walls of the airway begins to change. The primary bronchi contain many C-shaped cartilage rings that firmly hold the airway open and give the bronchi a cross-sectional shape like a flattened circle or a letter D. As the bronchi branch into secondary and tertiary bronchi, the cartilage becomes more widely spaced and more smooth muscle and elastin protein is found in the walls. The bronchioles differ from the structure of the bronchi in that they do not contain any cartilage at all. The presence of smooth muscles and elastin allow the smaller bronchi and bronchioles to be more flexible and contractile.

The main function of the bronchi and bronchioles is to carry air from the trachea into the lungs. Smooth muscle tissue in their walls helps to regulate airflow into the lungs. When greater volumes of air are required by the body, such as during exercise, the smooth muscle relaxes to dilate the bronchi and bronchioles. The dilated airway provides less resistance to airflow and allows more air to pass into and out of the lungs. The smooth muscle fibres are able to contract during rest to prevent hyperventilation. The bronchi and bronchioles also use the mucus and cilia of their epithelial lining to trap and move dust and other contaminants away from the lungs.

LUNGS

The lungs are a pair of large, spongy organs found in the thorax lateral to the heart and superior to the diaphragm. Each lung is surrounded by a pleural membrane that provides the lung with space to expand as well as a negative pressure space relative to the body's exterior. The negative pressure allows the lungs to passively fill with air as they relax. The left and right lungs are slightly different in size and shape due to the heart pointing to the left side of the body. The left lung is therefore slightly smaller than the right lung and is made up of 2 lobes while the right lung has 3 lobes. The interior of the lungs is made up of spongy tissues containing many capillaries and around 30 million tiny sacs known as alveoli. The alveoli are cup-shaped structures found at the end of the terminal bronchioles and surrounded by capillaries. The alveoli are lined with thin simple squamous epithelium that allows air entering the alveoli to exchange its gases with the blood passing through the capillaries.

MUSCLES OF RESPIRATION

Surrounding the lungs are sets of muscles that are able to cause air to be inhaled or exhaled from the lungs. The principal muscle of respiration in the human body is the diaphragm, a thin sheet of skeletal muscle that forms the floor of the thorax. When the diaphragm contracts, it moves inferiorly a few inches into the abdominal cavity, expanding the space within the thoracic cavity and pulling air into the lungs. Relaxation of the diaphragm allows air to flow back out the lungs during exhalation. Between the ribs are many small intercostal muscles that assist the diaphragm with expanding and compressing the lungs. These muscles are divided into 2 groups: the internal intercostal muscles and the external intercostal muscles. The internal intercostal muscles are the deeper set of muscles and depress the ribs to compress the thoracic cavity and force air to be exhaled from the lungs. The external intercostals are found superficial to the internal intercostals and function to elevate the ribs, expanding the volume of the thoracic cavity and causing air to be inhaled into the lungs.

ORGANS AND STRUCTURES OF THE RESPIRATORY SYSTEM

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

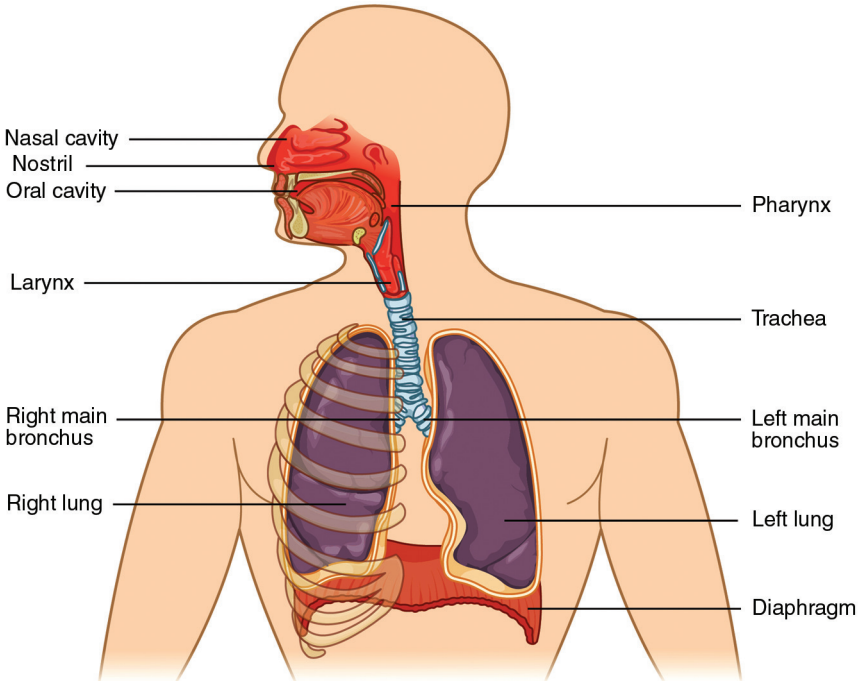


Fig. Major Respiratory Structures. The major respiratory structures span the nasal cavity to the diaphragm.

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

CONDUCTING ZONE

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

THE NOSE AND ITS ADJACENT STRUCTURES

The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose. The external nose consists of the surface and skeletal structures that result in the outward appearance of the nose and contribute to its numerous functions. The root is the region of the nose located between the eyebrows. The bridge is the part of the nose that connects the root to the rest of the nose. The dorsum nasi is the length of the nose. The apex is the tip of the nose. On either side of the apex, the nostrils are formed by the alae (singular = ala). An ala is a cartilaginous structure that forms the lateral side of each naris (plural = nares), or nostril opening. The philtrum is the concave surface that connects the apex of the nose to the upper lip.

Underneath the thin skin of the nose are its skeletal features. While the root and bridge of the nose consist of bone, the protruding portion of the nose is composed of cartilage. As a result, when looking at a skull, the nose is missing. The nasal bone is one of a pair of bones that lies under the root and bridge of the nose. The nasal bone articulates superiorly with the frontal bone and laterally with the maxillary bones. Septal cartilage is flexible hyaline cartilage connected to the nasal bone, forming the dorsum nasi. The alar cartilage consists of the apex of the nose; it surrounds the naris.

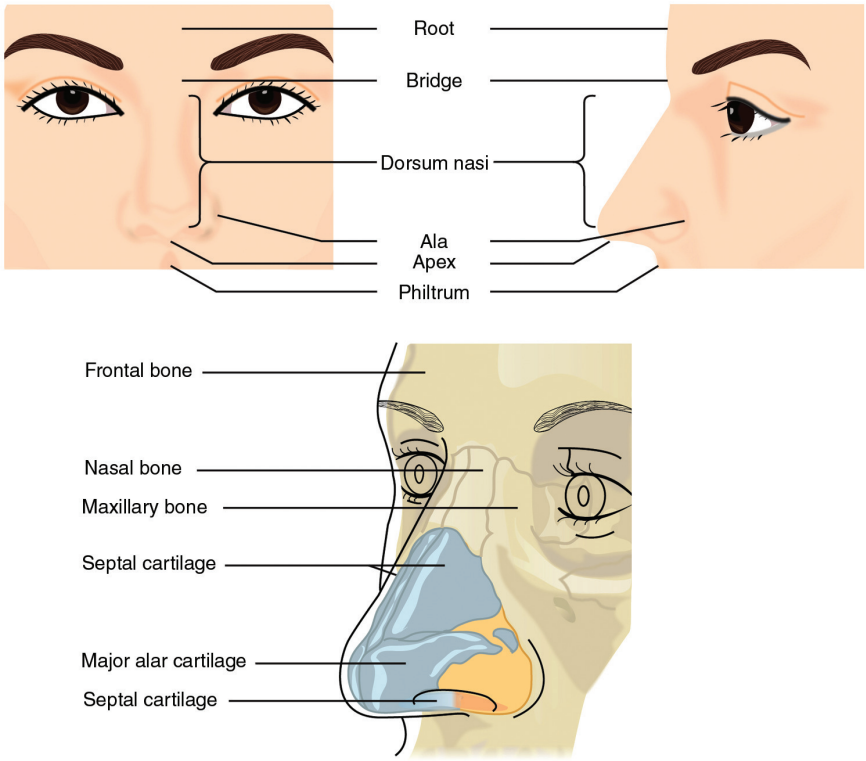


Fig. Nose. This illustration shows features of the external nose (top) and skeletal features of the nose (bottom).

The nares open into the nasal cavity, which is separated into left and right sections by the nasal septum. The nasal septum is formed anteriorly by a portion of the septal cartilage (the flexible portion you can touch with your fingers) and posteriorly by the perpendicular plate of the ethmoid bone (a cranial bone located just posterior to the nasal bones) and the thin vomer bones (whose name refers to its plough shape). Each lateral wall of the nasal cavity has three bony projections, called the superior, middle, and inferior nasal conchae.

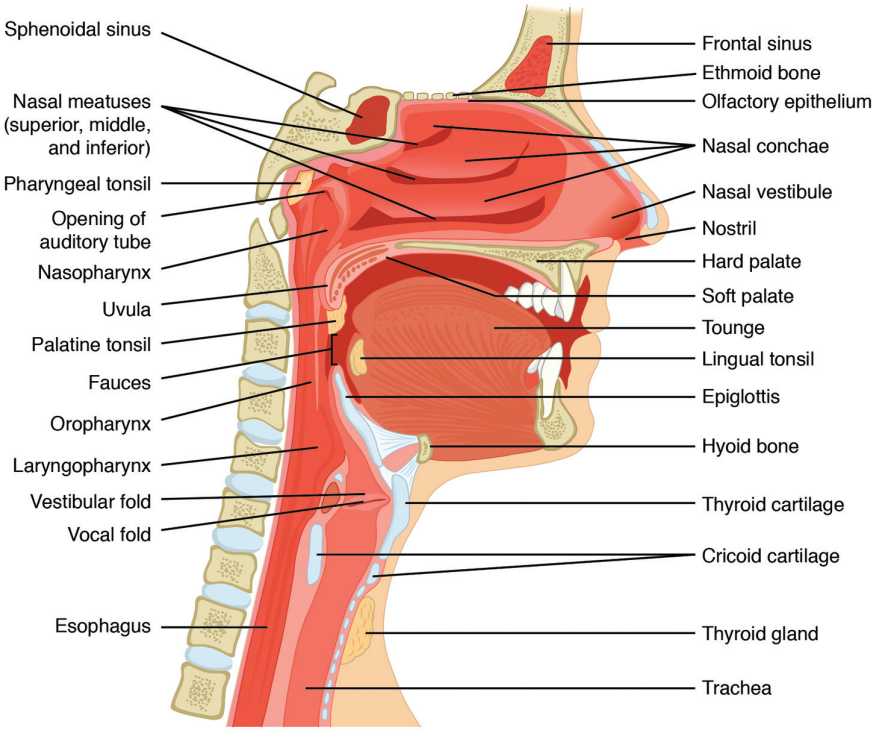


Fig. Upper Airway.

The inferior conchae are separate bones, whereas the superior and middle conchae are portions of the ethmoid bone. Conchae serve to increase the surface area of the nasal cavity and to disrupt the flow of air as it enters the nose, causing air to bounce along the epithelium, where it is cleaned and warmed. The conchae and meatuses also conserve water and prevent dehydration of the nasal epithelium by trapping water during exhalation. The floor of the nasal cavity is composed of the palate. The hard palate at the anterior region of the nasal cavity is composed of bone. The soft palate at the posterior portion of the nasal cavity consists of muscle tissue. Air exits the nasal cavities via the internal nares and moves into the pharynx.

Several bones that help form the walls of the nasal cavity have air-containing spaces called the paranasal sinuses, which serve to warm and humidify incoming air. Sinuses are lined with a mucosa. Each paranasal sinus is named for its associated bone: frontal sinus, maxillary sinus, sphenoidal sinus, and ethmoidal sinus. The sinuses produce mucus and lighten the weight of the skull.

The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odours is found deeper in the nasal cavity.

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

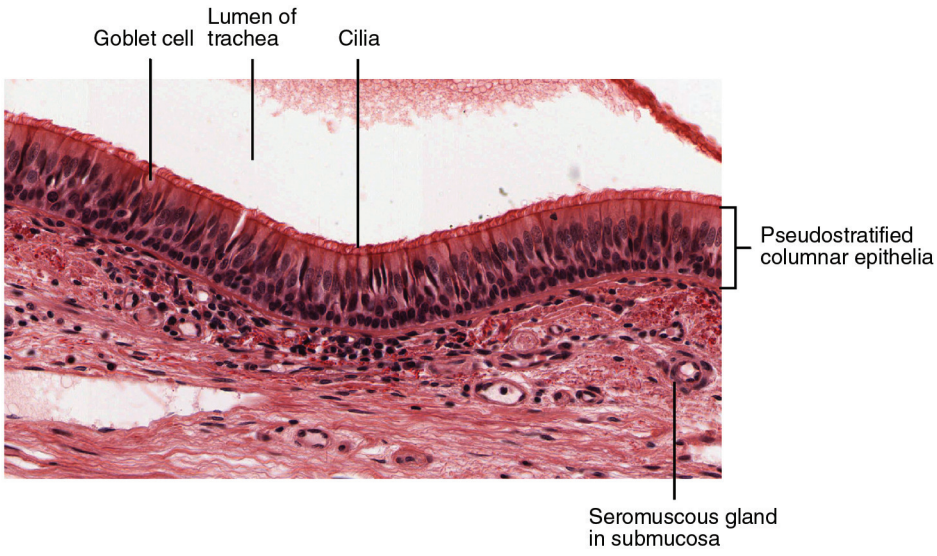


Fig. Pseudostratified Ciliated Columnar Epithelium. Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus.

PHARYNX

The pharynx is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities. The pharynx is divided into three major regions: the nasopharynx, the oropharynx, and the laryngopharynx.

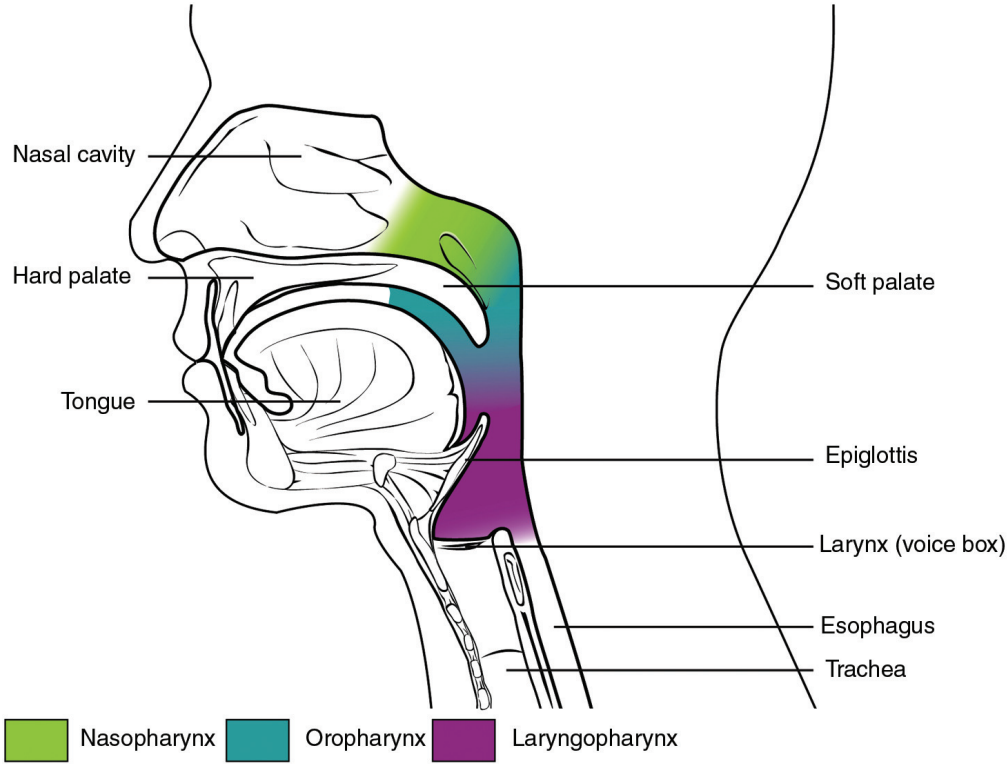


Fig. Divisions of the Pharynx. The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

The nasopharynx is flanked by the conchae of the nasal cavity, and it serves only as an airway. At the top of the nasopharynx are the pharyngeal tonsils. A pharyngeal tonsil, also called an adenoid, is an aggregate of lymphoid reticular tissue similar to a lymph node that lies at the superior portion of the nasopharynx. The function of the pharyngeal tonsil is not well understood, but it contains a rich supply of lymphocytes and is covered with ciliated epithelium that traps and destroys invading pathogens that enter during inhalation. The pharyngeal tonsils are large in children, but interestingly, tend to regress with age and may even disappear. The uvula is a small bulbous, teardrop-shaped structure located at the apex of the soft palate. Both the uvula and soft palate move like a pendulum during swallowing, swinging upward to close off the nasopharynx to prevent ingested materials from entering the nasal cavity. In addition, auditory (Eustachian) tubes that connect to each middle ear cavity open into the nasopharynx. This connection is why colds often lead to ear infections.

The oropharynx is a passageway for both air and food. The oropharynx is bordered superiorly by the nasopharynx and anteriorly by the oral cavity. The fauces is the opening at the connection between the oral cavity and the oropharynx. As the nasopharynx becomes the oropharynx, the epithelium changes from pseudostratified ciliated columnar epithelium to stratified squamous epithelium. The oropharynx contains two distinct sets of tonsils, the palatine and lingual tonsils. A palatine tonsil is one of a pair of structures located laterally in the oropharynx in the area of the fauces. The lingual tonsil is located at the base of the tongue. Similar to the pharyngeal tonsil, the palatine and lingual tonsils are composed of lymphoid tissue, and trap and destroy pathogens entering the body through the oral or nasal cavities.

The laryngopharynx is inferior to the oropharynx and posterior to the larynx. It continues the route for ingested material and air until its inferior end, where the digestive and respiratory systems diverge. The stratified squamous epithelium of the oropharynx is continuous with the laryngopharynx. Anteriorly, the laryngopharynx opens into the larynx, whereas posteriorly, it enters the esophagus.

LARYNX

The larynx is a cartilaginous structure inferior to the laryngopharynx that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs. The structure of the larynx is formed by several pieces of cartilage. Three large cartilage pieces—the thyroid cartilage (anterior), epiglottis (superior), and cricoid cartilage (inferior)—form the major structure of the larynx. The thyroid cartilage is the largest piece of cartilage that makes up the larynx. The thyroid cartilage consists of the laryngeal prominence, or "Adam's apple," which tends to be more prominent in males. The thick cricoid cartilage forms a ring, with a wide posterior region and a thinner anterior region. Three smaller, paired cartilages—the arytenoids, corniculates, and cuneiforms—attach to the epiglottis and the vocal cords and muscle that help move the vocal cords to produce speech.

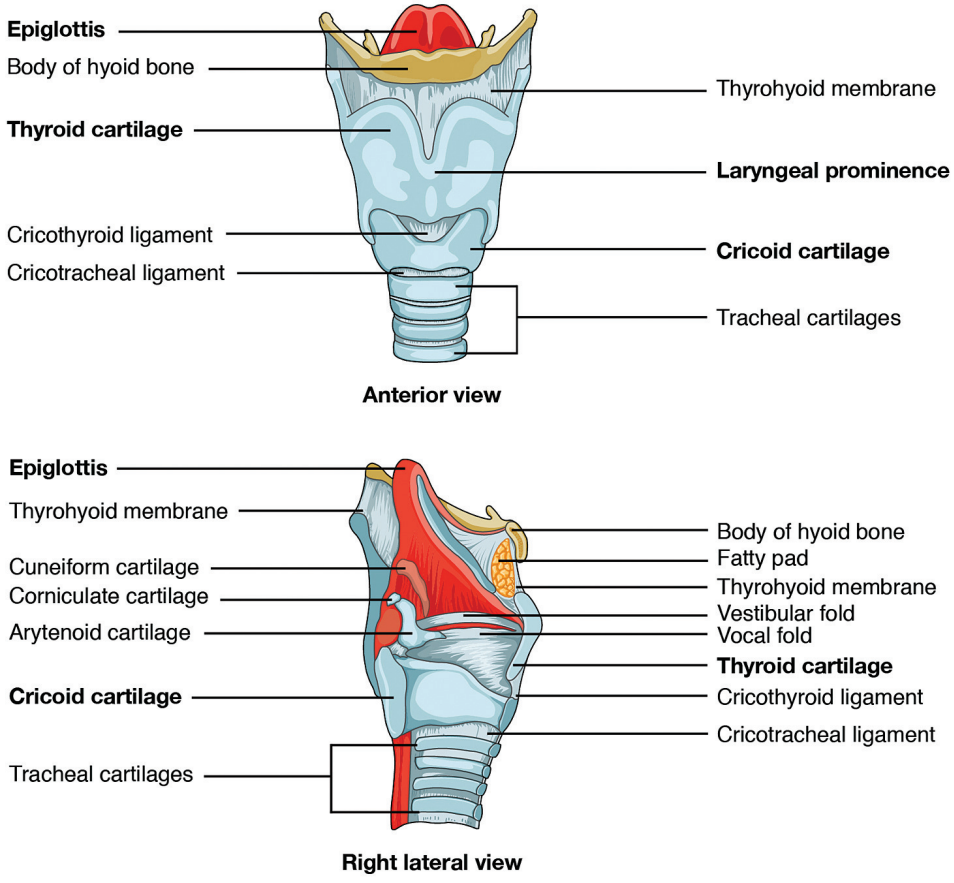


Fig. Larynx. The Larynx Extends from the Laryngopharynx and the Hyoid bone to the Trachea.

The epiglottis, attached to the thyroid cartilage, is a very flexible piece of elastic cartilage that covers the opening of the trachea. When in the "closed" position, the unattached end of the epiglottis rests on the glottis. The glottis is composed of the vestibular folds, the true vocal cords, and the space between these folds. A vestibular fold, or false vocal cord, is one of a pair of folded sections of mucous membrane. A true vocal cord is one of the white, membranous folds attached by muscle to the thyroid and arytenoid cartilages of the larynx on their outer edges. The inner edges of the true vocal cords are free, allowing oscillation to produce sound. The size of the membranous folds of the true vocal cords differs between individuals, producing voices with different pitch ranges. Folds in males tend to be larger than those in females, which create a deeper voice. The act of swallowing causes the pharynx and larynx to lift upward, allowing the pharynx to expand and the epiglottis of the larynx to swing downward, closing the opening to the trachea. These movements produce a larger area for food to pass through, while preventing food and beverages from entering the trachea.

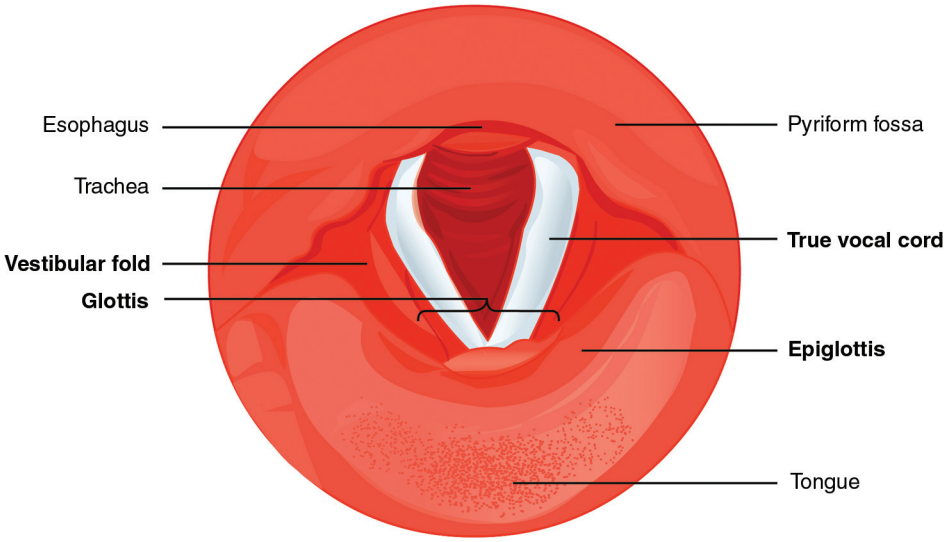


Fig. Vocal Cords. The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.

Continuous with the laryngopharynx, the superior portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the laryngopharynx, where it can be swallowed down the esophagus.

TRACHEA

The trachea (windpipe) extends from the larynx towards the lungs. The trachea is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The trachealis muscle and elastic connective tissue together form the fibroelastic membrane, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages.

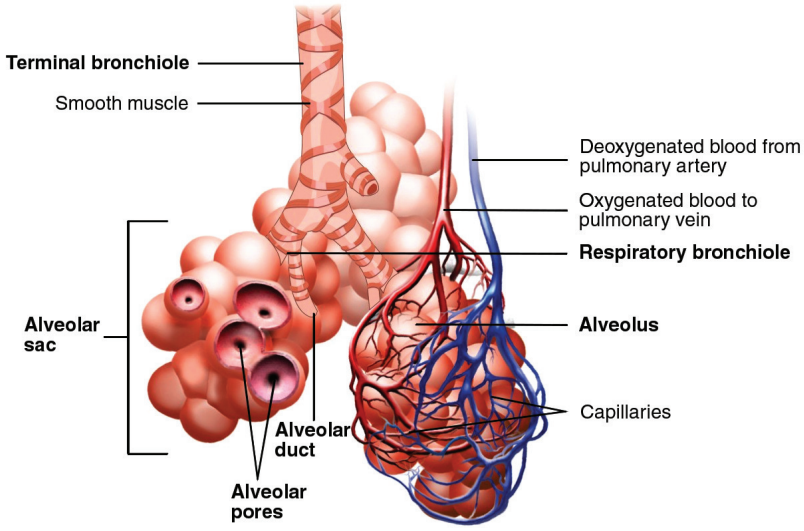


Fig. Trachea. (a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells.

The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.

BRONCHIAL TREE

The trachea branches into the right and left primary bronchi at the carina. These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells. The carina is a raised structure that contains specialized nervous tissue that induces violent coughing if a foreign body, such as food, is present. Rings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The bronchi continue to branch into bronchial a tree. A bronchial tree (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens. A bronchiole branches from the tertiary bronchi. Bronchioles, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles, which lead to the structures of gas exchange. There are more than 1000 terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

RESPIRATORY ZONE

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

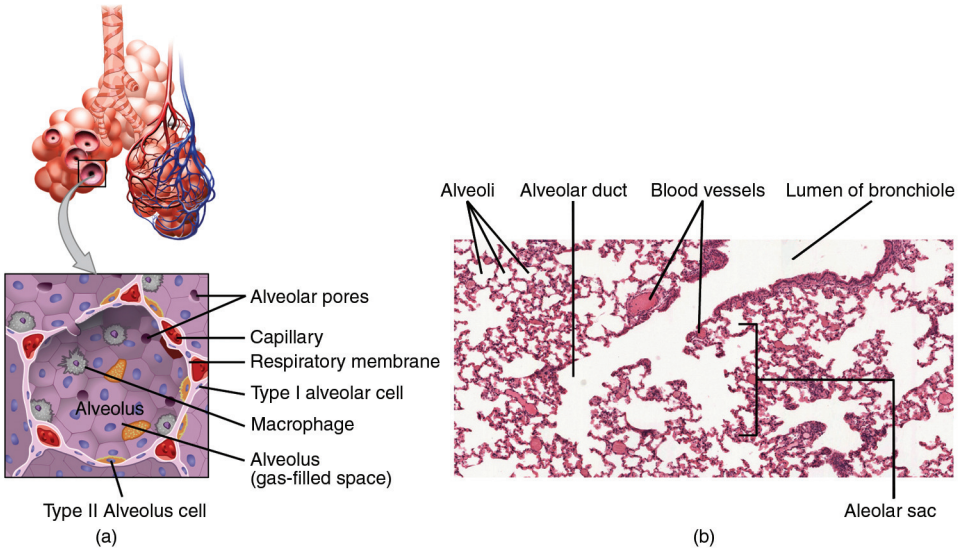


Fig. Respiratory Zone. Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

ALVEOLI

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

An alveolar sac is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 µm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbours by alveolar pores, which help maintain equal air pressure throughout the alveoli and lung.

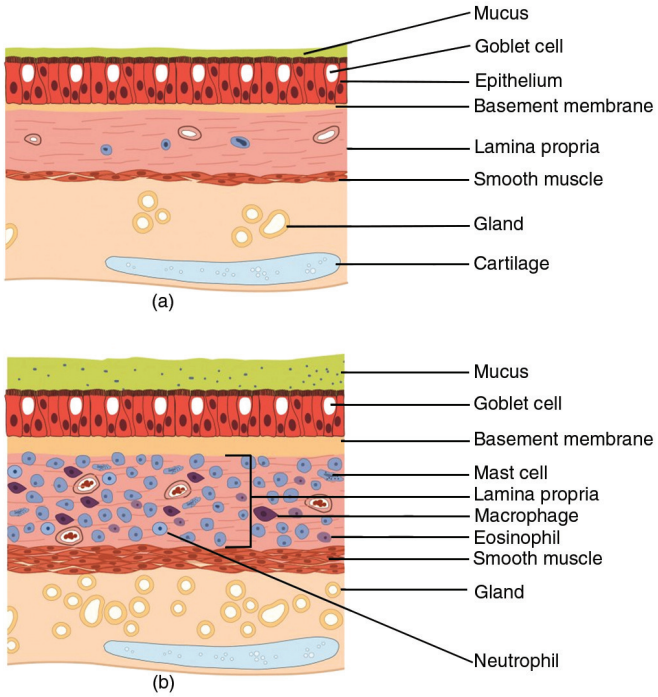


Fig. Structures of the Respiratory Zone. (a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue.

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

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

THE RESPIRATORY SYSTEM - STRUCTURE AND FUNCTION

The respiratory system is the system in the human body that enables us to breathe. The act of breathing includes: inhaling and exhaling air in the body; the absorption of oxygen from the air in order to produce energy; the discharge of carbon dioxide, which is the byproduct of the process.

THE PARTS OF THE RESPIRATORY SYSTEM

The respiratory system is divided into two parts:

- *Upper Respiratory Tract:* This includes the nose, mouth, and the beginning of the trachea.

- *Lower Respiratory Tract:* This includes the trachea, the bronchi, broncheoli and the lungs (the act of breathing takes place in this part of the system).
  The organs of the lower respiratory tract are located in the chest cavity. They are delineated and protected by the ribcage, the chest bone (sternum), and the muscles between the ribs and the diaphragm (that constitute a muscular partition between the chest and the abdominal cavity).
- *The Trachea:* The tube connecting the throat to the bronchi.
- *The Bronchi:* The trachea divides into two bronchi (tubes). One leads to the left lung, the other to the right lung. Inside the lungs each of the bronchi divides into smaller bronchi.
- *The Broncheoli:* The bronchi branches off into smaller tubes called broncheoli which end in the pulmonary alveolus.
- *Pulmonary Alveoli:* Tiny sacs (air sacs) delineated by a single-layer membrane with blood capillaries at the other end.
  The exchange of gases takes place through the membrane of the pulmonary alveolus, which always contains air: oxygen (O_2) is absorbed from the air into the blood capillaries and the action of the heart circulates it through all the tissues in the body. At the same time, carbon dioxide (CO_2) is transmitted from the blood capillaries into the alveoli and then expelled through the bronchi and the upper respiratory tract.
  The inner surface of the lungs where the exchange of gases takes place is very large, due to the structure of the air sacs of the alveoli.
- *The Lungs:* A pair of organs found in all vertebrates.
- *The Structure of the Lungs Includes the Bronchial Tree:* Air tubes branching off from the bronchi into smaller and smaller air tubes, each one ending in a pulmonary alveolus.

The Act of Breathing

The act of Breathing has Two Stages – inhalation and Exhalation:

- *Inhalation:* The intake of air into the lungs through expansion of chest volume.
- *Exhalation:* The expulsion of air from the lungs through contraction of chest volume.

Inhalation and exhalation involves muscles:

1. Rib Muscles = the muscles between the ribs in the chest.
2. Diaphragm Muscle

Muscle movement: The diaphragm and rib muscles are constantly contracting and relaxing (approximately 16 times per minute), thus causing the chest cavity to increase and decrease.

During Inhalation – The muscles contract:

Contraction of the Diaphragm Muscle: Causes the diaphragm to flatten, thus enlarging the chest cavity.

Contraction of the Rib Muscles: Causes the ribs to rise, thus increasing the chest volume.

The chest cavity expands, thus reducing air pressure and causing air to be passively drawn into the lungs. Air passes from the high pressure outside the lungs to the low pressure inside the lungs.

During Exhalation – the Muscles Relax

The muscles are no longer contracting, they are relaxed. The diaphragm curves and rises, the ribs descend – and chest volume decreases. The chest cavity contracts thus increasing air pressure and causing the air in the lungs to be expelled through the upper respiratory tract. Exhalation, too, is passive. Air passes from the high pressure in the lungs to the low pressure in the upper respiratory tract. Inhalation and exhalation are involuntary and therefore their control requires an effort.

THE ACT OF BREATHING – ILLUSTRATION AND ANIMATION

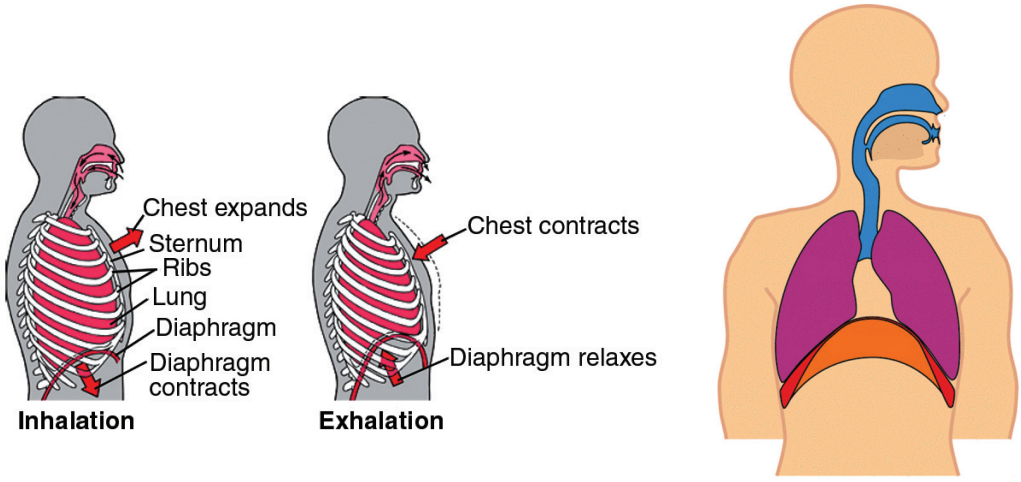


Fig. Changes in chest volume during inhalation and exhalation – Note that It only shows the movement of the diaphragm, not that of the rib muscles.

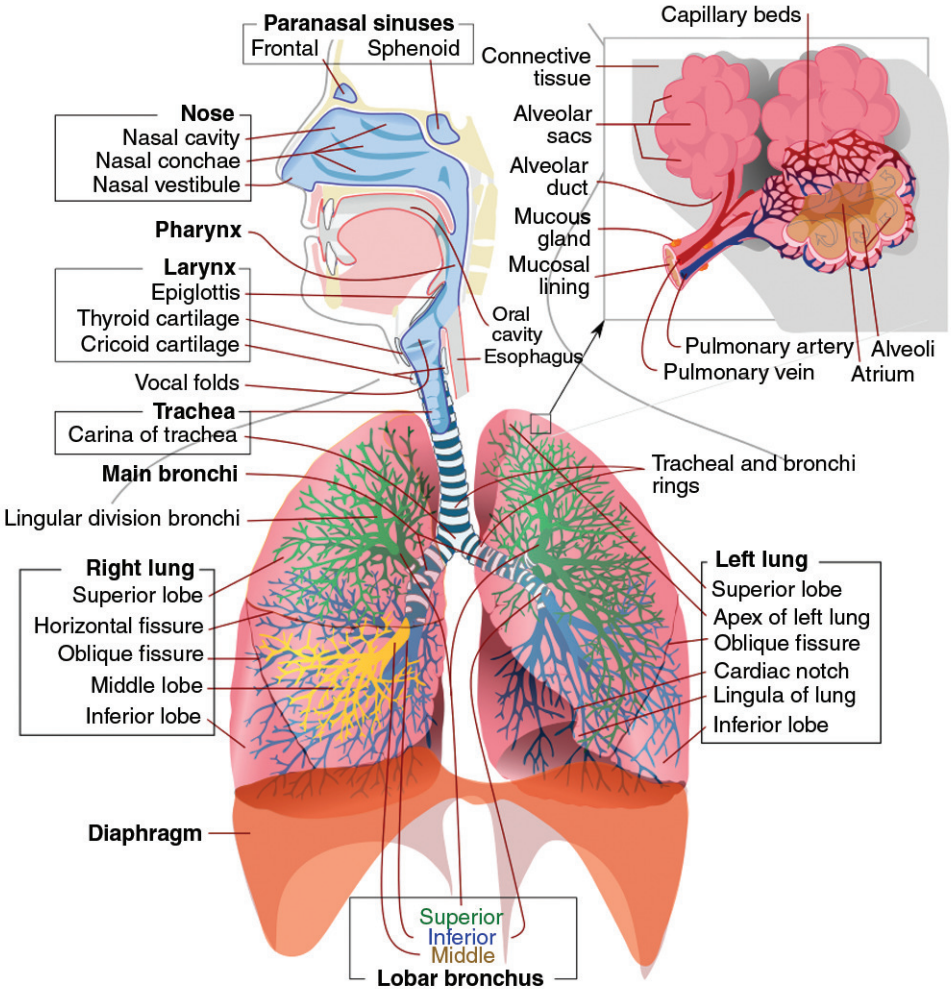


Fig. The Respiratory System- Illustration.

Measure

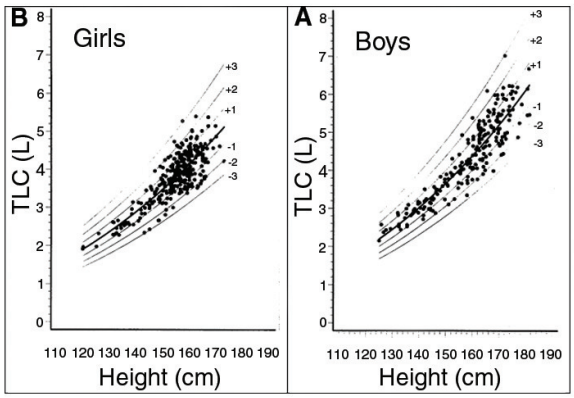
The respiratory airways include the respiratory apertures (mouth and nose), the trachea and a branching system of long, flexible tubes (bronchi) that branch of to shorter and narrower tubes (broncheoli) until they end in sacs called the pulmonary alveoli. The lungs encompass the entire system of tubes branching out from the main bronchi to the alveoli. Measuring the functioning of the lungs is a medical tool for diagnosing problems in the respiratory system.

Measurements of Lung Function

Air volume (in litres) – lung capacity:

- *Maximum lung volume* is known as TLC (total lung capacity). It can be obtained by maximum strenuous inhalation.
  The maximum lung volume of a healthy adult is up to 5-6 litres. In children the maximum lung volume is up to 2-3 litres, depending on age. In infants it is up to 600-1000 millilitres.
  Note: Differences in lung volume can only be caused by gender, age, and height.
- *Essential Air Volume* is the maximum volume utilized by the lungs for inhalation, also known as VC (vital capacity).
- *Residual Volume* (RV) is the volume of air remaining in the lungs after strenuous exhalation when the lungs feel completely empty. Residual volume prevents the broncheoli and the alveoli from sticking together. Residual volume is approximately 1.5 litres (adults).
- The differential between total lung capacity and residual volume is the *maximal volume utilized by the lungs in order to breath. It is known as vital capacity* (VC). In an adult, the VC is between 3.5 and 4.5 litres.
- *Tidal Volume* or VT is the volume of air displaced between normal inspiration and expiration. In a healthy adult the tidal volume is approximately 500 millilitres.

TLC (Total Lung Capacity) of Children



Examining Lung Function

The most common, accessible and efficient method of measuring lung function is by means of a spirometer. Its purpose is to diagnose obstructive diseases of the respiratory system. It produces a diagram (graphic depiction) of the volume of air expired in a given time (litre/minute) The spirometer shows the rate at which air is expelled from the lungs. It measures the total lung capacity up to the residual volume (this test does not show the rate at which oxygen is absorbed). If the airways are blocked the rate of the airflow of the lungs decreases. This will

show on the diagram and thus indicate that there is a problem in the airways. The most common obstruction stems from excessive phlegm, or from swelling of the inner wall of the air ways. The most common problem of blockage of the air ways is asthma. people suffering from asthma it take longer to empty the lungs than healthy people. For example, during the first second of exhalation, only half of the vital air capacity in their lungs is expelled as opposed to 90% in healthy people. The rest is exhaled much later. A spirometer examination takes only a few seconds. It is completely safe but there is a need for the patient to cooperate in order to obtain accurate results.

Stages of the Examination:

1. The patient is asked to inhale as deeply as possible.
2. The patient is asked to exhale strenuously into the spirometer.
3. The patient is asked to continue to expel air for a few seconds, despite the strong urge to breathe in.
4. The test is repeated twice or three times.

Respiratory Rate

Children in the upper classes of elementary school breathe about 20 times per minute. Every breath causes an inhalation of approximately 7 millilitres of air volume per kilogram of body weight. A child who weighs 30 kilos inhales approximately 210 millilitres of air volume (210 × 30). In other words, in the duration of a minute some 4200 millilitres of air volume enters and be expelled from the lungs.

Athletes breathe slightly deeper and slower. With every breath they inhale approximately 10 millilitres of air per kilogram. Thus an athletic child who weighs 30 kilos will only breathe 15 times in the duration space of a minute. Each inhalation will require some 300 milliliters of air volume. In the space of a minute 4500 millilitres of air volume will enter and be expelled from the his lungs. We can deduce from this that athletes ventilate their airways in a much more efficient way.

When we are under strain we breathe faster and more deeply. Since the lungs contain a reserve of air, we do not become tired because lack of air (oxygen) is causing respiratory restriction, but because of strain and tiredness in our respiratory and heart muscles. When we are under emotional stress (before an exam, in distress, or feeling very frightened) we breathe faster, but our breathing is shallower. For example, under stress we inhale 30 times per minute but at a rate of only 4 millilitres per kilo. In other words, overall only 3600 millilitres per minute are passing through our airways, so we feel "short of breath." During severe asthma attacks, the breathing of asthma patients is shallower and at a higher rate. Their breathing is thus not very efficient.

ANATOMY AND APPLIED ASPECTS OF PLEURA AND LUNGS

PLEURA

Each lung is enclosed in a serous pleural sac consisting two continuous membrane called visceral and parietal pleura. The two layers are continuous with each other around the hilum of the lung and enclose a potential space between them known as the pleural cavity. The pleura are lined by mesothelium. The visceral pleura invest all the surfaces of the lung forming their shiny outer surface and the parietal pleura lines the pulmonary cavities. The pleural cavity contains a layer of serous pleural fluid, which lubricates the pleural surfaces and allows the layers of pleura to slide smoothly over each other during respiration. Its surface tension also provides the cohesion that keeps the lung surface in contact with the thoracic wall.

The *visceral pleura* or pulmonary pleura closely covers the lung and is adherent to all its surfaces, including the surfaces within the horizontal and oblique fissures. The visceral pleura dip into the lung fissures so that the lobes of the lung are also covered with it. The visceral pleura are continuous with the parietal pleura at the hilum of the lung.

The parietal pleura line the pulmonary cavities. The parietal pleura consists of four parts:

1. *Costal pleura*– Covers the internal surfaces of the thoracic wall.
2. *Mediastinal pleura*– Covers the lateral aspects of the mediastinum.
3. *Diaphragmatic pleura*– Covers the superior or thoracic surface of the diaphragm on each side of the mediastinum.
4. *Cervical pleura (pleural cupula or dome of pleura)*- Extends from the superior thoracic aperture into the root of the neck, forming a cup shaped pleural dome over the apex of the lung.

The *pleural cavity* is the potential space between the layers of pleura and contains a capillary layer of serous pleural fluid, which lubricates the pleural surfaces and allows the layers of pleura to slide smoothly over each other during respiration.

The Pulmonary Ligament

- The parietal pleura extends downwards beyond the root as a fold called the pulmonary ligament.

Recesses of Pleura

There are two folds or recesses of parietal pleura which act as reserve spaces for the lung to expand during deep inspiration.

- *Costomediastinal Recess:* Lies anteriorly, behind the sternum and costal cartilages.
- *Costo Diaphragmatic Recess:* Lies inferiorly between the costal and diaphragmatic pleura.

Blood Supply and Lymphatic Drainage of Pleura

The pleura is supplied by intercostals, internal thoracic and musculophrenic arteries. The veins drain into the azygous and internal thoracic veins. The lymphatics drain into the intercostals, internal mammary, posterior mediastinal and diaphragmatic nodes.

Nerve Supply of Pleura

The parietal pleura is supplied by intercostals and phrenic nerves. The parietal pleura is pain sensitive. The pulmonary pleura is supplied by autonomous nerves derived from the spinal segments T4 and T5. This part of the pleura is not sensitive to pain.

APPLIED ANATOMY

Pleuritis or Pleurisy

This is the inflammation of the pleura. Acute pleuritis is marked by sharp, stabbing pain, especially on exertion.

Pneumothorax

This is a condition with the presence of air in the pleural cavity. Entry of air into the pleural cavity, resulting from a penetrating wound of the parietal pleura or rupture of a lung results in partial collapse of the lung.

Hemothorax

Presence of blood in the pleural cavity. Hemothorax results more often from injury to a major intercostal vessel than laceration of lung.

Hydrothorax

This is a condition with accumulation of significant amount of fluid in the pleural cavity.

Injuries to the Pleura

The cervical pleura reaches relatively higher levels in infants and young children because of the shortness of their necks. Consequently, the pleura is vulnerable to injury during the first few years. The small areas of pleura exposed in the costo vertebral angles inferiomedial to the 12th ribs are posterior to the superior poles of kidneys. The pleura is in danger here from an incision in the posterior abdominal wall when surgical procedures expose a kidney.

Pleural Adhesion

If the parietal and visceral pleura adhere the lymphatic vessels in the lung and visceral pleura drains into the axillary lymph nodes. The presence of carbon particles in these nodes is presumptive evidence of pleural adhesion.

Parencentesis Thoracic

Aspiration of any fluid from the pleural cavity is called parencentesis thoracis. It is usually done in the 6^{th} intercostal space in the midaxillary line. The needle is passed through the lower part of the space to avoid injury to the principal neurovascular bundle.

ANATOMY AND APPLIED ASPECTS OF THE LUNGS

Synonym: Pulmones

The lungs are the essential organs of respiration; they are two in number, placed one on either side within the thorax, and separated from each other by the heart and other contents of the mediastinum. The lungs are spongy in texture. In the young the lungs are brown or grey in colour. Gradually they become mottled black because of the deposition of the inhaled carbon particles. The right lung weighs about 625 g, it is about 50 g heavier than the left lung.

Each lung is conical in shape. It has:

- An apex at the upper end
- A base resting on the diaphragm
- *Three Borders:* Anterior, Posterior and Inferior
- *Three Surfaces:* Costal medial and diaphragmatic
- The *apex* is rounded and rises into the root of the neck about 1 inch above the level of the middle third of the clavicle. The structures associated with it are the first rib, blood vessels and nerves in the root of the neck.
- The *base* is concave and semi lunar in shape. It rests on the diaphragm which separates the right lung from the right lobe of the liver, and the left lung from the left lobe of the liver, fundus of the stomach, and the spleen.
- The *anterior border* is very thin. It is shorter than the posterior border. On the right side it is vertical and corresponds to the anterior line of pleural reflection. The anterior border of the left lung shows a wide cardiac notch below the level of 4^{th} costal cartilage. The heart and the pericardium are uncovered by the lung in the region of this notch.

- The *posterior border* is where the costal and the mediastinal surfaces meet posteriorly. It is thick and ill defined. It corresponds to the medial margin of the heads of the ribs.
- The *inferior border* circumscribes the diaphragmatic surface of the lung and separates the base from the costal and the medial surfaces.
- The *costal surface* is convex and is closely associated with the costal cartilages, the ribs and the intercostals muscles.
- The *medial surface* is concave and has a roughly triangular shaped area, called the hilum, at the level of 5^{th}, 6^{th} and 7^{th} thoracic vertebrae. This surface is divided into a posterior or vertebral part and an anterior or mediastinal part.
- *Diaphragmatic surface* forms the base of the lung rests on the dome of the diaphragm. The concavity is deeper in the right lung because of the higher position of the right diaphragmatic dome, which overlies the large liver.

Root of the Lung

The lungs attach to the heart and trachea by structures that comprise the roots of the lungs. The root of the lung is formed by structures entering and leaving the lung at its hilum. The root is enclosed within the area of continuity between the parietal and visceral layers of pleura called the pleural sleeve or mesopneumonium or mesentery of the lung. The hilum of the lung is the area on the medial surface of each lung, the point at which the structures forming the root.

These include:

- Bronchus
- Pulmonary artery
- Pulmonary veins
- Bronchial artery
- Bronchial veins
- Lymph vessels
- Parasympathetic and sympathetic nerves.

The area between the lungs is the mediastinum. It is occupied by the heart, great vessels, trachea, right and left bronchi, esophagus, lymph nodes, lymph vessels and nerves.

FISSURES AND LOBES OF THE LUNGS

The right lung is divided into three distinct lobes by two fissures (oblique and horizontal):

- Superior
- Middle
- Inferior

The left lung is smaller as heart is situated left of the midline. It is divided into only two lobes by the oblique fissure.

- Superior
- Inferior

The oblique fissure cuts into the whole thickness of the lung except at the hilum. It passes obliquely downwards and forwards, crossing the posterior border about 2 ½ inches below the apex and the inferior border about 2 inches from the medial plane. Due to the oblique plane of the fissure the lower lobe is more posterior and the upper lobe more anterior.

In the *right lung*, the horizontal fissure passes from the anterior border up to the oblique fissure and separated a wedge shaped middle lobe from the upper lobe. The fissure runs horizontally at the level of 4^{th} costal cartilage and meets the oblique fissure in the mid-axillary line. The tongue shaped projection of the left lung below the

cardiac notch is called the lingula. It corresponds to the middle lobe of the right lung. The lungs expand maximally in the inferior direction because movements of the thoracic wall and the diaphragm are maximal towards the base of the lung. The presence of the oblique fissure of each lung allows a more uniform expansion of the whole lung.

Interior of Lung

The lungs are composed of the bronchi and smaller air passages, alveoli, connective tissue, blood vessels, lymph vessels and nerves.

Trachea and Bronchi

The main bronchi or the primary bronchi, one to each lung, pass inferomedially from the bifurcation of the trachea at the level of the sternal angle to the hila of the lungs. The walls of the trachea and bronchi are supported by horseshoe or C- shaped rings of hyaline cartilage. The right main bronchus is wider, shorter and runs more vertically than the left main bronchus as it passes directly to the hilum of the lung.

The left main bronchus passes inferolaterally, inferior to the arch of aorta and anterior to the esophagus and thoracic aorta, to reach the hilum. The main bronchi enter the hila of the lungs and branch in a constant fashion within the lungs to form the bronchial tree. Each main bronchus divides into lobar bronchi (secondary bronchi), two on the left and three on the right, each of which supplies a lobe. Each lobar bronchus divides into several segmental bronchi (tertiary bronchi) that supply the bronchopulmonary segments.

Bronchopulmonary Segments

These are well defined sectors of the lung, each one of which is aerated by a tertiary or segmental bronchus. Each segment is pyramidal in shape with its apex directed towards the root of the lung and its base at the pleural surface. It is the largest subdivision of a lobe. It is separated from adjacent segments by connective tissue septa. It is supplied independently by a segmental bronchus and a tertiary branch of pulmonary artery. It is named according to the segmental bronchus supplying it. It is drained by the intersegmental parts of the pulmonary veins that lie in the connective tissue between and drain adjacent segments. It is surgically respectable.

Beyond the direct branches of the lobar bronchi, there are 20-25 generations of the branches that eventually end in terminal bronchioles. Each terminal bronchiole give rise to several generations of respiratory bronchioles and each respiratory bronchiole provides 2 to 11 alveolar ducts, each of which give rises to 5 or 6 alveolar sacs lined by alveoli.

Pulmonary Unit

Each respiratory bronchiole aerates a small part of the lung known as a pulmonary unit. The respiratory bronchiole ends in microscopic passages like- alveolar ducts, atria, air succules and pulmonary alveoli. The alveolus is the basic structural unit of gas exchange in the lung. New alveoli continue to develop until the age of 8 yrs, by which there are about 300 million alveoli.

Arterial Supply of the Lungs

Each lung has a large pulmonary artery supplying blood to it and two pulmonary veins draining blood from it. The right and left pulmonary arteries arise from the pulmonary trunk at the level of the sternal angle and carry venous blood to the lungs for oxygenation. Each pulmonary artery becomes part of the root of the corresponding lung and gives off its first branch to the superior lobe before entering the hilum. Within the lung

each artery descends posterolateral to the main bronchus and divides into lobar and segmental arteries. Consequently, an arterial branch goes to each lobe and bronchopulmonary segments. The artery and the bronchi are paired in the lung, branching simultaneously and running parallel courses.

The left bronchial arteries arise from the thoracic aorta and the right bronchial artery may arise from a superior posterior intercostals artery or from the thoracic aorta or from a left superior bronchial artery.

Venous Drainage of the Lungs

Usually there are two bronchial veins on each side carrying oxygenated blood from the lungs to the left atrium of the heart. The right bronchial vein drains into the azygos vein. The left bronchial vein drains either into the left superior intercostals vein or into the hemiazygos vein. The greater part of the venous blood from the lung is drained by the pulmonary veins. Beginning in the pulmonary capillaries, the veins unite into larger and larger vessels.

Lymphatic Drainage of the Lungs

- There are two sets of lymphatics, both of which drain into the bronchopulmonary nodes.
- Superficial vessels drain the peripheral lung tissue lying beneath the pulmonary pleura. The vessels pass round the borders of the lung and margins of the fissures to reach the hilum.
- Deep lymphatic drain the bronchial tree, the pulmonary vessels and the connective tissue septa. They run towards the hilum where they drain into the bronchopulmonary nodes.

Nerve Supply of the Lungs

Parasympathetic nerves are derived from the vagus. These fibres are:

- Motor to the bronchial muscles, and on stimulation cause bronchospasm
- Secretomotor to the mucus glands of the bronchial tree
- Sensory fibres are responsible for the stretch reflex of the lungs and for the cough reflex.
- Sympathetic nerves are derived from spinal segments T2 to T5. These are inhibitory to the smooth muscle and the glands of the bronchial tree.
- Both parasympathetic and the sympathetic nerves first form anterior and posterior pulmonary plexuses situated in front of and behind the lung roots. From the plexus, nerves are distributed to the lungs along the blood vessels and bronchi.

SURFACE ANATOMY OF THE PLEURAE AND LUNGS

- The cervical pleurae and the apices of the lungs pass through the superior thoracic aperture into the supraclavicular fossa, which are located superior and posterior to the clavicles and lateral to the tendons of the sternomastoid muscles.
- The anterior border of the lungs lies adjacent to the anterior line of reflection of the parietal pleura as far inferiorly as the 4th costal cartilages. The anterior border of the left lung is more deep indented by its cardiac notch. On the right side, the pleural reflection continues inferiorly from the 4th to the 6th costal cartilage, paralleled closely by the anterior border of the right lung.
- The pleural reflections reach the MCL at the level of 8th costal cartilage, the 10th rib at the MAL, and 12th rib at the scapular line.
- The inferior margins of the lungs reach the MCL at the level of 6th rib, MAL at 8th rib and the scapular line at the 10th rib.

- The oblique fissure of the lungs extends from the level of the spinous process of the T2 vertebra posteriorly to the 6th costal cartilage anteriorly.
- The horizontal fissure of the right lung extends from the oblique fissure along the 4th rib and costal cartilage anteriorly.

APPLIED ANATOMY

Variation in the Lobes of the Lung

Occasionally an extra fissure divides a lung or a fissure is absent. The most common accessory lobe is the azygos lobe, which appears in the right lung in about 1% of people. In these cases, the azygos vein arches over the apex of the right lung and not over the right hilum, isolating the medial part of the apex as an azygos lobe.

Aspiration of Foreign Bodies

Since the right bronchus is wider and shorter and runs more vertically than the left bronchus, foreign bodies are more likely to enter and lodge in it or in one of its branches.

Bronchoscopy

When examining with a bronchoscope, one observes a keel like ridge called the carina. It is a cartilaginous projection of the last tracheal ring. Morphological changes in the carina are important diagnostic signs to bronchoscopists in assisting with the differential diagnosis of respiratory disease.

Lung Resection

Knowledge of the anatomy of the bronchopulmonary segments is essential for precise interpretation of radiographs and other diagnostic images of the lungs and for surgical resection of the diseased segments. Bronchial and pulmonary disorders such as tumors or abscesses often localize in a bronchopulmonary segment, which may be surgically resected. During treatment of the lung cancer, the surgeon may remove a whole lung (pneumonectomy), a lobe (lobectomy) or a segment (segmentectomy).

Bronchial Asthma

Bronchial asthma IS n increasingly common condition of the lungs in which widespread narrowing of the airways is present. Asthma is caused by varying degrees by contraction of the smooth muscle, edema of the mucosa, and mucus in the lumen of the bronchi and bronchioles. These changes are caused by the local release of spasmogens and vasoactive substances influencing the tone and calibre of the blood vessels (eg; histamine and prostaglandins). The absence of cartilages in the walls of bronchioles is a potential hazard. In asthma, there is difficult expiration because the bronchioles which are opened during inspiration also have to remain open during expiration if they are to permit a rapid outflow of air owing to elastic recoil of the lung tissues. That's why more wheeze and breathing difficulties are experienced during expiration.

Pulmonary Thromboembolism

Obstruction of a pulmonary artery by a thrombus is a common cause of morbidity and mortality. An embolus in a pulmonary artery forms when a thrombus, fat globule, or air bubble travels in the blood to the lungs from a leg vein. The thrombus may block a pulmonary artery or its branch. The immediate result is partial or complete

obstruction of the blood to the lungs. When a large embolus occludes a pulmonary artery, the patient suffers from acute respiratory distress and may die in a few minutes.

Floatation of the Lungs

Fresh healthy lungs always contain some air. Diseased lungs filled with fluid, fetal lungs, and lungs from a still born infant will not float. The lungs of a live born infant who dies shortly after birth floats. These observations are of medico legal significance in determining whether a dead infant was stillborn or whether it was born alive and started to breathe.

Pneumonia

- This occurs when protective processes fail to prevent inhaled or blood born microbes reaching and colonizing the lungs.
- *Types:* lobar pneumonia and bronchopneumonia.

Lobar Pneumonia

This is the infection of one or more lobes by str.pneumoniae mainly type 1, 2 and 3. The infection leads to the production of watery inflammatory exudate in the alveoli. This accumulates and fills the lobule then overflows into the adjacent lobules spreading the microbes. It is of sudden onset and pleuritic pain accompanies inflammation of the visceral pleura. If not treated, the disease goes through a series of stages followed by resolution and reinflation of the lobes in 2-3 weeks.

Bronchopneumonia

Infection is spread from the bronchi to terminal bronchioles and alveoli. As these become inflamed, fibrous exudates accumulates and there is an influx of leukocytes. Small foci of consolidation develop. There is frequently incomplete resolution with fibrosis. Bronchiectasis is a common complication leading to further acute attacks. Bronchopneumonia occurs more commonly in infancy and old age, and death is fairly common.

MICROBES CAUSING PNEUMONIA

1. *Staphylococcus Aureus:* Infection is preceded by influenza, measles, whooping cough or chronic lung disease. Incomplete resolution may cause abscess formation.
2. *Friedlander's Bacillus (klebsiella pneumoniae):* This commensal is sometimes present in the upper respiratory tract, especially where there is advanced dental caries. It commonly causes pneumonia in men over 50 years and is often associated with diabetes mellitus and alcoholism.
3. *Legionella Pneumonophila:* These microbes are widely seen in water tanks, shower heads and air conditioning systems. They may cause severe form of pneumonia (Legionnaires ' disease), complicated by GI disturbances, headache, mental confusion and renal failure.
4. *Streptococcus Pyogenes:* Infection usually preceded by influenza or measles. In severe cases death may occur within few days.
5. *Pseudomonas Pyocyanae:* This is a commensal in the bowel that may cause a type of pneumonia acquired by cross infection in hospitals especially in patients with mechanically assisted ventilation or tracheostomy.
6. *Streptococcus Pneumonia (Pneumococcus):* This is a commensal in the respiratory tract which may cause lobar pneumonia or bronchopneumonia, usually preceded by viral infection.

LUNG ABSCESS

Local suppuration and necrosis within the lung substance is most commonly caused by str.viridans, str. Pyogenes, str. Pneumoniae, staph. Aureus.

MYCOBACTERIUM TUBERCULOSIS

Man is the main host. The microbes cause pulmonary tuberculosis and are spread either by droplet infection from an individual with active tuberculosis, or in dust contaminated by infected sputum.

Primary Tuberculosis

When microbes are inhaled they colonize a lung bronchiole, usually towards the apex of the lung. There may be no evidence of clinical disease during the initial stage of non- specific inflammation. T- Lymphocytes respond to the microbes and the individual becomes sensitized. Macrophages surround the microbes at the site of infection forming Ghon foci or tubercles. Some macrophages containing live microbes are spread in lymph and infect hilar lymph nodes. So primary complex consist of the Ghon foci and infected hilar lymph nodes. Primary tubercle is usually asymptomatic.

There are various outcomes:

- The disease may be permanently arrested, the foci becoming fibrosed and calcified.
- Microbes may survive in the foci and become the source of post primary infection months or years later.
- The disease may spread throughout the lung or to other parts of the body. The disease spreads to other parts of the body via lymph and blood leading to wide spread of the infection and the development of numerous small foci throughout the body (miliary tuberculosis).

*Secondary or Post primary tuberculosis: T*his phase occurs only in people previously sensitized by a primary lesion.

ACUTE BRONCHITIS

This is usually a secondary bacterial infection of the bronchi. It is usually preceded by a common cold or influenza.

CHRONIC BRONCHITIS

It is defined clinically as the presence of cough with sputum for 3 months in 2 successive years. It is a progressive inflammatory disease resulting from prolonged irritation of the bronchial epithelium. It develops mostly in middle aged men who are chronic heavy smokers and may have a familial predisposition. Ventilation of the lung is severely impaired, causing breathlessness, leading to hypoxia, pulmonary hypertension and right heart failure.

BRONCHIECTASIS

There is permanent abnormal dilatation of the bronchi and bronchioles. It is associated with chronic bacterial infection and there may be history of childhood bronchiolitis and bronchopneumonia, cystic fibrosis or bronchial tumour. The lower lobe of the lung is usually affected. Suppuration is common.

BRONCHIAL CARCINOMA

Primary bronchial carcinoma is a common form of malignancy. The tumour usually develops in a main bronchus, forming a large friable mass that project into the lumen sometimes causing obstruction. As the tumour

grows it may erode a blood vessel causing hemoptysis. The cause is not known but there is strong positive association with cigarette smoking and passive smoking. The modes of spread are infiltration of local tissues and the transport of tumour fragments in blood and lymph. Local spread may be within the lung, to the other lung or to the mediastinal structures. Tumour fragments may spread along the lymph vessels to the successive lymph nodes in which they may cause metastatic tumours. The most common sites of the blood born metastases are liver, brain, adrenal glands, bones and kidneys.

ATELECTASIS

There is defect in the expansion of the lungs. There are two types based on the time of onset:

- Immediately after birth.
- Within minutes or hours of birth.

PNEUMOCONIOSIS

This is a group of lung diseases caused by inhaling organic or inorganic atmospheric pollutants. Some of them are:

- *Coal workers Pneumoconiosis:* Soft bituminous Coal.
- *Siilicosis:* Dust Containing Silicon Compounds.
- *Asbestosis:* Asbestos.
- *Pleural Mesothelioma:* Asbestos.
- *Byssinosis:* Cotton Fibres.

Extrinsic Allergic Alveolitis

This is a group of conditions caused by inhaling materials contaminated by moulds and fungi:

- *Farmers Lung*: mouldy hay
- *Bagassosis:* Mouldy sugar waste
- *Bird Handler's Lung:* mould in bird droppings
- *Malt Worker's Lung:* mouldy barley.

6

Digestive System

DIGESTION DEFINITION

The energy required for all the processes and activities that take place in our bodies is derived from the foods we ingest. The digestive system allows us to utilize food from such diverse sources as meat from an animal and the roots of a plant, and utilize them as an energy source. Whether it is the ability to coordinate the chewing of the food without injuring our tongue and lips or the propulsion of the food from the stomach into the duodenum while releasing the appropriate enzymes, our digestive system allows us to manage the process without much thought and often while performing other tasks.

PROCESS OF DIGESTION

The process of digestion is a fascinating and complex one that takes the food we place in our mouth and turns it into energy and waste products. This process takes place in the gastrointestinal tract, a long, connected, tubular structure that starts with the mouth and ends with the anus. The food is propelled forward within the system, altered by enzymes and hormones into usable particles and absorbed along the way. Other organs that support the digestive process are the liver, gallbladder, and pancreas. The time it takes for food to travel from entering the mouth to be excreted as waste is around 30 to 40 hours.

THE MOUTH

The mouth is the entry point for food, but the digestive system often gets ready before the first piece of food even enters our mouth. Saliva is released by the salivary glands into our oral cavity when we smell food. Once the food enters the mouth, chewing (mastication) breaks food into smaller particles that can be more easily attacked by the enzymes in saliva. Our teeth can perform a cutting as well as grinding function to accomplish this task. The tongue assists in mixing the food with the saliva and then the tongue and roof of the mouth (soft palate) help move the food along to the pharynx and esophagus.

THE PHARYNX AND ESOPHAGUS

The pharynx (throat) is the transition area from the mouth to the esophagus. From the pharynx there are two paths that the food bolus can take; 1) the wrong path, which is down the windpipe into the lungs, or 2) the correct path into the esophagus and then the stomach. The act of swallowing is a complex process that closes the windpipe (to protect our lungs) and moves food into the esophagus. This process is mostly automatic (reflex) but it is also partially under our direct control.

Once it enters the esophagus, food is moved down the esophagus and into our stomach. The esophagus is a muscular tube that contracts in a synchronized fashion (peristalsis) to move food down towards the stomach.

While the muscles behind the food product contract, the muscles ahead of the food relax, causing the forward propulsion of the food. Peristalsis is the main mechanism by which food moves through our digestive system.

Once the food approaches the stomach, a muscular valve (the lower esophageal sphincter) relaxes and lets the food pass into the stomach. This sphincter has the important function of closing the stomach so no food or stomach acid reenters the esophagus (and therefore avoiding heartburn or regurgitation).

THE STOMACH AND SMALL INTESTINE

From glands that line the stomach, acid and enzymes are secreted that continue the breakdown process of the food. The stomach muscles further mix the food. At the end of this process, the food you placed in your mouth has been transformed to a thick creamy fluid called chyme. This thick fluid is then pushed into the duodenum (the first part of the small intestine). With the help of enzymes from the pancreas and bile from the liver, further breakdown of the food occurs in the small intestine. The small intestine has three segments. The first segment is the duodenum where further breakdown of the food takes place. The next two parts of the small intestine (jejunum and ileum) are mostly responsible for the absorption of nutrients from the processed food into the bloodstream through the walls of the intestine. After the small intestine, the leftover waste leaves the upper gastrointestinal tract (upper GI tract) which is made up of everything above the large intestine, and moves into the large intestine or colon (the beginning of the lower GI tract).

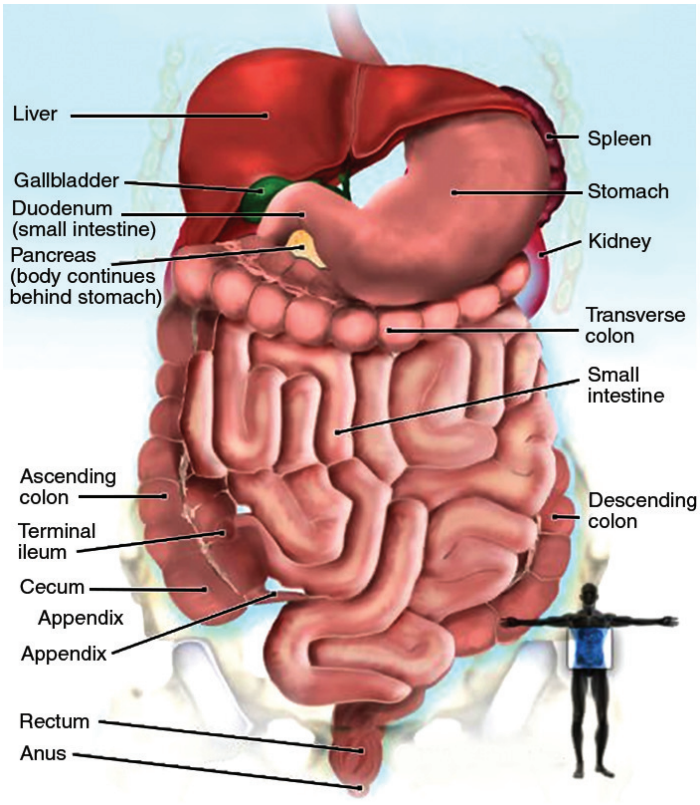


Fig. Anatomy of the Abdomen.

THE COLON, RECTUM, AND ANUS

The role of the lower GI tract is to solidify the waste product (by absorbing water), store the waste product until it can be evacuated (going to the bathroom) and help with the evacuation process.

The large intestine (colon) has four parts:

1. Ascending colon,

2. Transverse colon,
3. Descending colon and
4. Sigmoid colon.

All together the colon is approximately 7 feet long and connects to the rectum. Here as in most other parts of the GI system, the waste product is moved along by peristalsis. As the waste product passes through the colon, water is absorbed and stool is formed.

The stool from the colon is stored in the rectum. The anal sphincter provides the control over releasing stool or holding it. Once stool arrives in the rectum, a feedback to the brain makes the person aware of the need for a bowel movement. Voluntary control over the anal sphincter lets us hold the stool until we go to the toilet.

THREE ACCESSORY DIGESTIVE ORGANS (PANCREAS, LIVER, GALLBLADDER)

Three other organs are instrumental in the digestive process:

1. *Pancreas:* Although the pancreas is mostly known for its blood sugar regulatory function with the production of insulin (as part of the endocrine system—he insulin goesdirectly from the gland into the bloodstream), it is the main producer of digestive enzymes as part of the exocrine system (the enzymes produced by the gland pass through a duct into the intestines). These enzymes are released into the duodenum and help with the digestion of fats, proteins, and carbohydrates.
2. *Liver:* The liver produces bile for fat digestion and elimination. In addition, nutrients are stored in the liver, and toxins and chemicals are filtered by liver.
3. *Gallbladder:* Bile is stored and released from the gallbladder. When fatty food enters the duodenum, the gallbladder contracts and releases bile.

THE STRUCTURE AND FUNCTION OF THE DIGESTIVE SYSTEM

The article provides an overview of the digestive system, with a brief description of the body part components from the top (the mouth) to the bottom (the anus).

ORGANS MAKE UP THE DIGESTIVE SYSTEM

Your digestive system is uniquely constructed to perform its specialized function of turning food into the energy you need to survive and packaging the residue for waste disposal. To help you understand how the many parts of the digestive system work together, here is an overview of the structure and function of this complex system.

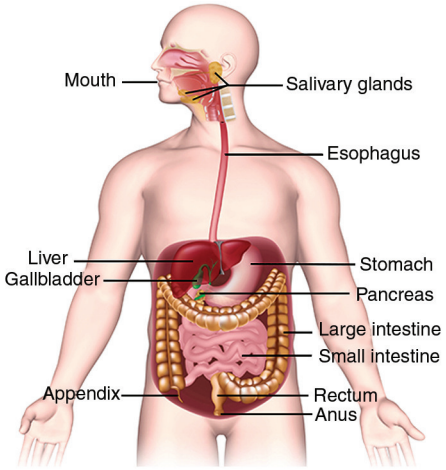


Fig. Structure of the Digestive System.

MOUTH

The mouth is the beginning of the digestive tract; and, in fact, digestion starts here when taking the first bite of food. Chewing breaks the food into pieces that are more easily digested, while saliva mixes with food to begin the process of breaking it down into a form your body can absorb and use.

ESOPHAGUS

Located in your throat near your trachea (windpipe), the esophagus receives food from your mouth when you swallow. By means of a series of muscular contractions called peristalsis, the esophagus delivers food to your stomach.

STOMACH

The stomach is a hollow organ, or "container," that holds food while it is being mixed with enzymes that continue the process of breaking down food into a usable form. Cells in the lining of the stomach secrete a strong acid and powerful enzymes that are responsible for the breakdown process. When the contents of the stomach are sufficiently processed, they are released into the small intestine.

SMALL INTESTINE

Made up of three segments- the duodenum, jejunum, and ileum - the small intestine is a 22-foot long muscular tube that breaks down food using enzymes released by the pancreas and bile from the liver. Peristalsis also is at work in this organ, moving food through and mixing it with digestive secretions from the pancreas and liver. The duodenum is largely responsible for the continuous breaking-down process, with the jejunum and ileum mainly responsible for absorption of nutrients into the bloodstream.

Contents of the small intestine start out semi-solid, and end in a liquid form after passing through the organ. Water, bile, enzymes, and mucous contribute to the change in consistency. Once the nutrients have been absorbed and the leftover-food residue liquid has passed through the small intestine, it then moves on to the large intestine, or colon.

PANCREAS

The pancreas secretes digestive enzymes into the duodenum, the first segment of the small intestine. These enzymes break down protein, fats, and carbohydrates. The pancreas also makes insulin, secreting it directly into the bloodstream. Insulin is the chief hormone for metabolizing sugar.

LIVER

The liver has multiple functions, but its main function within the digestive system is to process the nutrients absorbed from the small intestine. Bile from the liver secreted into the small intestine also plays an important role in digesting fat. In addition, the liver is the body's chemical "factory." It takes the raw materials absorbed by the intestine and makes all the various chemicals the body needs to function. The liver also detoxifies potentially harmful chemicals. It breaks down and secretes many drugs.

GALLBLADDER

The gallbladder stores and concentrates bile, and then releases it into the duodenum to help absorb and digest fats.

COLON (LARGE INTESTINE)

The colon is a 6-foot long muscular tube that connects the small intestine to the rectum. The large intestine is made up of the cecum, the ascending (right) colon, the transverse (across) colon, the descending (left) colon, and the sigmoid colon, which connects to the rectum.

Stool, or waste left over from the digestive process, is passed through the colon by means of peristalsis, first in a liquid state and ultimately in a solid form. As stool passes through the colon, water is removed. Stool is stored in the sigmoid (S-shaped) colon until a "mass movement" empties it into the rectum once or twice a day. It normally takes about 36 hours for stool to get through the colon. The stool itself is mostly food debris and bacteria. These bacteria perform several useful functions, such as synthesizing various vitamins, processing waste products and food particles, and protecting against harmful bacteria. When the descending colon becomes full of stool, or feces, it empties its contents into the rectum to begin the process of elimination.

RECTUM

The rectum (Latin for "straight") is an 8-inch chamber that connects the colon to the anus. It is the rectum's job to receive stool from the colon, to let the person know that there is stool to be evacuated, and to hold the stool until evacuation happens. When anything (gas or stool) comes into the rectum, sensors send a message to the brain. The brain then decides if the rectal contents can be released or not. If they can, the sphincters relax and the rectum contracts, disposing its contents. If the contents cannot be disposed, the sphincter contracts and the rectum accommodates so that the sensation temporarily goes away.

ANUS

The anus is the last part of the digestive tract. It is a 2-inch long canal consisting of the pelvic floor muscles and the two anal sphincters (internal and external). The lining of the upper anus is specialized to detect rectal contents. It lets you know whether the contents are liquid, gas, or solid. The anus is surrounded by sphincter muscles that are important in allowing control of stool. The pelvic floor muscle creates an angle between the rectum and the anus that stops stool from coming out when it is not supposed to. The internal sphincter is always tight, except when stool enters the rectum. It keeps us continent when we are asleep or otherwise unaware of the presence of stool. When we get an urge to go to the bathroom, we rely on our external sphincter to hold the stool until reaching a toilet, where it then relaxes to release the contents.

HUMAN DIGESTIVE SYSTEM

Human digestive system, the system used in the human body for the process of digestion. The human digestive system consists primarily of the digestive tract, or the series of structures and organs through which food and liquids pass during their processing into forms absorbable into the bloodstream. The system also consists of the structures through which wastes pass in the process of elimination and other organs that contribute juices necessary for the digestive process.

STRUCTURES AND FUNCTIONS OF THE HUMAN DIGESTIVE SYSTEM

The digestive tract begins at the lips and ends at the anus. It consists of the mouth, or oral cavity, with its teeth, for grinding the food, and its tongue, which serves to knead food and mix it with saliva; the throat, or pharynx; the esophagus; the stomach; the small intestine, consisting of the duodenum, the jejunum, and the ileum; and the large intestine, consisting of the cecum, a closed-end sac connecting with the ileum, the ascending colon, the transverse colon, the descending colon, and the sigmoid colon, which terminates in the rectum.

Glands contributing digestive juices include the salivary glands, the gastric glands in the stomach lining, the pancreas, and the liver and its adjuncts—the gallbladder and bile ducts. All of these organs and glands contribute to the physical and chemical breaking down of ingested food and to the eventual elimination of non-digestible wastes. Their structures and functions are described step by step in this chapter.

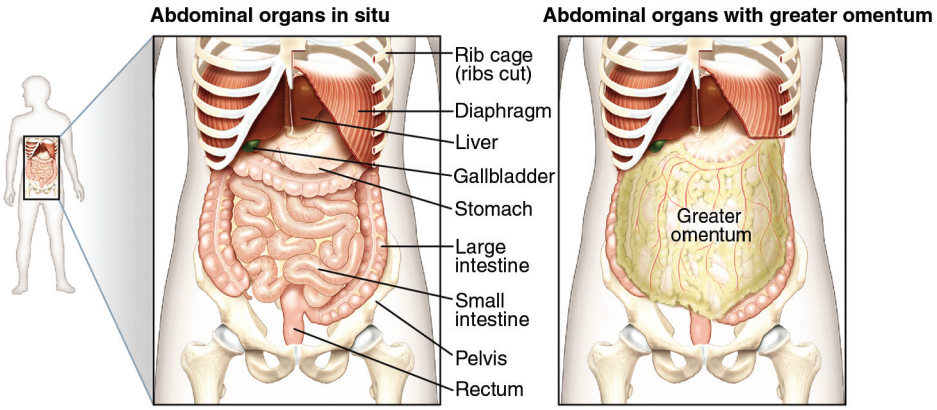


Fig. The abdominal organs are supported and protected by the bones of the pelvis and ribcage and are covered by the greater omentum, a fold of peritoneum that consists mainly of fat.

MOUTH AND ORAL STRUCTURES

Little digestion of food actually takes place in the mouth. However, through the process of mastication, or chewing, food is prepared in the mouth for transport through the upper digestive tract into the stomach and small intestine, where the principal digestive processes take place.

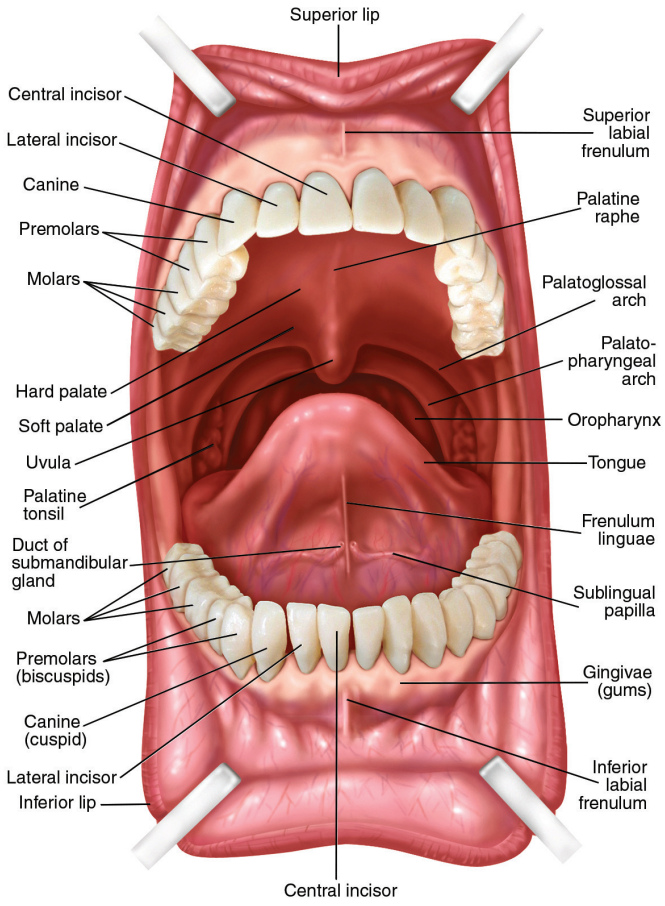


Fig. Anterior view of the oral Cavity.

Chewing is the first mechanical process to which food is subjected. Movements of the lower jaw in chewing are brought about by the muscles of mastication (the masseter, the temporal, the medial and lateral pterygoids, and the buccinator). The sensitivity of the periodontal membrane that surrounds and supports the teeth, rather than the power of the muscles of mastication, determines the force of the bite.

Mastication is not essential for adequate digestion. Chewing does aid digestion, however, by reducing food to small particles and mixing it with the saliva secreted by the salivary glands. The saliva lubricates and moistens dry food, while chewing distributes the saliva throughout the food mass. The movement of the tongue against the hard palate and the cheeks helps to form a rounded mass, or bolus, of food.

THE LIPS AND CHEEKS

The lips, two fleshy folds that surround the mouth, are composed externally of skin and internally of mucous membrane, or mucosa. The mucosa is rich in mucus-secreting glands, which together with saliva ensure adequate lubrication for the purposes of speech and mastication.

The cheeks, the sides of the mouth, are continuous with the lips and have a similar structure. A distinct fat pad is found in the subcutaneous tissue (the tissue beneath the skin) of the cheek; this pad is especially large in infants and is known as the sucking pad. On the inner surface of each cheek, opposite the second upper molar tooth, is a slight elevation that marks the opening of the parotid duct, leading from the parotid salivary gland, which is located in front of the ear. Just behind this gland are four to five mucus-secreting glands, the ducts of which open opposite the last molar tooth.

THE ROOF OF THE MOUTH

The roof of the mouth is concave and is formed by the hard and soft palate. The hard palate is formed by the horizontal portions of the two palatine bones and the palatine portions of the maxillae, or upper jaws. The hard palate is covered by a thick, somewhat pale mucous membrane that is continuous with that of the gums and is bound to the upper jaw and palate bones by firm fibrous tissue. The soft palate is continuous with the hard palate in front. Posteriorly it is continuous with the mucous membrane covering the floor of the nasal cavity. The soft palate is composed of a strong, thin, fibrous sheet, the palatine aponeurosis, and the glossopalatine and pharyngopalatine muscles. A small projection called the uvula hangs free from the posterior of the soft palate.

THE FLOOR OF THE MOUTH

The floor of the mouth can be seen only when the tongue is raised. In the midline is a prominent, elevated fold of mucous membrane (frenulum linguae) that binds each lip to the gums, and on each side of this is a slight fold called a sublingual papilla, from which the ducts of the submandibular salivary glands open. Running outward and backward from each sublingual papilla is a ridge (the plica sublingualis) that marks the upper edge of the sublingual (under the tongue) salivary gland and onto which most of the ducts of that gland open.

THE GUMS

The gums consist of mucous membranes connected by thick fibrous tissue to the membrane surrounding the bones of the jaw. The gummembrane rises to form a collar around the base of the crown (exposed portion) of each tooth. Rich in blood vessels, the gum tissues receive branches from the alveolar arteries; these vessels, called alveolar because of their relationship to the alveoli dentales, or tooth sockets, also supply the teeth and the spongy bone of the upper and lower jaws, in which the teeth are lodged.

THE TEETH

The teeth are hard, white structures found in the mouth. Usually used for mastication, the teeth of different vertebrate species are sometimes specialized. The teeth of snakes, for example, are very thin and sharp and usually curve backward; they function in capturing prey but not in chewing, because snakes swallow their food whole. The teeth of carnivorous mammals, such as cats and dogs, are more pointed than those of primates, including humans; the canines are long, and the premolars lack flat grinding surfaces, being more adapted to cutting and shearing (often the more posterior molars are lost). On the other hand, herbivores such as cows and horses have very large, flat premolars and molars with complex ridges and cusps; the canines are often totally absent. Sharp pointed teeth, poorly adapted for chewing, generally characterize meat eaters such as snakes, dogs, and cats; and broad, flat teeth, well adapted for chewing, characterize herbivores. The differences in the shapes of teeth are functional adaptations. Few animals can digest cellulose, yet the plant cells used as food by herbivores are enclosed in cellulose cell walls that must be broken down before the cell contents can be exposed to the action of digestive enzymes. By contrast, the animal cells in meat are not encased in non-digestible matter and can be acted upon directly by digestive enzymes. Consequently, chewing is not so essential for carnivores as it is for herbivores. Humans, who are omnivores (eaters of plants and animal tissue), have teeth that belong, functionally and structurally, somewhere between the extremes of specialization attained by the teeth of carnivores and herbivores.

Each tooth consists of a crown and one or more roots. The crown is the functional part of the tooth that is visible above the gum. The root is the unseen portion that supports and fastens the tooth in the jawbone. The shapes of the crowns and the roots vary in different parts of the mouth and from one animal to another. The teeth on one side of the jaw are essentially a mirror image of those located on the opposite side. The upper teeth differ from the lower and are complementary to them. Humans normally have two sets of teeth during their lifetime. The first set, known as the deciduous, milk, or primary dentition, is acquired gradually between the ages of six months and two years. As the jaws grow and expand, these teeth are replaced one by one by the teeth of the secondary set. There are five deciduous teeth and eight permanent teeth in each quarter of the mouth, resulting in a total of 32 permanent teeth to succeed the 20 deciduous ones.

THE TONGUE

The tongue, a muscular organ located on the floor of the mouth, is an extremely mobile structure and is an important accessory organ in such motor functions as speech, chewing, and swallowing. In conjunction with the cheeks, it is able to guide and maintain food between the upper and lower teeth until mastication is complete. The motility of the tongue aids in creating a negative pressure within the oral cavity and thus enables infants to suckle. Especially important as a peripheral sense organ, the tongue contains groups of specialized epithelial cells, known as taste buds, that carry stimuli from the oral cavity to the central nervous system. Furthermore, the tongue's glands produce some of the saliva necessary for swallowing.

The tongue consists of a mass of interwoven striated (striped) muscles interspersed with fat. The mucous membrane that covers the tongue varies in different regions. The tongue is attached to the lower jaw, the hyoid bone (a U-shaped bone between the lower jaw and the larynx), the skull, the soft palate, and the pharynx by its extrinsic muscles. It is bound to the floor of the mouth and to the epiglottis (a plate of cartilage that serves as a lid for the larynx) by folds of mucous membrane.

SALIVARY GLANDS

Food is tasted and mixed with saliva that is secreted by several sets of glands. Besides the many minute glands that secrete saliva, there are three major pairs of salivary glands: the parotid, the submandibular, and the

sublingual glands. The parotid glands, the largest of the pairs, are located at the side of the face, below and in front of each ear. The parotid glands are enclosed in sheaths that limit the extent of their swelling when inflamed, as in mumps. The submandibular glands, which are rounded in shape, lie near the inner side of the lower jawbone, in front of the sternomastoid muscle (the prominent muscle of the jaw). The sublingual glands lie directly under the mucous membrane covering the floor of the mouth beneath the tongue.

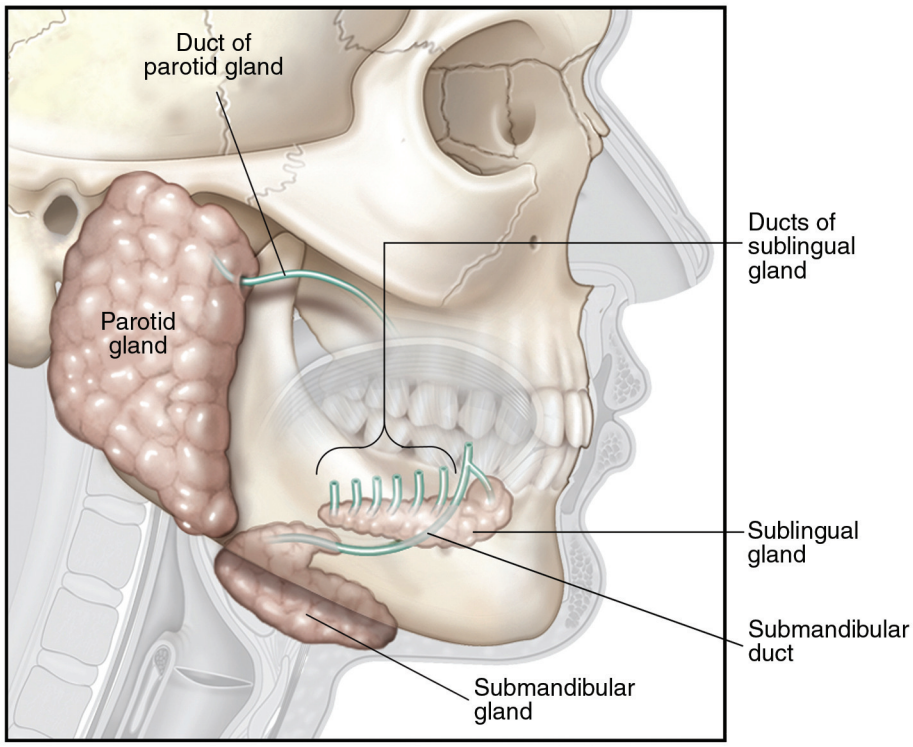


Fig. The Three major Pairs of Salivary Glands.

The salivary glands are of the type called racemose, from the Latin *racemosus* ("full of clusters"), because of the clusterlike arrangement of their secreting cells in rounded sacs, called acini, attached to freely branching systems of ducts. The walls of the acini surround a small central cavity known as an alveolus. In the walls of the acini are pyramidal secreting cells and some flat, star-shaped contractile cells called myoepithelial, or basket, cells. The latter cells are thought to contract, like the similar myoepithelial cells of the breast, which by their contraction expel milk from the milk ducts.

The secreting cells may be of the serous or the mucous type. The latter type secretes mucin, the chief constituent of mucus; the former, a watery fluid containing the enzyme amylase. The secreting cells of the parotid glands are of the serous type; those of the submandibular glands, of both serous and mucous types, with the serous cells outnumbering the mucous cells by four to one. The acini of the sublingual glands are composed primarily of mucous cells.

The salivary glands are controlled by the two divisions of the autonomic nervous system, the sympathetic and the parasympathetic. The parasympathetic nerve supply regulates secretion by the acinar cells and causes the blood vessels to dilate. Functions regulated by the sympathetic nerves include secretion by the acinar cells, constriction of blood vessels, and, presumably, contraction of the myoepithelial cells. Normally secretion of saliva is constant, regardless of the presence of food in the mouth. The amount of saliva secreted in 24 hours usually amounts to 1–1.5 litres. When something touches the gums, the tongue, or some region of the mouth lining, or when chewing occurs, the amount of saliva secreted increases. The stimulating substance need not be food—dry sand in the mouth or even moving the jaws and tongue when the mouth is empty increases the salivary flow. This coupling of direct stimulation to the oral mucosa with increased salivation is known as the

unconditioned salivary reflex. When an individual learns that a particular sight, sound, smell, or other stimulus is regularly associated with food, that stimulus alone may suffice to stimulate increased salivary flow. This response is known as the conditioned salivary reflex.

SALIVA

Saliva dissolves some of the chewed food and acts as a lubricant, facilitating passage through the subsequent portions of the digestive tract. Saliva also contains a starch-digesting enzyme called amylase (ptyalin), which initiates the process of enzymatic hydrolysis; it splits starch (a polysaccharide containing many sugar molecules bound in a continuous chain) into molecules of the double sugar maltose. Many carnivores, such as dogs and cats, have no amylase in their saliva; therefore, their natural diet contains very little starch. Substances must be in solution for the taste buds to be stimulated; saliva provides the solvent for food materials.

The composition of saliva varies, but its principal components are water, inorganic ions similar to those commonly found in blood plasma, and a number of organic constituents, including salivary proteins, free amino acids, and the enzymes lysozyme and amylase. Although saliva is slightly acidic, the bicarbonates and phosphates contained within it serve as buffers and maintain the pH, or hydrogen ion concentration, of saliva relatively constant under ordinary conditions.

The concentrations of bicarbonate, chloride, potassium, and sodium in saliva are directly related to the rate of their flow. There is also a direct relation between bicarbonate concentration and the partial pressure of carbon dioxide in the blood. The concentration of chloride in the blood varies from 5 millimoles per litre at low flow rates to 70 millimoles per litre when the flow rate is high. The sodium concentrations in similar circumstances vary from 5 millimoles per litre to 100 millimoles per litre. The concentration of potassium in the blood is often higher than that in the blood plasma, up to 20 millimoles per litre, which accounts for the sharp and metallic taste of saliva when flow is brisk.

The constant flow of saliva keeps the oral cavity and teeth moist and comparatively free from food residues, sloughed epithelial cells, and foreign particles. By removing material that may serve as culture media, saliva inhibits the growth of bacteria. Saliva serves a protective function, for the enzyme lysozyme has the ability to lyse, or dissolve, certain bacteria. The secretion of saliva also provides a mechanism whereby certain organic and inorganic substances can be excreted from the body, including mercury, lead, potassium iodide, bromide, morphine, ethyl alcohol, and certain antibiotics such as penicillin, streptomycin, and chlortetracycline.

Although saliva is not essential to life, its absence results in a number of inconveniences, including dryness of the oral mucous membrane, poor oral hygiene because of bacterial overgrowth, a greatly diminished sense of taste, and difficulties with speech.

PHARYNX

The pharynx, or throat, is the passageway leading from the mouth and nose to the esophagus and larynx. The pharynx permits the passage of swallowed solids and liquids into the esophagus, or gullet, and conducts air to and from the trachea, or windpipe, during respiration. The pharynx also connects on either side with the cavity of the middle ear by way of the Eustachian tube and provides for equalization of air pressure on the eardrum membrane, which separates the cavity of the middle ear from the external ear canal. The pharynx has roughly the form of a flattened funnel.

It is attached to the surrounding structures but is loose enough to permit gliding of the pharyngeal wall against them in the movements of swallowing. The principal muscles of the pharynx, involved in the mechanics of swallowing, are the three pharyngeal constrictors, which overlap each other slightly and form the primary musculature of the side and rear pharyngeal walls.

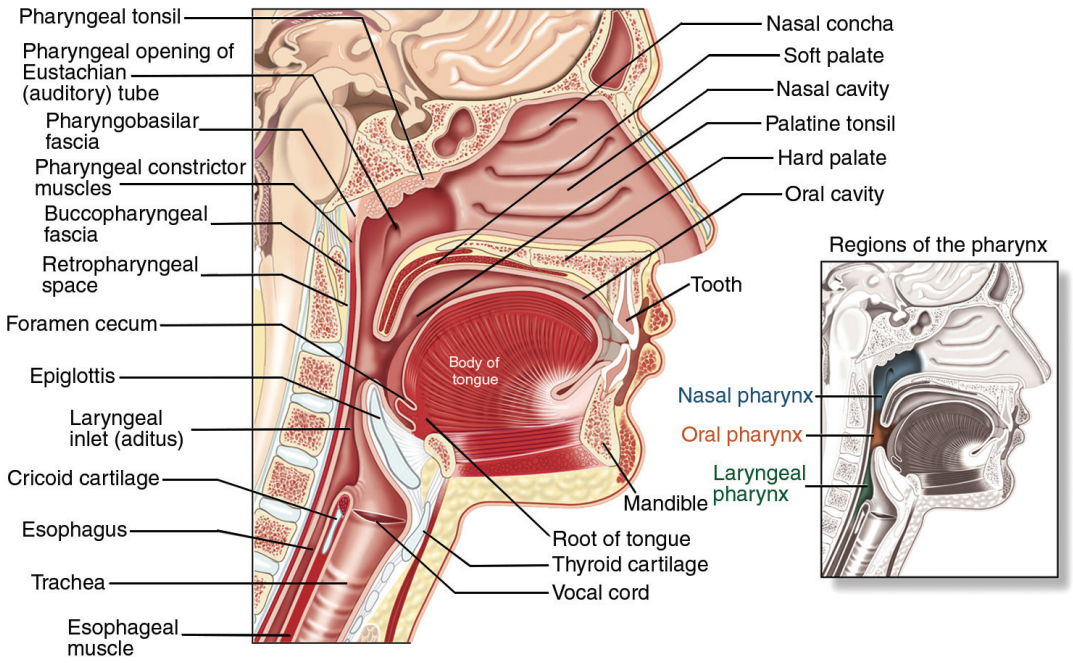


Fig. Sagittal section of the pharynx.

There are three main divisions of the pharynx: the oral pharynx, the nasal pharynx, and the laryngeal pharynx. The latter two are airways, whereas the oral pharynx is shared by both the respiratory and digestive tracts. On either side of the opening between the mouth cavity and the oral pharynx is a palatine tonsil, so called because of its proximity to the palate. Each palatine tonsil is located between two vertical folds of mucous membrane called the glossopalatine arches. The nasal pharynx, above, is separated from the oral pharynx by the soft palate. Another pair of tonsils are located on the roof of the nasal pharynx. The pharyngeal tonsils, also known as the adenoids, are part of the body's immune system. When the pharyngeal tonsils become grossly swollen (which occurs often during childhood) they occlude the airway. The laryngeal pharynx and the lower part of the oral pharynx are hidden by the root of the tongue.

The first stage of deglutition, or swallowing, consists of passage of the bolus into the pharynx and is initiated voluntarily. The front part of the tongue is retracted and depressed, mastication ceases, respiration is inhibited, and the back portion of the tongue is elevated and retracted against the hard palate. This action, produced by the strong muscles of the tongue, forces the bolus from the mouth into the pharynx. Entry of the bolus into the nasal pharynx is prevented by the elevation of the soft palate against the posterior pharyngeal wall. As the bolus is forced into the pharynx, the larynx moves upward and forward under the base of the tongue. The superior pharyngeal constrictor muscles contract, initiating a rapid pharyngeal peristaltic, or squeezing, contraction that moves down the pharynx, propelling the bolus in front of it. The walls and structures of the lower pharynx are elevated to engulf the oncoming mass of food. The epiglottis, a lidlike covering that protects the entrance to the larynx, diverts the bolus to the pharynx. The cricopharyngeal muscle, or upper esophageal sphincter, which has kept the esophagus closed until this point, relaxes as the bolus approaches and allows it to enter the upper esophagus. The pharyngeal peristaltic contractioncontinues into the esophagus and becomes the primary esophageal peristaltic contraction.

ESOPHAGUS

The esophagus, which passes food from the pharynx to the stomach, is about 25 cm (10 inches) in length; the width varies from 1.5 to 2 cm (about 1 inch). The esophagus lies behind the trachea and heart and in front of the spinal column; it passes through the diaphragm before entering the stomach.

The esophagus contains four layers—the mucosa, submucosa, muscularis, and tunica adventitia. The mucosa is made up of stratified squamous epithelium containing numerous mucous glands. The submucosa is a thick, loose fibrous layer connecting the mucosa to the muscularis. Together the mucosa and submucosa form long longitudinal folds, so that a cross section of the esophagus opening would be star-shaped. The muscularis is composed of an inner layer, in which the fibres are circular, and an outer layer of longitudinal fibres. Both muscle groups are wound around and along the alimentary tract, but the inner one has a very tight spiral, so that the windings are virtually circular, whereas the outer one has a very slowly unwinding spiral that is virtually longitudinal. The outer layer of the esophagus, the tunica adventitia, is composed of loose fibrous tissue that connects the esophagus with neighbouring structures. Except during the act of swallowing, the esophagus is normally empty, and its lumen, or channel, is essentially closed by the longitudinal folds of the mucosal and submucosal layers.

The upper third of the esophagus is composed of striated (voluntary) muscle. The middle third is a mixture of striated and smooth (involuntary) muscle, and the lower third consists only of smooth muscle. The esophagus has two sphincters, circular muscles that act like drawstrings in closing channels. Both sphincters normally remain closed except during the act of swallowing. The upper esophageal sphincter is located at the level of the cricoid cartilage (a single ringlike cartilage forming the lower part of the larynx wall). This sphincter is called the cricopharyngeus muscle. The lower esophageal sphincter encircles the 3 to 4 cm of the esophagus that pass through an opening in the diaphragm called the diaphragmatic hiatus. The lower esophageal sphincter is maintained in tension at all times, except in response to a descending contraction wave, at which point it relaxes momentarily to allow the release of gas (belching) or vomiting. The lower esophageal sphincter has an important role, therefore, in protecting the esophagus from the reflux of gastric contents with changes in body position or with alterations of intragastric pressure.

Transport through the esophagus is accomplished by the primary esophageal peristaltic contractions, which, as noted above, originate in the pharynx. These contractions are produced by an advancing peristaltic wave that creates a pressure gradient and sweeps the bolusahead of it. Transport of material through the esophagus takes approximately 10 seconds. When the bolus arrives at the junction with the stomach, the lower esophageal sphincter relaxes and the bolus enters the stomach. If the bolus is too large, or if the peristaltic contraction is too weak, the bolus may become arrested in the middle or lower esophagus. When this occurs, secondary peristaltic contractions originate around the bolus in response to the local distension of the esophageal wall and propel the bolus into the stomach.

When a liquid is swallowed, its transport through the esophagus depends somewhat on the position of the body and the effects of gravity. When swallowed in a horizontal or head-down position, liquids are handled in the same manner as solids, with the liquid moving immediately ahead of the advancing peristaltic contraction. (The high pressures and strong contractions of the esophageal peristaltic wave make it possible for animals with very long necks, such as the giraffe, to transport liquids through the esophagus for many feet.) When the body is in the upright position, however, liquids enter the esophagus and fall by gravity to the lower end; there they await the arrival of the peristaltic contraction and the opening of the lower esophageal sphincter (8 to 10 seconds) before being emptied into the stomach.

STOMACH

ANATOMY

The stomach receives ingested food and liquids from the esophagus and retains them for grinding and mixing with gastric juice so that food particles are smaller and more soluble. The main functions of the stomach are to commence the digestion of carbohydrates and proteins, to convert the meal into chyme, and to discharge the

chyme into the small intestine periodically as the physical and chemical condition of the mixture is rendered suitable for the next phase of digestion. The stomach is located in the left upper part of the abdomen immediately below the diaphragm. In front of the stomach are the liver, part of the diaphragm, and the anterior abdominal wall. Behind it are the pancreas, the left kidney, the left adrenal gland, the spleen, and the colon. The stomach is more or less concave on its right side, convex on its left. The concave border is called the lesser curvature; the convex border, the greater curvature. When the stomach is empty, its mucosal lining is thrown into numerous longitudinal folds, known as rugae; these tend to disappear when the stomach is distended.

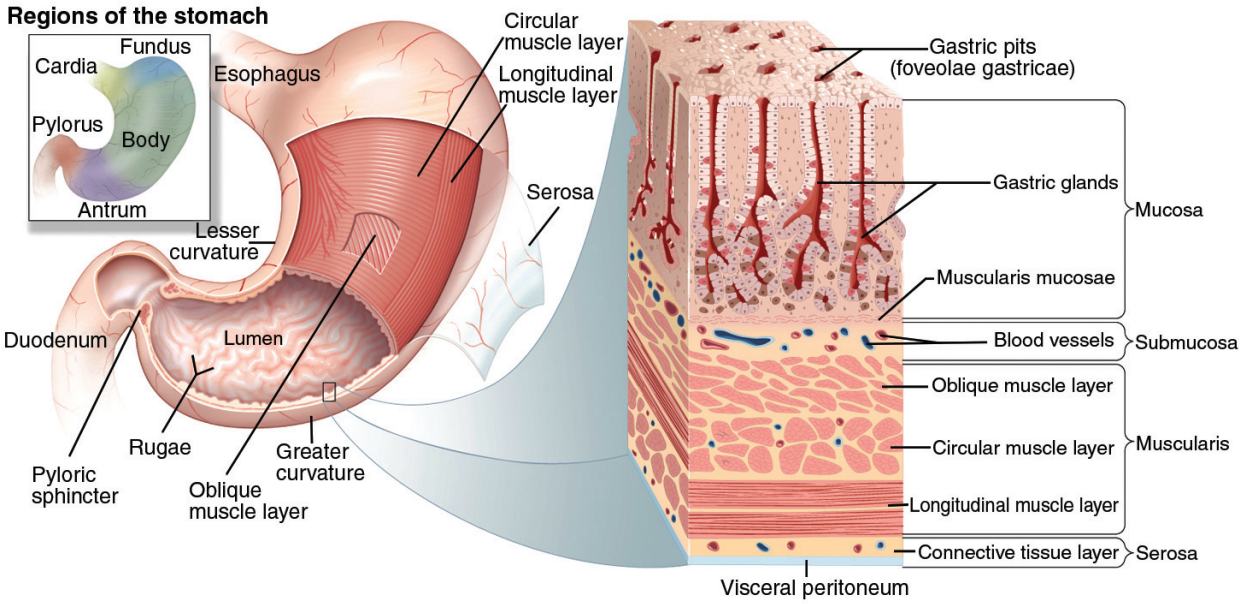


Fig. Regions of the Stomach Anatomy.

The cardia is the opening from the esophagus into the stomach. The uppermost part of the stomach, located above the entrance of the esophagus, is the fundus. The fundus adapts to the varying volume of ingested food by relaxing its muscular wall; it frequently contains a gas bubble, especially after a meal. The largest part of the stomach is known simply as the body; it serves primarily as a reservoir for ingested food and liquids. The antrum, the lowermost part of the stomach, is somewhat funnel-shaped, with its wide end joining the lower part of the body and its narrow end connecting with the pyloric canal, which empties into the duodenum (the upper division of the small intestine). The pyloric portion of the stomach (antrum plus pyloric canal) tends to curve to the right and slightly upward and backward and thus gives the stomach its J-shaped appearance. The pylorus, the narrowest portion of the stomach, is the outlet from the stomach into the duodenum. It is approximately 2 cm (almost 1 inch) in diameter and is surrounded by thick loops of smooth muscle.

The muscles of the stomach wall are arranged in three layers, or coats. The external coat, called the longitudinal muscle layer, is continuous with the longitudinal muscle coat of the esophagus. Longitudinal muscle fibres are divided at the cardia into two broad strips. The one on the right, the stronger, spreads out to cover the lesser curvature and the adjacent posterior and anterior walls of the stomach. Longitudinal fibres on the left radiate from the esophagus over the dome of the fundus to cover the greater curvature and continue on to the pylorus, where they join the longitudinal fibres coming down over the lesser curvature. The longitudinal layer continues on into the duodenum, forming the longitudinal muscle of the small intestine.

The middle, or circular muscular layer, the strongest of the three muscular layers, completely covers the stomach. The circular fibres of this coat are best developed in the lower portion of the stomach, particularly over the antrum and pylorus. At the pyloric end of the stomach, the circular muscle layer becomes greatly thickened to form the pyloric sphincter. This muscular ring is slightly separated from the circular muscle of the duodenum by connective tissue.

The innermost layer of smooth muscle, called the oblique muscular layer, is strongest in the region of the fundus and progressively weaker as it approaches the pylorus. The stomach is capable of dilating to accommodate more than one litre (about one quart) of food or liquids without increasing pressure on the stomach. This receptive relaxation of the upper part of the stomach to accommodate a meal is partly due to a neural reflex that is triggered when hydrochloric acid comes into contact with the mucosa of the antrum, possibly through the release of the hormone known as vasoactive intestinal peptide. The distension of the body of the stomach by food activates a neural reflex that initiates the muscle activity of the antrum.

BLOOD AND NERVE SUPPLY

Many branches of the celiac trunk bring arterial blood to the stomach. The celiac trunk is a short, wide artery that branches from the abdominal portion of the aorta, the main vessel conveying arterial blood from the heart to the systemic circulation. Blood from the stomach is returned to the venous system through the portal vein, which carries the blood to the liver.

The nerve supply to the stomach is provided by both the parasympathetic and sympathetic divisions of the autonomic nervous system. The parasympathetic nerve fibres are carried in the vagus, or 10th cranial, nerve. As the vagus nerve passes through the opening in the diaphragm together with the esophagus, branches of the right vagus nerve spread over the posterior part of the stomach, while the left vagus nerve supplies the anterior part. Sympathetic branches from a nerve network called the celiac, or solar, plexus accompany the arteries of the stomach into the muscular wall.

STOMACH CONTRACTIONS

Three types of motor activity of the stomach have been observed. The first is a small contraction wave of the stomach wall that originates in the upper part of the stomach and slowly moves down over the organtoward the pyloric sphincter. This type of contraction produces a slight indentation of the stomach wall. Retrograde waves frequently sweep from the pyloric sphincter to the antrum and up to its junction with the body of the stomach, which results in a back-and-forth movement of the gastric contents that has a mixing and crushing effect. The second type of motor activity is also a contracting wave, but it is peristaltic in nature. The contraction originates in the upper part of the stomach as well and is slowly propagated over the organ towards the pyloric sphincter. This type of gastric contraction produces a deep indentation in the wall of the stomach. As the peristaltic wave approaches the antrum, the indentation completely obstructs the stomach lumen, or cavity, and thus compartmentalizes it. The contracting wave then moves over the antrum, propelling the material ahead of it through the pyloric sphincter into the duodenum. This type of contraction serves as a pumping mechanism for emptying the contents of the gastric antrum through the pyloric sphincter. Both the mixing and the peristaltic contractions of the stomach occur at a constant rate of three contractions per minute when recorded from the gastric antrum. A wave of peristalsis sweeps along the lower half of the stomach and along the entire intestine to the proximal colon at two-hour intervals after meals. These peristaltic waves can be halted by eating and can be induced by the hormone motilin.

The third type of gastric motor activity is best described as a tonic, or sustained, contraction of all the stomach muscles. The tonic contraction decreases the size of the stomach lumen, as all parts of the gastric wall seem to contract simultaneously. This activity accounts for the stomach's ability to accommodate itself to varying volumes of gastric content. The tonic contraction is independent of the other two types of contractions; however, mixing contractions and peristaltic contractions normally occur simultaneously with the tonic contraction. As food is broken down, smaller particles flow through the pyloric sphincter, which opens momentarily as a peristaltic wave descends through the antrum towards it. This permits "sampling" of the gastric contents by the duodenum.

GASTRIC MUCOSA

The inner surface of the stomach is lined by a mucous membraneknown as the gastric mucosa. The mucosa is always covered by a layer of thick mucus that is secreted by tall columnar epithelial cells. Gastric mucus is a glycoprotein that serves two purposes: the lubrication of food masses in order to facilitate movement within the stomach and the formation of a protective layer over the lining epithelium of the stomach cavity. This protective layer is a defence mechanism the stomach has against being digested by its own protein-lyzing enzymes, and it is facilitated by the secretion of bicarbonate into the surface layer from the underlying mucosa. The acidity, or hydrogen ion concentration, of the mucous layer measures pH7 (neutral) at the area immediately adjacentto the epithelium and becomes more acidic (pH2) at the luminal level. When the gastric mucus is removed from the surface epithelium, small pits, called foveolae gastricae, may be observed with a magnifying glass. There are approximately 90 to 100 gastric pits per square millimetre (58,000 to 65,000 per square inch) of surface epithelium. Three to seven individual gastric glands empty their secretions into each gastric pit. Beneath the gastric mucosa is a thin layer of smooth muscle called the muscularis mucosae, and below this, in turn, is loose connective tissue, the submucosa, which attaches the gastric mucosa to the muscles in the walls of the stomach.

The gastric mucosa contains six different types of cells. In addition to the tall columnar surface epithelial cells mentioned above, there are five common cell types found in the various gastric glands.

1. Mucoid cells secrete gastric mucus and are common to all types of gastric glands. Mucoid cells are the main cell type found in the gastric glands in the cardiac and pyloric areas of the stomach. The necks of the glands in the body and fundic parts of the stomach are lined with mucoid cells.
2. Zymogenic, or chief, cells are located predominantly in gastric glands in the body and fundic portions of the stomach. These cells secrete pepsinogen, from which the proteolytic (protein-digesting) enzymepepsin is formed. There are two varieties of pepsinogen, known as pepsinogen I and pepsinogen II. Both are produced in the mucous and zymogenic cells in the glands of the body of the stomach, but the mucous glands located elsewhere in the stomach produce only pepsinogen II. Those stimuli that cause gastric acid secretion—in particular, vagal nervestimulation—also promote the secretion of the pepsinogens.
3. Gastrin cells, also called G cells, are located throughout the antrum. These endocrine cells secrete the acid-stimulating hormone gastrin as a response to lowered acidity of the gastric contents when food enters the stomach and gastric distention. Gastrin then enters the bloodstream and is carried in the circulation to the mucosa of the body of the stomach, where it binds to receptor sites on the outer membrane of the parietal cells. The gastrin-receptor complex that is formed triggers an energy-consuming reaction moderated by the presence of the enzyme ATPase, bound to the membrane that leads to the production and secretion of hydrogen ions in the parietal cells.
4. Parietal, or oxyntic, cells, found in the glands of the body and fundic portions of the stomach, secrete hydrogen ions that combine with chloride ions to form hydrochloric acid (HCl). The acid that is produced drains into the lumen of the gland and then passes through to the stomach. This process occurs only when one or more types of receptors on the outer membrane of the parietal cell are bound to histamine, gastrin, or acetylcholine. Prostaglandins, hormonelike substances that are present in virtually all tissues and body fluids, inhibit the secretion of hydrochloric acid. The drugs omeprazole (Losec™ or Prilosec™) and lansoprazole (Prevacid™) also inhibit acid secretion by the parietal cells and are used as treatments for peptic ulcer. Parietal cells produce most of the water found in gastric juice; they also produce glycoproteins called intrinsic factor, which are essential to the maturation of red blood cells, vitamin B_{12}absorption, and the health of certain cells in the central and peripheralnervous systems.

5. Endocrine cells called enterochromaffin-like cells because of their staining characteristics are scattered throughout the body of the stomach. Enterochromaffin-like cells secrete several substances, including the hormone serotonin.

GASTRIC SECRETION

The gastric mucosa secretes 1.2 to 1.5 litres of gastric juice per day. Gastric juice renders food particles soluble, initiates digestion (particularly of proteins), and converts the gastric contents to a semiliquid mass called chyme, thus preparing it for further digestion in the small intestine. Gastric juice is a variable mixture of water, hydrochloric acid, electrolytes (sodium, potassium, calcium, phosphate, sulfate, and bicarbonate), and organic substances (mucus, pepsins, and protein). This juice is highly acidic because of its hydrochloric acid content, and it is rich in enzymes. As noted above, the stomach walls are protected from digestive juices by the membrane on the surface of the epithelial cells bordering the lumen of the stomach; this membrane is rich in lipoproteins, which are resistant to attack by acid. The gastric juice of some mammals (*e.g.*, calves) contains the enzyme rennin, which clumps milk proteins and thus takes them out of solution and makes them more susceptible to the action of a proteolytic enzyme.

The process of gastric secretion can be divided into three phases (cephalic, gastric, and intestinal) that depend upon the primary mechanisms that cause the gastric mucosa to secrete gastric juice. The phases of gastric secretion overlap, and there is an interrelation and some interdependence between the neural and humoral pathways.

The cephalic phase of gastric secretion occurs in response to stimuli received by the senses—that is, taste, smell, sight, and sound. This phase of gastric secretion is entirely reflex in origin and is mediated by the vagus (10th cranial) nerve. Gastric juice is secreted in response to vagal stimulation, either directly by electrical impulses or indirectly by stimuli received through the senses. Ivan Petrovich Pavlov, the Russian physiologist, originally demonstrated this method of gastric secretion in a now-famous experiment with dogs.

The gastric phase is mediated by the vagus nerve and by the release of gastrin. The acidity of the gastric contents after a meal is buffered by proteins so that overall it remains around pH3 (acidic) for approximately 90 minutes. Acid continues to be secreted during the gastric phase in response to distension and to the peptides and amino acids that are liberated from protein as digestion proceeds. The chemical action of free amino acids and peptides excites the liberation of gastrin from the antrum into the circulation. Thus, there are mechanical, chemical, and hormonal factors contributing to the gastric secretory response to eating. This phase continues until the food has left the stomach.

The intestinal phase is not fully understood, because of a complex stimulatory and inhibitor process. Amino acids and small peptides that promote gastric acid secretion are infused into the circulation, however, at the same time chyme inhibits acid secretion. The secretion of gastric acid is an important inhibitor of gastrin release. If the pH of the antral contents falls below 2.5, gastrin is not released. Some of the hormones that are released from the small intestine by products of digestion (especially fat), in particular glucagon and secretin, also suppress acid secretion.

ABSORPTION AND EMPTYING

Although the stomach absorbs few of the products of digestion, it can absorb many other substances, including glucose and other simple sugars, amino acids, and some fat-soluble substances. The pH of the gastric contents determines whether some substances are absorbed. At a low pH, for example, the environment is acidic and aspirin is absorbed from the stomach almost as rapidly as water, but, as the pH of the stomach rises and the environment becomes more basic, aspirin is absorbed more slowly. Water moves freely from the gastric contents across the gastric mucosa into the blood. The net absorption of water from the stomach is small, however,

because water moves just as easily from the blood across the gastric mucosa to the lumen of the stomach. The absorption of water and alcohol can be slowed if the stomach contains foodstuffs and especially fats, probably because gastric emptying is delayed by fats, and most water in any situation is absorbed from the small intestine.

The rate of emptying of the stomach depends upon the physical and chemical composition of the meal. Fluids empty more rapidly than solids, carbohydrates more rapidly than proteins, and proteins more rapidly than fats. When food particles are sufficiently reduced in size and are nearly soluble and when receptors in the duodenal bulb (the area of attachment between the duodenum and the stomach) have a fluidity and a hydrogen ion concentration of a certain level, the duodenal bulb and the second part of the duodenum relax, allowing emptying of the stomach to start. During a duodenal contraction, the pressure in the duodenal bulb rises higher than that in the antrum. The pylorusprevents reflux into the stomach by shutting. The vagus nerve has an important role in the control of emptying, but there is some indication that the sympathetic division of the autonomic nervous system is also involved. Several of the peptide hormones of the digestive tract also have an effect on intragastric pressure and gastric movements, but their role in physiological circumstances is unclear.

SMALL INTESTINE

The small intestine is the principal organ of the digestive tract. The primary functions of the small intestine are mixing and transporting of intraluminal contents, production of enzymes and other constituentsessential for digestion, and absorption of nutrients. Most of the processes that solubilize carbohydrates, proteins, and fats and reduce them to relatively simple organic compounds occur in the small intestine.

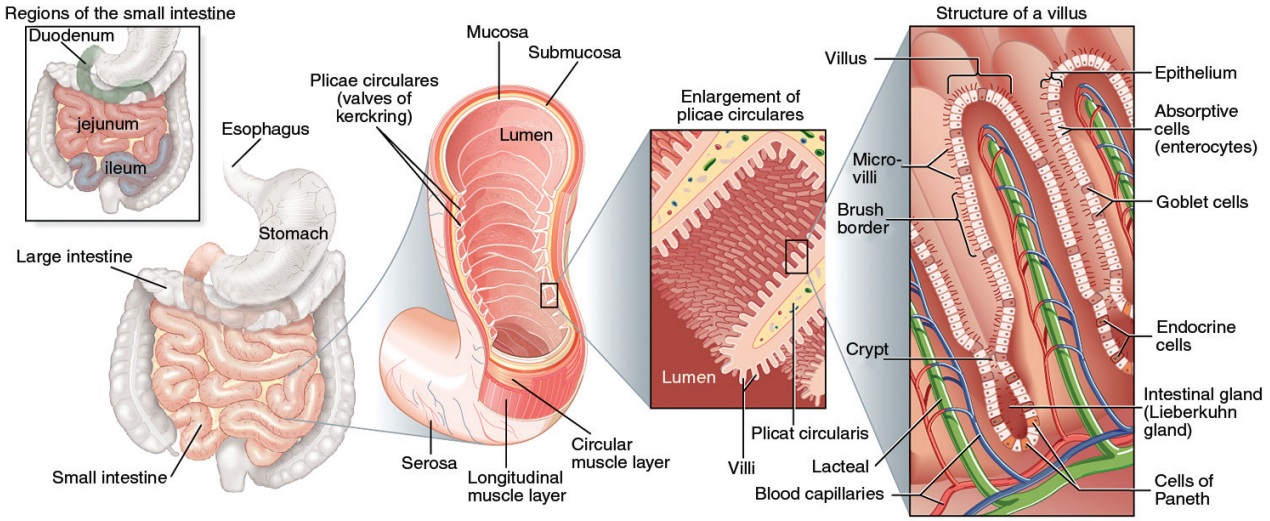


Fig. Structures of the small intestine. The inner wall of the small intestine is covered by numerous folds of mucous membrane called plicae circulares. The surface of these folds contains tiny projections called villi and microvilli, which further increase the total area for absorption. Absorbed nutrients are moved into circulation by blood capillaries and lacteals, or lymph channels.

ANATOMY

The small intestine, which is 670 to 760 cm (22 to 25 feet) in length and 3 to 4 cm (about 2 inches) in diameter, is the longest part of the digestive tract. It begins at the pylorus, the juncture with the stomach, and ends at the ileocecal valve, the juncture with the colon. The main functional segments of the small intestine are the duodenum, the jejunum, and the ileum.

The duodenum is 23 to 28 cm (9 to 11 inches) long and forms a C-shaped curve that encircles the head of the pancreas. Unlike the rest of the small intestine, it is retroperitoneal (that is, it is behind the peritoneum, the membrane lining the abdominal wall). Its first segment, known as the duodenal bulb, is the widest part of the

small intestine. It is horizontal, passing backward and to the right from the pylorus, and lies somewhat behind the wide end of the gallbladder. The second part of the duodenum runs vertically downward in front of the hilum of the right kidney (the point of entrance or exit for blood vessels, nerves, and the ureters); it is into this part through the duodenal papilla (papilla of Vater) that the pancreatic juice and bile flow. The third part of the duodenum runs horizontally to the left in front of the aorta and the inferior vena cava (the principal channel for return to the heart of venous blood from the lower part of the body and the legs), while the fourth part ascends to the left side of the second lumbar vertebra (at the level of the small of the back), then bends sharply downward and forward to join the second part of the small intestine, the jejunum. An acute angle, called the duodenojejunal flexure, is formed by the suspension of this part of the small intestine by the ligament of Treitz.

The jejunum forms the upper two-fifths of the rest of the small intestine; it, like the ileum, has numerous convolutions and is attached to the posterior abdominal wall by the mesentery, an extensive fold of serous-secreting membrane. The ileum is the remaining three-fifths of the small intestine, though there is no absolute point at which the jejunum ends and the ileum begins. In broad terms, the jejunum occupies the upper and left part of the abdomen below the subcostal plane (that is, at the level of the 10th rib), while the ileum is located in the lower and right part. At its termination the ileum opens into the large intestine.

The arrangement of the muscular coats of the small intestine is uniform throughout the length of the organ. The inner, circular layer is thicker than the outer, longitudinal layer. The outermost layer of the small intestine is lined by the peritoneum.

BLOOD AND NERVE SUPPLY

The superior mesenteric artery (a branch of the abdominal aorta) and the superior pancreaticduodenal artery (a branch of the hepatic artery) supply the small intestine with blood. These vessels run between layers of the mesentery, the membrane that connects the intestines with the wall of the abdominal cavity, and give off large branches that form a row of connecting arches from which branches arise to enter the wall of the small bowel. The blood from the intestine is returned by means of the superior mesenteric vein, which, with the splenic vein, forms the portal vein, which drains into the liver.

The small intestine has both sympathetic and parasympathetic innervation. The vagus nerve provides parasympathetic innervation. Sympathetic innervation is provided by branches from the superior mesenteric plexus, a nerve network underneath the solar plexus that follows the blood vessels into the small intestine and finally terminates in the Auerbach plexus, which is located between the circular and longitudinal muscle coats, and the Meissner plexus, which is located in the submucosa. Numerous fibrils, both adrenergic (sympathetic) and cholinergic (parasympathetic), connect these two plexuses.

CONTRACTIONS AND MOTILITY

The contractions of the circular and longitudinal muscles are regulated by electrical impulses that begin with the passage of calcium ions into the muscle cell. The duodenal pacemaker sends electrical impulses down the small intestine at a rate of 11 cycles per minute in the duodenum, gradually decreasing to 8 cycles per minute in the ileum. These electrical changes are propagated in the longitudinal muscle layer of the wall of the small intestine. Occurring simultaneously with the slow-wave electrical activity may be fast, spikelike electrical charges. This type of electrical activity originates in the circular muscle layer of the intestinal wall and occurs when the circular layer contracts to form a segmenting contraction. The depolarization of the muscle cell membranes, or an excess of positive charges on the inside of the cell, causes the myofibrils (the contracting components of the myofilaments that constitute the muscle tissues) to contract. The rate of these contractions is governed by the rate of depolarization of the muscle cell membrane. The two spiral muscle layers then contract, causing the motor activity that permits the mixing and transporting of the food in the small intestine.

The primary purposes of the movements of the small intestine are to provide mixing and transport of intraluminal contents. A characteristic of small intestine motility is the inherent ability of the smooth muscleconstituting the wall of the intestine to contract spontaneously and rhythmically. This phenomenon is independent of any extrinsic nervesupply to the small intestine. In the myenteric plexus (a network of nerve fibres in the wall of the intestine), there are several other messenger substances and receptors capable of modulating smooth muscle activity, including somatostatin, serotonin (5-hydroxytryptamine), and the enkephalins. With at least seven such substances in and around the smooth muscle, there is some confusion as to their respective roles. The contractions of the small intestine create pressure gradients from one adjacent segment of the organ to another. The pressure gradients, in turn, are primarily responsible for transport within the small intestine. Two types of motor activity have been recognized: segmenting contractions and peristaltic contractions.

The predominant motor action of the small intestine is the segmenting contraction, which is a localized circumferential contraction, principally of the circular muscle of the intestinal wall. Segmenting contractions mix, separate, and churn the intestinal chyme. The contraction involves only a short segment of the intestinal wall, less than 1 to 2 cm (about 1 inch), and constricts the lumen, tending to divide its contents. As the chyme moves from the duodenum to the ileum, there is a gradual decrease in the number of segmenting contractions. This has been described as the "gradient" of small intestine motility. Although segmenting contractions usually occur in an irregular manner, they can occur in a regular or rhythmic pattern and at a maximum rate for that particular site of the small intestine (rhythmic segmentation). Rhythmic segmentation may occur only in a localized segment of small intestine, or it may occur in a progressive manner, with each subsequent segmenting contraction occurring slightly below the preceding one (progressive segmentation).

A peristaltic contraction may be defined as an advancing ring, or wave, of contraction that passes along a segment of the gastrointestinal tract. It normally occurs only over a short segment (approximately every 6 cm) and moves at a rate of about 1 or 2 cm per minute. This type of motor activity in the small intestine results in the transport of intraluminal contents downward, usually one segment at a time.

When an inflammatory condition of the small bowel exists, or when irritating substances are present in the intraluminal contents, a peristaltic contraction may travel over a considerable distance of the small intestine; this is called the peristaltic rush. Diarrhea due to common infections is frequently associated with peristaltic rushes. Most cathartics produce their diarrheic effect by irritating the intestinal mucosa or by increasing the contents, particularly with fluid.

ABSORPTION

Although the small intestine is only 3 to 4 cm in diameter and approximately 7 metres in length, it has been estimated that its total absorptive surface area is approximately 4,500 square metres (5,400 square yards). This enormous absorptive surface is provided by the unique structure of the mucosa, which is arranged in concentric folds that have the appearance of transverse ridges. These folds, known as plicae circulares, are approximately 5 to 6 cm (2 inches) long and about 3 mm (0.1 inch) thick. Plicae circulares are present throughout the small intestine except in the first portion, or bulb, of the duodenum, which is usually flat and smooth, except for a few longitudinal folds. Also called valves of Kerckring, the plicae circulares are largest in the lower part of the duodenum and in the upper part of the jejunum. They become smaller and finally disappear in the lower part of the ileum. The folds usually run one-half to two-thirds of the way around the intestinal wall; occasionally, a single fold may spiral the wall for three or four complete turns. It has been estimated that the small intestine contains approximately 800 plicae circulares and that they increase the surface area of the lining of the small bowel by five to eight times the outer surface area.

Another feature of the mucosa that greatly multiplies its surface area is that of tiny projections called villi. The villi usually vary from 0.5 to 1 mm in height. Their diameters vary from approximately one-eighth to one-third their height. The villi are covered by a single layer of tall columnar cells called goblet cells because of their rough resemblance to empty goblets after they have discharged their contents. Goblet cells are found scattered among the surface epithelial cells covering the villi and are a source of mucin, the chief constituent of mucus.

At the base of the mucosal villi are depressions called intestinal glands, or Lieberkühn's glands. The cells that line these glands continue up and over the surface of the villi. In the bottom of the glands, epithelial cells called cells of Paneth are filled with alpha granules, or eosinophilic granules, so called because they take up the rose-coloured stain eosin. Though they may contain lysozyme, an enzyme toxic to bacteria, and immunoglobins, their precise function is uncertain.

There are three other cell types in the Lieberkühn's glands: undifferentiated cells, which have the potential to undergo changes for the purpose of replacing losses of any cell type; the goblet cells mentioned above; and endocrine cells. The main functions of the undifferentiated cells in these glands are cell renewal and secretion. Undifferentiated cells have an average life of 72 hours before becoming exhausted and being cast off.

The appearance and shape of the villi vary in different levels of the small intestine. In the duodenum the villi are closely packed, large, and frequently leaflike in shape. In the jejunum the individual villus measures between 350 and 600 μm in height (there are about 25,000 μm in an inch) and has a diameter of 110 to 135 μm. The inner structure of the individual villus consists of loose connective tissue containing a rich network of blood vessels, a central lacteal (or channel for lymph), smooth muscle fibres, and scattered cells of various types. The smooth muscle cells surround the central lacteal and provide for the pumping action required to initiate the flow of lymph out of the villus. A small central arteriole (minute artery) branches at the tip of the villus to form a capillary network; the capillaries, in turn, empty into a collecting venule that runs to the bottom of the villus.

A remarkable feature of the mucosa villi is the rough, specialized surface of the epithelial cells. This plasma membrane, known as the brush border, is thicker and richer in proteins and lipids than is the plasma membrane on the epithelial cells at the side and base of the villus. Water and solutes pass through pores in the surface epithelium of the mucosa by active transport and solvent drag; *i.e.*, solutes are carried in a moving stream of water that causes an increased concentration of solute on the side of the membrane from which the water had originally come. The size of the pores is different in the ileum from in the jejunum; this difference accounts for the various rates of absorption of water at the two sites. The enterocytes are joined near their apex by a contact zone known as a "tight junction." These junctions are believed to have pores that are closed in the resting state and dilated when absorption is required. The brush border is fused to a layer of glycoprotein, known as the "fuzzy coat," where certain nutrients are partly digested. It consists of individual microvilli approximately 0.1 μm in diameter and 1 μm in height; each epithelial cell may have as many as 1,000 microvilli. The microvilli play an important role in the digestion and absorption of intestinal contents by enlarging the absorbing surface approximately 25 times. They also secrete the enzymes disaccharidase and peptidase that hydrolyze disaccharides and polypeptides to monosaccharides and dipeptides to amino acids, respectively. Molecular receptors for specific substances are found on the microvilli surfaces at different levels in the small intestine. This may account for the selective absorption of particular substances at particular sites—for example, intrinsic-factor-bound vitamin B_{12} in the terminal ileum. Such receptors may also explain the selective absorption of iron and calcium in the duodenum and upper jejunum. Furthermore, there are transport proteins in the microvillus membrane associated with the passage of sodium ions, D-glucose, and amino acids.

Actin is found in the core of the microvillus, and myosin is found in the brush border; because contractility is a function of these proteins, the microvilli have motor activity that presumably initiates the stirring and mixing actions within the lumen of the small intestine.

Beneath the mucosa of the small intestine, as beneath that of the stomach, are the muscularis and the submucosa. The submucosa consists of loose connective tissue and contains many blood vessels and lymphatics. Brunner's glands, located in the submucosa of the duodenum, are composed of acini (round sacs) and tubules that are twisting and have multiple branching. These glands empty into the base of Lieberkühn's glands in the duodenum. Their exact function is not known, but they do secrete a clear fluid that contains mucus, bicarbonate, and a relatively weak proteolytic (protein-splitting) enzyme. In the submucosa of the jejunum, solitary nodules (lumps) of lymphatic tissue are located. There is more lymphatic tissue in the ileum, in aggregates of nodules known as Peyer patches.

SECRETIONS

There are many sources of digestive secretions into the small intestine. Secretions into the small intestine are controlled by nerves, including the vagus, and hormones. The most effective stimuli for secretion are local mechanical or chemical stimulations of the intestinal mucous membrane. Such stimuli always are present in the intestine in the form of chyme and food particles. The gastric chyme that is emptied into the duodenum contains gastric secretions that will continue their digestive processes for a short time in the small intestine. One of the major sources of digestive secretion is the pancreas, a large gland that produces both digestive enzymes and hormones.

The pancreas empties its secretions into the duodenum through the major pancreatic duct (duct of Wirsung) in the duodenal papilla (papilla of Vater) and the accessory pancreatic duct a few centimetres away from it. Pancreatic juice contains enzymes that digest proteins, fats, and carbohydrates. Secretions of the liver are delivered to the duodenum by the common bile duct via the gallbladder and are also received through the duodenal papilla.

The composition of the succus entericus, the mixture of substances secreted into the small intestine, varies somewhat in different parts of the intestine. Except in the duodenum, the quantity of the fluid secreted is minimal, even under conditions of stimulation. In the duodenum, for example, where the Brunner's glands are located, the secretion contains more mucus. In general, the secretion of the small intestine is a thin, colourless or slightly straw-coloured fluid, containing flecks of mucus, water, inorganic salts, and organic material. The inorganic salts are those commonly present in other body fluids, with the bicarbonate concentration higher than it is in blood. Aside from mucus, the organic matter consists of cellular debris and enzymes, including a pepsinlike protease (from the duodenum only), an amylase, a lipase, at least two peptidases, sucrase, maltase, enterokinase, alkaline phosphatase, nucleophosphatases, and nucleocytases.

LARGE INTESTINE

The large intestine, or colon, serves as a reservoir for the liquids emptied into it from the small intestine. It has a much larger diameter than the small intestine (approximately 2.5 cm, or 1 inch, as opposed to 6 cm, or 3 inches, in the large intestine), but at 150 cm (5 feet), it is less than one-quarter the length of the small intestine. The primary functions of the colon are to absorb water; to maintain osmolality, or level of solutes, of the blood by excreting and absorbing electrolytes (substances, such as sodium and chloride, that in solution take on an electrical charge) from the chyme; and to store fecal material until it can be evacuated by defecation. The large intestine also secretes mucus, which aids in lubricating the intestinal contents and facilitates their transport through the bowel.

Each day approximately 1.5 to 2 litres (about 2 quarts) of chyme pass through the ileocecal valve that separates the small and large intestines. The chyme is reduced by absorption in the colon to around 150 ml (5 fluid ounces). The residual indigestible matter, together with sloughed-off mucosal cells, dead bacteria, and food residues not digested by bacteria, constitute the feces.

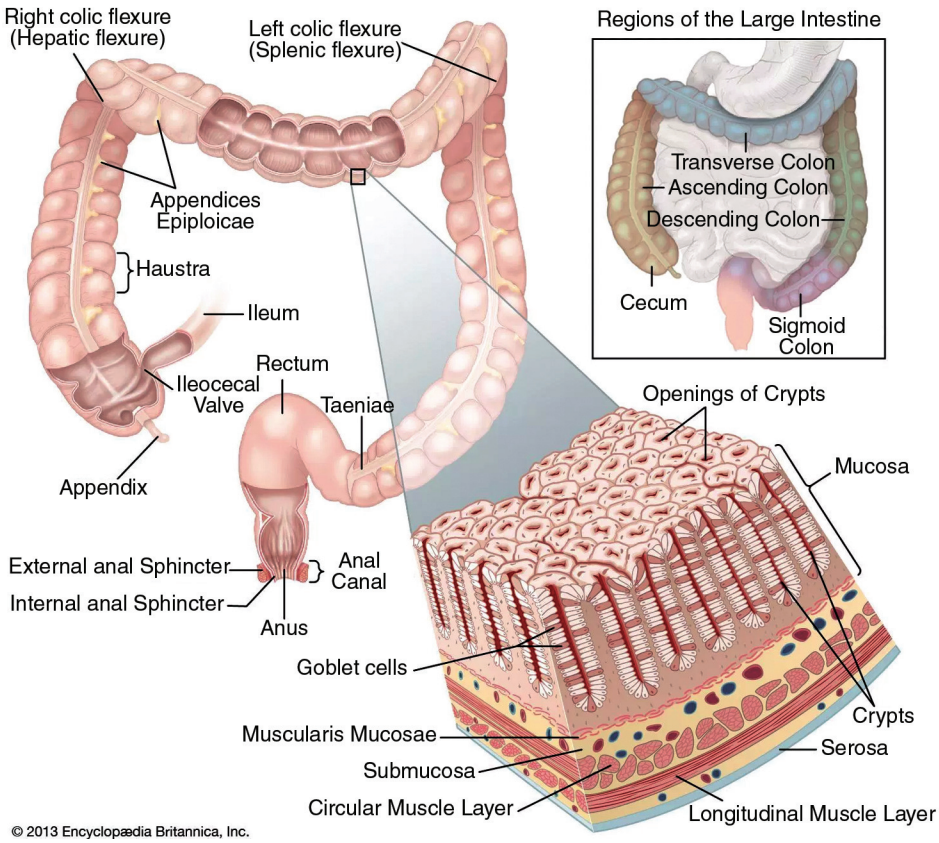


Fig. Structures of the human large intestine, rectum, and anusThe mucosa of the large intestine is punctuated with numerous crypts that absorb water and are lined with mucus-secreting goblet cells. At the lower end of the rectum, the circular and longitudinal muscle layers terminate in the internal and external anal sphincters.

The colon also contains large numbers of bacteria that synthesize niacin (nicotinic acid), thiamin (vitamin B_1) and vitamin K, vitamins that are essential to several metabolic activities as well as to the function of the central nervous system.

ANATOMY

The large intestine can be divided into the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon. The cecum, the first part of the large intestine, is a sac with a closed end that occupies the right iliac fossa, the hollow of the inner side of the ilium (the upper part of the hipbone). Guarding the opening of the ileum (the terminal portion of the small intestine) into the cecum is the ileocecal valve. The circular muscle fibres of the ileum and those of the cecum combine to form the circular sphincter muscle of the ileocecal valve.

The ascending colon extends up from the cecum at the level of the ileocecal valve to the bend in the colon called the hepatic flexure, which is located beneath and behind the right lobe of the liver; behind, it is in contact with the rear abdominal wall and the right kidney. The ascending colon is covered by peritoneum except on its posterior surface. The transverse colon is variable in position, depending largely on the distention of the stomach, but usually is located in the subcostal plane—that is, at the level of the 10th rib. On the left side of the abdomen, it ascends to the bend called the splenic flexure, which may make an indentation in the spleen. The transverse colon is bound to the diaphragm opposite the 11th rib by a fold of peritoneum.

The descending colon passes down and in front of the left kidney and the left side of the posterior abdominal wall to the iliac crest (the upper border of the hipbone). The descending colon is more likely than the ascending colon to be surrounded by peritoneum.

The sigmoid colon is commonly divided into iliac and pelvic parts. The iliac colon stretches from the crest of the ilium, or upper border of the hipbone, to the inner border of the psoas muscle, which lies in the left iliac fossa. Like the descending colon, the iliac colon is usually covered by peritoneum. The pelvic colon lies in the true pelvis (lower part of the pelvis) and forms one or two loops, reaching across to the right side of the pelvis and then bending back and, at the midline, turning sharply downward to the point where it becomes the rectum.

The layers that make up the wall of the colon are similar in some respects to those of the small intestine; there are distinct differences, however. The external aspect of the colon differs markedly from that of the small intestine because of features known as the taeniae, haustra, and appendices epiploicae. The taeniae are three long bands of longitudinal muscle fibres, about 1 cm in width, that are approximately equally spaced around the circumference of the colon. Between the thick bands of the taeniae, there is a thin coating of longitudinal muscle fibres. Because the taeniae are slightly shorter than the large intestine, the intestinal wall constricts and forms circular furrows of varying depths called haustra, or sacculations. The appendices epiploicae are collections of fatty tissue beneath the covering membrane. On the ascending and descending colon, they are usually found in two rows, whereas on the transverse colon they form one row.

The inner surface of the colon has many crypts that are lined with mucous glands and numerous goblet cells, and it lacks the villi and plicae circulares characteristic of the small intestine. It contains many solitary lymphatic nodules but no Peyer patches. Characteristic of the colonic mucosa are deep tubular pits, increasing in depth towards the rectum.

The inner layer of muscle of the large intestine is wound in a tight spiral around the colon, so that contraction results in compartmentalization of the lumen and its contents. The spiral of the outer layer, on the other hand, follows a loose undulating course, and contraction of this muscle causes the contents of the colon to shift forward and backward. The bulk of the contents, in particular the amount of undigested fibre, influences these muscular activities.

BLOOD AND NERVE SUPPLY

The arterial blood supply to the large intestine is supplied by branches of the superior and inferior mesenteric arteries (both of which are branches of the abdominal aorta) and the hypogastric branch of the internal iliac artery (which supplies blood to the pelvic walls and viscera, the genital organs, the buttocks, and the inside of the thighs). The vessels form a continuous row of arches from which vessels arise to enter the large intestine. Venous blood is drained from the colon from branches that form venous arches similar to those of the arteries. These eventually drain into the superior and inferior mesenteric veins, which ultimately join with the splenic vein to form the portal vein. The innervation of the large intestine is similar to that of the small intestine.

CONTRACTIONS AND MOTILITY

Local contractions and retrograde propulsions ensure mixing of the contents and good contact with the mucosa. Colonic motility is stimulated by mastication and by the presence of fat, unabsorbed bile salts, bile acids, and the peptide hormones gastrin and cholecystokinin. The hormones secretin, glucagon, and vasoactive intestinal peptide act to suppress motility. The electrical activity of the muscles of the colon is more complex than that of the small intestine. Variations from the basic rhythmic movements of the colon are present in the lower (distal) half of the colon and in the rectum. Slow-wave activity that produces contractions from the ascending colon to the descending colon occurs at the rate of 11 cycles per minute, and slow-wave activity in the sigmoid colon and rectum occurs at 6 cycles per minute. Local contractions migrate distally in the colon at the rate of 4 cm (1.6 inches) per second. Retrograde, or reverse, movements occur mainly in the upper (proximal) colon.

ORGANS OF THE DIGESTIVE SYSTEM

The organs of the digestive system can be divided into upper and lower digestive tracts. The upper digestive tract consists of the esophagus, stomach, and the small intestine; the lower tract includes all of the large intestine, the rectum, and anus. The human body uses a variety of mental and physiological cues to initiate the process of digestion. Throughout our gastrointestinal (GI) tract, each organ serves a specific purpose to bring our food from the plate to a digestible substance from which nutrients can be extracted.

THE DIGESTIVE TUBE

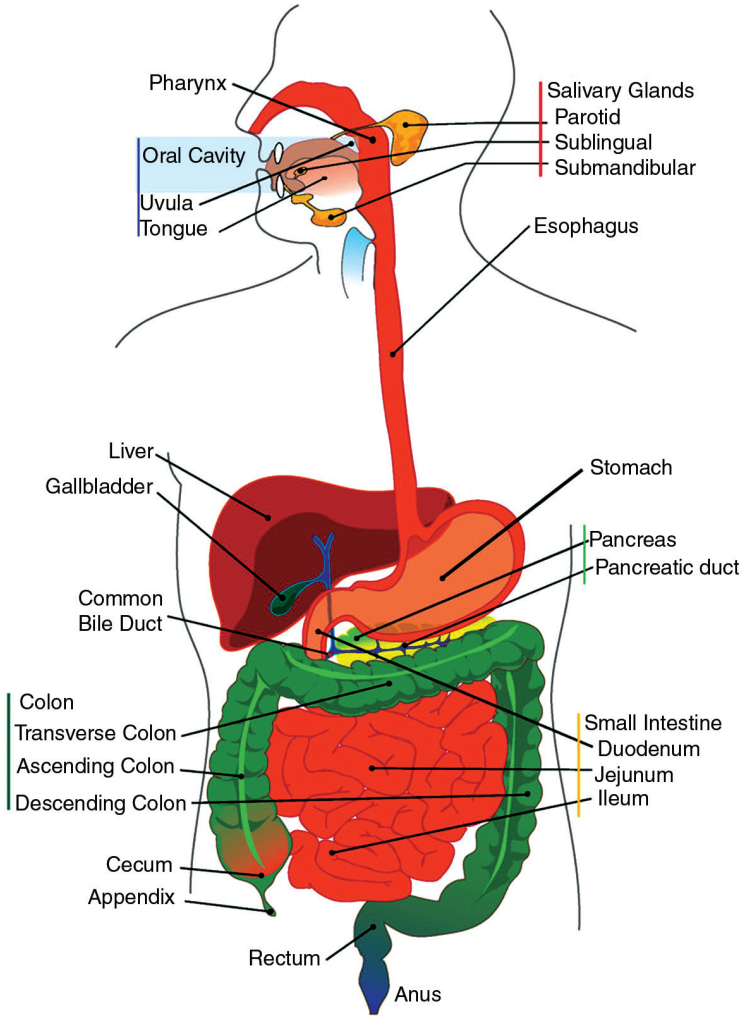


Fig. The organs of the gastrointestinal tract: This diagram shows the relationship between the various organs of the digestive system. It shows how the oral cavity connects to the esophagus and descends into the stomach and then the small intestine. It then connects to the large intestine, then the rectum, and, finally, the anus.

Our digestive system is like a long tube, with different segments doing different jobs. The major organs within our digestive system can be split into two major segments of this tube: the upper gastrointestinal tract, and the lower gastrointestinal tract.

The Upper Gastrointestinal Tract

The upper gastrointestinal, or GI, tract is made up of three main parts:

1. The esophagus.

2. The stomach.
3. The small intestine.

The Lower Gastrointestinal Tract

The lower GI tract contains the remainder of the system:

1. The large intestine.
2. The rectum.
3. The anus.

The exact dividing line between upper and lower tracts can vary, depending on which medical specialist is examining the GI tract.

FOOD BREAKDOWN AND ABSORPTION: THE UPPER GI TRACT

When we take a bite of food, the food material gets chewed up and processed in the mouth, where saliva begins the process of chemical and mechanical breakdown. The chewing process is also known as mastication. When we mix up food with saliva, the resulting mushy wad is called a bolus. The bolus gets swallowed, and begins its journey through the upper gastrointestinal tract.

The Esophagus

The upper GI tract begins with the esophagus, the long muscular tube that carries food to the stomach. The throat cavity in which our esophagus originates is known as the pharynx. As we swallow, the bolus moves down our esophagus, from the pharynx to the stomach, through waves of muscle movement known as peristalsis. Next the bolus reaches the stomach itself.

The Stomach

The stomach is a muscular, hollow bag that is an important part of the upper GI tract. Many organisms have a variety of stomach types, with many segments or even multiple stomachs. As humans, we have only one stomach.

Here our bolus gets mixed with digestive acids, furthering breakdown of the bolus, and turning the bolus material into a slimy mess called chyme. The chyme moves on into the small intestine, where nutrients are absorbed.

The Small Intestine

The small intestine is an impressive digestive tube, spanning an average of 20 feet in length. The twists and turns of the small intestine, along with tiny interior projections known as villi, help to increase the surface area for nutrient absorption.

This snaking tube is made up of three parts, in order from the stomach:

1. The duodenum.
2. The jejunum.
3. The ileum.

As the chyme makes its way through each segment of the small intestine, pancreatic juices from the pancreas start to break down proteins. Soapy bile from the liver, stored in the gallbladder, gets squirted into the small intestine to help emulsify—or break apart—fats. Now thoroughly digested, with its nutrients absorbed along the path of the small intestine, what remains of our food gets passed into the lower GI tract.

WASTE COMPACTION AND REMOVAL: THE LOWER GASTROINTESTINAL TRACT

The Large Intestine (Colon)

Following nutrient absorption, the food waste reaches the large intestine, or colon. The large intestine is responsible for compacting waste material, removing water, and producing feces —our solid-waste product. Accessory organs like the cecum and appendix, which are remnants of our evolutionary past, serve as special pockets at the beginning of the large intestine. The compacted and dried-out waste passes to the rectum, and out of the body through the anus. Healthy gut bacteria in the large intestine also help to metabolize our waste as it finishes its journey.

LYMPHATIC SYSTEM

The lymphatic system is part of the vascular system and an important part of the immune system, comprising a large network of lymphatic vessels that carry a clear fluid called lymph (from Latin, *lympha* meaning "water") directionally towards the heart. The lymphatic system was first described in the seventeenth century independently by Olaus Rudbeck and Thomas Bartholin. Unlike the circulatory system, the lymphatic system is not a closed system. The human circulatory system processes an average of 20 litres of blood per day through capillary filtration, which removes plasma while leaving the blood cells. Roughly 17 litres of the filtered plasma is reabsorbed directly into the blood vessels, while the remaining three litres remain in the interstitial fluid. One of the main functions of the lymph system is to provide an accessory return route to the blood for the surplus three litres.

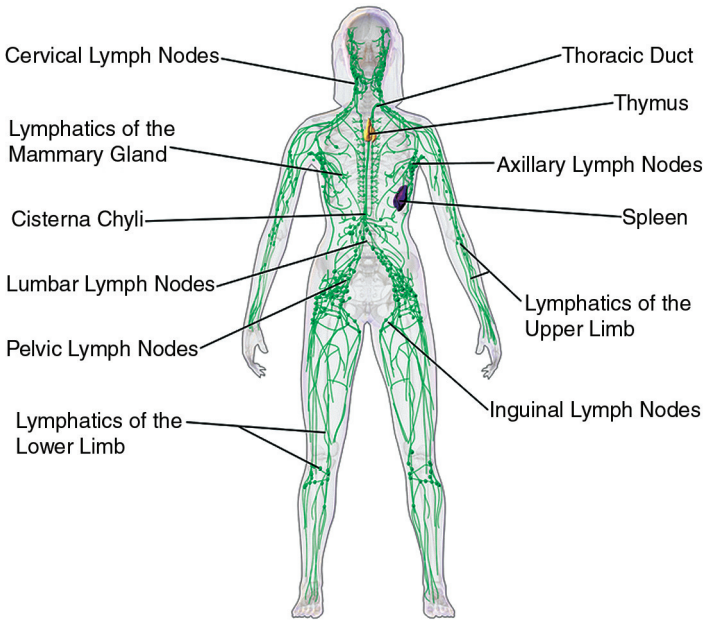


Fig. Lymphatic System.

The other main function is that of defence in the immune system. Lymph is very similar to blood plasma: it contains lymphocytes. It also contains waste products and cellular debris together with bacteria and proteins. Associated organs composed of lymphoid tissue are the sites of lymphocyte production. Lymphocytes are concentrated in the lymph nodes. The spleen and the thymus are also lymphoid organs of the immune system. The tonsils are lymphoid organs that are also associated with the digestive system. Lymphoid tissues contain

lymphocytes, and also contain other types of cells for support. The system also includes all the structures dedicated to the circulation and production of lymphocytes (the primary cellular component of lymph), which also includes the bone marrow, and the lymphoid tissue associated with the digestive system.

The blood does not come into direct contact with the parenchymal cells and tissues in the body (except in case of an injury causing rupture of one or more blood vessels), but constituents of the blood first exit the microvascular exchange blood vessels to become interstitial fluid, which comes into contact with the parenchymal cells of the body. Lymph is the fluid that is formed when interstitial fluid enters the initial lymphatic vessels of the lymphatic system. The lymph is then moved along the lymphatic vessel network by either intrinsic contractions of the lymphatic passages or by extrinsic compression of the lymphatic vessels via external tissue forces (*e.g.*, the contractions of skeletal muscles), or by lymph hearts in some animals. The organization of lymph nodes and drainage follows the organization of the body into external and internal regions; therefore, the lymphatic drainage of the head, limbs, and body cavity walls follows an external route, and the lymphatic drainage of the thorax, abdomen, and pelvic cavities follows an internal route. Eventually, the lymph vessels empty into the lymphatic ducts, which drain into one of the two subclavian veins, near their junction with the internal jugular veins.

STRUCTURE

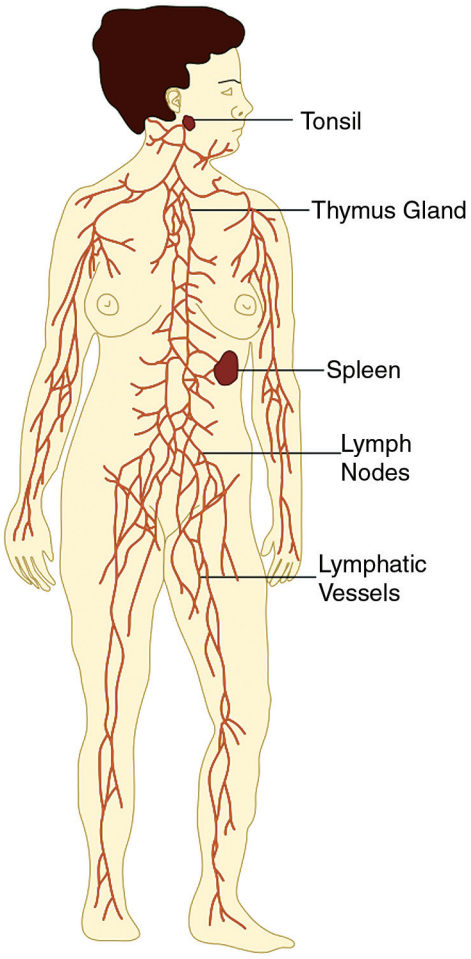


Fig. Lymphatic System.

The lymphatic system consists of lymphatic organs, a conducting network of lymphatic vessels, and the circulating lymph. The primary or central lymphoid organs generate lymphocytes from immature progenitor cells. The thymus and the bone marrow constitute the primary lymphoid organs involved in the production and early clonal selection of lymphocyte tissues. Bone marrow is responsible for both the creation of T cells and the

production and maturation of B cells. From the bone marrow, B cells immediately join the circulatory system and travel to secondary lymphoid organs in search of pathogens. T cells, on the other hand, travel from the bone marrow to the thymus, where they develop further. Mature T cells join B cells in search of pathogens. The other 95% of T cells begin a process of apoptosis, a form of programmed cell death.

Secondary or peripheral lymphoid organs, which include lymph nodes and the spleen, maintain mature naive lymphocytes and initiate an adaptive immune response. The peripheral lymphoid organs are the sites of lymphocyte activation by antigens. Activation leads to clonal expansion and affinity maturation. Mature lymphocytes recirculate between the blood and the peripheral lymphoid organs until they encounter their specific antigen.

Secondary lymphoid tissue provides the environment for the foreign or altered native molecules (antigens) to interact with the lymphocytes. It is exemplified by the lymph nodes, and the lymphoid follicles in tonsils, Peyer's patches, spleen, adenoids, skin, *etc.* that are associated with the mucosa-associated lymphoid tissue (MALT). In the gastrointestinal wall the appendix has mucosa resembling that of the colon, but here it is heavily infiltrated with lymphocytes.

Tertiary lymphoid organs (TLO) are abnormal lymph node–like structures that form in peripheral tissues at sites of chronic inflammation, such as chronic infection, transplanted organs undergoing graft rejection, some cancers, and autoimmune and autoimmune-related diseases. TLOs are regulated differently from the normal process whereby lymphoid tissues are formed during ontogeny, being dependent on cytokines and hematopoietic cells, but still drain interstitial fluid and transport lymphocytes in response to the same chemical messengers and gradients. TLOs typically contains far fewer lymphocytes, and assumes an immune role only when challenged with antigens that result in inflammation. It achieves this by importing the lymphocytes from blood and lymph.

LYMPHOID TISSUE

THYMUS

The thymus is a primary lymphoid organ and the site of maturation for T cells, the lymphocytes of the adaptive immune system. The thymus increases in size from birth in response to postnatal antigen stimulation, then to puberty and regresses thereafter. The loss or lack of the thymus results in severe immunodeficiency and subsequent high susceptibility to infection. In most species, the thymus consists of lobules divided by septa which are made up of epithelium and is therefore an epithelial organ. T cells mature from thymocytes, proliferate and undergo selection process in the thymic cortex before entering the medulla to interact with epithelial cells.

The thymus provides an inductive environment for development of T cells from hematopoietic progenitor cells. In addition, thymic stromal cells allow for the selection of a functional and self-tolerant T cell repertoire. Therefore, one of the most important roles of the thymus is the induction of central tolerance.

The thymus is largest and most active during the neonatal and pre-adolescent periods. By the early teens, the thymus begins to atrophy and thymic stroma is mostly replaced by adipose tissue. Nevertheless, residual T lymphopoiesis continues throughout adult life.

Spleen

The main functions of the spleen are:

1. To produce immune cells to fight antigens
2. To remove particulate matter and aged blood cells, mainly red blood cells.
3. To produce blood cells during fetal life.

The spleen synthesizes antibodies in its white pulp and removes antibody-coated bacteria and antibody-coated blood cells by way of blood and lymph node circulation. A study published in 2009 using mice found

that the spleen contains, in its reserve, half of the body's monocytes within the red pulp. These monocytes, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages while promoting tissue healing. The spleen is a center of activity of the mononuclear phagocyte system and can be considered analogous to a large lymph node, as its absence causes a predisposition to certain infections.

Like the thymus, the spleen has only efferent lymphatic vessels. Both the short gastric arteries and the splenic artery supply it with blood. The germinal centers are supplied by arterioles called *penicilliary radicles*. Up to the fifth month of prenatal development the spleen creates red blood cells. After birth the bone marrow is solely responsible for hematopoiesis. As a major lymphoid organ and a central player in the reticuloendothelial system, the spleen retains the ability to produce lymphocytes. The spleen stores red blood cells and lymphocytes. It can store enough blood cells to help in an emergency. Up to 25% of lymphocytes can be stored at any one time.

Lymph Nodes

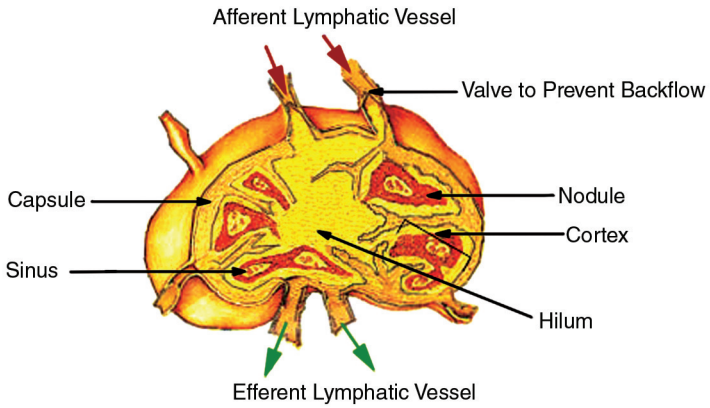


Fig. A lymph node showing afferent and efferent lymphatic vessels.

A lymph node is an organized collection of lymphoid tissue, through which the lymph passes on its way back to the blood. Lymph nodes are located at intervals along the lymphatic system. Several afferent lymph vessels bring in lymph, which percolates through the substance of the lymph node, and is then drained out by an efferent lymph vessel. There are between five and six hundred lymph nodes in the human body, many of which are grouped in clusters in different regions as in the underarm and abdominal areas. Lymph node clusters are commonly found at the base of limbs (groin, armpits) and in the neck, where lymph is collected from regions of the body likely to sustain pathogen contamination from injuries.

The substance of a lymph node consists of lymphoid follicles in an outer portion called the cortex. The inner portion of the node is called the medulla, which is surrounded by the cortex on all sides except for a portion known as the hilum. The hilum presents as a depression on the surface of the lymph node, causing the otherwise spherical lymph node to be bean-shaped or ovoid. The efferent lymph vessel directly emerges from the lymph node at the hilum. The arteries and veins supplying the lymph node with blood enter and exit through the hilum. The region of the lymph node called the paracortex immediately surrounds the medulla. Unlike the cortex, which has mostly immature T cells, or thymocytes, the paracortex has a mixture of immature and mature T cells. Lymphocytes enter the lymph nodes through specialised high endothelial venules found in the paracortex.

A lymph follicle is a dense collection of lymphocytes, the number, size and configuration of which change in accordance with the functional state of the lymph node. For example, the follicles expand significantly when encountering a foreign antigen. The selection of B cells, or *B lymphocytes*, occurs in the germinal centre of the lymph nodes. Lymph nodes are particularly numerous in the mediastinum in the chest, neck, pelvis, axilla, inguinal region, and in association with the blood vessels of the intestines.

Other Lymphoid Tissue

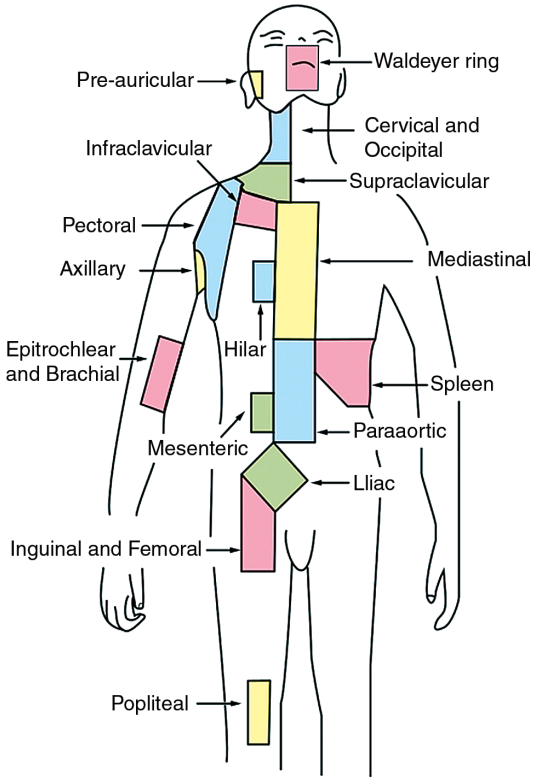


Fig. Regional Lymph Nodes.

Lymphoid tissue associated with the lymphatic system is concerned with immune functions in defending the body against infections and the spread of tumours. It consists of connective tissue formed of reticular fibres, with various types of leukocytes, (white blood cells), mostly lymphocytes enmeshed in it, through which the lymph passes. Regions of the lymphoid tissue that are densely packed with lymphocytes are known as *lymphoid follicles*. Lymphoid tissue can either be structurally well organized as lymph nodes or may consist of loosely organized lymphoid follicles known as the mucosa-associated lymphoid tissue.

The central nervous system also has lymphatic vessels, as discovered by the University of Virginia Researchers. The search for T-cell gateways into and out of the meninges uncovered functional meningeal lymphatic vessels lining the dural sinuses, anatomically integrated into the membrane surrounding the brain.

Lymphatic Vessels

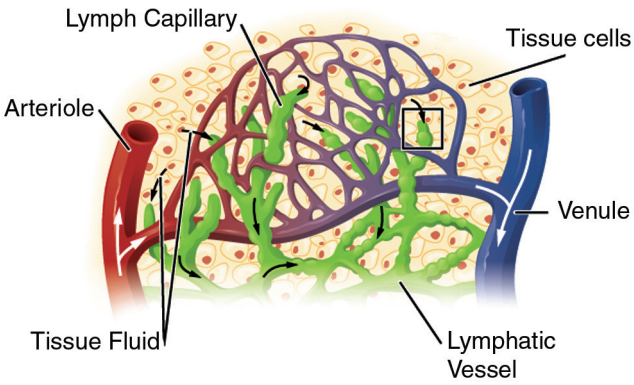


Fig. Lymph capillaries in the tissue spaces.

The lymphatic vessels, also called lymph vessels, conduct lymph between different parts of the body. They include the tubular vessels of the lymph capillaries, and the larger collecting vessels–the right lymphatic duct and the thoracic duct (the left lymphatic duct). The lymph capillaries are mainly responsible for the absorption of interstitial fluid from the tissues, while lymph vessels propel the absorbed fluid forward into the larger collecting ducts, where it ultimately returns to the bloodstream via one of the subclavian veins. These vessels are also called the lymphatic channels or simply *lymphatics*.

The lymphatics are responsible for maintaining the balance of the body fluids. Its network of capillaries and collecting lymphatic vessels work to efficiently drain and transport extravasated fluid, along with proteins and antigens, back to the circulatory system. Numerous intraluminal valves in the vessels ensure a unidirectional flow of lymph without reflux. Two valve systems are used to achieve this one directional flow—a primary and a secondary valve system. The capillaries are blind-ended, and the valves at the ends of capillaries use specialised junctions together with anchoring filaments to allow a unidirectional flow to the primary vessels. The collecting lymphatics, however, act to propel the lymph by the combined actions of the intraluminal valves and lymphatic muscle cells.

Development

Lymphatic tissues begin to develop by the end of the fifth week of embryonic development. Lymphatic vessels develop from lymph sacs that arise from developing veins, which are derived from mesoderm. The first lymph sacs to appear are the paired jugular lymph sacs at the junction of the internal jugular and subclavian veins. From the jugular lymph sacs, lymphatic capillary plexuses spread to the thorax, upper limbs, neck and head. Some of the plexuses enlarge and form lymphatic vessels in their respective regions. Each jugular lymph sac retains at least one connection with its jugular vein, the left one developing into the superior portion of the thoracic duct.

The next lymph sac to appear is the unpaired retroperitoneal lymph sac at the root of the mesentery of the intestine. It develops from the primitive vena cava and mesonephric veins. Capillary plexuses and lymphatic vessels spread from the retroperitoneal lymph sac to the abdominal viscera and diaphragm. The sac establishes connections with the cisterna chyli but loses its connections with neighbouring veins. The last of the lymph sacs, the paired posterior lymph sacs, develop from the iliac veins. The posterior lymph sacs produce capillary plexuses and lymphatic vessels of the abdominal wall, pelvic region, and lower limbs. The posterior lymph sacs join the cisterna chyli and lose their connections with adjacent veins. With the exception of the anterior part of the sac from which the cisterna chyli develops, all lymph sacs become invaded by mesenchymal cells and are converted into groups of lymph nodes. The spleen develops from mesenchymal cells between layers of the dorsal mesentery of the stomach. The thymus arises as an outgrowth of the third pharyngeal pouch.

7

Nervous System and Its Components

The nervous system transmits signals between the brain and the rest of the body, including internal organs. In this way, the nervous system's activity controls the ability to move, breathe.

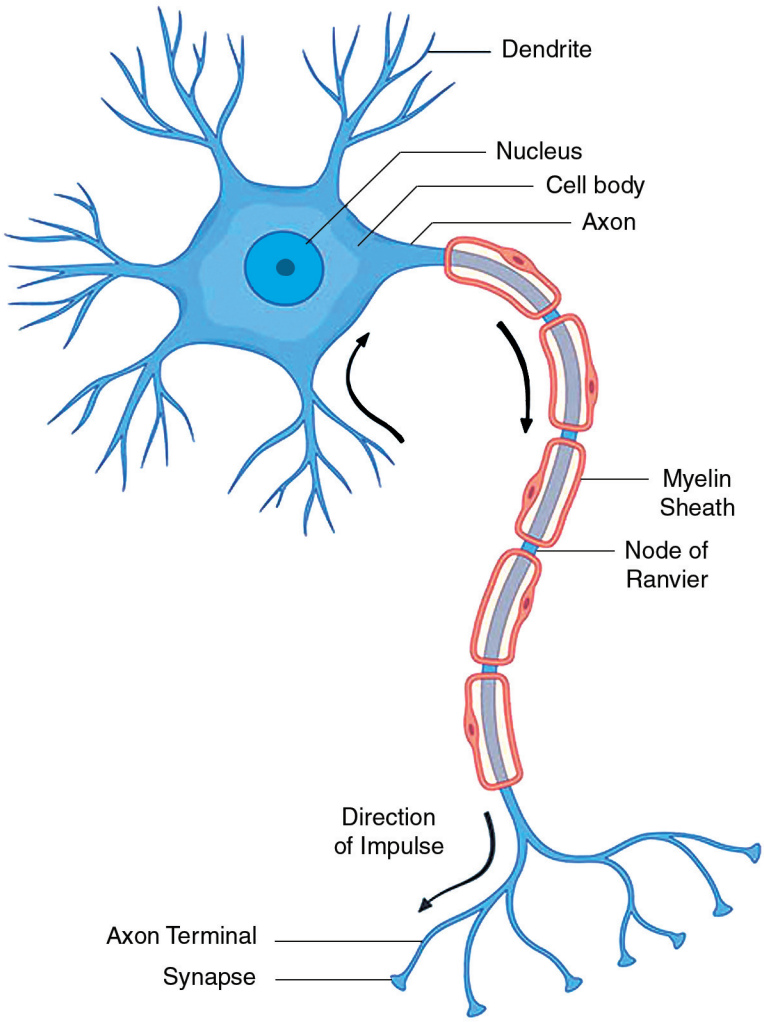


Fig. The nervous System.

The basic unit of the nervous system is a nerve cell, or neuron. The human brain contains about 100 billion neurons. A neuron has a cell body, which includes the cell nucleus, and special extensions called axons (pronounced *AK-sonz*) and dendrites (pronounced *DEN-drahytz*). Bundles of axons, called nerves, are found throughout the body. Axons and dendrites allow neurons to communicate, even across long distances.

Different types of neurons control or perform different activities. For instance, motor neurons transmit messages from the brain to the muscles to generate movement. Sensory neurons detect light, sound, odour, taste, pressure, and heat and send messages about those things to the brain. Other parts of the nervous system control involuntary processes. These include keeping a regular heartbeat, releasing hormones like adrenaline, opening the pupil in response to light, and regulating the digestive system.

When a neuron sends a message to another neuron, it sends an electrical signal down the length of its axon. At the end of the axon, the electrical signal changes to a chemical signal. The axon then releases the chemical signal with chemical messengers called neurotransmitters (pronounced *noor-oh-TRANS-mit-erz*) into the synapse (pronounced *SIN-aps*)—the space between the end of an axon and the tip of a dendrite from another neuron. The neurotransmitters move the signal through the synapse to the neighboring dendrite, which converts the chemical signal back into an electrical signal. The electrical signal then travels through the neuron and goes through the same conversion processes as it moves to neighboring neurons.

COMPONENTS OF THE NERVOUS SYSTEM

IDENTIFY THE TWO PRIMARY PARTS OF THE NERVOUS SYSTEM AND DESCRIBE THE FUNCTION AND STRUCTURE OF NEURONS AND GLIAL CELLS

The nervous system is made up of neurons, specialized cells that can receive and transmit chemical or electrical signals, and glia, cells that provide support functions for the neurons by playing an information processing role that is complementary to neurons. A neuron can be compared to an electrical wire—it transmits a signal from one place to another. Glia can be compared to the workers at the electric company who make sure wires go to the right places, maintain the wires, and take down wires that are broken. Although glia have been compared to workers, recent evidence suggests that also usurp some of the signaling functions of neurons.

There is great diversity in the types of neurons and glia that are present in different parts of the nervous system. There are four major types of neurons, and they share several important cellular components.

DIVERSITY OF NERVOUS SYSTEMS

Nervous systems throughout the animal kingdom vary in structure and complexity, as illustrated by the variety of animals shown in Figure. Some organisms, like sea sponges, lack a true nervous system. Others, like jellyfish, lack a true brain and instead have a system of separate but connected nerve cells (neurons) called a "nerve net." Echinoderms such as sea stars have nerve cells that are bundled into fibres called nerves.

Flatworms of the phylum Platyhelminthes have both a central nervous system (CNS), made up of a small "brain" and two nerve cords, and a peripheral nervous system (PNS) containing a system of nerves that extend throughout the body. The insect nervous system is more complex but also fairly decentralized. It contains a brain, ventral nerve cord, and ganglia (clusters of connected neurons). These ganglia can control movements and behaviours without input from the brain. Octopi may have the most complicated of invertebrate nervous systems—they have neurons that are organized in specialized lobes and eyes that are structurally similar to vertebrate species.

Compared to invertebrates, vertebrate nervous systems are more complex, centralized, and specialized. While there is great diversity among different vertebrate nervous systems, they all share a basic structure: a CNS that contains a brain and spinal cord and a PNS made up of peripheral sensory and motor nerves. One interesting difference between the nervous systems of invertebrates and vertebrates is that the nerve cords of many

invertebrates are located ventrally whereas the vertebrate spinal cords are located dorsally. There is debate among evolutionary biologists as to whether these different nervous system plans evolved separately or whether the invertebrate body plan arrangement somehow "flipped" during the evolution of vertebrates.

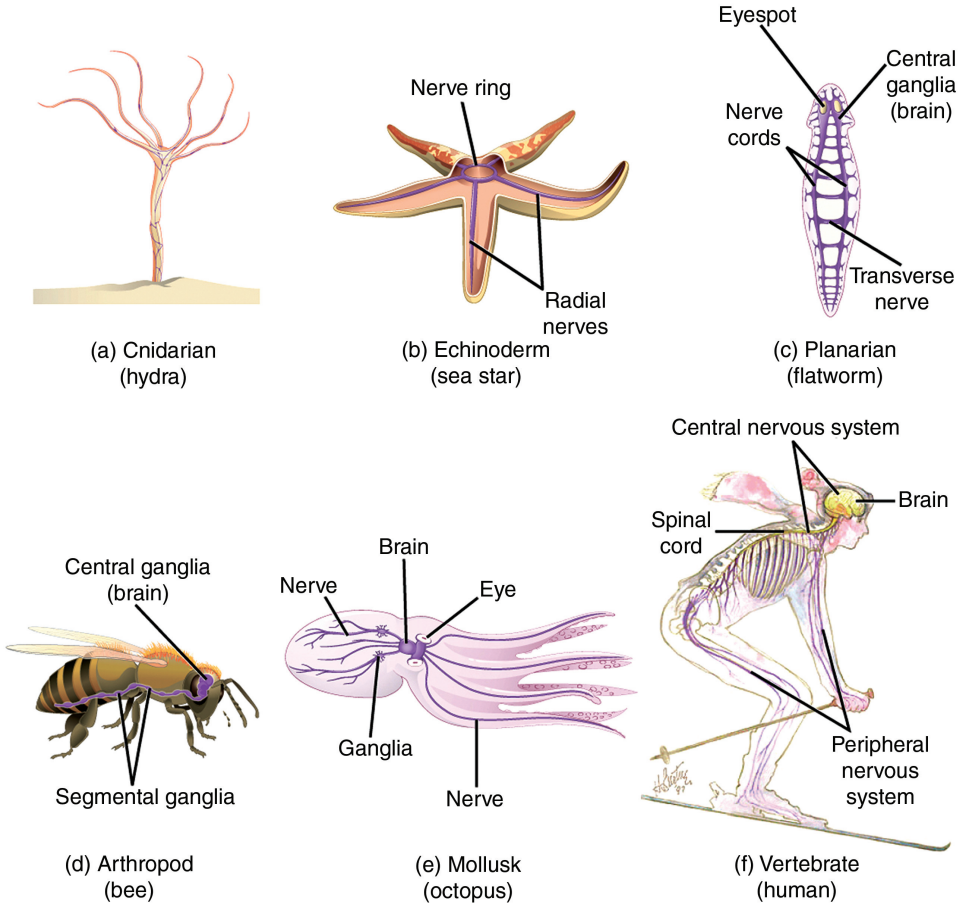


Fig. Nervous systems vary in structure and complexity. In (a) cnidarians, nerve cells form a decentralized nerve net. In (b) echinoderms, nerve cells are bundled into fibres called nerves. In animals exhibiting bilateral symmetry such as (c) planarians, neurons cluster into an anterior brain that processes information. In addition to a brain, (d) arthropods have clusters of nerve cell bodies, called peripheral ganglia, located along the ventral nerve cord. Mollusks such as squid and (e) octopi, which must hunt to survive, have complex brains containing millions of neurons. In (f) vertebrates, the brain and spinal cord comprise the central nervous system, while neurons extending into the rest of the body comprise the peripheral nervous system. (credit e: modification of work by Michael Vecchione, Clyde F.E. Roper, and Michael J. Sweeney, NOAA; credit f: modification of work by NIH).

THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

The nervous system has three main functions: sensory input, integration of data and motor output. Sensory input is when the body gathers information or data, by way of neurons, glia and synapses. The nervous system is composed of excitable nerve cells (neurons) and synapses that form between the neurons and connect them to centers throughout the body or to other neurons. These neurons operate on excitation or inhibition, and although nerve cells can vary in size and location, their communication with one another determines their function. These nerves conduct impulses from sensory receptors to the brain and spinal cord. The data is then processed by way of integration of data, which occurs only in the brain. After the brain has processed the information, impulses are then conducted from the brain and spinal cord to muscles and glands, which is called motor output. Glia cells are found within tissues and are not excitable but help with myelination, ionic regulation and extracellular fluid.

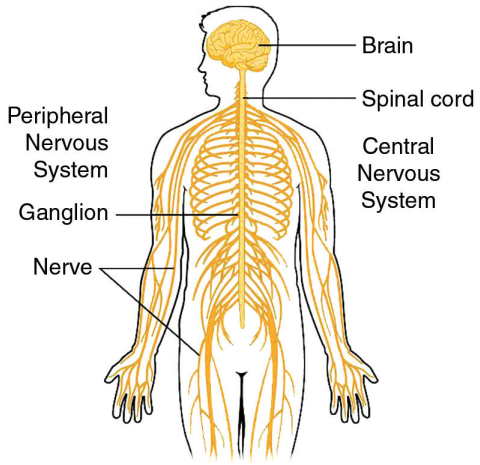


Fig. The central and Peripheral Nervous Systems.

The nervous system is comprised of two major parts, or subdivisions, the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and spinal cord. The brain is the body's "control center." The CNS has various centers located within it that carry out the sensory, motor and integration of data. These centers can be subdivided to Lower Centers (including the spinal cord and brain stem) and Higher centers communicating with the brain via effectors.

The PNS is a vast network of spinal and cranial nerves that are linked to the brain and the spinal cord. It contains sensory receptors which help in processing changes in the internal and external environment. This information is sent to the CNS via afferent sensory nerves. The PNS is then subdivided into the autonomic nervous system and the somatic nervous system. The autonomic has involuntary control of internal organs, blood vessels, smooth and cardiac muscles. The somatic has voluntary control of skin, bones, joints, and skeletal muscle. The two systems function together, by way of nerves from the PNS entering and becoming part of the CNS, and vice versa.

NEURONS

The nervous system of the common laboratory fly, *Drosophila melanogaster*, contains around 100,000 neurons, the same number as a lobster. This number compares to 75 million in the mouse and 300 million in the octopus. A human brain contains around 86 billion neurons. Despite these very different numbers, the nervous systems of these animals control many of the same behaviours—from basic reflexes to more complicated behaviours like finding food and courting mates. The ability of neurons to communicate with each other as well as with other types of cells underlies all of these behaviours.

Most neurons share the same cellular components. But neurons are also highly specialized—different types of neurons have different sizes and shapes that relate to their functional roles.

Parts of a Neuron

Like other cells, each neuron has a cell body (or soma) that contains a nucleus, smooth and rough endoplasmic reticulum, Golgi apparatus, mitochondria, and other cellular components. Neurons also contain unique structures receiving and sending the electrical signals that make neuronal communication possible. Dendrites are tree-like structures that extend away from the cell body to receive messages from other neurons at specialized junctions called synapses. Although some neurons do not have any dendrites, some types of neurons have multiple dendrites. Dendrites can have small protrusions called dendritic spines, which further increase surface area for possible synaptic connections.

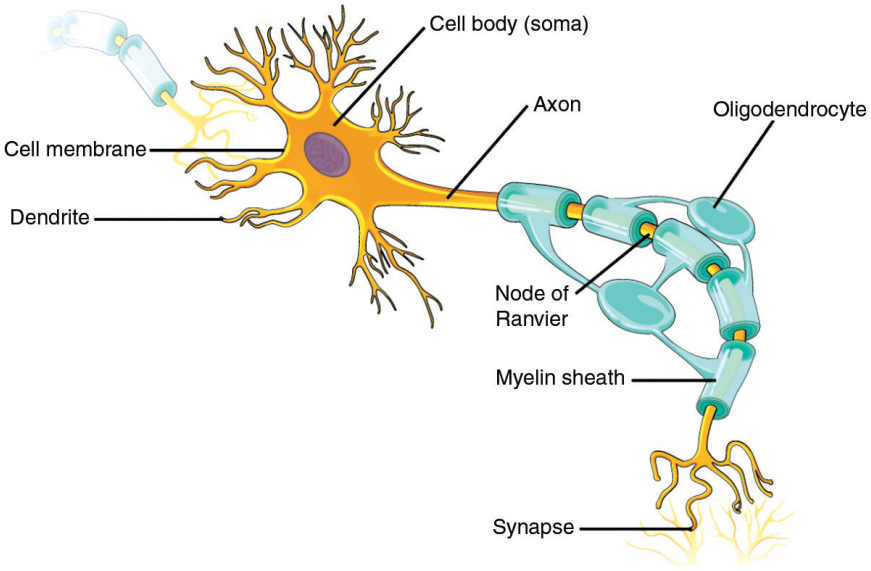
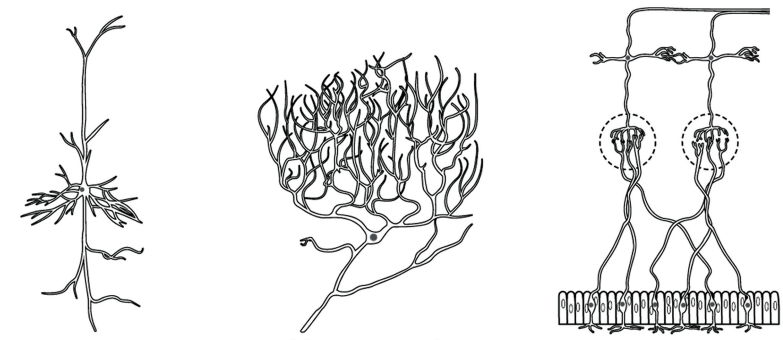


Fig. Neurons contain organelles common to many other cells, such as a nucleus and mitochondria. They also have more specialized structures, including dendrites and axons.

Once a signal is received by the dendrite, it then travels passively to the cell body. The cell body contains a specialized structure, the axon hillock that integrates signals from multiple synapses and serves as a junction between the cell body and an axon. An axon is a tube-like structure that propagates the integrated signal to specialized endings called axon terminals. These terminals in turn synapse on other neurons, muscle, or target organs. Chemicals released at axon terminals allow signals to be communicated to these other cells. Neurons usually have one or two axons, but some neurons, like amacrine cells in the retina, do not contain any axons. Some axons are covered with myelin, which acts as an insulator to minimize dissipation of the electrical signal as it travels down the axon, greatly increasing the speed on conduction. This insulation is important as the axon from a human motor neuron can be as long as a meter—from the base of the spine to the toes. The myelin sheath is not actually part of the neuron. Myelin is produced by glial cells. Along the axon there are periodic gaps in the myelin sheath. These gaps are called nodes of Ranvier and are sites where the signal is "recharged" as it travels along the axon. It is important to note that a single neuron does not act alone—neuronal communication depends on the connections that neurons make with one another (as well as with other cells, like muscle cells). Dendrites from a single neuron may receive synaptic contact from many other neurons. For example, dendrites from a Purkinje cell in the cerebellum are thought to receive contact from as many as 200,000 other neurons.

TYPES OF NEURONS



(a) Pyramindal cell of the cerebral cortex

(b) Purkinje cell of the cerebellar cortex

(c) Olfactory neurons

Fig. There is great diversity in the size and shape of neurons throughout the nervous system. Examples include (a) a pyramidal cell from the cerebral cortex, (b) a Purkinje cell from the cerebellar cortex, and (c) olfactory cells from the olfactory epithelium and olfactory bulb.

There are different types of neurons, and the functional role of a given neuron is intimately dependent on its structure. There is an amazing diversity of neuron shapes and sizes found in different parts of the nervous system (and across species).

While there are many defined neuron cell subtypes, neurons are broadly divided into four basic types: unipolar, bipolar, multipolar, and pseudounipolar. Unipolar neurons have only one structure that extends away from the soma. These neurons are not found in vertebrates but are found in insects where they stimulate muscles or glands. A bipolar neuron has one axon and one dendrite extending from the soma. An example of a bipolar neuron is a retinal bipolar cell, which receives signals from photoreceptor cells that are sensitive to light and transmits these signals to ganglion cells that carry the signal to the brain. Multipolar neurons are the most common type of neuron. Each multipolar neuron contains one axon and multiple dendrites. Multipolar neurons can be found in the central nervous system (brain and spinal cord). An example of a multipolar neuron is a Purkinje cell in the cerebellum, which has many branching dendrites but only one axon. Pseudounipolar cells share characteristics with both unipolar and bipolar cells. A pseudounipolar cell has a single process that extends from the soma, like a unipolar cell, but this process later branches into two distinct structures, like a bipolar cell. Most sensory neurons are pseudounipolar and have an axon that branches into two extensions: one connected to dendrites that receive sensory information and another that transmits this information to the spinal cord.

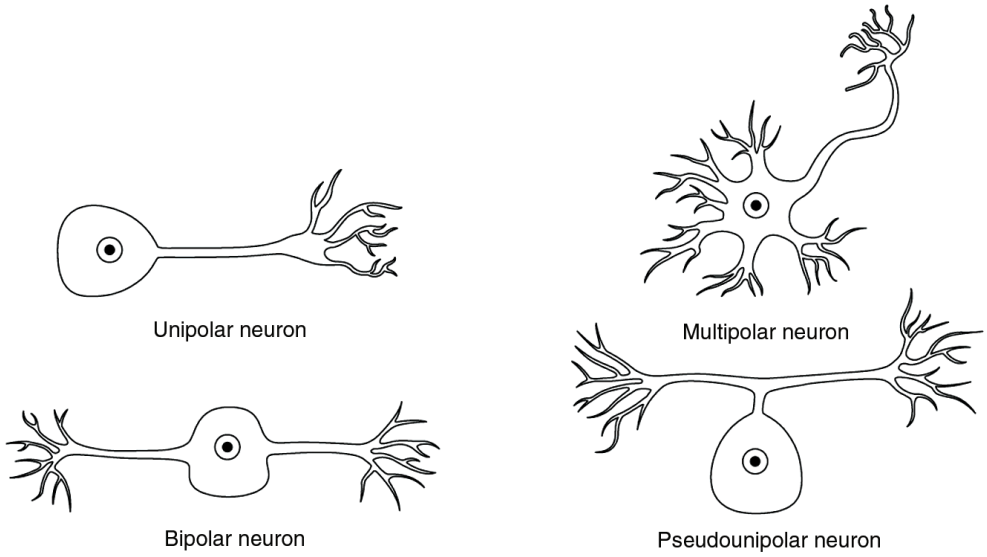


Fig. Neurons are broadly divided into four main types based on the number and placement of axons: (1) unipolar, (2) bipolar, (3) multipolar, and (4) pseudounipolar.

NEUROGENESIS

At one time, scientists believed that people were born with all the neurons they would ever have. Research performed during the last few decades indicates that neurogenesis, the birth of new neurons, continues into adulthood. Neurogenesis was first discovered in songbirds that produce new neurons while learning songs. For mammals, new neurons also play an important role in learning: about 1000 new neurons develop in the hippocampus (a brain structure involved in learning and memory) each day. While most of the new neurons will die, researchers found that an increase in the number of surviving new neurons in the hippocampus correlated with how well rats learned a new task. Interestingly, both exercise and some antidepressant medications also promote neurogenesis in the hippocampus. Stress has the opposite effect. While neurogenesis is quite limited compared to regeneration in other tissues, research in this area may lead to new treatments for disorders such as Alzheimer's, stroke, and epilepsy.

How do scientists identify new neurons? A researcher can inject a compound called bromodeoxyuridine (BrdU) into the brain of an animal. While all cells will be exposed to BrdU, BrdU will only be incorporated into the DNA of newly generated cells that are in S phase. A technique called immunohistochemistry can be used to attach a fluorescent label to the incorporated BrdU, and a researcher can use fluorescent microscopy to visualize the presence of BrdU, and thus new neurons, in brain tissue.

The fluorescently labeled new neurons in a rat hippocampus. Cells that are actively dividing have bromodoxyuridine (BrdU) incorporated into their DNA and are labeled in red. Cells that express glial fibrillary acidic protein (GFAP) are labeled in green. Astrocytes, but not neurons, express GFAP. Thus, cells that are labeled both red and green are actively dividing astrocytes, whereas cells labeled red only are actively dividing neurons.

GLIAL CELLS

While glia are often thought of as the supporting cast of the nervous system, the number of glial cells in the brain actually outnumbers the number of neurons by a factor of ten. Neurons would be unable to function without the vital roles that are fulfilled by these glial cells. Glia guide developing neurons to their destinations, buffer ions and chemicals that would otherwise harm neurons, and provide myelin sheaths around axons. Scientists have recently discovered that they also play a role in responding to nerve activity and modulating communication between nerve cells. When glia do not function properly, the result can be disastrous—most brain tumors are caused by mutations in glia.

Types of Glia

There are several different types of glia with different functions.

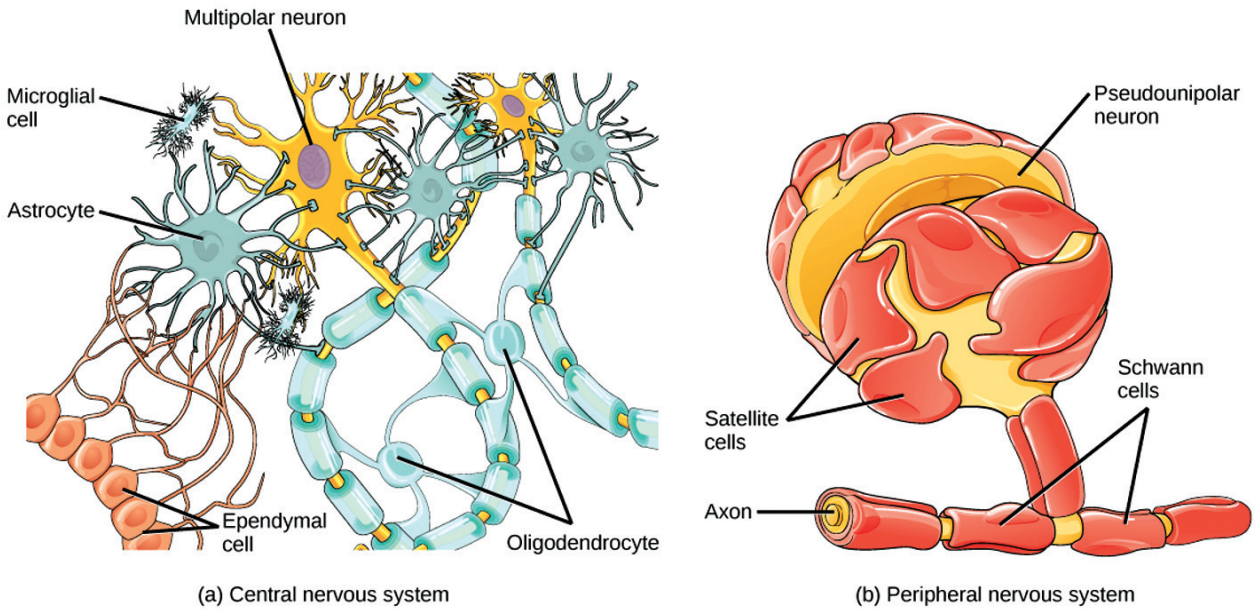


Fig. Glial cells support neurons and maintain their environment. Glial cells of the (a) central nervous system include oligodendrocytes, astrocytes, ependymal cells, and microglial cells. Oligodendrocytes form the myelin sheath around axons. Astrocytes provide nutrients to neurons, maintain their extracellular environment, and provide structural support. Microglia scavenge pathogens and dead cells. Ependymal cells produce cerebrospinal fluid that cushions the neurons. Glial cells of the (b) peripheral nervous system include Schwann cells, which form the myelin sheath, and satellite cells, which provide nutrients and structural support to neurons.

Astrocytes, make contact with both capillaries and neurons in the CNS. They provide nutrients and other substances to neurons, regulate the concentrations of ions and chemicals in the extracellular fluid, and provide

structural support for synapses. Astrocytes also form the blood-brain barrier—a structure that blocks entrance of toxic substances into the brain. Astrocytes, in particular, have been shown through calcium imaging experiments to become active in response to nerve activity, transmit calcium waves between astrocytes, and modulate the activity of surrounding synapses.

Satellite glia provide nutrients and structural support for neurons in the PNS. Microglia scavenge and degrade dead cells and protect the brain from invading microorganisms. Oligodendrocytes myelin sheaths around axons in the CNS. One axon can be myelinated by several oligodendrocytes, and one oligodendrocyte can provide myelin for multiple neurons. This is distinctive from the PNS where a single Schwann cell provides myelin for only one axon as the entire Schwann cell surrounds the axon. Radial glia serve as scaffolds for developing neurons as they migrate to their end destinations. Ependymal cells line fluid-filled ventricles of the brain and the central canal of the spinal cord. They are involved in the production of cerebrospinal fluid, which serves as a cushion for the brain, moves the fluid between the spinal cord and the brain, and is a component of the choroid plexus.

PARTS OF THE NERVOUS SYSTEM

The two halves of the nervous system work together in order for your body to properly communicate its sensations and needs. The forebrain, midbrain, hindbrain, and spinal cord form the central nervous system (CNS), which is one of two great divisions of the nervous system as a whole. The brain is protected by the skull, while the spinal cord, which is about 17 inches (43 cm) long, is protected by the vertebral column.

The other great division of the human brain is the peripheral nervous system (PNS), which consists of nerves and small concentrations of gray matter called ganglia, a term specifically used to describe structures in the PNS. Overall the nervous system is a vast biological computing device formed by a network of gray matter regions interconnected by white matter tracts.

The brain sends messages via the spinal cord to peripheral nerves throughout the body that serve to control the muscles and internal organs. The somatic nervous system is made up of neurons connecting the CNS with the parts of the body that interact with the outside world. Somatic nerves in the cervical region are related to the neck and arms; those in the thoracic region serve the chest; and those in the lumbar and sacral regions interact with the legs.

The autonomic nervous system is made of neurons connecting the CNS with internal organs. It is divided into two parts. The sympathetic nervous system mobilizes energy and resources during times of stress and arousal, while the parasympathetic nervous system conserves energy and resources during relaxed states, including sleep. Messages are carried throughout the nervous system by the individual units of its circuitry: neurons.

PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system is made up of thick bundles of axons, called nerves, carrying messages back and forth between the CNS and the muscles, organs, and senses in the periphery of the body (*i.e.*, everything outside the CNS). The PNS has two major subdivisions: the somatic nervous system and the autonomic nervous system.

The somatic nervous system is associated with activities traditionally thought of as conscious or voluntary. It is involved in the relay of sensory and motor information to and from the CNS; therefore, it consists of motor neurons and sensory neurons. Motor neurons, carrying instructions from the CNS to the muscles, are efferent fibres (efferent means "moving away from"). Sensory neurons, carrying sensory information to the CNS, are afferent fibres (afferent means "moving towards"). Each nerve is basically a two-way superhighway, containing thousands of axons, both efferent and afferent.

The autonomic nervous system controls our internal organs and glands and is generally considered to be outside the realm of voluntary control. It can be further subdivided into the sympathetic and parasympathetic

divisions. The sympathetic nervous system is involved in preparing the body for stress-related activities; the parasympathetic nervous system is associated with returning the body to routine, day-to-day operations. The two systems have complementary functions, operating in tandem to maintain the body's homeostasis. Homeostasis is a state of equilibrium, in which biological conditions (such as body temperature) are maintained at optimal levels.

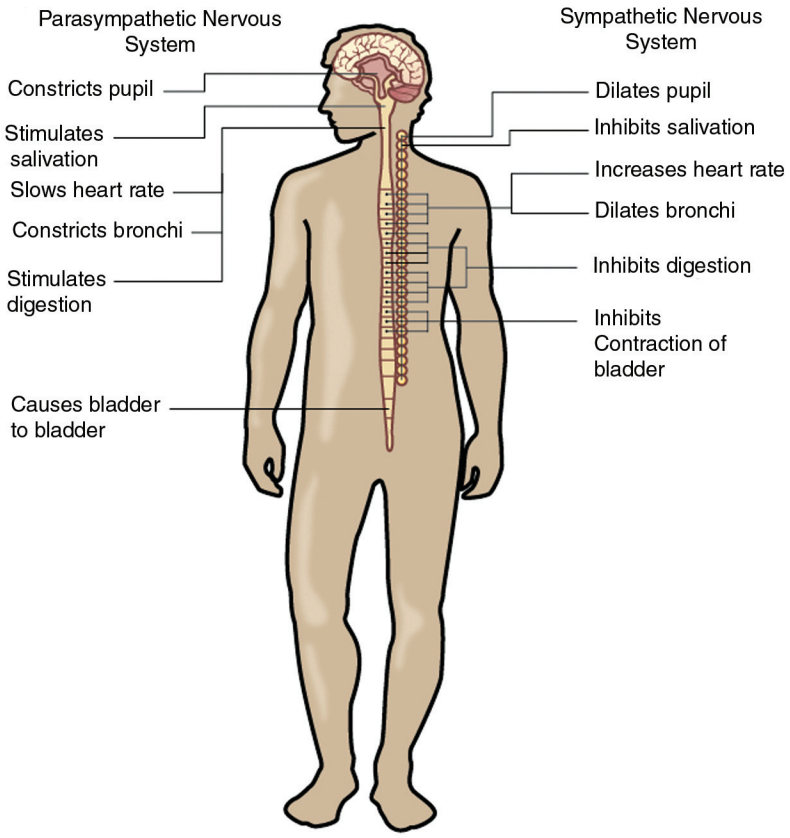


Fig. The sympathetic and parasympathetic divisions of the autonomic nervous system have the opposite effects on various systems.

The sympathetic nervous system is activated when we are faced with stressful or high-arousal situations. The activity of this system was adaptive for our ancestors, increasing their chances of survival. Imagine, for example, that one of our early ancestors, out hunting small game, suddenly disturbs a large bear with her cubs. At that moment, his body undergoes a series of changes—a direct function of sympathetic activation—preparing him to face the threat. His pupils dilate, his heart rate and blood pressure increase, his bladder relaxes, his liver releases glucose, and adrenaline surges into his bloodstream. This constellation of physiological changes, known as the fight or flight response, allows the body access to energy reserves and heightened sensory capacity so that it might fight off a threat or run away to safety.

While it is clear that such a response would be critical for survival for our ancestors, who lived in a world full of real physical threats, many of the high-arousal situations we face in the modern world are more psychological in nature. For example, think about how you feel when you have to stand up and give a presentation in front of a roomful of people, or right before taking a big test. You are in no real physical danger in those situations, and yet you have evolved to respond to any perceived threat with the fight or flight response. This kind of response is not nearly as adaptive in the modern world; in fact, we suffer negative health consequences when faced constantly with psychological threats that we can neither fight nor flee. Recent research suggests that an increase in susceptibility to heart disease (Chandola, Brunner, and Marmot, 2006) and impaired function of the immune system (Glaser and

Kiecolt-Glaser, 2005) are among the many negative consequences of persistent and repeated exposure to stressful situations. Once the threat has been resolved, the parasympathetic nervous system takes over and returns bodily functions to a relaxed state. Our hunter's heart rate and blood pressure return to normal, his pupils constrict, he regains control of his bladder, and the liver begins to store glucose in the form of glycogen for future use. These processes are associated with activation of the parasympathetic nervous system.

BLOOD SUPPLY TO THE BRAIN

A lack of oxygen to the CNS can be devastating, and the cardiovascular system has specific regulatory reflexes to ensure that the blood supply is not interrupted. There are multiple routes for blood to get into the CNS, with specializations to protect that blood supply and to maximize the ability of the brain to get an uninterrupted perfusion.

ARTERIAL SUPPLY

The major artery carrying recently oxygenated blood away from the heart is the aorta. The very first branches off the aorta supply the heart with nutrients and oxygen.

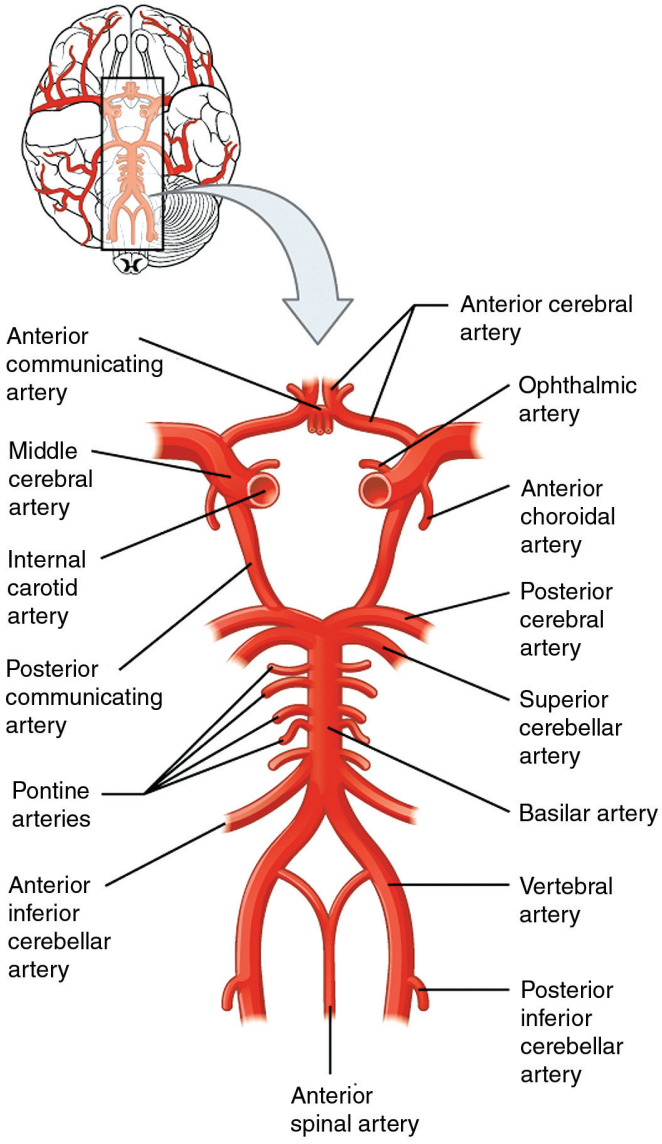


Fig. Circle of Willis. The blood supply to the brain enters through the internal carotid arteries and the vertebral arteries, eventually giving rise to the circle of Willis.

The next branches give rise to the common carotid arteries, which further branch into the internal carotid arteries. The external carotid arteries supply blood to the tissues on the surface of the cranium. The bases of the common carotids contain stretch receptors that immediately respond to the drop in blood pressure upon standing. The orthostatic reflex is a reaction to this change in body position, so that blood pressure is maintained against the increasing effect of gravity (orthostatic means "standing up"). Heart rate increases—a reflex of the sympathetic division of the autonomic nervous system—and this raises blood pressure.

The internal carotid artery enters the cranium through the carotid canal in the temporal bone. A second set of vessels that supply the CNS are the vertebral arteries, which are protected as they pass through the neck region by the transverse foramina of the cervical vertebrae. The vertebral arteries enter the cranium through the foramen magnum of the occipital bone. Branches off the left and right vertebral arteries merge into the anterior spinal arterysupplying the anterior aspect of the spinal cord, found along the anterior median fissure. The two vertebral arteries then merge into the basilar artery, which gives rise to branches to the brain stem and cerebellum. The left and right internal carotid arteries and branches of the basilar artery all become the circle of Willis, a confluence of arteries that can maintain perfusion of the brain even if narrowing or a blockage limits flow through one part.

VENOUS RETURN

After passing through the CNS, blood returns to the circulation through a series of dural sinuses and veins. The superior sagittal sinus runs in the groove of the longitudinal fissure, where it absorbs CSF from the meninges. The superior sagittal sinus drains to the confluence of sinuses, along with the occipital sinuses and straight sinus, to then drain into the transverse sinuses. The transverse sinuses connect to the sigmoid sinuses, which then connect to the jugular veins. From there, the blood continues towards the heart to be pumped to the lungs for reoxygenation.

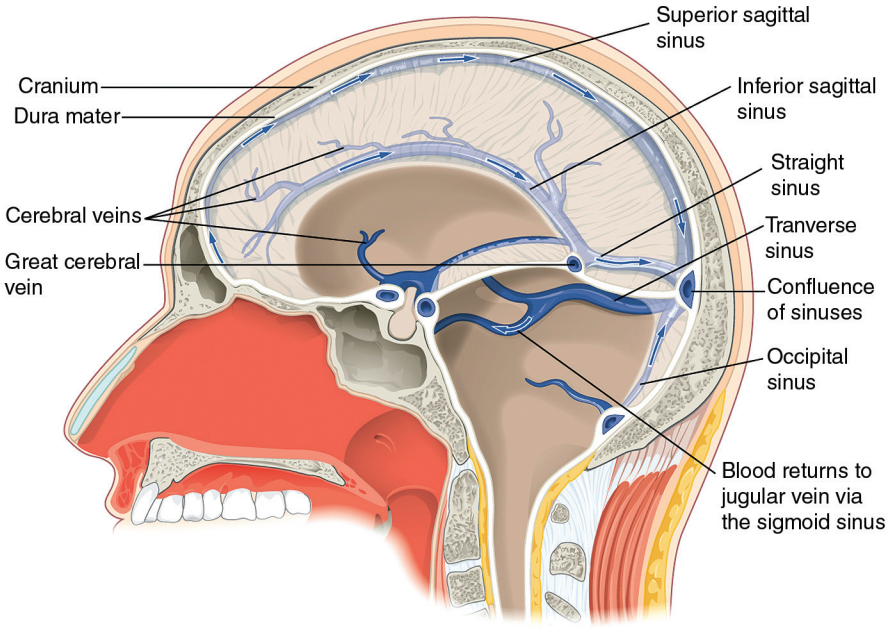


Fig. Dural Sinuses and Veins. Blood drains from the brain through a series of sinuses that connect to the jugular veins.

PROTECTIVE COVERINGS OF THE BRAIN AND SPINAL CORD

The outer surface of the CNS is covered by a series of membranes composed of connective tissue called the meninges, which protect the brain. The dura mater is a thick fibrous layer and a strong protective

sheath over the entire brain and spinal cord. It is anchored to the inner surface of the cranium and vertebral cavity. The arachnoid mater is a membrane of thin fibrous tissue that forms a loose sac around the CNS. Beneath the arachnoid is a thin, filamentous mesh called the arachnoid trabeculae, which looks like a spider web, giving this layer its name. Directly adjacent to the surface of the CNS is the pia mater, a thin fibrous membrane that follows the convolutions of gyri and sulci in the cerebral cortex and fits into other grooves and indentations.

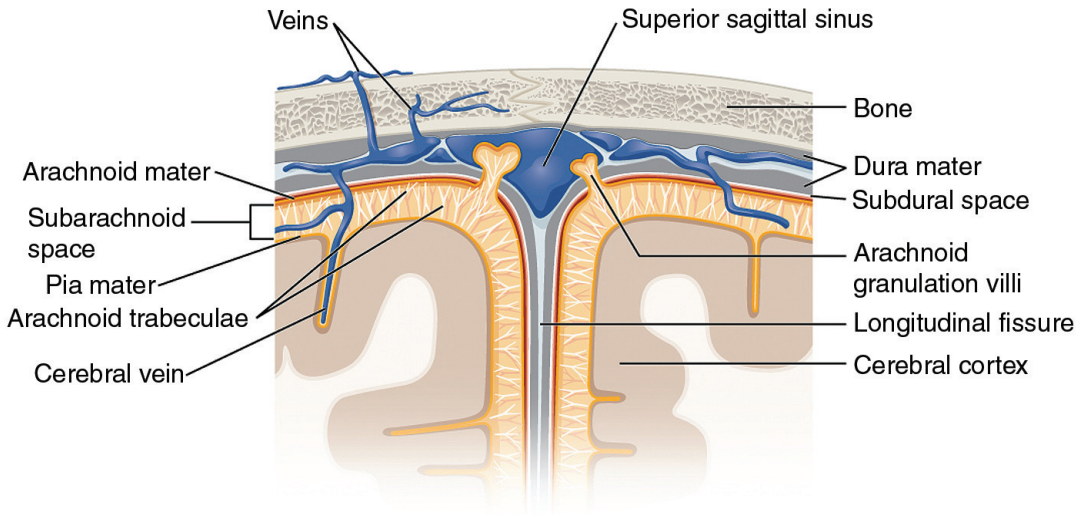


Fig. Meningeal Layers of Superior Sagittal Sinus. The layers of the meninges in the longitudinal fissure of the superior sagittal sinus are shown, with the dura mater adjacent to the inner surface of the cranium, the pia mater adjacent to the surface of the brain, and the arachnoid and subarachnoid space between them. An arachnoid villus is shown emerging into the dural sinus to allow CSF to filter back into the blood for drainage.

DURA MATER

Like a thick cap covering the brain, the dura mater is a tough outer covering. The name comes from the Latin for "tough mother" to represent its physically protective role. It encloses the entire CNS and the major blood vessels that enter the cranium and vertebral cavity. It is directly attached to the inner surface of the bones of the cranium and to the very end of the vertebral cavity.

There are infoldings of the dura that fit into large crevasses of the brain. Two infoldings go through the midline separations of the cerebrum and cerebellum; one forms a shelf-like tent between the occipital lobes of the cerebrum and the cerebellum, and the other surrounds the pituitary gland. The dura also surrounds and supports the venous sinuses.

ARACHNOID MATER

The middle layer of the meninges is the arachnoid, named for the spider-web–like trabeculae between it and the pia mater. The arachnoid defines a sac-like enclosure around the CNS. The trabeculae are found in the subarachnoid space, which is filled with circulating CSF. The arachnoid emerges into the dural sinuses as the arachnoid granulations, where the CSF is filtered back into the blood for drainage from the nervous system.

The subarachnoid space is filled with circulating CSF, which also provides a liquid cushion to the brain and spinal cord. Similar to clinical blood work, a sample of CSF can be withdrawn to find chemical evidence of neuropathology or metabolic traces of the biochemical functions of nervous tissue.

PIA MATER

The outer surface of the CNS is covered in the thin fibrous membrane of the pia mater. It is thought to have a continuous layer of cells providing a fluid-impermeable membrane. The name pia mater comes from the Latin for "tender mother," suggesting the thin membrane is a gentle covering for the brain. The pia extends into every convolution of the CNS, lining the inside of the sulci in the cerebral and cerebellar cortices. At the end of the spinal cord, a thin filament extends from the inferior end of CNS at the upper lumbar region of the vertebral column to the sacral end of the vertebral column. Because the spinal cord does not extend through the lower lumbar region of the vertebral column, a needle can be inserted through the dura and arachnoid layers to withdraw CSF. This procedure is called a lumbar puncture and avoids the risk of damaging the central tissue of the spinal cord. Blood vessels that are nourishing the central nervous tissue are between the pia mater and the nervous tissue.

THE SOMATOSENSORY TRACT

The spinothalamic tract is a sensory pathway originating in the spinal cord. It transmits information to the thalamus about pain, temperature, itch, and crude touch. The pathway decussates at the level of the spinal cord. Somatosensory organization is divided into the dorsal column–medial lemniscus tract (the touch/proprioception/vibration sensory pathway) and the anterolateral system, or ALS (the pain/temperature sensory pathway). Both sensory pathways use three different neurons to get information from sensory receptors at the periphery to the cerebral cortex. These neurons are designated primary, secondary, and tertiary sensory neurons. In both pathways, primary sensory neuron cell bodies are found in the dorsal rootganglia, and their central axons project into the spinal cord.

FUNCTION

The types of sensory information transmitted via the spinothalamic tract are described as affective sensation. This means that the sensation is accompanied by a compulsion to act. For instance, an itch is accompanied by a need to scratch, and a painful stimulus makes us want to withdraw from the pain.

There are two Subsystems:

1. Direct (for direct, conscious appreciation of pain).
2. Indirect (for affective and arousal impact of pain).

Indirect projections are further divided into:

- Spino-reticulo-thalamo-cortical (part of the ascending reticular arousal system, also known as ARAS).
- Spino-mesencephalic-limbic (for affective impact of pain).

THE CORTICOSPINAL TRACT

The corticospinal tract conducts impulses from the brain to the spinal cord. It contains mostly motor axons. The corticospinal tract is made up of two separate tracts in the spinal cord: the lateral corticospinal tract and the anterior corticospinal tract. The corticospinal tract also contains the Betz cell (the largest pyramidal cells) that are not found in any other region of the body. An understanding of these tracts leads to an understanding of why one side of the body is controlled by the opposite side of the brain.

The corticospinal tract is concerned specifically with discrete, voluntary, skilled movements, such as the precise movement of fingers and toes. The brain sends impulses to the spinal cord that relay the message. This is imperative in understanding that the left hemisphere of the brain controls the RIGHT side of the body, while the right hemisphere of the brain controls the LEFT side of the body. The signals cross in the medulla oblongata, and this process is also known as decussation.

Spinal cord tracts are identified in this drawing. They are the pyramidal tracts, extrapyramidal tracts, spinocerebellar tracts, the lateral spinothalamic tract, and the anterior spinothalamic tract.

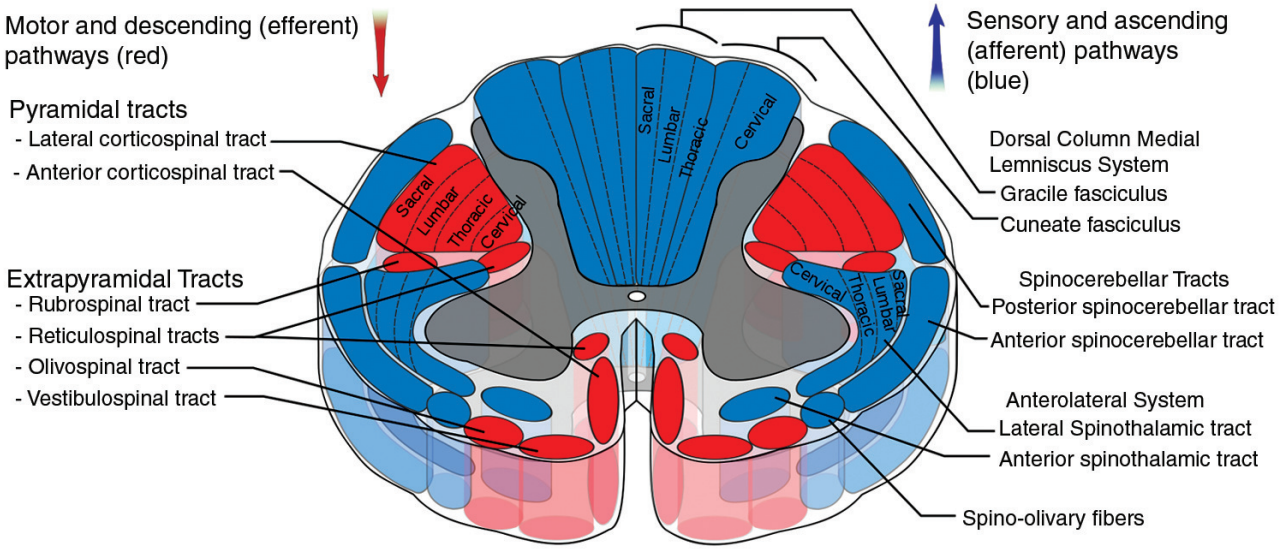


Fig. Spinal Cord Tracts.

FUNCTION

The primary purpose of the corticospinal tract is to maintain voluntary motor control of the body and limbs. However, connections to the somatosensory cortex suggest that the pyramidal tracts are also responsible for modulating sensory information from the body. Some of these connections cross the midline; therefore, each side of the brain is responsible for controlling muscles for the limbs on opposite sides of the body. However, control of trunk muscles is on the same side of the body.

After a patient's pyramidal tracts are injured, the patient is paralyzed on the corresponding side of the body. Fortunately, they can re-learn some crude, basic motions, but not fine movements. This implies that the connections to these tracts are crucial for fine movement, and only partial recovery is possible if they are damaged.

AUTONOMIC NERVOUS SYSTEM

In the autonomic nervous system, a preganglionic neuron of the CNS synapses with a postganglionic neuron of the PNS. The postganglionic neuron, in turn, acts on a target organ. Autonomic responses are mediated by the sympathetic and the parasympathetic systems, which are antagonistic to one another. The sympathetic system activates the "fight or flight" response, while the parasympathetic system activates the "rest and digest" response.

The autonomic nervous system serves as the relay between the CNS and the internal organs. It controls the lungs, the heart, smooth muscle, and exocrine and endocrine glands. The autonomic nervous system controls these organs largely without conscious control; it can continuously monitor the conditions of these different systems and implement changes as needed. Signaling to the target tissue usually involves two synapses: a preganglionic neuron (originating in the CNS) synapses to a neuron in a ganglion that, in turn, synapses on the target organ, as illustrated in Figure. There are two divisions of the autonomic nervous system that often have opposing effects: the sympathetic nervous system and the parasympathetic nervous system.

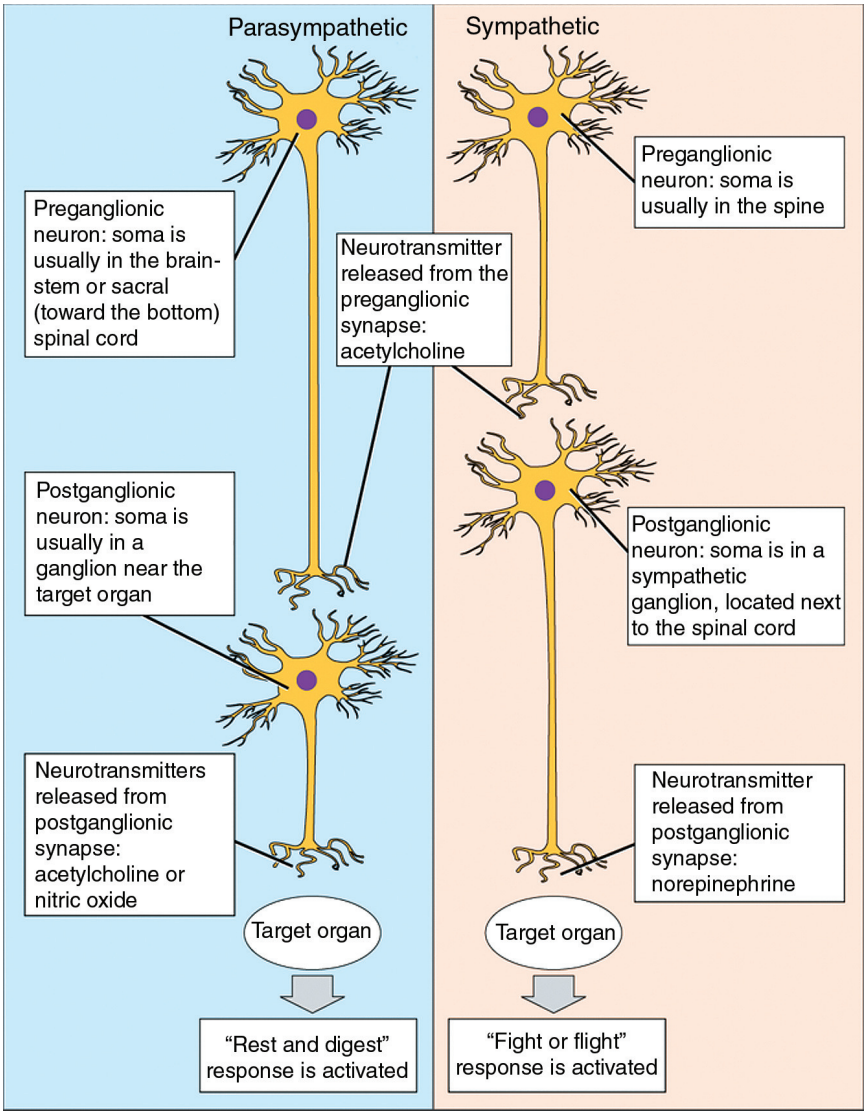


Fig. The sympathetic and parasympathetic systems.

SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system is responsible for the "fight or flight" response that occurs when an animal encounters a dangerous situation. One way to remember this is to think of the surprise a person feels when encountering a snake ("snake" and "sympathetic" both begin with "s"). Examples of functions controlled by the sympathetic nervous system include an accelerated heart rate and inhibited digestion. These functions help prepare an organism's body for the physical strain required to escape a potentially dangerous situation or to fend off a predator.

Most preganglionic neurons in the sympathetic nervous system originate in the spinal cord. The axons of these neurons release acetylcholine on postganglionic neurons within sympathetic ganglia (the sympathetic ganglia form a chain that extends alongside the spinal cord). The acetylcholine activates the postganglionic neurons. Postganglionic neurons then release norepinephrine onto target organs. As anyone who has ever felt a rush before a big test, speech, or athletic event can attest, the effects of the sympathetic nervous system are quite pervasive. This is both because one preganglionic neuron synapses on multiple postganglionic neurons, amplifying the effect of the original synapse, and because the adrenal gland also releases norepinephrine (and the closely related hormone epinephrine) into the blood stream.

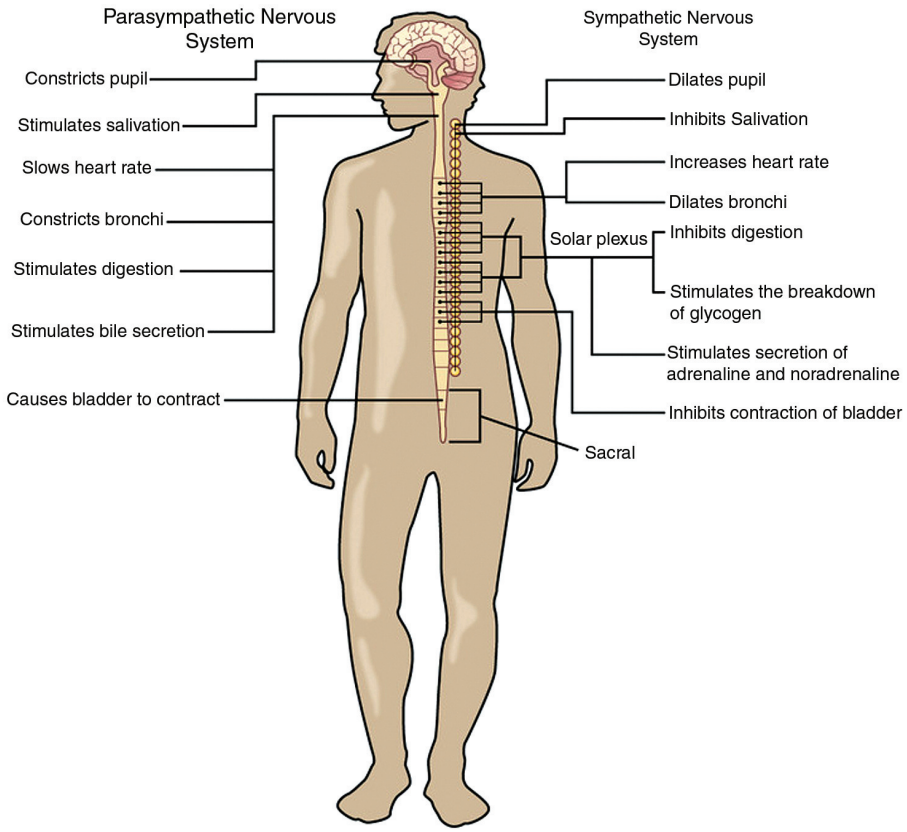


Fig. The sympathetic and Parasympathetic Nervous Systems Often have Opposing effects on Target Organs.

The physiological effects of this norepinephrine release include dilating the trachea and bronchi (making it easier for the animal to breathe), increasing heart rate, and moving blood from the skin to the heart, muscles, and brain (so the animal can think and run). The strength and speed of the sympathetic response helps an organism avoid danger, and scientists have found evidence that it may also increase LTP—allowing the animal to remember the dangerous situation and avoid it in the future.

PARASYMPATHETIC NERVOUS SYSTEM

While the sympathetic nervous system is activated in stressful situations, the parasympathetic nervous system allows an animal to "rest and digest." The parasympathetic system's functions conserve energy: slowing down the heart rate, reducing contractile forces of both cardiac and gastrointestinal muscle, and reducing conduction velocity of the sinoatrial node and atrioventricular node.

One way to remember this is to think that during a restful situation like a picnic, the parasympathetic nervous system is in control ("picnic" and "parasympathetic" both start with "p"). Parasympathetic preganglionic neurons have cell bodies located in the brainstem and in the sacral (towards the bottom) spinal cord. The axons of the preganglionic neurons release acetylcholine on the postganglionic neurons, which are generally located very near the target organs. Most postganglionic neurons release acetylcholine onto target organs, although some release nitric oxide. Acetylcholine acts on two types of receptors, the muscarinic and nicotinic cholinergic receptors. Most transmissions occur in two stages: When stimulated, the preganglionic neuron releases acetylcholine at the ganglion, which acts on nicotinic receptors of postganglionic neurons. The postganglionic neuron then releases acetylcholine to stimulate the muscarinic receptors of the target organ. The parasympathetic nervous system resets organ function after the sympathetic nervous system is activated (the common adrenaline dump you feel after a "fight-or-flight" event). Effects of acetylcholine release on target organs include slowing of heart rate, lowered blood pressure, and stimulation of digestion.

8

Introduction to Pathology

Pathology is the study and diagnosis of disease through examination of organs, tissues, bodily fluids, and whole bodies (autopsies). The history of pathology can be traced to the earliest application of the scientific method to the field of medicine, a development which occurred in the Middle East during the Islamic Golden Age and in Western Europe during the Italian Renaissance.

Early systematic human dissections were carried out by the Ancient Greek physicians Herophilus of Chalcedon and Erasistratus of Chios in the early part of the third century BC. The first physician known to have made postmortem dissections was the Arabian physician Avenzoar (1091–1161). Rudolf Virchow (1821–1902) is generally recognized to be the father of microscopic pathology. Most early pathologists were also practicing physicians or surgeons.

GENERAL PATHOLOGY

General pathology is a broad and complex scientific field which seeks to understand the mechanisms of injury to cells and tissues, as well as the body's means of responding to and repairing injury. Areas of study include cellular adaptation to injury, necrosis, inflammation, wound healing and neoplasia. It forms the foundation of pathology, the application of this knowledge to diagnose diseases in humans and animals. The term "general pathology" is also used to describe the practice of both anatomical and clinical pathology.

ANATOMIC PATHOLOGY

Anatomic pathology (U.S.) is a medical specialty that is concerned with the diagnosis of disease based on the gross, microscopic, chemical, immunologic and molecular examination of organs, tissues, and whole bodies (autopsy).

Anatomic pathology is itself divided in subspecialties, the main ones being surgical pathology, cytopathology and forensic pathology. To be licensed to practice pathology, one has to complete medical school and secure a license to practice medicine. An approved residency programme and certification (in the U.S., the American board of Pathology or the American Osteopathic Board of Pathology) is usually required to obtain employment or hospital privileges.

Anatomic pathology is one of two branches of pathology, the other being clinical pathology, the diagnosis of disease through the laboratory analysis of bodily fluids and/or tissues. Often, pathologists practice both anatomic and clinical pathology, a combination known as general pathology. The distinction between anatomic and clinical pathology is increasingly blurred by the introduction of technologies that require new expertise and the need to provide patients and referring physicians with integrated diagnostic reports. Similar specialties exist in veterinary pathology.

CLINICAL PATHOLOGY

Clinical pathology or Laboratory medicine, is a medical specialty that is concerned with the diagnosis of disease based on the laboratory analysis of bodily fluids such as blood and urine, and tissues using the tools of chemistry, microbiology, hematology and molecular pathology. Clinical pathologists work in close collaboration with medical technologists, hospital administrations, and referring physicians to ensure the accuracy and optimal utilization of laboratory testing.

Clinical pathology is one of the two major divisions of pathology, the other being anatomic pathology. Often, pathologists practice both anatomic and clinical pathology, a combination sometimes known as general pathology.

FORENSIC PATHOLOGY

Forensic pathology is a branch of pathology concerned with determining the cause of death by examination of a cadaver. The autopsy is performed by the pathologist at the request of a coroner usually during the investigation of criminal law cases and civil law cases in some jurisdictions. Forensic pathologists are also frequently asked to confirm the identity of a cadaver.

VETERINARY PATHOLOGY

Veterinary pathologists are doctors of veterinary medicine who specialize in the diagnosis of diseases through the examination of animal tissue and body fluids. Like for medical pathology, veterinary pathology is divided in two branches, anatomical pathology and clinical pathology. Veterinary pathologists are critical participants in the drug development process.

PATHOLOGY AS A MEDICAL SPECIALTY

Pathologists are physicians who diagnose and characterize disease in living patients by examining biopsies or bodily fluid. The vast majority of cancer diagnoses are made or confirmed by a pathologist. Pathologists may also conduct autopsies to investigate causes of death. Pathology is a core discipline of medical school and many pathologists are also teachers. As managers of medical laboratories, pathologists play an important role in the development of Laboratory information systems. Although the medical practice of pathology grew out of the tradition of investigative pathology, most modern pathologists do not perform original research.

HUMAN PATHOLOGY

The investigation of disease in humans has, understandably, been one of the primary focal points in medicine for thousands of years. The image gallery presented in this chapter attempts to illustrate, through use of the brightfield microscope, many of the pathological conditions that are readily observed in stained human specimens. Each image was chosen for artistic merit, photographic quality, and content. Note that several of the images in this gallery might not depict every aspect of the pathological condition under which they are catalogued.

ADENOMYOSIS

Adenomyosis generally affects scattered areas of the uterine wall, typically making the condition unsuitable for localized surgery. A complete hysterectomy is usually the treatment of choice, estimates indicating that the procedure is 80 percent effective in eliminating common symptoms of adenomyosis. Depending on the severity of the specific symptoms and the reproductive intentions of the patient, other treatments may be recommended.

ALVEOLAR CELL CARCINOMA

In the United States, lung cancer is the leading cause of cancer-related death among both men and women. The popularity of smoking is usually considered accountable for the prevalence of the disease, since cigarettes have been linked to about 90 percent of lung cancer cases in men and 80 percent in women. A few specific types of lung cancer, however, such as alveolar cell carcinoma, appear to have no relationship to smoking.

BASAL CELL CARCINOMA

Basal cell carcinoma is the most common type of cancer that occurs in humans. In the United States alone, an estimated 900,000 people develop basal cell carcinoma each year, and by most accounts, that number will continue to grow as the Earth's protective ozone layer becomes increasingly compromised. Individuals with fair skin that tends to burn rather than tan, blue or green eyes, and blonde hair are among those that are most likely to acquire the disease.

BENIGN PROSTATIC HYPERPLASIA

Many men with benign prostatic hyperplasia experience urinary problems related to the condition. As the prostate enlarges, the gland places increasing pressure on the urethra, often resulting in difficulty beginning or ending urination, an inability to completely empty the bladder, decreased urine flow, and frequent urination. In the most severe cases, complete blockage of the urethra occurs, which may lead to kidney damage.

TYPES OF PATHOLOGY

There are three main subtypes of pathology: anatomical pathology, clinical pathology, and molecular pathology. These subtypes can be broken down into even more specific categories; pathology is a diverse field because so many different diseases and ways of studying diseases exist.

ANATOMICAL PATHOLOGY

Anatomical pathology is the study of anatomical features, such as tissue removed from the body, or even an entire body in the case of an autopsy, to diagnose and increase knowledge of disease. Anatomical pathology can include looking at cells under a microscope, but it also involves looking at organs in general (*e.g.* a ruptured spleen). It also includes investigation of the chemical properties of cells, and their immunological markers. *There are several broad subcategories of anatomical pathology:*

- Surgical pathology is the examination of tissues removed during surgery. A common example is the examination of a small piece of tumor tissue to determine whether the tumor is malignant (cancerous) or benign and make a diagnosis. This procedure is called a biopsy.
- Histopathology is the examination of cells under a microscope that have been stained with dye to make them visible or easier to see. Often, antibodies are used to label different parts of the cells with different colours of dye or fluorescence. After the microscope became widespread in pathology, many different methods of preserving and dyeing tissue were developed.
- Cytopathology is the study of small groups of cells shed in bodily fluids or obtained through scraping, such as those taken during a cervical Pap smear. A Pap smear detects cervical cancer and some types of infections. The cells are taken by swabbing the cervix, and are then processed and examined under a microscope to check for abnormalities.

CLINICAL PATHOLOGY

Clinical pathology diagnoses disease through laboratory analysis of bodily fluids and tissues. For example, the chemical components of blood may be analyzed, along with analyzing cells and identifying any microorganisms such as bacteria that are present in a sample. Sometimes, the field of clinical pathology is also referred to as the field of laboratory medicine. *Major types include the following:*

- Chemical pathology, or clinical chemistry, involves the chemical analysis of bodily fluids, through testing and microscopy. Commonly, chemical pathology involves the study of blood and its immune components like white blood cells.
- Hematology is also related to the study of blood, but it has more to do with identifying blood diseases specifically than chemical pathology does. Hematologists also study the lymph system and bone marrow, which are other parts of the hematopoietic system.
- Immunology, or immunopathology, is the study of immune system disorders. It deals with immune responses to foreign molecules, allergies, immunodeficiencies, and organ transplant rejection.

MOLECULAR PATHOLOGY

Molecular pathology is the study of abnormalities of tissues and cells at the molecular level. It is a broad category that is used to refer to the study of disease of any organ or tissue in the body by examining what molecules are present in cells. It can combine aspects of both anatomical and clinical pathology. Some techniques that can be used in molecular pathology include polymerase chain reaction (PCR) to amplify DNA, fluorescence labeling, karyotype imaging of chromosomes, and DNA microarrays (small samples of DNA placed onto biochips).

CAREERS IN PATHOLOGY

Pathologists are medical doctors; to be a pathologist, one needs to go to school for a medical degree and complete residency. Only MDs can truly be described as pathologists. However, many different careers exist in the field of pathology, for those with various levels of education. With a high school degree and subsequent specialized training, one can become a phlebotomist, a person who draws blood from patients for training. With a two-year associate's degree, one can become a laboratory technician. Laboratory technicians perform laboratory testing, often under supervision. A person with a bachelor's degree, often in biology or biochemistry, can become a research laboratory technologist or a clinical/medical laboratory technologist. In this position, one can assist in performing research and clinical testing. Those who go on to get a Master's degree can become a laboratory manager or pathologist's assistant. Those who go even further to get a Ph.D. can become a research laboratory scientist, where they will design experiments involving pathology in order to expand upon scientific knowledge and help doctors better treat disease.

9

Cell Injury

Cell injury is defined as a variety of stress, a cell encounter as a result in changes in its internal and external environment. All cells of body have an inbuilt mechanism to deal with changes in environment to an extent.

CELL ADAPTION

The cellular response to cell injury depends upon followings:

1. The type of cell and tissue involved.
2. On extent and type of cell injury.

Cellular responses to injury as follows:

1. The cell may adapt to changes which are expressed morphologically and then revert back to normal after the stress is removed. (Cellular Adaptation).
2. When the stress is mild to moderate, the injured cell may recover (Reversible Cell Injury), while when the injury is persistent, the cell may die. (Irreversible Cell Injury).
3. The residual effect of reversible cell injury may persist in the cell as evidence of cell injury at sub cellular level (Sub cellular Changes) or metabolites may accumulate within cell. (Intracellular Accumulation).

In mammalian cell under normal condition, cells are dynamic structures existing in fluid environment. A cell is enclosed by cell membrane that extends internally to enclose nucleus and other organelles suspended in cytosol.

THE VASCULAR RESPONSE TO INJURY

GENERAL INTRODUCTION

A long tradition defines the scope of pathology as both a clinical specialty and an area of biomedical research. Although rooted in the correlation of anatomical and histological changes with clinically apparent disease (and hence the iconic images of autopsy and microscope), modern pathology studies the causes of disease (etiology) and the expression/evolution of such (pathogenesis) at the molecular level using the tools of molecular genetics and biochemical analysis as well as at the cellular and organ system levels. Because (as is apparent to the clinician) the first symptoms and signs of disease are often those of the body's response to injury, the pathologist is acutely interested in characterizing this response since, more often than not, such provides critical clues as to the etiological agent and likely mode of pathogenesis.

As a clinical endeavor, pathology is both a diagnostic and prognostic specialty, which by defining and classifying the disease process, hopes to suggest (and help evaluate) therapeutic approaches to the physician. But in a broad sense, pathology seeks to understand the basis of the disease process. At times, this broad scope of interest leads to a "pathocentric" view of medicine.

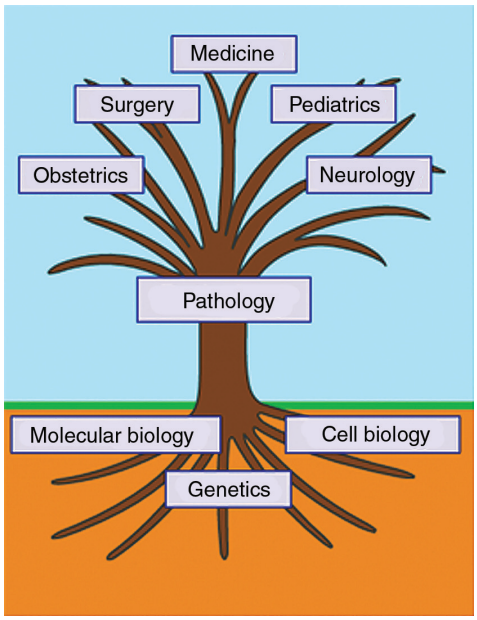


Fig. "Pathocentric" view of Medicine.

This chapter will present an overview of how the pathologist views mechanisms of irreversible cell injury (cell death), reversible cell injury, and the organism's response to both. Oxygen deprivation to tissue (ischemia) leading to a form of tissue damage termed an infarct is of notable clinical significance (*e.g.*, in myocardial infarcts, "heart attacks") and will serve as an important model. Second, this chapter will briefly consider injury resulting from the process of host defence, either as appropriately targeted to tissue injury or inappropriately directed towards self-components either as "bystander effects" or "autoimmunity."

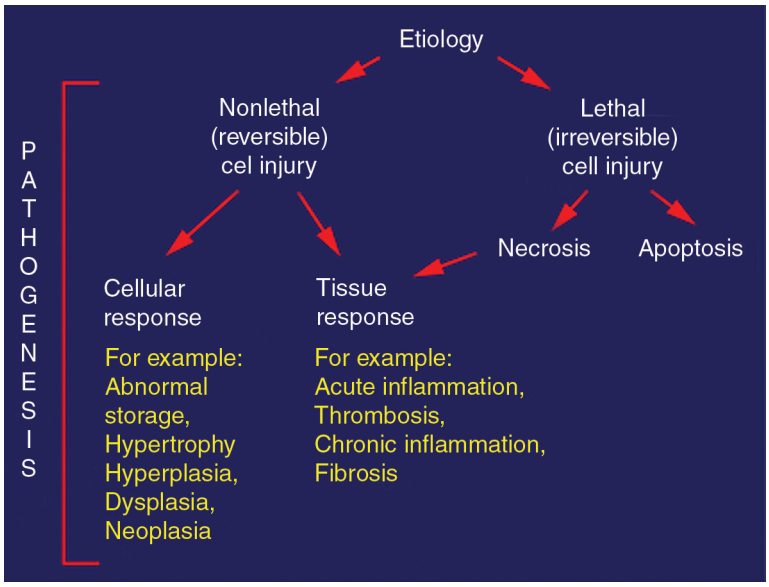


Fig. A Simplified but Useful Overview.

CELL INJURY AND CELL DEATH: AN INTRODUCTION

An interest in the effects of disease and trauma is nothing new. People have been pathologists observing the effects of disease since the dawn of recorded history, likely before. Egyptian medical texts described infectious diseases (tetanus is an often quoted example). The Tanach (Hebrew Bible) tells of a disease visited upon the

Philistines that may well have been bubonic plague. The Iliad describes the surgeon Machaon treating Menaleus' arrow wound. Egyptian physicians described the host reaction to such wounds (suppuration, inflammation) as early as the third millennium BC and may have treated such wounds with antiseptic agents.

CELL DAMAGE

Cell damage (also known as cell injury) is a variety of changes of stress that a cell suffers due to external as well internal environmental changes. Among other causes, this can be due to physical, chemical, infectious, biological, nutritional or immunological factors. Cell damage can be reversible or irreversible. Depending on the extent of injury, the cellular response may be adaptive and where possible, homeostasis is restored. Cell death occurs when the severity of the injury exceeds the cell's ability to repair itself. Cell death is relative to both the length of exposure to a harmful stimulus and the severity of the damage caused. Cell death may occur by necrosis or apoptosis.

CAUSES

- Physical agents such as heat or radiation can damage a cell by literally cooking or coagulating their contents.
- Impaired nutrient supply, such as lack of oxygen or glucose, or impaired production of adenosine triphosphate (ATP) may deprive the cell of essential materials needed to survive.

TARGETS

The most notable components of the cell that are targets of cell damage are the DNA and the cell membrane:

- *DNA Damage:* In human cells, both normal metabolic activities and environmental factors such as ultraviolet light and other radiations can cause DNA damage, resulting in as many as one million individual molecular lesions per cell per day.
- *Membrane Damage:* Damage to the cell membrane disturbs the state of cell electrolytes, *e.g.* calcium, which when constantly increased, induces apoptosis.

TYPES OF DAMAGE

Some cell damage can be reversed once the stress is removed or if compensatory cellular changes occur. Full function may return to cells but in some cases a degree of injury will remain.

SUB-LETHAL (REVERSIBLE)

Cellular Swelling

Cellular swelling (or cloudy swelling) may occur due to cellular hypoxia, which damages the sodium-potassium membrane pump; it is reversible when the cause is eliminated. Cellular swelling is the first manifestation of almost all forms of injury to cells. When it affects many cells in an organ, it causes some pallor, increased turgor, and increase in weight of the organ. On microscopic examination, small clear vacuoles may be seen within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum. This pattern of non-lethal injury is sometimes called hydropic change or vacuolar degeneration. Hydropic degeneration is a severe form of cloudy swelling. It occurs with hypokalemia due to vomiting or diarrhea.

The ultrastructural changes of reversible cell injury include:

- Blebbing
- Blunting

- Distortion of microvilli
- Loosening of intercellular attachments
- Mitochondrial changes
- Dilation of the endoplasmic reticulum.

Fatty Change

The cell has been damaged and is unable to adequately metabolize fat. Small vacuoles of fat accumulate and become dispersed within cytoplasm. Mild fatty change may have no effect on cell function; however more severe fatty change can impair cellular function. In the liver, the enlargement of hepatocytes due to fatty change may compress adjacent bile canaliculi, leading to cholestasis. Depending on the cause and severity of the lipid accumulation, fatty change is generally reversible. Fatty Change is also known as fatty degeneration, fatty metamorphosis, or fatty steatosis.

LETHAL

Necrosis

Necrosis is characterised by cytoplasmic swelling, irreversible damage to the plasma membrane, and organelle breakdown leading to cell death. The stages of cellular necrosis include *pyknosis*; clumping of chromosomes and shrinking of the nucleus of the cell, *karyorrhexis*; fragmentation of the nucleus and break up of the chromatin into unstructured granules, and *karyolysis*; dissolution of the cell nucleus. Cytosolic components that leak through the damaged plasma membrane into the extracellular space can incur an inflammatory response.

There are six types of necrosis:

- Coagulative Necrosis
- Liquefactive Necrosis
- Caseous Necrosis
- Fat Necrosis
- Fibroid Necrosis
- Gangrenous Necrosis.

Apoptosis

Apoptosis is the programmed cell death of superfluous or potentially harmful cells in the body. It is an energy dependent process mediated by proteolytic enzymes called caspases, which trigger cell death through the cleaving of specific proteins in the cytoplasm and nucleus. The dying cells shrink and condense into apoptotic bodies. The cell surface is altered so as to display properties which lead to rapid phagocytosis by macrophages or neighbouring cells. Unlike necrotic cell death, neighbouring cells are not damaged by apoptosis as cytosolic products are safely isolated by membranes prior to undergoing phagocytosis. In the average adult between 50 and 70 billion cells die each day due to apoptosis. Inhibition of apoptosis can result in a number of cancers, autoimmune diseases, inflammatory diseases, and viral infections. Hyperactive apoptosis can lead to neurodegenerative diseases, hematologic diseases, and tissue damage.

REPAIR

When a cell is damaged the body will try to repair or replace the cell to continue normal functions. If a cell dies the body will remove it and replace it with another functioning cell, or fill the gap with connective tissue to

provide structural support for the remaining cells. The motto of the repair process is to fill a gap caused by the damaged cells to regain structural continuity. Normal cells try to regenerate the damaged cells but this cannot always happen. Asexual reproduction is what repairs cells.

Regeneration

Regeneration of parenchyma cells, or the functional cells, of an organism. The body can make more cells to replace the damaged cells keeping the organ or tissue intact and fully functional.

Replacement

When a cell cannot be regenerated the body will replace it with stromal connective tissue to maintain tissue/organ function. Stromal cells are the cells that support the parenchymal cells in any organ. Fibroblasts, immune cells, pericytes, and inflammatory cells are the most common types of stromal cells.

BIOCHEMICAL CHANGES IN CELLULAR INJURY

ATP (adenosine triphosphate) depletion is a common biological alteration that occurs with cellular injury. This change can happen despite the inciting agent of the cell damage. A reduction in intracellular ATP can have a number of functional and morphologic consequences during cell injury. *These effects include:*

- Failure of the ATP dependent pumps (Na^+/K^+ pump and Ca^{2+} pump), resulting in a net influx of Na^+ and Ca^{2+} ions and osmotic swelling.
- ATP-depleted cells begin to undertake anaerobic metabolism to derive energy from glycogen which is known as 'glycogenolysis'.
- A consequent decrease in the intracellular pH of the cell arises, which mediates harmful enzymatic processes.
- Early clumping of nuclear chromatin then occurs, known as 'pyknosis', and leads to eventual cell death.

DNA DAMAGE AND REPAIR

DNA Damage

DNA damage (or RNA damage in the case of some virus genomes) appears to be a fundamental problem for life. As noted by Haynes, the subunits of DNA are not endowed with any peculiar kind of quantum mechanical stability, and thus DNA is vulnerable to all the "chemical horrors" that might befall any such molecule in a warm aqueous medium. These chemical horrors are DNA damages that include various types of modification of the DNA bases, single- and double-strand breaks, and inter-strand cross-links. DNA damages are distinct from mutations although both are errors in the DNA. Whereas DNA damages are abnormal chemical and structural alterations, mutations ordinarily involve the normal four bases in new arrangements. Mutations can be replicated, and thus inherited when the DNA replicates. In contrast, DNA damages are altered structures that cannot, themselves, be replicated.

Several different repair processes can remove DNA damages. However, those DNA damages that remain unrepaired can have detrimental consequences. DNA damages may block replication or gene transcription. These blockages can lead to cell death. In multicellular organisms, cell death in response to DNA damage may occur by a programmed process, apoptosis. Alternatively, when a DNA polymerase replicates a template strand containing a damaged site, it may inaccurately bypass the damage and, as a consequence, introduce an incorrect base leading to a mutation. Experimentally, mutation rates increase substantially in cells defective in DNA mismatch repair or in Homologous recombinational repair (HRR).

In both prokaryotes and eukaryotes, DNA genomes are vulnerable to attack by reactive chemicals naturally produced in the intracellular environment and by agents from external sources. An important internal source of DNA damage in both prokaryotes and eukaryotes is reactive oxygen species (ROS) formed as byproducts of normal aerobic metabolism. For eukaryotes, oxidative reactions are a major source of DNA damage. In humans, about 10,000 oxidative DNA damages occur per cell per day. In the rat, which has a higher metabolic rate than humans, about 100,000 oxidative DNA damages occur per cell per day. In aerobically growing bacteria, ROS appear to be a major source of DNA damage, as indicated by the observation that 89% of spontaneously occurring base substitution mutations are caused by introduction of ROS-induced single-strand damages followed by error-prone replication past these damages. Oxidative DNA damages usually involve only one of the DNA strands at any damaged site, but about 1–2% of damages involve both strands. The double-strand damages include double-strand breaks (DSBs) and inter-strand crosslinks. For humans, the estimated average number of endogenous DNA DSBs per cell occurring at each cell generation is about 50. This level of formation of DSBs likely reflects the natural level of damages caused, in large part, by ROS produced by active metabolism.

Repair of DNA Damages

Five major pathways are employed in repairing different types of DNA damages. These five pathways are nucleotide excision repair, base excision repair, mismatch repair, non-homologous end joining and homologous recombinational repair (HRR) and reference. Only HRR can accurately repair double strand damages, such as DSBs. The HRR pathway requires that a second homologous chromosome be available to allow recovery of the information lost by the first chromosome due to the double-strand damage.

DNA damage appears to play a key role in mammalian aging, and an adequate level of DNA repair promotes longevity. In addition, an increased incidence of DNA damage and/or reduced DNA repair cause an increased risk of cancer. Furthermore, the ability of HRR to accurately and efficiently repair double-strand DNA damages likely played a key role in the evolution of sexual reproduction. In extant eukaryotes, HRR during meiosis provides the major benefit of maintaining fertility.

REVERSIBLE CELL INJURY (RCI)

If ischemia or hypoxia is for short period of time, the cell can be reverting back to its normal condition which is known as RCI. In coronary arteries, myocardial contractility is reversed if circulation is quickly restored. It also depends upon the organ which undergoes hypoxia. Ex, skeletal muscle can with stand for half an hour with cell injury but brain cells can undergo permanent damage within 10 minutes.

The pathogenesis of RCI is described below:

- Decrease supply of oxygen, decreases cells aerobic respiration by mitochondria due to decrease ATP generation.
- To maintain the supply of energy to the cell anaerobic glycolysis takes place to generate ATP.
- Decreases glycogen level. This result in increase accumulation of lactic acid. Thus, decreases intracellular pH.
- This causes clumping of nuclear chromatin.
- Decrease ATP causes failure of energy requiring Na-pump. There by causing accumulation of Na and diffusion of K outside the cell resulting in cellular swelling.
- If hypoxia continues, intracellular protein synthesis decreases due to damage to ribosomes and polysomes.
- Continue hypoxia causes cytoskeleton changes with loss of microvilli and formation of blebs on the surface of the cell.
- This swelling results in swelling at mitochondria and ER (endoplasmic reticulum). If reperfusion at this stage, changes can be reverse otherwise results in irreversible cell injury.

Decreased Generation of Cellular ATP: The first point of attack of hypoxia is the cells aerobic respiration. ATP is essentially requires for variety of cellular functions such as ion transport, protein synthesis, lipid synthesis and phosphor lipid metabolism. ATP in human derived from two sources, aerobic respiration or oxidative phosphorylation in mitochondria and anaerobic glycolytic pathway.

ATP is also generated from creatine phosphate through action of creatinine kinase.

Reduced Intracellular pH: Due to decrease aerobic respiration by mitochondria results in anaerobic glycolytic pathway for generation of ATP for energy requirement. This result in rapid depletion of glycogen and accumulation of lactic acid which lowering the intracellular pH. Early fall in intracellular pH results in clumping of nuclear chromatin.

Damage plasma membrane Na+ pump: Normally, Na+ is kept lower intracellular than extracellularly. Na+/K+ pump (Na/K Atpase). This Na+/K+ pump regulates active transport of Na to outside the cell(by using ATP) and diffusion of K in to the cell. By decrease supply of ATP, failure of Na/K Atpase takes place which cause accumulation of Na+ inside the cell with diffusion of K+ outside the cell.

Increase accumulation of Na+ leads to increase intracellular water level for maintain isoosmotic condition which leads to cellular swelling and dilation of ER (Hydropic swelling).

Reduce Protein Synthesis: As continued hypoxia, ribosomes are detached from granular ER and polysomes are degraded to monosomes. Thus causing reduction in protein synthesis.

Functional Coseqences: RCI may result in functional disturbances like myocardial contractility ceases within 60 sec of coronary occulation but can be reverse if circulation is restored.

Ultra Structural Changes

They are as follow,

ER: detachment of membrane bounded polysomes from surface of rough ER.

Mitochondria: Mitochondrial swelling and phospholipid rich amorphous densities.

Plasma Membrane: Loss of microvilli and projection of blebs take place.

Nucleus: Segregration of granular and fibillar components of nucleolus and decrease synthesis of ribosomal RNA.

CELL DAMAGE AND TISSUE REPAIR

Toxic damage to cells can cause individual cell death and if sufficient cells are lost, the result can be tissue or organ failure, ultimately leading to death of the organism. It is nearly impossible to separate a discussion of cellular toxicity and biochemical toxicity. Most observable cellular changes and cell death are due to specific biochemical changes within the cell or in the surrounding tissue. However, there are a few situations where a toxic chemical or physical agent can cause cell damage without actually affecting a specific chemical in the cell or its membrane. Physical agents such as heat and radiation may damage a cell by coagulating their contents (similar to cooking). In this case, there are no specific chemical interactions. Impaired nutrient supply (such as glucose and oxygen) may deprive the cell of essential materials needed for survival.

TOXIC EFFECTS

The majority of toxic effects, especially due to xenobiotics, are due to specific biochemical interactions without causing recognizable damage to a cell or its organelles.

Examples of these Toxic Effects Include:

- Interference with a chemical that transmits a message across a neural synapse such as the inhibition of the enzymeacetylcholinesterase by organophosphate pesticides.
- When one toxic chemical inhibits or replaces another essential chemical such as the replacement of oxygen on the hemoglobin molecule with carbon monoxide.

The human body is extremely complex. In addition to over 200 different cell types and about as many types of tissues, there are literally thousands of different biochemicals, which may act alone or in concert to keep the body functions operating correctly. To illustrate the cell's structures and functions and the chemical toxicity of all tissues and organs would be impossible in this brief tutorial. This chapter presents only a general overview of toxic effects along with some specific types of toxicity that include cancer and neurotoxicity.

CAPACITY FOR REPAIR

Some tissues have a great capacity for repair, such as most epithelial tissues. Others have limited or no capacity to regenerate and repair, such as nervous tissue. Most organs have a functional reserve capacity so that they can continue to perform their body function although perhaps in somewhat diminished ability. *For example:*

- Half of a person's liver can be damaged, and the body can regenerate sufficient new liver or repair the damaged section by fibrous replacement to maintain most of the capacity of the original liver.
- The hypertrophy of one kidney to assume the capacity lost when the other kidney has been lost or surgically removed.

TOXIC DAMAGE TO CELLS AND TISSUES

Toxic damage to cells and tissues can be transient and non-lethal or, in severe situations, the damage may cause death of the cells or tissues. The various effects that can occur with damage to cells. *There are four main final endpoints to the cellular or biochemical toxicity:*

1. The Tissue may be completely repaired and return to normal.
2. The Tissue may be incompletely repaired but is capable of sustaining its function with reduced capacity.
3. Death of the organism or the complete loss of a tissue or organ. In some instances, the organism can continue to live with the aid of medical treatment, for example, replacement of insulin or by organ transplantations.
4. Neoplasm or cancers may result, many of which will result in death of the organism and some of which may be cured by medical treatment.

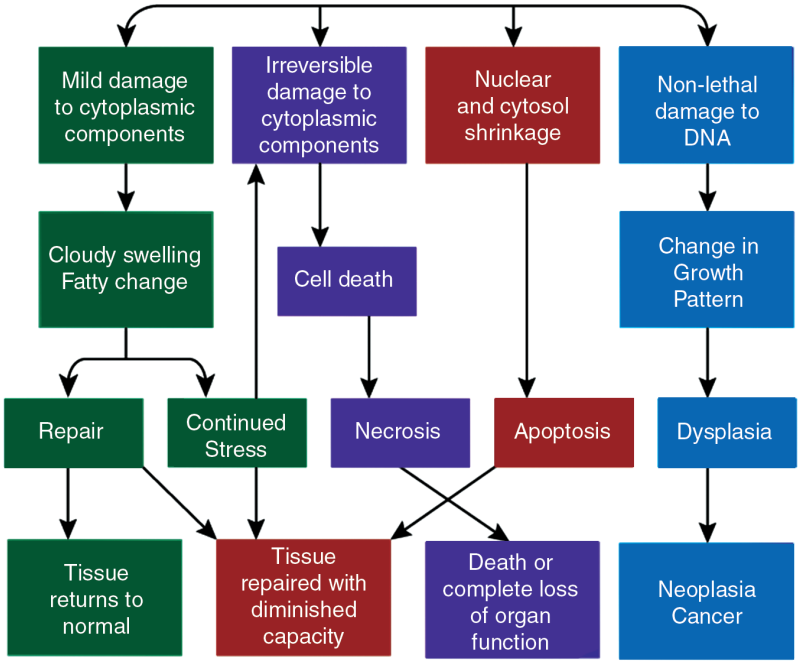


Fig. Toxic Damage to Cells.

REVERSIBLE CELL DAMAGE

The response of cells to toxic injury may be transient and reversible once the stress has been removed or the compensatory cellular changes are made. In some cases, the full capability of the damaged cells returns. In other cases, a degree of permanent injury remains with a diminished cellular or tissue capacity.

Cellular swelling, which is associated with hypertrophy, is due to cellular hypoxia, which damages the sodium-potassium membrane pump. This in turn changes the intracellular electrolyte balance with an influx of fluids into the cell, causing it to swell. Cell swelling is reversible when the cause is eliminated.

Fatty change is more serious and occurs with severe cellular injury. In this situation, the cell has become damaged and is unable to adequately metabolize fat. The result is that small vacuoles of fat accumulate and become dispersed within the cytoplasm. While fatty change can occur in several organs, it is usually observed in the liver. This is because most fat is synthesized and metabolized in liver cells. Fatty change can be reversed but it is a much slower process than the reversal of cellular swelling.

LETHAL INJURY (CELL DEATH)

In many situations, the damage to a cell may be so severe that the cell cannot survive. Cell death occurs mainly by two methods: necrosis and apoptosis. Necrosis is a progressive failure of essential metabolic and structural cell components usually in the cytoplasm. Necrosis generally involves a group of contiguous cells or occurs at the tissue level. Such progressive deterioration in structure and function rapidly leads to cell death or "necrotic cells." Necrosis begins as a reduced production of cellular proteins, changes in electrolyte gradient, or loss of membrane integrity (especially increased membrane permeability). Cytoplasmic organelles (such as mitochondria and endoplasmic reticulum) swell while others (especially ribosomes) disappear. This early phase progresses to fluid accumulation in the cells making them pale-staining or showing vacuoles, which pathologists call "cloudy swelling" or "hydropic degeneration." In some cells, they no longer can metabolize fatty acids so that lipids accumulate in the cytoplasmic vacuoles, referred to as "fatty accumulation" or "fatty degeneration." In the final stages of "cell dying," the nucleus becomes shrunken (pyknosis) or fragmented (karyorrhexis).

Apoptosis or "programmed cell death" is a process of self-destruction of the cell nucleus. Apoptosis is an individual or single cell death in that dying cells are not contiguous but are scattered throughout a tissue. Apoptosis is a normal process in cell turnover in that cellshave a finite lifespan and spontaneously die. During embryonic development, certain cells are programmed to die and are not replaced, such as the cells between each developing finger. If the programmed cells do not die, the fetus ends up with incomplete or fingers joined together in a web fashion.

In apoptosis, the cells shrink from a decrease of cytosol and the nucleus. The organelles (other than the nucleus) appear normal in apoptosis. The cell disintegrates into fragments referred to as "apoptotic bodies." These apoptotic bodies and the organelles are phagocytized by adjacent cells and local macrophages without initiation of an inflammatory response as is seen in necrosis. The cellsundergo apoptosis and just appear to "fade away." Some toxicants induce apoptosis or, in other cases, they inhibit normal physiological apoptosis.

Following necrosis, the tissue attempts to regenerate with the same type of cells that have died. When the injury is minimal, the tissuemay effectively replace the damaged or lost cells. In severely damaged tissues or long-term chronic situations, the ability of the tissueto regenerate the same cell types and tissue structure may be exceeded, so that a different and imperfect repair occurs.

- An example of this is with chronic alcoholic damage to liver tissue in which the body can no longer replace hepatocytes with hepatocytes but rather connective tissue replacement occurs. Fibrocytes with collagen replace the hepatocytes and normal liver structure with scar tissue. The

fibrotic scar tissue shores up the damage but it cannot replace the function of the lost hepatic tissue. With constant fibrotic change, the liver function is continually diminished so that eventually the liver can no longer maintain homeostasis. This fibrotic replacement of the liver is known as cirrhosis. The normal dark-red, glistening smooth appearance of the liver has been replaced with light, irregular fibrous scar tissue that permeates the entire liver.

Fig. A healthy liver (left) and a liver with cirrhosis (right).

We have so far discussed primarily changes to individual cells. However, a tissue and an organ consist of different types of cells that work together to achieve a particular function. As with a football team, when one member falters, the others rally to compensate. It is the same with a tissue. Damage to one cell type prompts reactions within the tissue to compensate for the injury. Within organs, there are two basic types of tissues: the parenchymal and stromal tissues. The parenchymal tissues contain the functional cells (for example, squamous dermal cells, liver hepatocytes, and pulmonary alveolar cells). The stromal cells are the supporting connective tissues (for example, blood vessels and elastic fibres).

CELL REPAIR

Repair of injured cells can be accomplished by either:

1. Regeneration of the parenchymal cells.
2. Repair and replacement by the stromal connective tissue.

The goal of the repair process is to fill the gap that results from the tissue damage and restore the structural continuity of the injured tissue. Normally a tissue attempts to regenerate the same cells that are damaged; however, in many cases, this cannot be achieved so that replacement with a stromal connective tissue is the best means for achieving the structural continuity.

The ability to regenerate varies greatly with the type of parenchymal cell. The regenerating cells come from the proliferation of nearby parenchymal cells, which serve to replace the lost cells. *Based on regenerating ability, there are three types of cells:*

1. *Labile Cells:* Cells that routinely divide and replace cells that have a limited lifespan (for example, skin epithelial cells, and hematopoietic stem cells).
2. *Stable Cells:* Cells that usually have a long lifespan with normally a low rate of division; they can rapidly divide upon demand.
3. *Permanent Cells:* Cells that never divide and do not have the ability for replication even when stressed or when some cells die.

Table below shows examples of cell types.

Table: Examples of Three cell Types of Parenchymal Cells.

Cell Type	Examples
Labile cells	Squamous epithelium of skin, mouth, vagina, and cervix Columnar epithelium of intestinal tract Transitional epithelium of urinary tract Bone marrow cells
Stable cells	Liver hepatocytes Alveolar cells of lung Epithelium of kidney tubules
Permanent cells,	Neurons Skeletal and cardiac muscle

The labile cells have a great potential for regeneration by replication and repopulation with the same cell type so long as the supporting structure remains intact. Stable cells can also respond and regenerate but to a lesser degree and are quite dependent on the supporting stromal framework. When the stromal framework is damaged, the regenerated parenchymal cells may be irregularly dispersed in the organ resulting in diminished organ function. The tissue response for the labile and stable cells is initially hyperplasiauntil the organ function becomes normal again. When permanent cells die they are not replaced in kind but instead connective tissue(usually fibrous tissue) moves in to occupy the damaged area. This is a form of metaplasia.

Examples of Replacement by Metaplasia are:

- *Cirrhosis of the Liver:* Liver cells (hepatocytes) are replaced by bands of fibrous tissue, which cannot carry out the metabolic functions of the liver.
- Cardiac Infarcts: Cardiac muscle cells do not regenerate and thus are replaced by fibrous connective tissue (scar). The scar cannot transmit electrical impulses or participate in contraction of the heart.
- *Pulmonary Fibrosis:* Damaged or dead epithelial cells lining the pulmonary alveoli are replaced by fibrous tissue. Gases cannot diffuse across the fibrous cells and thus gas exchange is drastically reduced in the lungs.

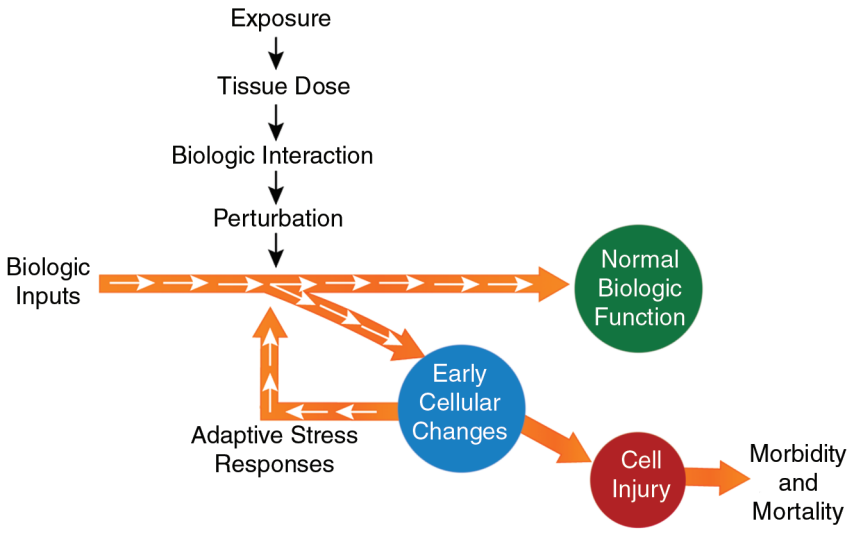


Fig. Activation of Toxicity Pathways.

10

Amyloidosis and Calcification

AMYLOIDOSIS

Amyloidosis is when an abnormal protein called amyloid builds up in your tissues and organs. When it does, it affects their shape and how they work. Amyloidosis is a serious health problem that can lead to life-threatening organ failure.

CAUSES AND TYPES OF AMYLOIDOSIS

Many different proteins can lead to amyloid deposits, but only a few have been linked to major health problems. The type of protein and where it collects tells the type of amyloidosis you have. Amyloid deposits may collect throughout your body or in just one area.

The different types of amyloidosis include:

AL amyloidosis (immunoglobulin light chain amyloidosis): This is the most common type and used to be called primary amyloidosis. AL stands for "amyloid light chains," which is the type of protein responsible for the condition. There's no known cause, but it happens when your bone marrow makes abnormal antibodies that can't be broken down. It's linked with a blood cancer called multiple myeloma. It can affect your kidneys, heart, liver, intestines, and nerves.

AA amyloidosis: Previously known as secondary amyloidosis, this condition is the result of another chronic infectious or inflammatory disease such as rheumatoid arthritis, Crohn's disease, or ulcerative colitis. It mostly affects your kidneys, but it can also upset your digestive tract, liver, and heart. AA means the amyloid type A protein causes this type.

Dialysis-related amyloidosis (DRA): This is more common in older adults and people who have been on dialysis for more than 5 years. This form of amyloidosis is caused by deposits of beta-2 microglobulin that build up in the blood. Deposits can build up in many different tissues, but it most commonly affects bones, joints, and tendons.

Familial, or Hereditary, Amyloidosis: This is a rare form passed down through families. It often affects the liver, nerves, heart, and kidneys. Many genetic defects are linked to a higher chance of amyloid disease. For example, an abnormal protein like transthyretin (TTR) can be the cause.

Age-related (senile) Systemic Amyloidosis: This is caused by deposits of normal TTR in the heart and other tissues. It happens most commonly in older men.

Organ-specific Amyloidosis: This causes deposits of amyloid protein in single organs, including the skin (cutaneous amyloidosis).

Though some types of amyloid deposits have been linked to Alzheimer's disease, the brain is rarely affected by amyloidosis that happens throughout your body.

RISK FACTORS FOR AMYLOIDOSIS

Men get amyloidosis more often than women. Your risk for amyloidosis goes up as you grow older. Amyloidosis affects 15% of patients with a form of cancer called multiple myeloma. Amyloidosis may also happen in people with end-stage kidney disease who are on dialysis for a long time.

SYMPTOMS OF AMYLOIDOSIS

Symptoms of amyloidosis are often subtle. They can also vary greatly depending on where the amyloid protein is collecting in the body. It is important to note that the symptoms described below may be due to a variety of health problems. Only your doctor can make a diagnosis of amyloidosis.

General Symptoms of Amyloidosis may Include:

- Changes in skin colour
- Severe fatigue
- Feeling of fullness
- Joint pain
- Low red blood cell count (anemia)
- Shortness of breath
- Swelling of the tongue
- Tingling and numbness in legs and feet
- Weak hand grip
- Severe weakness
- Sudden weight loss.

CARDIAC (HEART) AMYLOIDOSIS

Amyloid deposits in the heart can make the walls of the heart muscle stiff. They can also make the heart muscle weaker and affect the electrical rhythm of the heart. This condition can cause less blood to flow to your heart. Eventually, your heart will no longer be able to pump normally. *If amyloidosis affects your heart, you may have:*

- Shortness of breath with light activity
- An irregular heartbeat
- Signs of heart failure, including swelling of the feet and ankles, weakness, fatigue, and nausea, among others.

RENAL (KIDNEY) AMYLOIDOSIS

Your kidneys filter waste and toxins from your blood. Amyloid deposits in the kidneys make it hard for them to do this job. When your kidneys do not work properly, water and dangerous toxins build up in your body. *If amyloidosis affects the kidneys, you may have:*

- Signs of kidney failure, including swelling of the feet and ankles and puffiness around the eyes.
- High levels of protein in your urine.

GASTROINTESTINAL AMYLOIDOSIS

Amyloid deposits along your gastrointestinal (GI) tract slow down the movement of food through your intestines. This interferes with digestion.

If amyloidosis affects your GI tract, you may have:

- Less Appetite

- Diarrhea
- Nausea
- Stomach pain
- Weight Loss.

If your liver is affected, that can cause liver enlargement and fluid buildup in the body.

AMYLOID NEUROPATHY

Amyloid deposits can damage the nerves outside your brain and spinal cord, called the peripheral nerves. The peripheral nerves carry information between your brain and spinal cord and the rest of your body. For example, they make your brain perceive pain if you burn your hand or stub your toes.

If Amyloidosis Affects your Nerves, you may have:

- Balance problems
- Problems controlling your bladder and bowel
- Sweating problems
- Tingling and weakness
- Lightheadedness when standing due to a problem with your body's ability to control blood pressure.

DIAGNOSING AMYLOIDOSIS

A thorough physical exam and a detailed and accurate account of your medical history are crucial in helping your doctor diagnose amyloidosis. Blood and urine tests can spot abnormal proteins. Depending on your symptoms, your doctor may also check your thyroid and liver.

Your doctor will do a biopsy to confirm a diagnosis of amyloidosis and know the specific type of protein you have. The tissue sample for the biopsy may be taken from your belly fat (the abdominal fat pad), bone marrow, or sometimes your mouth, rectum, or other organs. It's not always necessary to biopsy the part of the body damaged by the amyloid deposits. Imaging tests can also help. They show the amount of damage to organs like your heart, liver, or spleen.

Your doctor will do a genetic test if they think you have a type that is passed down through families. Treatment for hereditary amyloidosis is different from treatment for other types of the disease. Once you're diagnosed, your doctor might check your heart with an echocardiogram or your liver and spleen with imaging tests.

AMYLOIDOSIS TREATMENT

There is no cure for amyloidosis. Your doctor will prescribe treatments to slow the development of the amyloid protein and manage your symptoms. If amyloidosis is related to another condition, then treatment will include targeting that underlying condition.

Specific treatment depends on what type of amyloidosis you have and how many organs are affected:

- High-dose chemotherapy with stem cell transplant can help remove the substance that leads to amyloid formation in some people with primary AL amyloidosis. Chemotherapy medicines alone may be used to treat other patients with primary AL amyloidosis.
- Secondary (AA) amyloidosis is treated by controlling the underlying disorder and with powerful anti-inflammatory medicines called steroids, which fight inflammation.
- A liver transplant may treat the disease if you have certain types of hereditary amyloidosis.
- New therapies can slow the production of the abnormal protein TTR.
- Your doctor might also recommend a kidney transplant.

Other treatments to help with symptoms Include:

- Diuretic medicine to remove extra water from your body
- Thickeners to add to fluids to prevent choking if you have trouble swallowing
- Compression stockings to relieve swelling in your legs or feet
- Changes to what you eat, especially if you have gastrointestinal amyloidosis.

Expect

Amyloidosis can be deadly, especially if it affects your heart or kidneys. Early diagnosis and treatment are important and can help improve survival. Researchers continue to question why some types of amyloid make people sick and how the formation of amyloid can be stopped. Studies to find new treatments are ongoing. If you have amyloidosis, consider asking your doctor if there are any clinical trials you can join.

Signs and Symptoms

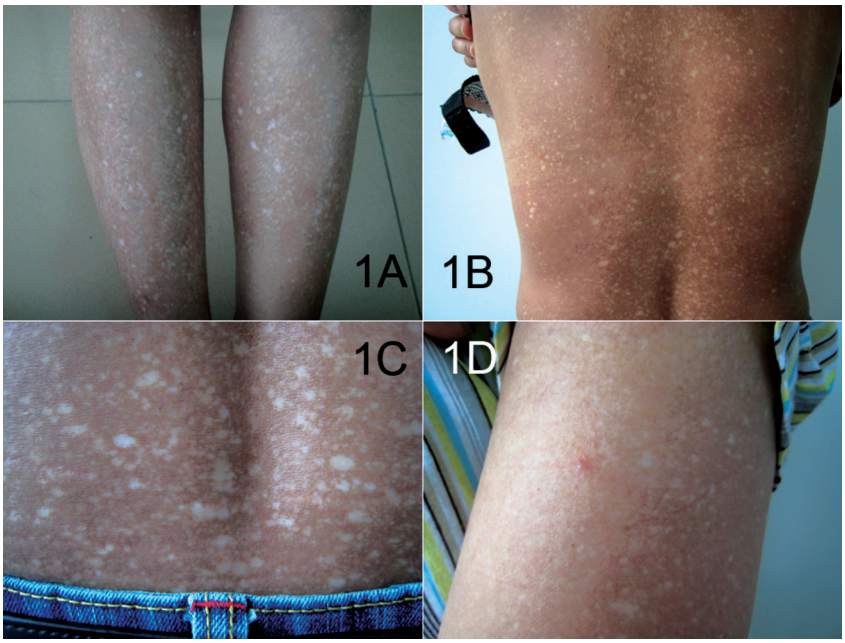


Fig. Skin features of amyloidosis cutis dyschromica. Hyperpigmented and hypopigmented macules on: (A) lower legs, (B) back and waist, (C) waist. (D) Individual blisters on upper arm

The presentation of amyloidosis is broad and depends on the site of amyloid accumulation. The kidney and heart are the most common organs involved. Amyloid deposition in the kidneys can cause nephrotic syndrome, which results from a reduction in the kidney's ability to filter and hold on to proteins. The nephrotic syndrome occurs with or without elevations in creatinine and blood urea concentration, two biochemical markers of kidney injury. In AA amyloidosis, the kidneys are involved in 91–96% of people, symptoms ranging from protein in the urine to nephrotic syndrome and rarely renal insufficiency. Amyloid deposition in the heart can cause both diastolic and systolic heart failure. EKG changes may be present, showing low voltage and conduction abnormalities like atrioventricular block or sinus node dysfunction. On echocardiography, the heart shows a restrictive filling pattern, with normal to mildly reduced systolic function. AA amyloidosis usually spares the heart. People with amyloidosis do not get central nervous system involvement but can develop sensory and autonomic neuropathies. Sensory neuropathy develops in a symmetrical pattern and progresses in a distal to proximal manner. Autonomic neuropathy can present as orthostatic hypotension but may manifest more gradually with non-specific gastrointestinal symptoms like constipation, nausea, or early satiety.

Accumulation of amyloids in the liver can lead to elevations in serum aminotransferases and alkaline phosphatase, two biomarkers of liver injury, which is seen in about one third of people. Liver enlargement is common. In contrast, spleen enlargement is rare, occurring in 5% of people. Splenic dysfunction, leading to the presence of Howell-Jolly bodies on blood smear, occurs in 24% of people with amyloidosis. Malabsorption is seen in 8.5% of AL amyloidosis and 2.4% of AA amyloidosis. One suggested mechanism for the observed malabsorption is that amyloid deposits in the tips of intestinal villi (fingerlike projections that increase the intestinal area available for absorption of food), begin to erode the functionality of the villi, presenting a sprue-like picture. A rare development is amyloid purpura, a susceptibility to bleeding with bruising around the eyes, termed "raccoon-eyes", caused by amyloid deposition in the blood vessels and a reduced activity of thrombin and factor X, two clotting proteins that lose their function after binding with amyloid.

Amyloid deposits in tissue can cause enlargement of structures. Twenty percent of people with AL amyloidosis have a enlarged tongue, that can lead to obstructive sleep apnea, difficulty swallowing, and altered taste. Tongue enlargement does not occur in ATTR or AA amyloidosis. Enlarged shoulders, "shoulder pad sign", results from amyloid deposition in synovial space. Deposition of amyloid in the throat can cause hoarseness. Aβ2MG amyloidosis (Hemodialysis associated amyloidosis) likes to deposit in synovial tissue, causing chronic synovitis, which can lead to repeated carpal tunnel syndrome.

Both the thyroid and adrenal gland can be infiltrated. It is estimated that 10–20% of individuals with amyloidosis have hypothyroidism. Adrenal infiltration may be harder to appreciate given that its symptoms of orthostatic hypotension and low blood sodium concentration may be attributed to autonomic neuropathy and heart failure. "Amyloid deposits occur in the pancreas of patients with diabetes mellitus, although it is not known if this is functionally important. The major component of pancreatic amyloid is a 37-amino acid residue peptide known as islet amyloid polypeptide or 'amylin.' This is stored with insulin in secretory granules in B cells and is co secreted with insulin." (Rang and Dale's Pharmacology, 2015.) Uncommonly, a collection of amyloid can grow large enough to be classed as an amyloidoma, a macroscopic lump of amyloid that can cause mass effect.

PATHOGENESIS

The cells in the body have two different ways of making proteins. Some proteins are made of one single piece or sequence of amino acids; in other cases, protein fragments are produced, and the fragments come and join together to form the whole protein. But such a protein can sometimes fall apart into the original protein fragments. This process of "flip flopping" happens frequently for certain protein types, especially the ones that cause amyloidosis.

The fragments or actual proteins are at risk of misfolding as they are synthesized, to make a poorly functioning protein. This causes proteolysis, which is the directed breakdown of proteins by cellular enzymes called proteases or by intramolecular digestion; proteases come and digest the misfolded fragments and proteins. The problem occurs when the proteins do not dissolve in proteolysis because the misfolded proteins sometimes become robust enough so that they are not dissolved by normal proteolysis. When the fragments do not dissolve, they get spit out of proteolysis and aggregate to form oligomers. The reason they aggregate is that the parts of the protein that do not dissolve in proteolysis are hydrophobic β-pleated sheets. They are usually sequestered in the middle of the protein, while parts of the protein that are more soluble are found near the outside. When they are exposed to water, these hydrophobic pieces tend to aggregate with other hydrophobic pieces. This ball of fragments gets stabilized by GAGs (glycosaminoglycans) and SAP (serum amyloid P), a component found in amyloid aggregations that is thought to stabilize them and prevent proteolytic cleavage. The stabilized balls of protein fragments are called oligomers. The oligomers can aggregate together and further stabilize to make amyloid fibrils.

Both the oligomers and amyloid fibrils are toxic to cells and can interfere with proper organ function.

DIAGNOSIS

Diagnosis of Amyloidosis Requires Tissue Biopsy: The biopsy is assessed for evidence of characteristic amyloid deposits. The tissue is treated with various stains. The most useful stain in the diagnosis of amyloid is Congo red, which, combined with polarized light, makes the amyloid proteins appear apple-green on microscopy. Also, thioflavin T stain may be used.

Tissue can come from any involved organ, but in systemic disease the first-line site of the biopsy is subcutaneous abdominal fat, known as a "fat pad biopsy", due to its ease of acquisition versus biopsy of the rectum, salivary gland or internal organs. An abdominal fat biopsy is not completely sensitive, and sometimes, biopsy of an involved organ (such as the kidney) is required to achieve a diagnosis. For example, in AL amyloidosis only 85% of people will have a positive fatpad biopsy using Congo red stain. By comparison, rectal biopsy has sensitivity of 74–94%.

The Type of the Amyloid Protein can be Determined in Various Ways: The detection of abnormal proteins in the bloodstream (on protein electrophoresis or light chain determination); binding of particular antibodies to the amyloid found in the tissue (immunohistochemistry); or extraction of the protein and identification of its individual amino acids. Immunohistochemistry can identify AA amyloidosis the majority of the time, but can miss many cases of AL amyloidosis. Laser microdissection with mass spectrometry is the most reliable method of identifying the different forms of amyloidosis.

AL is the most common form of amyloidosis, and a diagnosis often begins with a search for plasma cell dyscrasia, memory B cells producing aberrant immunoglobulins or portions of immunoglobulins. Immunofixation electrophoresis of urine or serum is positive in 90% of people with AL amyloidosis. Immunofixation electrophoresis is more sensitive than regular electrophoresis but may not be available in all centers. Alternatively immunohistochemical staining of a bone marrow biopsy looking for dominant plasma cells can be sought in people with a high clinical suspicion for AL amyloidosis but negative electrophoresis.

ATTR, or familial transthyretin-associated amyloidosis, is suspected in people with family history of idiopathic neuropathies or heart failure who lack evidence of plasma cell dyscrasias. ATTR can be identified using isoelectric focusing which separates mutated forms of transthyretin. Findings can be corroborated by genetic testing to look for specific known mutations in transthyretin that predispose to amyloidosis.

AA is suspected on clinical grounds in individuals with longstanding infections or inflammatory diseases. AA can be identified by immunohistochemistry staining.

CLASSIFICATION OF AMYLOIDOSIS

Amyloidosis is classified according to the type of accumulated protein and according to the underlying disease. These are all relatievly rare illnesses, but some occur more frequently than others.

AL amyloidosis stands for Amyloid Light Chain Amyloidosis. The accumulating proteins are small proteins, known as light chains, and can be one of two types: either kappa or lambda. They are created by a type of white blood cells, called plasma cells in the bone marrow. Everyone has plasma cells, in their bone marrow, that create kappa and lambda protein. Plasma cells are important to our immune system, as they create the natural antibodies that protect us against infections. In patients with AL amyloidosis, dysplasia takes place, which leads to formation of a changed protein with an abnormal composition and form. This means that the proteins have a tendency to accumulate. The underlying problem is the dysplasia of the plasma cells, and this type of amyloidosis can be treated with a type of chemotherapy, which destroys the transformed plasma cells. The dysplasia is not malignant, and AL amyloidosis is not a cancer, but the illness is serious due to the accumulation.

ATTR amyloidosis stands for Amyloid Transthyretin Amyloidosis. Transthyretin is a bigger protein than the light chains. We all create transthyretin, which is the originator of the most dominant protein we have in our serum, *i.e.* albumin. Transthyretin is also known as prealbumin. There are two types of transthyretin amyloidosis:

a hereditary type and an acquired age-related type. The hereditary type is caused by an abnormality in the gene that codes the formation of transthyretin. The transthyretin protein, which is formed, therefore has a slightly different structure than normally, and it is this difference that is significant enough that the protein has a tendency to cause accumulation. There are two main types of the hereditary type; one that most frequently attacks the nerve pathways and leads to chronic nerve stress, and another type, which most frequently affects the heart and causes enlargement of the heart as well as heart failure. Even though this type of amyloidosis is inherent, symptoms occur relatively late in adulthood, *e.g.* at 40-60 years of age. The non-hereditary type of ATTR amyloidosis is typically seen in older patients and is therefore named "Senile amyloidosis". It typically also affects the heart.

AA amyloidosis stands for Apoprotein A amyloidosis and is also known as secondary amyloidosis. Occurs in patients with long-term chronic infections, chronic inflammations and chronic, active rheumatism. This type is more frequent in developing countries, but has become rarer in Denmark, as treatment of infections and rheumatism has improved significantly. In connection with AA amyloidosis, it is important to ensure that the underlying triggering illness is treated as well as possible.

Beta 2 microglobulin amyloidosis is caused by accumulation of the protein, Beta 2 microglobulin. This type is typically seen in patients with chronic kidney disease and is caused by the amount of Beta 2 microglobulin in the blood increasing in connection with kidney failure.

CALCIFICATION

Calcification happens when calcium builds up in body tissue, blood vessels, or organs. This buildup can harden and disrupt your body's normal processes. Calcium is transported through the bloodstream. It's also found in every cell. As a result, calcification can occur in almost any part of the body.

According to the National Academy of Medicine Trusted Source (formerly the Institute of Medicine), about 99 percent of your body's calcium is in your teeth and bones. The other 1 percent is in the blood, muscles, fluid outside the cells, and other body tissues.

Some disorders cause calcium to deposit in places where it doesn't typically belong. Over time, this can add up and cause problems. You may need treatment to prevent complications if you have this extra calcium buildup.

TYPES OF CALCIFICATION

Calcifications can form in many places throughout your body, including:

- Small and large arteries
- Heart valves
- Brain, where it's known as cranial calcification
- Joints and tendons, such as knee joints and rotator cuff tendons
- Soft tissues like breasts, muscles, and fat
- Kidney, bladder and Gallbladder

Some Calcium Buildup is Harmless: These deposits are believed to be the body's response to inflammation, injury, or certain biological processes. However, some calcifications can disrupt organ function and affect blood vessels.

According to the Division of Cardiology at UCLA School of Medicine, most adults older than 60 have calcium deposits in their blood vessels.

CAUSES OF CALCIFICATION

Many factors play a role in calcification.

These Include:

- Infections.
- Calcium metabolism disorders that cause hypercalcemia (too much calcium in the blood)
- Genetic or autoimmune disorders affecting the skeletal system and connective tissues
- Persistent Inflammation.

According to Harvard University, a common misconception is that calcifications are caused by a calcium-rich diet. However, researchers haven't found a link between dietary calcium and a higher risk for calcium deposits.

This is also True for Kidney Stones: Most kidney stones are made of calcium oxalate. People who get calcium oxalate stones release more calcium in their urine than those who don't. This disparity happens no matter how much calcium people have in their diets.

DIAGNOSING CALCIFICATION

Calcifications are usually found via X-rays. X-ray tests use electromagnetic radiation to take pictures of your internal organs and usually cause no discomfort. Your doctor will likely detect any calcification issues right away with X-rays. Your doctor may also order blood tests. For example, if you have kidney stones, these tests can determine your overall kidney function. Sometimes calcium deposits are found in areas of cancer. A calcification is usually tested to rule out cancer as a cause. Your doctor will order a biopsy (often through a fine needle) to collect a tissue sample. The sample is then sent to a laboratory for testing. If there aren't any cancer cells detected, your doctor will label the calcification as benign.

BREAST CALCIFICATIONS

Breast calcifications occur when calcium builds up within the soft tissue of the breast. There are two main types of breast calcifications: macrocalcifications (large calcium buildups) and microcalcifications (small calcium buildups). According to the National Cancer Institute Trusted Source, macrocalcifications in the breasts are most common in women over 50 years old. Men can get breast calcifications too, but it's not as common.

Breast calcifications happen for a number of reasons. Breast injuries, cell secretions, infections, and inflammation can all cause breast calcifications. You might also get calcifications if you've had breast cancer or radiation therapy for cancer. Most breast calcifications aren't cancerous. This is especially true for macrocalcifications.

Microcalcifications are often not cancerous either, but some microcalcification patterns may be signs of early breast cancer. Breast calcifications are too small to be found during a regular breast exam. Your doctor usually spots these deposits during a mammogram of your breast tissue. Your doctor may ask you to schedule a follow-up appointment if any calcifications need to be checked again.

Your doctor may also take a biopsy for testing of calcifications that might be suspicious looking. And your doctor may suggest minor surgery to remove calcifications in order to look at them more closely. Getting regular mammograms at an appropriate age can help track breast calcifications if they're present. The earlier that breast changes of concern are discovered, the more likely you are to have a positive outcome.

TREATING CALCIFICATION

Calcification Treatment Depends on Several Factors:

- Where do the calcium deposits occur?
- What is their underlying cause?
- What, if any, complications arise?

Your doctor will require regular follow-up appointments to check for potential complications once calcifications have been found. Minor artery calcifications aren't considered dangerous. Heart valves can also develop calcifications. In this case, you may need surgery to open or replace the valve if the calcium buildup is severe enough to affect the valve's function.

Kidney stone treatments help break down calcium buildup in the kidneys. Your doctor may prescribe a diuretic called thiazide to help prevent future calcium kidney stones. This diuretic signals the kidneys to release urine while holding on to more calcium. Calcium deposits in your joints and tendons don't always cause painful symptoms, but they can affect range of motion and cause discomfort. Treatments may include taking anti-inflammatory medicines and applying ice packs. If the pain doesn't go away, your doctor may recommend surgery.

PREVENTING CALCIFICATIONS

If you're over 65 years old, see your doctor regularly for blood tests to evaluate your calcium levels along with other tests. If you're under 65 years old and were born with a heart defect or kidney-related issues, calcifications can be more common for you than for others of your age. If you are aware of any of these conditions, ask your doctor about getting tested for calcifications.

Some medications can affect your body's calcium levels. Cholesterol medication, blood pressure medication, and hormone replacement therapy are common medications that affect how calcium is used in your body. Talk to your doctor if you're taking any of these medications or having related treatments to understand the effects of these treatments on your calcium levels.

If you frequently take calcium carbonate supplements (such as Tums), you risk raising your calcium to high levels. Problems with the kidney or the parathyroid (four small glands on the back of the thyroid) can also cause calcium levels in your blood to rise too high. The amount of calcium you need per day is based on your age. Talk to your doctor about what dose of calcium is right for you based on your age, gender, and other health issues. Smoking is associated with increased calcifications in the heart and major arteries. As smoking is known to be a major risk factor for developing heart disease, these calcifications may also play a role. Overall, quitting smoking has both short- and long-term benefits, especially for your heart, blood vessels, and brain.

There is no proven way to prevent calcifications, as they're a result of a variety of biological processes. Quitting smoking and changing diet may impact formation of calcifications, depending on the location of the buildup. Kidney stones may form less often with certain dietary changes. Talk to your doctor about ways to incorporate a healthy diet into your lifestyle.

OUTLOOK FOR CALCIFICATION

Calcifications don't cause symptoms on their own. They're often detected when X-rays are being done for other reasons. Talk to your doctor if you have any underlying health problems. For example, you may be susceptible to calcifications if you have heart disease, kidney disease, or if you smoke. Your outlook depends on the location and severity of the calcifications. Hardened calcium deposits can interrupt vital processes in the brain and heart. Calcifications in your blood vessels can lead to coronary heart disease. You and your doctor can talk about the best ways to manage the health issues that may put you at risk for calcifications.

THE BOTTOM LINE

Calcification is a buildup of calcium in body tissue. The buildup can form hardened deposits in soft tissues, arteries, and other areas. Some calcifications don't cause painful symptoms, while others can lead to serious complications. Treatment depends on the location, severity, and underlying cause of the deposits.

DYSTROPHIC CALCIFICATION

Dystrophic calcification (DC) is the calcification occurring in degenerated or necrotic tissue, as in hyalinized scars, degenerated foci in leiomyomas, and caseous nodules. This occurs as a reaction to tissue damage, including as a consequence of medical device implantation. Dystrophic calcification can occur even if the amount of calcium in the blood is not elevated. (A systemic mineral imbalance would elevate calcium levels in the blood and all tissues and cause metastatic calcification.) Basophilic calcium salt deposits aggregate, first in the mitochondria, and progressively throughout the cell. These calcifications are an indication of previous microscopic cell injury. It occurs in areas of cell necrosis in which activated phosphatases bind calcium ions to phospholipids in the membrane.

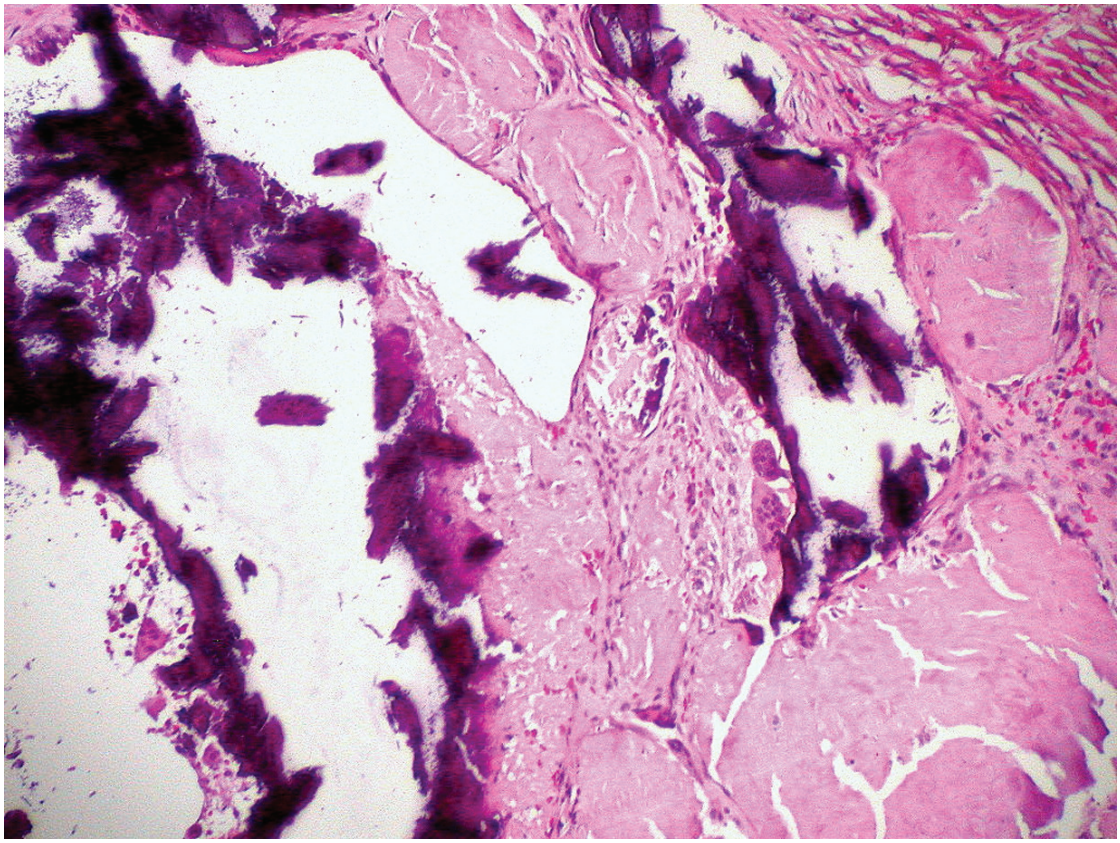


Fig. Amyloidosis, Dystrophic Calcification.

Calcification can occur in dead or degenerated tissue.

CALCIFICATION IN DEAD TISSUE

1. Caseous necrosis in T.B. is most common site of dystrophic calcification.
2. Liquefactive necrosis in chronic abscesses may get calcified.
3. Fat necrosis following acute pancreatitis or traumatic fat necrosis in breasts results in deposition of calcium soaps.
4. Infarcts may undergo D.C.
5. Thrombi, especially in veins, may produce phlebolithis.
6. Haematomas in the vicinity of bones may undergo D.C.
7. Dead parasites like schistosoma eggs may calcify.
8. Congenital toxoplasmosis, CMV or rubella may be seen on X-ray as calcifications in the brain.

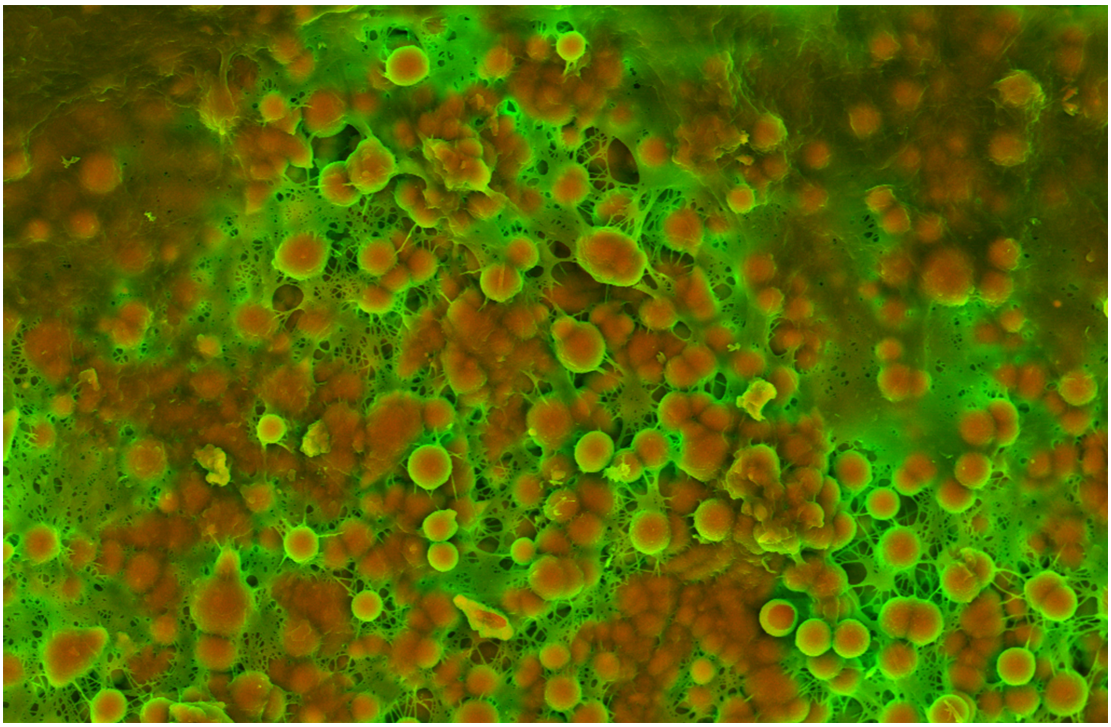


Fig. Density-Dependent Colour Scanning Electron Micrograph SEM (DDC-SEM) of cardiovascular calcification, showing in orange calcium phosphate spherical particles (denser material) and, in green, the extracellular matrix (less dense material).

CALCIFICATION IN DEGENERATED TISSUE

1. Dense scars may undergo hyaline degeneration and calcification.
2. Atheroma in aorta and coronaries frequently undergo calcification.
3. Cysts can show calcification.
4. Calcinosis cutis is condition in which there are irregular nodular deposits of calcium salts in skin and subcutaneous tissue.
5. Senile degenerative changes may be accompanied by calcification.
6. The inherited disorder pseudoxanthoma elasticum may lead to angioid streaks with calcification of Bruch's membrane, the elastic tissue below the retinal ring.

VASCULAR CALCIFICATIONS

If your doctor tells you that you have vascular calcifications, you're right to be concerned. Vascular calcifications are mineral deposits on the walls of your arteries and veins. These mineral deposits sometimes stick to fatty deposits, or plaques, that are already built up on the walls of a blood vessel. Vascular calcifications are common but potentially serious. They can increase your risk of stroke and blood clots, according to Cardiovascular Research. It's important to learn what causes calcification in the body and how to treat it.

Calcifications can occur in the intimal (inside) or medial (middle layer) part of the blood vessel. Each location has different associated risks. Medial calcifications, for example, are most often associated with kidney disease, diabetes, hypertension, and advanced age. Intimal calcifications are associated with blocked arteries and blood clots. When calcifications in the breast are found during a mammogram, doctors examine these closely as they can signal breast cancer. In the body, calcification is actually part of the aging process. Calcifications accumulate in the vessels, heart, or valves as calcium travels through the bloodstream.

RISK FACTORS AND COMPLICATIONS OF VASCULAR CALCIFICATION

Postmenopausal women with osteoporosis and people with type 1 or type 2 diabetes or metabolic syndrome are at a greater risk of developing vascular calcifications. However, they are more common in those with chronic kidney disease. Long-term smoking and elevated LDL cholesterol levels are associated with an increase in the incidence of calcifications.

According to the journal Arteriosclerosis, Thrombosis, and Vascular Biology, vascular calcifications can raise the rise of:

- Heart attack
- Stroke
- Dementia
- Renal insufficiency
- Inadequate blood supply to arms and legs

You may not always notice symptoms of vascular calcification. If vascular calcification causes arteries to harden, the heart will have to work harder to pump blood. Eventually, you might develop symptoms of peripheral artery disease (PAD) or stroke. The most common PAD symptom is pain or cramping in your leg muscles when walking or climbing stairs. If plaque is dislodged, it can cause a stroke. Symptoms of a stroke include sudden weakness, confusion, or dizziness, along with vision and speech impairment.

VASCULAR CALCIFICATION TREATMENT AND PREVENTION

Doctors treat plaque-clogged blood vessels in a variety of ways, including vascular surgery and medicine.

Lifestyle Changes: Quitting smoking, eating healthier foods, and starting to exercise—can decrease the chances of plaque and calcifications forming. If you take calcium supplements, your doctor can advise the proper dosage or if you should continue taking them.

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Inflammation and Repair

Inflammation is the body's mechanism for coping with agents that could damage it. In other words, inflammation is a protective response to rid the body of the cause of cell injury and the resultant necrotic cells that cell injury produces. Although the processes of acute and chronic inflammation are an important protective mechanism used by the body to deal with potentially damaging agents, they are potentially damaging to the body and must be closely regulated. The basic steps in acute inflammation allow white blood cells to move from the blood to the tissue location where they are required. Acute inflammation can resolve completely if the inciting agent is removed, or it can have one of several other sequelae, including chronic inflammation.

GENERAL CONCEPTS OF ACUTE AND CHRONIC INFLAMMATION

Overview: The body must undergo changes locally through vasodilation and increased vascular permeability in the area of the agent inciting the inflammatory reaction to allow white blood cells to accumulate. The white blood cells must then leave the blood vessel, cross the basement membrane, and be drawn to the area where they are needed. The process by which white blood cells are drawn to the area where they are needed is referred to as chemotaxis. Acute inflammation has a rapid onset, lasts for minutes to days, and is characterized by exudation of fluid and protein from vessels and emigration of neutrophils. Acute inflammation is a protective process that is designed to rid the body of the inciting agent and set up the process of repair. Chronic inflammation has a longer time course (days to years) and involves different cell types than does acute inflammation (lymphocytes and macrophages versus neutrophils).

Cardinal Signs of Acute Inflammation: Rubor (red discoloration), calor (heat), dolor (pain), tumor (mass effect), and loss of function.

Causes of Acute Inflammation: Infection, trauma, physical and chemical agents, necrosis, foreign bodies, and immune reactions.

INFLAMMATION

Inflammation, a response triggered by damage to living tissues. The inflammatory response is a defence mechanism that evolved in higher organisms to protect them from infection and injury. Its purpose is to localize and eliminate the injurious agent and to remove damaged tissue components so that the body can begin to heal. The response consists of changes in blood flow, an increase in permeability of blood vessels, and the migration of fluid, proteins, and white blood cells (leukocytes) from the circulation to the site of tissue damage. An inflammatory response that lasts only a few days is called acuteinflammation, while a response of longer duration is referred to as chronic inflammation.

Although acute inflammation is usually beneficial, it often causes unpleasant sensations, such as the pain of a sore throat or the itching of an insect bite. Discomfort is usually temporary and disappears when the inflammatory response has done its job. But in some instances inflammation can cause harm. Tissue destruction can occur when the regulatory

mechanisms of the inflammatory response are defective or the ability to clear damaged tissue and foreign substances is impaired. In other cases an inappropriate immune response may give rise to a prolonged and damaging inflammatory response. Examples include allergic, or hypersensitivity, reactions, in which an environmental agent such as pollen, which normally poses no threat to the individual, stimulates inflammation, and autoimmune reactions, in which chronic inflammation is triggered by the body's immune response against its own tissues.

CAUSES

The factors that can stimulate inflammation include microorganisms, physical agents, chemicals, inappropriate immunological responses, and tissue death. Infectious agents such as viruses and bacteria are some of the most common stimuli of inflammation. Viruses give rise to inflammation by entering and destroying cells of the body; bacteria release substances called endotoxins that can initiate inflammation. Physical trauma, burns, radiation, and frostbite can damage tissues and also bring about inflammation, as can corrosive chemicals such as acids, alkalis, and oxidizing agents. As mentioned above, malfunctioning immunological responses can incite an inappropriate and damaging inflammatory response. Inflammation can also result when tissues die from a lack of oxygen or nutrients, a situation that often is caused by loss of blood flow to the area.

SIGNS

The four cardinal signs of inflammation—redness (Latin *rubor*), heat(*calor*), swelling (*tumor*), and pain (*dolor*)—were described in the 1st century AD by the Roman medical writer Aulus Cornelius Celsus. Redness is caused by the dilation of small blood vessels in the area of injury. Heat results from increased blood flow through the area and is experienced only in peripheral parts of the body such as the skin. Fever is brought about by chemical mediators of inflammation and contributes to the rise in temperature at the injury. Swelling, called edema, is caused primarily by the accumulation of fluid outside the blood vessels. The pain associated with inflammation results in part from the distortion of tissues caused by edema, and it also is induced by certain chemical mediators of inflammation, such as bradykinin, serotonin, and the prostaglandins.

Like what you're reading? Start your free trial today for unlimited access to Britannica. A fifth consequence of inflammation is the loss of function of the inflamed area, a feature noted by German pathologist Rudolf Virchow in the 19th century. Loss of function may result from pain that inhibitsmobility or from severe swelling that prevents movement in the area.

THE ACUTE INFLAMMATORY RESPONSE

VASCULAR CHANGES

When tissue is first injured, the small blood vessels in the damaged area constrict momentarily, a process called vasoconstriction. Following this transient event, which is believed to be of little importance to the inflammatory response, the blood vessels dilate (vasodilation), increasing blood flow into the area. Vasodilation may last from 15 minutes to several hours.

Next, the walls of the blood vessels, which normally allow only water and salts to pass through easily, become more permeable. Protein-rich fluid, called exudate, is now able to exit into the tissues. Substances in the exudate include clotting factors, which help prevent the spread of infectious agents throughout the body. Other proteins include antibodies that help destroy invading microorganisms.

As fluid and other substances leak out of the blood vessels, blood flow becomes more sluggish and white blood cells begin to fall out of the axial stream in the centre of the vessel to flow nearer the vessel wall. The white blood cells then adhere to the blood vessel wall, the first step in their emigration into the extravascular space of the tissue.

CELLULAR CHANGES

The most important feature of inflammation is the accumulation of white blood cells at the site of injury. Most of these cells are phagocytes, certain "cell-eating" leukocytes that ingest bacteria and other foreign particles and also clean up cellular debris caused by the injury. The main phagocytes involved in acute inflammation are the neutrophils, a type of white blood cell that contains granules of cell-destroying enzymes and proteins. When tissue damage is slight, an adequate supply of these cells can be obtained from those already circulating in the blood. But, when damage is extensive, stores of neutrophils—some in immature form—are released from the bone marrow, where they are generated.

To perform their tasks, not only must neutrophils exit through the blood vessel wall but they must actively move from the blood vessel towards the area of tissue damage. This movement is made possible by chemical substances that diffuse from the area of tissue damage and create a concentration gradient followed by the neutrophils. The substances that create the gradient are called chemotactic factors, and the one-way migration of cells along the gradient is called chemotaxis.

Large numbers of neutrophils reach the site of injury first, sometimes within an hour after injury or infection. After the neutrophils, often 24 to 28 hours after inflammation begins, there comes another group of white blood cells, the monocytes, which eventually mature into cell-eating macrophages. Macrophages usually become more prevalent at the site of injury only after days or weeks and are a cellular hallmark of chronic inflammation.

CHEMICAL MEDIATORS OF INFLAMMATION

Although injury starts the inflammatory response, chemical factors released upon this stimulation bring about the vascular and cellular changes outlined above. The chemicals originate primarily from blood plasma, white blood cells (basophils, neutrophils, monocytes, and macrophages), platelets, mast cells, endothelial cells lining the blood vessels, and damaged tissue cells.

One of the best-known chemical mediators released from cells during inflammation is histamine, which triggers vasodilation and increases vascular permeability. Stored in granules of circulating basophils and mast cells, histamine is released immediately when these cells are injured. Other substances involved in increasing vascular permeability are lysosomal compounds, which are released from neutrophils, and certain small proteins in the complement system, namely C3a and C5a. Many cytokines secreted by cells involved in inflammation also have vasoactive and chemotactic properties.

The prostaglandins are a group of fatty acids produced by many types of cells. Some prostaglandins increase the effects of other substances that promote vascular permeability. Others affect the aggregation of platelets, which is part of the clotting process. Prostaglandins are associated with the pain and fever of inflammation. Anti-inflammatory drugs, such as aspirin, are effective in part because they inhibit an enzyme involved in prostaglandin synthesis. Prostaglandins are synthesized from arachidonic acid, as are the leukotrienes, another group of chemical mediators that have vasoactive properties.

The plasma contains four interrelated systems of proteins—complement, the kinins, coagulation factors, and the fibrinolytic system—that generate various mediators of inflammation. Activated complement proteins serve as chemotactic factors for neutrophils, increase vascular permeability, and stimulate the release of histamine from mast cells. They also adhere to the surface of bacteria, making them easier targets for phagocytes. The kinin system, which is activated by coagulation factor XII, produces substances that increase vascular permeability. The most important of the kinins is bradykinin, which is responsible for much of the pain and itching experienced with inflammation. The coagulation system converts the plasma protein fibrinogen into fibrin, which is a major component of the fluid exudate. The fibrinolytic system contributes to inflammation primarily through the formation of plasmin, which breaks down fibrin into products that affect vascular permeability.

EVENTS FOLLOWING ACUTE INFLAMMATION

Once acute inflammation has begun, a number of outcomes may follow. These include healing and repair, suppuration, and chronic inflammation. The outcome depends on the type of tissue involved and the amount of tissue destruction that has occurred, which are in turn related to the cause of the injury.

HEALING AND REPAIR

During the healing process, damaged cells capable of proliferation regenerate. Different types of cells vary in their ability to regenerate. Some cells, such as epithelial cells, regenerate easily, whereas others, such as liver cells, do not normally proliferate but can be stimulated to do so after damage has occurred. Still other types of cells are incapable of regeneration. For regeneration to be successful, it is also necessary that the structure of the tissue be simple enough to reconstruct. For example, uncomplicated structures such as the flat surface of the skin are easy to rebuild, but the complex architecture of a gland is not. In some cases, the failure to replicate the original framework of an organ can lead to disease. This is the case in cirrhosis of the liver, in which regeneration of damaged tissue results in the construction of abnormal structures that can lead to hemorrhaging and death.

Repair, which occurs when tissue damage is substantial or the normal tissue architecture cannot be regenerated successfully, results in the formation of a fibrous scar. Through the repair process, endothelial cells give rise to new blood vessels, and cells called fibroblasts grow to form a loose framework of connective tissue. This delicate vascularized connective tissue is called granulation tissue. It derives its name from the small red granular areas that are seen in healing tissue (*e.g.*, the skin beneath a scab). As repair progresses, new blood vessels establish blood circulation in the healing area, and fibroblasts produce collagen that imparts mechanical strength to the growing tissue. Eventually a scar consisting almost completely of densely packed collagen is formed. The volume of scar tissue is usually less than that of the tissue it replaces, which can cause an organ to contract and become distorted. For example, scarring of the intestines can cause the tubular structure to become obstructed through narrowing. The most dramatic cases of scarring occur in response to severe burns or trauma.

SUPPURATION

The process of pus formation, called suppuration, occurs when the agent that provoked the inflammation is difficult to eliminate. Pus is a viscous liquid that consists mostly of dead and dying neutrophils and bacteria, cellular debris, and fluid leaked from blood vessels. The most common cause of suppuration is infection with the pyogenic (pus-producing) bacteria, such as *Staphylococcus* and *Streptococcus*.

Once pus begins to collect in a tissue, it becomes surrounded by a membrane, giving rise to a structure called an abscess. Because an abscess is virtually inaccessible to antibodies and antibiotics, it is very difficult to treat. Sometimes a surgical incision is necessary to drain and eliminate it. Some abscesses, such as boils, can burst of their own accord. The abscess cavity then collapses, and the tissue is replaced through the process of repair.

CHRONIC INFLAMMATION

If the agent causing an inflammation cannot be eliminated, or if there is some interference with the healing process, an acute inflammatory response may progress to the chronic stage. Repeated episodes of acute inflammation also can give rise to chronic inflammation. The physical extent, duration, and effects of chronic inflammation vary with the cause of the injury and the body's ability to ameliorate the damage.

In some cases, chronic inflammation is not a sequel to acute inflammation but an independent response. Some of the most common and disabling human diseases, such as tuberculosis, rheumatoid arthritis, and chronic lung disease, are characterized by this type of inflammation. Chronic inflammation can be brought about by infectious organisms that are able to resist host defences and persist in tissues for an extended period. These

organisms include *Mycobacterium tuberculosis* (the causative agent of tuberculosis), fungi, protozoa, and metazoal parasites. Other inflammatory agents are materials foreign to the body that cannot be removed by phagocytosis or enzymatic breakdown. These include substances that can be inhaled, such as silica dust, and materials that can gain entry to wounds, such as metal or wood splinters.

In autoimmune reactions the stimulus to chronic inflammation is a normal component of the body to which the immune system has become sensitized. Autoimmune reactions give rise to chronic inflammatory diseases such as rheumatoid arthritis. The hallmark of chronic inflammation is the infiltration of the tissue site by macrophages, lymphocytes, and plasma cells (mature antibody-producing B lymphocytes). These cells are recruited from the circulation by the steady release of chemotactic factors. Macrophages are the principal cells involved in chronic inflammation and produce many effects that contribute to the progression of tissue damage and to consequent functional impairment. Granulomatous inflammation is a distinct type of chronic inflammation. It is marked by the formation of granulomas, which are small collections of modified macrophages called epithelioid cells and are usually surrounded by lymphocytes. Granulomas often contain giant, or Langhans, cells that form from the coalescence of epithelioid cells. A classic example of granulomatous inflammation is tuberculosis, and the granulomas formed are called tubercles. Granulomas also typically arise from fungal infections, and they are present in schistosomiasis, syphilis, and rheumatoid arthritis.

ACUTE INFLAMMATION

During an immune response, often a set of processes occur that create a condition known as inflammation. These processes include many of the innate effector mechanisms we have been discussing. But also some additional events occur as well. Here we pull together the various processes that collectively are called inflammation. Inflammation is divided into acute inflammation, which occurs over seconds, minutes, hours, and days, and chronic inflammation, which occurs over longer times.

EVENTS IN ACUTE INFLAMMATION

Acute inflammation begins within seconds to minutes following the injury of tissues. The damage may be purely physical, or it may involve the activation of an immune response.

Three main processes occur:

- Increased blood flow due to dilation of blood vessels (arterioles) supplying the region
- Increased permeability of the capillaries, allowing fluid and blood proteins to move into the interstitial spaces.
- Migration of neutrophils (and perhaps a few macrophages) out of the capillaries and venules and into interstitial spaces.

INCREASED BLOOD FLOW AND EDEMA

The first two of the above effects are readily visible within a few minutes following a scratch that does not break the skin. At first, the scratch is visible as a pale red line. Then the surrounding few millimeters of tissue on both sides of the scratch becomes red as blood flow increases locally. Finally, the area swells as additional fluid accumulates in the interstitial spaces of the region, a condition known as edema. The increased permeability of the capillaries occurs because the endothelial cells separate from one another at their edges.

CELL ADHESION MOLECULES

As described when we were discusssing the migration of neutrophils from blood vessels into the tissues, the first step is the binding of the neutrophils to the endothelium of the blood vessels. The binding is due to

molecules, called cell adhesion molecules (CAMs), found on the surfaces of neutrophils and on endothelial cells in injured tissue. The binding occurs in two steps. In the first, adhesion molecules called selectins lightly tether the neutrophil to the endothelium, so that it begins rolling along the surface. In a second step, a much tighter binding occurs through the interaction of ICAMs on the endothelial cells with integrins on the neutrophil.

In this light micrograph of a blood vessel in the lungs you can see a layer of neutrophils adhering to the inner surface of the blood vessel.

Notice in the above micrograph that you can also observe neutrophils outside as well as inside the blood vessel. Once bound to the endothelium, neutrophils squeeze through gaps between adjacent endothelial cells into the interstitial fluid, a process called diapedesis. Sometimes pus forms at the site of acute inflammation, especially if a foreign body is present to continually aggravate the tissue. This light micrograph of pus from an inflammed appendix shows that pus is packed with neutrophils, the primary cells typically present during acute inflammation. (How can you tell these are neutrophils?)

CHEMOTAXIS

Once outside the blood vessel, a neutrophil is guided towards an infection by various diffusing chemotactic factors. Examples include the chemokines and the complement peptide C5a, which is released when the complement system is activated either via specific immunity or innate immunity.

EOSINOPHILS

However, in some circumstances eosinophils rather than neutrophils predominate in acute inflammation. This tends to occur with parasitic worms, against which neutrophils have little success, or with a response involving the antibody IgE. Eosinophils release several proteins, such as major basic protein, which are often effective against parasites. Eosinophils also release several regulatory molecules that increase endothelial permeability. Note that eosinophils are also linked to certain types of allergies.

INFLAMMATORY PARACRINES

What causes the characteristic sequence of events in acute inflammation? Various cells at the site of tissue damage or of a specific immune response release regulatory molecules that act locally as paracrines.

- Macrophages and lymphocytes are important sources of inflammatory paracrines. The macrophages release IL-1 and TNF-alpha, which have powerful, widespread effects.
- Also important are mast cells, which are found throughout the body, especially under epithelia. Mast cells are filled with large vesicles containing histamine and other inflammatory paracrines. Factors associated with tissue damage can trigger the exocytosis. But sometimes it is a specific immune response that triggers the release of the inflammatory paracrines.
- Also, various arachidonic acid derivatives are important. Both prostaglandins (notably PG D2) and leukotrienes (LT) can be important, depending on the tissue. Note the effectiveness of aspirin and various NSAIDs in quieting inflammation.
- Complement peptides, C3a and C5a.
- Various other molecules including nitric oxide, certain platelet products, kinins, and certain other substances we will not discuss (serotonin, *etc*).

MEDIATORS OF INFLAMMATION

Once leukocytes have arrived at a site of infection or inflammation, they release mediators which control the later accumulation and activation of other cells. However, in inflammatory reactions initiated by the immune

system, the ultimate control is exerted by the antigen itself, in the same way as it controls the immune response itself. For this reason, the cellular accumulation at the site of chronic infection, or in autoimmune reactions (where the antigen cannot ultimately be eradicated), is quite different from that at sites where the antigenic stimulus is rapidly cleared.

There are four major plasma enzyme systems which have an important role in haemostasis and control of inflammation. These are the complement system, the clotting system, the fibrinolytic (plasmin) system and the kinin system.

Inflammatory mediators are soluble, diffusible molecules that act locally at the site of tissue damage and infection, and at more distant sites. They can be divided into exogenous and endogenous mediators.

Bacterial products and toxins can act as *exogenous mediators* of inflammation. Notable among these is *endotoxin*, or LPS of Gram-negative bacteria. The immune system of higher organisms has probably evolved in a veritable sea of endotoxin, so it is perhaps not surprising that this substance avokes powerful responses. For example, endotoxin can trigger complement activation, resulting in the formation of anaphylatoxins C3a and C5a which cause vasodilation and increase vascular permeability. Endotoxin also activates the Hageman factor, leading to activation of both the coagulation and fibrinolytic pathways as well as the kinin system. In addition, endotoxin elicit T cell proliferation, and have been described as superantigen for T cells.

Endogenous mediators of inflammation are produced from within the (innate and adaptive) immune system itself, as well as other systems. For example, they can be derived from molecules that are normally present in the plasma in an inactive form, such as peptide fragments of some components of complement, coagulation, and kinin systems. Mediators of inflammatory responses are also released at the site of injury by a number of cell types that either contain them as preformed molecules within storage granules, *e.g.* histamine, or which can rapidly switch on the machinery required to synthesize the mediators when they are required, for example to produce metabolites of arachidonic acid.

Mononuclear phagocytes (monocytes and macrophages) are central to inflammation, as they produce many components which participate in or regulate the different plasma enzyme systems, and hence the mediators of the inflammatory response. They are also actively phagocytic and are involved in microbial killing, as are neutrophils. While the latter can be thought of as short-lived kamikaze cells that need to be continually replaced from the bone marrow, mononuclear phagocytes are long-lived and some can proliferate *in situ*. Other cells such as mast cells and basophils are much less phagocytic, but together with platelets, these cells are particularly important for secretion of vasoactive mediators. The function of these cell types is at least partially under the control of cytokines. All inflammatory cells have receptors for Fc domains of immunoglobulins and for complement components, and they possess specialized granules containing an immerse variety of products that are released perhaps by common mechanisms. Cytotoxic T lymphocytes and NK cells, in general, also possess granules which are important for their cytotoxic function. In general, lymphocytes are involved in the *adaptive* response to inflammation, and the early events of inflammation are mediated in part by molecules produced by cells of the *innate* arm of the immune system.

Early phase mediators are produced by mast cells and platelets. They are especially important in acute inflammation and include mainly histamine, serotonin and other vasoactive substances. *Platelets may contribute to inflammatory responses resulting as a consequence of tissue injury, through a variety of mechanisms including:*

1. The release of vasoactive amines and other permeability factors,
2. The release of lysosomal enzymes,
3. The release of coagulation factors which lead to localized and generalized fibrin deposition, and
4. The formation of platelet aggregates or trombi which result in the blocking of vessels and capillaries.

To the early phase mediators also belong chemoatractants (*e.g.* C5a) and cytokines such as IL-1, IL-6, and TNF-α.

Late phase mediators are responsible for the regulation of vascular events occuring later - from about 6-12 hours after initiation of inflammation. The later vascular events are mediated, at least in part, by products of arachidonic acid.

The chemical mediators of inflammation. There is considerable functional redundancy of the mediators by inflammation. This explains why certain patients may have complete absence of a humoral component (*e.g.*, complement component C3), yet minimal problems with increased susceptibility to infection.

Table: Mediators of Inflammation.

Function	Mediators
Increased vascular permeability of small blood vessels	Histamine, serotonin, bradykinin, C3a, C5a, PGE_2, LTC4, LTD_4, prostacyclins, activated Hageman factor, high-molecular-weight kininogen fragments, fibrinopeptides
Vasoconstriction	TXA_2, LTB_4, LTC_4, LTD_4, C5a, N-formylpeptides
Smooth muscle contraction	C3a, C5a, Histamine, LTB_4, LTC_4, LTD_4, TXA_2, serotonin, PAF, bradykinin.
Increased endothelial cell stickiness	IL-1, TNF-α, MCP, endotoxin, LTB4,
Mast cell degranulation	C5a, C3a
Phagocytes	
Stem cell proliferation	IL-3, G-CSF, GM-CSF, M-CSF
Recruitment from bone narrow	CSFs, IL-1
Adherence/aggregation	iC3b, IgG, fibronectin, lectins
Chemotaxis	C5a, LTB_4, IL-8 and other chemokines, PAF, Histamine (for eosinophils), laminin, N-formyl peptides, collagen fragments, lymphocyte-derived chemotactic factor, fibrinopeptides
Lysosomal granule release	C5a, IL-8, PAF, most chemoattractants, phagocytosis
Production of reactive oxygen	C5a, TNF-α, PAF, IL-8, phagocytic particles; IFN-γ enhances.
phagocytosis	C3b, iC3b, IgG (Fc portion), Fibronectin; IFN-γ increases Fc receptor expression
Granuloma formation	IFN-γ, TNF-α, IL-1
Pyrogens	IL-1, TNF-α, PGE_2, IL-6
Pain	PGE_2, bradykinin.

Edema formation can be separated from phagocyte recruitment. Vasodilation in response to histamine, bradykinin, PGE_2 and PGI_2, and complement fragments C3a and C5a results from a direct action of these substances on endothelial cells and smooth muscle vasculature with resulting leakage of plasma. This is accompanied by release of mediators, such as C5a, LTB_4, and PAF, that act directly on the phagocytic cells. In addition N-formyl peptides are released from bacteria and mitochondria of damaged tissues. These mediators are potent chemoattractants that mobilize neutrophils, monocytes, and eosinophils, cause release of lysosomal contents, and activate the respiratory burst of the phagocytes with resulting production of toxic oxygen products.

Following intravenous endotoxin, a characteristic change in body temperature and white blood count is observed. The body temperature begins to increase after about one hour and reaches a maximum at about four hours. The leukocyte count shows a characteristic decrease at about 30 min, due to neutrophil and monocyte adherence to endothelial cells in the lung and spleen. This is followed by a leukocytosis characterized by the presence of immature neutrophils at about four hours, which can persist throughout 24 hr with gradual return to baseline by 48 hr. The leukocytosis is predominantly due to mobilization of immature neutrophils from the bone marrow. The critical components of the inflammatory response—fever, neutrophil margination in the circulary vessels, and then mobilization from the bone marrow—are associated with readily detected changes in circulating levels of certain mediators of inflammation. For example, TNF-α peaks within two hours and is likely the predominant pyrogen associated with the febrile response. Plasma levels of the chemoattractant IL-8 increase early and peak by four hours. Early increases in IL-8 may relate to the transient decrease in the neutrophil count at 30 min (margination).

Mediator accumulation at local inflammatory processes in skin blisters is somewhat different from the systemic effects following intravenous endotoxin. Mediators detected in blister fluid within 3 to 5 hr of the inflammatory response included LTB_4, C5a, IL-8 and IL-6. In contrast IL-1ß, GM-CSF, and TNF-α were not detected until after 8 hr in the blister. Thus the endotoxin and skin blister models of inflammation demonstrate that there are clear differences in the mediators that can be detected systemically and locally.

CHRONIC INFLAMMATION

If the condition causing acute inflammation is not resolved, the inflammation may pass to a longer term chronic phase. Also, some pathogies by their nature tend to directly provoke chronic rather than acute inflammation. Many of the features of acute inflammation continue as the inflammation becomes chronic, including increased blood flow and increased capillary permeability. Accumulation of white blood cells also continues, but the composition of the cells changes.

As the last page describes, neutrophils quickly enter the infected tissue, and these short-lived cells predominate initially. However, soon macrophages and lymphocytes begin to be recruited. The sequence by which they bind to cell adhesion molecules and pass through the endothelium is the same as for neutrophils. Thus, the primary cells of chronic inflammation are macrophages and lymphocytes.

Macrophages live far longer than neutrophils. As their name suggests, macrophages phagocytize pathogens and other material at the site of the inflammation. Because they are long-lived, indigestible material may remain inside macrophages in vesicles for long periods. As described previously, macrophages are important secretory cells releasing inflammatory paracrines, growth factors, and a variety of other proteins.

Macrophages are avid phagocytes, and, even if they can't digest all the material phagocytized, they will continue to engulf more. Here is a light micrograph of macrophages distended with lipid from broken down myelin at the site of necrotic tissue due to a blocked blood vessel in the brain. Observe the large amount of nearly clear cytoplasm.

Lymphocytes entering the inflammed tissue can serve several roles. Most notable, perhaps, are the T cells that activate macrophages. This is important for dealing with difficult pathogens. But this issue will arise most frequently in the context of autoimmune diseases, in which activated macrophages often are a major factor causing the damage. B cells making antibodies also can be present in inflammed tissue, adding antibodies locally to those that enter from the blood.

GRANULOMATOUS INFLAMMATION

In certain cases of chronic inflammation, macrophages collect in layers surrounding the problematical material. Sometimes the macrophages will fuse, forming giant cells. The structure so formed, with layers of macrophages surrounding a central core, is called a granuloma. Granulomas are a characteristic feature of a tuberculosis, in which macrophages can't destroy the phagocytized bacteria, apparently because the bacteria somehow prevent lysosomes from fusing with the phagocytic vesicles. What happens in chronic granulomatous disease?

WOUND HEALING

Wound healing is a complex process in which the skin, and the tissues under it, repair themselves after injury. In this chapter, wound healing is depicted in a discrete timeline of physical attributes (phases) constituting the post-trauma repairing process. In undamaged skin, the epidermis (surface layer) and dermis (deeper layer) form a protective barrier against the external environment. When the barrier is broken, a regulated sequence of biochemical events is set into motion to repair the damage. This process is divided into predictable phases: blood clotting (hemostasis), inflammation, tissue growth (proliferation), and tissue remodeling (maturation). Blood clotting may be considered to be part of the inflammation stage instead of a separate stage.

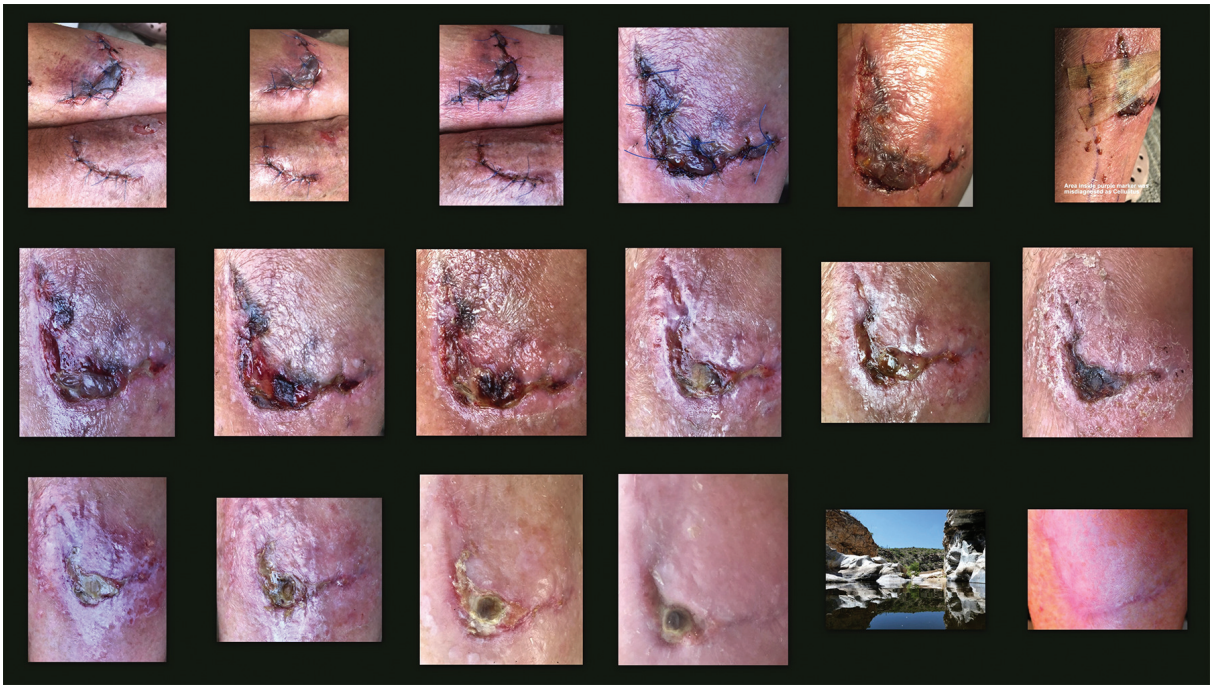

Fig. Deep wound on shin with stitches healing over five weeks.

The wound healing process is not only complex but also fragile, and it is susceptible to interruption or failure leading to the formation of non-healing chronic wounds. Factors that contribute to non-healing chronic wounds are diabetes, venous or arterial disease, infection, and metabolic deficiencies of old age.

Wound care encourages and speeds wound healing via cleaning and protection from reinjury or infection. Depending on each patient's needs, it can range from the simplest first aid to entire nursing specialties such as wound, ostomy, and continence nursing and burn centercare.

STAGES

- *Hemostasis (Blood Clotting):* Within the first few minutes of injury, platelets in the blood begin to stick to the injured site. This activates the platelets, causing a few things to happen. They change into an amorphous shape, more suitable for clotting, and they release chemical signals to promote clotting. This results in the activation of fibrin, which forms a mesh and acts as "glue" to bind platelets to each other. This makes a clot that serves to plug the break in the blood vessel, slowing/preventing further bleeding.
- *Inflammation:* During this phase, damaged and dead cells are cleared out, along with bacteria and other pathogens or debris. This happens through the process of phagocytosis, where white blood cells "eat" debris by engulfing it. Platelet-derived growth factors are released into the wound that cause the migration and division of cells during the proliferative phase.
- *Proliferation (Growth of New Tissue):* In this phase, angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction occur. In angiogenesis, vascular endothelial cells form new blood vessels. In fibroplasia and granulation tissue formation, fibroblasts grow and form a new, provisional extracellular matrix(ECM) by excreting collagen and fibronectin. Concurrently, re-epithelialization of the epidermis occurs, in which epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue. In wound contraction, myofibroblasts decrease the size of the wound by gripping the wound edges and contracting using a mechanism that resembles that in smooth muscle cells. When the cells' roles are close to complete, unneeded cells undergo apoptosis.

- *Maturation (Remodeling):* During maturation and remodeling, collagen is realigned along tension lines, and cells that are no longer needed are removed by programmed cell death, or apoptosis.

Timing and Reepithelialization

Timing is important to wound healing. Critically, the timing of wound reepithelialization can decide the outcome of the healing. If the epithelization of tissue over a denuded area is slow, a scar will form over many weeks, or months; If the epithelization of a wounded area is fast, the healing will result in regeneration.

EARLY VS CELLULAR PHASE

Wound healing is classically divided into hemostasis, inflammation, proliferation, and remodeling. Although a useful construct, this model employs considerable overlapping among individual phases. A complementary model has recently been described where the many elements of wound healing are more clearly delineated. The importance of this new model becomes more apparent through its utility in the fields of regenerative medicine and tissue engineering. In this construct, the process of wound healing is divided into two major phases: the *early phase* and the *cellular phase*:

The early phase, which begins immediately following skin injury, involves cascading molecular and cellular events leading to hemostasis and formation of an early, makeshift extracellular matrix that provides structural staging for cellular attachment and subsequent cellular proliferation.

The cellular phase involves several types of cells working together to mount an inflammatory response, synthesize granulation tissue, and restore the epithelial layer. Subdivisions of the cellular phase are: Macrophages and inflammatory components (within 1–2 days), Epithelial-mesenchymal interaction: re-epithelialization (phenotype change within hours, migration begins on day 1 or 2), Fibroblasts and myofibroblasts: progressive alignment, collagen production, and matrix contraction (between day 4 and day 14), Endothelial cells and angiogenesis (begins on day 4), Dermal matrix: elements of fabrication (begins on day 4, lasting 2 weeks) and alteration/remodeling (begins after week 2, lasting weeks to months—depending on wound size).

INFLAMMATORY PHASE

Just before the inflammatory phase is initiated, the clotting cascade occurs in order to achieve hemostasis, or stop blood loss by way of a fibrin clot. Thereafter, various soluble factors (including chemokines and cytokines) are released to attract cells that phagocytise debris, bacteria, and damaged tissue, in addition to releasing signaling molecules that initiate the proliferative phase of wound healing.

Clotting Cascade

When tissue is first wounded, blood comes in contact with collagen, triggering blood platelets to begin secreting inflammatory factors. Platelets also express sticky glycoproteinson their cell membranes that allow them to aggregate, forming a mass. Fibrin and fibronectin cross-link together and form a plug that traps proteins and particles and prevents further blood loss. This fibrin-fibronectin plug is also the main structural support for the wound until collagen is deposited. Migratory cells use this plug as a matrix to crawl across, and platelets adhere to it and secrete factors. The clot is eventually lysed and replaced with granulation tissue and then later with collagen.

Platelets, the cells present in the highest numbers shortly after a wound occurs, release mediators into the blood, including cytokines and growth factors. Growth factors stimulate cells to speed their rate of division. Platelets release other proinflammatory factors like serotonin, bradykinin, prostaglandins, prostacyclins, thromboxane, and histamine, which serve several purposes, including increasing cell proliferation and migration to the area and causing blood vessels to become dilated and porous. In many ways, extravasated platelets in

trauma perform a similar function to tissue macrophages and mast cells exposed to microbial molecular signatures in infection: they become activated, and secrete molecular mediators – vasoactive amines, eicosanoids, and cytokines – that initiate the inflammatory process.

Vasoconstriction and Vasodilation

Immediately after a blood vessel is breached, ruptured cell membranes release inflammatory factors like thromboxanes and prostaglandins that cause the vessel to spasm to prevent blood loss and to collect inflammatory cells and factors in the area. This vasoconstriction lasts five to ten minutes and is followed by vasodilation, a widening of blood vessels, which peaks at about 20 minutes post-wounding. Vasodilation is the end result of factors released by platelets and other cells. The main factor involved in causing vasodilation is histamine. Histamine also causes blood vessels to become porous, allowing the tissue to become edematous because proteins from the bloodstream leak into the extravascular space, which increases its osmolar load and draws water into the area. Increased porosity of blood vessels also facilitates the entry of inflammatory cells like leukocytes into the wound site from the bloodstream.

Polymorphonuclear Neutrophils

Within an hour of wounding, polymorphonuclear neutrophils (PMNs) arrive at the wound site and become the predominant cells in the wound for the first two days after the injury occurs, with especially high numbers on the second day. They are attracted to the site by fibronectin, growth factors, and substances such as kinins. Neutrophils phagocytise debris and kill bacteria by releasing free radicals in what is called a 'respiratory burst. They also cleanse the wound by secreting proteases that break down damaged tissue. Functional neutrophils at the wound site only have life-spans of around 2 days, so they usually undergo apoptosis once they have completed their tasks and are engulfed and degraded by macrophages. Other leukocytes to enter the area include helper T cells, which secrete cytokines to cause more T cells to divide and to increase inflammation and enhance vasodilation and vessel permeability. T cells also increase the activity of macrophages.

Macrophages

One of the macrophage's roles is to phagocytize other expended phagocytes, bacteria and damaged tissue, and they also debride damaged tissue by releasing proteases. Macrophages function in regeneration and are essential for wound healing. They are stimulated by the low oxygen content of their surroundings to produce factors that induce and speed angiogenesis and they also stimulate cells that reepithelialize the wound, create granulation tissue, and lay down a new extracellular matrix. By secreting these factors, macrophages contribute to pushing the wound healing process into the next phase. They replace PMNs as the predominant cells in the wound by two days after injury.

The spleen contains half the body's monocytes in reserve ready to be deployed to injured tissue. Attracted to the wound site by growth factors released by platelets and other cells, monocytes from the bloodstream enter the area through blood vessel walls. Numbers of monocytes in the wound peak one to one and a half days after the injury occurs. Once they are in the wound site, monocytes mature into macrophages. Macrophages also secrete a number of factors such as growth factors and other cytokines, especially during the third and fourth post-wounding days. These factors attract cells involved in the proliferation stage of healing to the area.

In wound healing that result in incomplete repair, scar contraction occurs, bringing varying gradations of structural imperfections, deformities and problems with flexibility. Macrophages may restrain the contraction phase. Scientists have reported that removing the macrophages from a salamander resulted in failure of a typical regeneration response (limb regeneration), instead bringing on a repair (scarring) response.

Decline of Inflammatory Phase

As inflammation dies down, fewer inflammatory factors are secreted, existing ones are broken down, and numbers of neutrophils and macrophages are reduced at the wound site. These changes indicate that the inflammatory phase is ending and the proliferative phase is underway. In vitro evidence, obtained using the dermal equivalent model, suggests that the presence of macrophages actually delays wound contraction and thus the disappearance of macrophages from the wound may be essential for subsequent phases to occur.

Because inflammation plays roles in fighting infection, clearing debris and inducing the proliferation phase, it is a necessary part of healing. However, inflammation can lead to tissuedamage if it lasts too long. Thus the reduction of inflammation is frequently a goal in therapeutic settings. Inflammation lasts as long as there is debris in the wound. Thus, if the individual's immune system is compromised and is unable to clear the debris from the wound and/or if excessive detritus, devitalized tissue, or microbial biofilm is present in the wound, these factors may cause a prolonged inflammatory phase and prevent the wound from properly commencing the proliferation phase of healing. This can lead to a chronic wound.

PROLIFERATIVE PHASE

About two or three days after the wound occurs, fibroblasts begin to enter the wound site, marking the onset of the proliferative phase even before the inflammatory phase has ended. As in the other phases of wound healing, steps in the proliferative phase do not occur in a series but rather partially overlap in time.

Angiogenesis

Also called neovascularization, the process of angiogenesis occurs concurrently with fibroblast proliferation when endothelial cells migrate to the area of the wound. Because the activity of fibroblasts and epithelial cells requires oxygen and nutrients, angiogenesis is imperative for other stages in wound healing, like epidermal and fibroblast migration. The tissue in which angiogenesis has occurred typically looks red (is erythematous) due to the presence of capillaries.

Angiogenesis Occurs in Overlapping Phases in Response to Inflammation:

1. *Latent Period:* During the haemostatic and inflammatory phase of the wound healing process, vasodilation and permeabilisation allow leukocyte extravasation and phagocytic debridement and decontamination of the wound area. Tissue swelling aids later angiogenesis by expanding and loosening the existing collagenous extracellular matrix.
2. *Endothelial Activation:* As the wound macrophages switches from inflammatory to healing mode, it begins to secrete endothelial chemotactic and growth factors to attract adjacent endothelial cells. Activated endothelial cells respond by retracting and reducing cell junctions, loosening themselves from their embedded endothelium. Characteristically the activated endothelial cells show enlarged nucleoli.
3. *Degradation of Endothelial Basement Membrane:* The wound macrophages, mast cells and the endothelial cells themselves secrete proteases to break down existing vascular basal lamina.
4. *Vascular Sprouting:* With the breakdown of endothelial basement membrane, detached endothelial cells from pre-existing capillaries and post-capillary venules can divide and migrate chemotactically towards the wound, laying down new vessels in the process. Vascular sprouting can be aided by ambient hypoxia and acidosis in the wound environment, as hypoxia stimulates the endothelial transcription factor, hypoxia inducible factor (HIF) to transactivate angiogenic genes such as VEGF and GLUT1. Sprouted vessels can self-organise into luminal morphologies, and fusion of blind channels give rise to new capillary networks.

5. *Vascular Maturation:* The endothelium of vessels mature by laying down new endothelial extracellular matrix, followed by basal lamina formation. Lastly the vessel establishes a pericyte layer.

Stem cells of endothelial cells, originating from parts of uninjured blood vessels, develop pseudopodia and push through the ECM into the wound site to establish new blood vessels.

Endothelial cells are attracted to the wound area by fibronectin found on the fibrin scab and chemotactically by angiogenic factors released by other cells, *e.g.* from macrophages and platelets when in a low-oxygen environment. Endothelial growth and proliferation is also directly stimulated by hypoxia, and presence of lactic acid in the wound. For example, hypoxia stimulates the endothelial transcription factor, hypoxia-inducible factor (HIF) to transactivate a set of proliferative genes including vascular endothelial growth factor (VEGF) and glucose transporter 1 (GLUT1).

To migrate, endothelial cells need collagenases and plasminogen activator to degrade the clot and part of the ECM. Zinc-dependent metalloproteinases digest basement membrane and ECM to allow cell migration, proliferation and angiogenesis.

When macrophages and other growth factor-producing cells are no longer in a hypoxic, lactic acid-filled environment, they stop producing angiogenic factors. Thus, when tissue is adequately perfused, migration and proliferation of endothelial cells is reduced. Eventually blood vessels that are no longer needed die by apoptosis.

Fibroplasia and Granulation Tissue Formation

Simultaneously with angiogenesis, fibroblasts begin accumulating in the wound site. Fibroblasts begin entering the wound site two to five days after wounding as the inflammatory phase is ending, and their numbers peak at one to two weeks post-wounding. By the end of the first week, fibroblasts are the main cells in the wound. Fibroplasia ends two to four weeks after wounding.

As a model the mechanism of fibroplasia may be conceptualised as an analogous process to angiogenesis-only the cell type involved is fibroblasts rather than endothelial cells. Initially there is a latent phase where the wound undergoes plasma exudation, inflammatory decontamination and debridement. Oedema increases the wound histologic accessibility for later fibroplastic migration. Second, as inflammation nears completion, macrophage and mast cells release fibroblast growth and chemotactic factors to activate fibroblasts from adjacent tissue. Fibroblasts at this stage loosen themselves from surrounding cells and ECM. Phagocytes further release proteases that break down the ECM of neighbouring tissue, freeing the activated fibroblasts to proliferate and migrate towards the wound. The difference between vascular sprouting and fibroblast proliferation is that the former is enhanced by hypoxia, whilst the latter is inhibited by hypoxia. The deposited fibroblastic connective tissue matures by secreting ECM into the extracellular space, forming granulation tissue. Lastly collagen is deposited into the ECM.

In the first two or three days after injury, fibroblasts mainly migrate and proliferate, while later, they are the main cells that lay down the collagen matrix in the wound site. Origins of these fibroblasts are thought to be from the adjacent uninjured cutaneous tissue (although new evidence suggests that some are derived from blood-borne, circulating adult stem cells/precursors). Initially fibroblasts utilize the fibrin cross-linking fibres (well-formed by the end of the inflammatory phase) to migrate across the wound, subsequently adhering to fibronectin. Fibroblasts then deposit ground substance into the wound bed, and later collagen, which they can adhere to for migration.

Granulation tissue functions as rudimentary tissue, and begins to appear in the wound already during the inflammatory phase, two to five days post wounding, and continues growing until the wound bed is covered. Granulation tissue consists of new blood vessels, fibroblasts, inflammatory cells, endothelial cells, myofibroblasts, and the components of a new, provisional extracellular matrix (ECM). The provisional ECM is different in composition from the ECM in normal tissue and its components originate from fibroblasts. Such components

include fibronectin, collagen, glycosaminoglycans, elastin, glycoproteins and proteoglycans. Its main components are fibronectin and hyaluronan, which create a very hydrated matrix and facilitate cell migration. Later this provisional matrix is replaced with an ECM that more closely resembles that found in non-injured tissue.

Growth factors (PDGF, TGF-β) and fibronectin encourage proliferation, migration to the wound bed, and production of ECM molecules by fibroblasts. Fibroblasts also secrete growth factors that attract epithelial cells to the wound site. Hypoxia also contributes to fibroblast proliferation and excretion of growth factors, though too little oxygen will inhibit their growth and deposition of ECM components, and can lead to excessive, fibrotic scarring.

Collagen Deposition

One of fibroblasts' most important duties is the production of collagen. Collagen deposition is important because it increases the strength of the wound; before it is laid down, the only thing holding the wound closed is the fibrin-fibronectin clot, which does not provide much resistance to traumatic injury. Also, cells involved in inflammation, angiogenesis, and connective tissue construction attach to, grow and differentiate on the collagen matrix laid down by fibroblasts.

Type III collagen and fibronectin generally begin to be produced in appreciable amounts at somewhere between approximately 10 hours and 3 days, depending mainly on wound size. Their deposition peaks at one to three weeks. They are the predominating tensile substances until the later phase of maturation, in which they are replaced by the stronger type I collagen.

Even as fibroblasts are producing new collagen, collagenases and other factors degrade it. Shortly after wounding, synthesis exceeds degradation so collagen levels in the wound rise, but later production and degradation become equal so there is no net collagen gain. This homeostasis signals the onset of the later maturation phase. Granulation gradually ceases and fibroblasts decrease in number in the wound once their work is done. At the end of the granulation phase, fibroblasts begin to commit apoptosis, converting granulation tissue from an environment rich in cells to one that consists mainly of collagen.

Epithelialization

The formation of granulation tissue into an open wound allows the reepithelialization phase to take place, as epithelial cells migrate across the new tissue to form a barrier between the wound and the environment. Basal keratinocytes from the wound edges and dermal appendages such as hair follicles, sweat glands and sebacious (oil) glands are the main cells responsible for the epithelialization phase of wound healing. They advance in a sheet across the wound site and proliferate at its edges, ceasing movement when they meet in the middle. In healing that results in a scar, sweat glands, hair follicles and nerves do not form. With the lack of hair follicles, nerves and sweat glands, the wound, and the resulting healing scar, provide a challenge to the body with regards to temperature control.

Keratinocytes migrate without first proliferating. Migration can begin as early as a few hours after wounding. However, epithelial cells require viable tissue to migrate across, so if the wound is deep it must first be filled with granulation tissue. Thus the time of onset of migration is variable and may occur about one day after wounding. Cells on the wound margins proliferate on the second and third day post-wounding in order to provide more cells for migration.

If the basement membrane is not breached, epithelial cells are replaced within three days by division and upward migration of cells in the stratum basale in the same fashion that occurs in uninjured skin. However, if the basement membrane is ruined at the wound site, reepithelization must occur from the wound margins and from skin appendages such as hair follicles and sweat and oil glands that enter the dermis that are lined with viable keratinocytes. If the wound is very deep, skin appendages may also be ruined and migration can only occur from wound edges.

Migration of keratinocytes over the wound site is stimulated by lack of contact inhibition and by chemicals such as nitric oxide. Before they begin to migrate, cells must dissolve their desmosomes and hemidesmosomes, which normally anchor the cells by intermediate filaments in their cytoskeleton to other cells and to the ECM. Transmembrane receptorproteins called integrins, which are made of glycoproteins and normally anchor the cell to the basement membrane by its cytoskeleton, are released from the cell's intermediate filaments and relocate to actin filaments to serve as attachments to the ECM for pseudopodia during migration. Thus keratinocytes detach from the basement membrane and are able to enter the wound bed.

Before they begin migrating, keratinocytes change shape, becoming longer and flatter and extending cellular processes like lamellipodia and wide processes that look like ruffles. Actin filaments and pseudopodia form. During migration, integrins on the pseudopod attach to the ECM, and the actin filaments in the projection pull the cell along. The interaction with molecules in the ECM through integrins further promotes the formation of actin filaments, lamellipodia, and filopodia.

Epithelial cells climb over one another in order to migrate. This growing sheet of epithelial cells is often called the epithelial tongue. The first cells to attach to the basement membrane form the stratum basale. These basal cells continue to migrate across the wound bed, and epithelial cells above them slide along as well. The more quickly this migration occurs, the less of a scar there will be.

Fibrin, collagen, and fibronectin in the ECM may further signal cells to divide and migrate. Like fibroblasts, migrating keratinocytes use the fibronectin cross-linked with fibrin that was deposited in inflammation as an attachment site to crawl across.

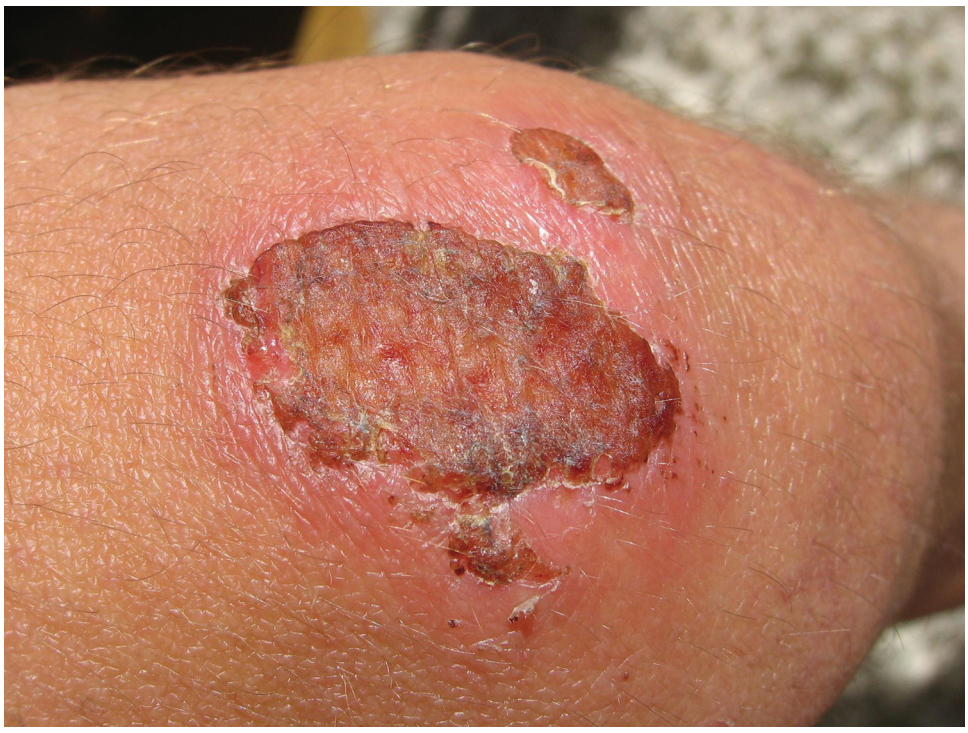

Fig. A Scab Covering a Healing Wound.

As keratinocytes migrate, they move over granulation tissue but stay underneath the scab, thereby separating the scab from the underlying tissue. Scabs are formed on locations that are exposed to harmful UVR and the main biological function of human wound scabs is to inhibit the exposure to UVR, thus protecting otherwise exposed cells in a wound from UVR-induced DNA damage. Epithelial cells have the ability to phagocytize debris such as dead tissue and bacterial matter that would otherwise obstruct their path. Because they must dissolve any scab that forms, keratinocyte migration is best enhanced by a moist environment, since a dry one

leads to formation of a bigger, tougher scab. To make their way along the tissue, keratinocytes must dissolve the clot, debris, and parts of the ECM in order to get through. They secrete plasminogen activator, which activates plasminogen, turning it into plasmin to dissolve the scab. Cells can only migrate over living tissue, so they must excrete collagenases and proteases like matrix metalloproteinases(MMPs) to dissolve damaged parts of the ECM in their way, particularly at the front of the migrating sheet. Keratinocytes also dissolve the basement membrane, using instead the new ECM laid down by fibroblasts to crawl across.

As keratinocytes continue migrating, new epithelial cells must be formed at the wound edges to replace them and to provide more cells for the advancing sheet. Proliferation behind migrating keratinocytes normally begins a few days after wounding and occurs at a rate that is 17 times higher in this stage of epithelialization than in normal tissues. Until the entire wound area is resurfaced, the only epithelial cells to proliferate are at the wound edges.

Growth factors, stimulated by integrins and MMPs, cause cells to proliferate at the wound edges. Keratinocytes themselves also produce and secrete factors, including growth factors and basement membrane proteins, which aid both in epithelialization and in other phases of healing. Growth factors are also important for the innate immune defence of skin wounds by stimulation of the production of antimicrobial peptides and neutrophil chemotactic cytokines in keratinocytes.

Keratinocytes continue migrating across the wound bed until cells from either side meet in the middle, at which point contact inhibition causes them to stop migrating. When they have finished migrating, the keratinocytes secrete the proteins that form the new basement membrane. Cells reverse the morphological changes they underwent in order to begin migrating; they reestablish desmosomes and hemidesmosomes and become anchored once again to the basement membrane. Basal cells begin to divide and differentiate in the same manner as they do in normal skin to reestablish the strata found in reepithelialized skin.

Contraction

Contraction is a key phase of wound healing with repair. If contraction continues for too long, it can lead to disfigurement and loss of function. Thus there is a great interest in understanding the biology of wound contraction, which can be modelled in vitro using the collagen gel contraction assay or the dermal equivalent model.

Contraction commences approximately a week after wounding, when fibroblasts have differentiated into myofibroblasts. In full thickness wounds, contraction peaks at 5 to 15 days post wounding. Contraction can last for several weeks and continues even after the wound is completely reepithelialized. A large wound can become 40 to 80% smaller after contraction. Wounds can contract at a speed of up to 0.75 mm per day, depending on how loose the tissue in the wounded area is. Contraction usually does not occur symmetrically; rather most wounds have an ‘axis of contraction’ which allows for greater organization and alignment of cells with collagen.

At first, contraction occurs without myofibroblast involvement. Later, fibroblasts, stimulated by growth factors, differentiate into myofibroblasts. Myofibroblasts, which are similar to smooth muscle cells, are responsible for contraction. Myofibroblasts contain the same kind of actin as that found in smooth muscle cells.

Myofibroblasts are attracted by fibronectin and growth factors and they move along fibronectin linked to fibrin in the provisional ECM in order to reach the wound edges. They form connections to the ECM at the wound edges, and they attach to each other and to the wound edges by desmosomes. Also, at an adhesion called the fibronexus, actin in the myofibroblast is linked across the cell membrane to molecules in the extracellular matrix like fibronectin and collagen. Myofibroblasts have many such adhesions, which allow them to pull the ECM when they contract, reducing the wound size. In this part of contraction, closure occurs more quickly than in the first, myofibroblast-independent part.

As the actin in myofibroblasts contracts, the wound edges are pulled together. Fibroblasts lay down collagen to reinforce the wound as myofibroblasts contract. The contraction stage in proliferation ends as myofibroblasts

stop contracting and commit apoptosis. The breakdown of the provisional matrix leads to a decrease in hyaluronic acid and an increase in chondroitin sulfate, which gradually triggers fibroblasts to stop migrating and proliferating. These events signal the onset of the maturation stage of wound healing.

MATURATION AND REMODELING

When the levels of collagen production and degradation equalize, the maturation phase of tissue repair is said to have begun. During maturation, type III collagen, which is prevalent during proliferation, is replaced by type I collagen. Originally disorganized collagen fibres are rearranged, cross-linked, and aligned along tension lines. The onset of the maturation phase may vary extensively, depending on the size of the wound and whether it was initially closed or left open, ranging from approximately 3 days to 3 weeks. The maturation phase can last for a year or longer, similarly depending on wound type.

As the phase progresses, the tensile strength of the wound increases. Collagen will reach approximately 20% of its tensile strength after 3 weeks, increasing to 80% by 12th week. The maximum scar strength is 80% of that of unwounded skin. Since activity at the wound site is reduced, the scar loses its red appearance as blood vessels that are no longer needed are removed by apoptosis.

The phases of wound healing normally progress in a predictable, timely manner; if they do not, healing may progress inappropriately to either a chronic wound such as a venous ulcer or pathological scarring such as a keloid scar.

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Immunopathology

Immunopathology is a branch of medicine that deals with immune responses associated with disease. It includes the study of the pathology of an organism, organ system, or disease with respect to the immune system, immunity, and immune responses. In biology, it refers to damage caused to an organism by its own immune response, as a result of an infection. It could be due to mismatch between pathogen and host species, and often occurs when an animal pathogen infects a human (*e.g.* avian flu leads to a cytokine storm which contributes to the increased mortality rate).

When a foreign antigen enters the body, there is either an antigen specific or non-specific response to it. These responses are the immune system fighting off the foreign antigens, whether they are deadly or not. Immunopathology could refer to how the foreign antigens cause the immune system to have a response or problems that can arise from an organism's own immune response on itself. There are certain problems or faults in the immune system that can lead to more serious illness or disease. These diseases can come from one of the following problems. The first would be Hypersensitivity reactions, where there would be a stronger immune response than normal. There are four different types (type one, two, three and four), all with varying types and degrees of an immune response.

The problems that arise from each type vary from small allergic reactions to more serious illnesses such as tuberculosis or arthritis. The second kind of complication in the immune system is Autoimmunity, where the immune system would attack itself rather than the antigen. Inflammation is a prime example of autoimmunity, as the immune cells used are self-reactive. A few examples of autoimmune diseases are Type 1 diabetes, Addison's disease and Celiac disease. The third and final type of complication with the immune system is Immunodeficiency, where the immune system lacks the ability to fight off a certain disease. The immune system's ability to combat it is either hindered or completely absent. The two types are Primary Immunodeficiency, where the immune system is either missing a key component or does not function properly, and Secondary Immunodeficiency, where disease is obtained from an outside source, like radiation or heat, and therefore cannot function properly. Diseases that can cause immunodeficiency include HIV, AIDS and leukemia.

In all vertebrates, there are two different kinds of immune responses: Innate and Adaptive immunity. Innate immunity is used to fight off non-changing antigens and is therefore considered non-specific. It is usually a more immediate response than the adaptive immune system, usually responding within minutes to hours. It is composed of physical blockades such as the skin, but also contains non-specific immune cells such as dendritic cells, macrophages, and basophils. The second form of immunity is Adaptive immunity. This form of immunity requires recognition of the foreign antigen before a response is produced. Once the antigen is recognized, a specific response is produced in order to destroy the specific antigen.

Because of this idea, adaptive immunity is considered to be specific immunity. A key part of adaptive immunity that separates it from innate is the use of memory to combat the antigen in the future. When the antigen is originally introduced, the organism does not have any receptors for the antigen so it must generate them from

the first time the antigen is present. The immune system then builds a memory of that antigen, which enables it to recognize the antigen quicker in the future and be able to combat it quicker and more efficiently. The more the system is exposed to the antigen, the quicker it will build up its responsiveness.

EXPECTED SYMPTOMS OF IMMUNOPATHOLOGY

When bacteria are killed, endotoxins and cytokines are released at the site of the infection. This contributes to a sense that one's original disease is getting worse. In fact, the increase in symptoms is only temporary. Although these symptoms may be similar to one's disease, unlike disease symptoms, they are a sign that something is being accomplished: the Th1 pathogens are being killed.

The immunopathological reaction is caused by release of toxins and the apoptosis (die off) of infected cells. People with effective detoxification and elimination systems may not experience significant aggravation of symptoms. Some of my patients just experience gradual improvement in health. Others experience mild loss of stamina, periodic night sweats or emotional swings.

I firmly believe that Th1 patients no matter what their diagnosis react similarly.

I would suggest evaluating present condition with that which was present prior to starting the MP. Most patients with a diagnosis of borrelia have significant physical or cognitive loss and have received other therapies prior to them starting the MP. Some of these therapies can result in delayed or reduced immunopathological reactions. *—Greg Blaney, MD*

As evidenced by high rates of depression and anxiety in the population at large, the brain itself is a frequent site of chronic bacterial infection. One of the challenges of having neurological immunopathology is a lack of awareness about the role infection and immunopathology play in one's mood, cognitive abilities, and ability to think clearly. It is very common for patients with neurological immunopathology not to recognize that their recovery will involve the temporary exacerbation of these types of symptoms. One's life events play a role in, say, depression, but often enough they are not the driving force behind it.

Along with neurological immunopathology, cardiac immunopathology and respiratory immunopathology are potentially life-threatening. Patients who have, or worry that they may have, these symptoms should work particularly closely with their physician and proceed on the MP cautiously.

UNEXPECTED SYMPTOMS OF IMMUNOPATHOLOGY

The MP can't create new inflammation because it can't make bacteria appear where there weren't any before. The presence of new symptoms is a clear indication that bacteria are being targeted in areas of the body not known to be infected. In the absence of undergoing some kind of curative therapy like the MP, it seems probable that these sites of sub-clinical infection would in time be part of the disease process.

If extra Benicar reduces a symptom, one can be sure it is due to immunopathology. But, lack of response to Benicar does not rule out immunopathology. Palliative medication may reduce symptoms of immunopathology also.

NECESSITY OF IMMUNOPATHOLOGY

Immunopathology is not a "side effect" of the MP – not in the traditional sense anyway. Also, the MP does not "cause" an exacerbation of disease symptoms. Patients are hardwired to equate symptoms with disease, but what many do not realize is that all disease symptoms are the result of an immune system response.

A rise in intensity of symptoms is not a sign that the disease process is advancing, but an indication that the immune system is active and killing bacteria. If a person gets infected with a virus, the rise in symptoms he or she displays is not caused by the virus, but the response of the immune system to the virus. The symptoms of

food poisoning including diarrhea and vomiting are very unpleasant, but are extremely effective in rapidly eliminating toxins. The Jarisch-Herxheimer response, a term which is sometimes used interchangeably with immunopathology, has been documented as necessary to recovery in over 10 diseases, to say nothing of evidence supporting the MP's effectiveness.

Based on everything we know about the way the bacteria have parasitized the immune system, and the way they affect the body's molecular chemistry, I am sad to say that it seems 'no pain, no gain.' I suspect we will find some palliative techniques as time goes by, especially for pain, but the starting point is relatively unpalatable, I am afraid. This is, of course, one of the reasons why nobody has been able to develop a therapy until now. Until you understand the pathogenesis, there is no way that 'no pain, no gain' makes any sense. But when you understand how the bugs are wreaking their havoc - it all becomes crystal clear. *—Trevor Marshall, PhD*

A potent anti-inflammatory, Benicar should palliate negative symptoms and minimize any tissue damage caused by the disease process.

ASSESSING IMMUNOPATHOLOGY

Immunopathology is necessary for making progress on the MP. Throughout the course of one's treatment, the goal is to generate a tolerable level of immunopathology. But how does one determine if immunopathology is tolerable or intolerable?

USING LAB TESTS TO TRACK IMMUNOPATHOLOGY

With chronically ill patients, it is common to disassociate from one's feelings and therefore it can be difficult to determine the sometimes subtle shifts associated with Herx reactions…. My use of lab tests is to help determine pace of therapy especially if degree of Herx reaction is difficult for patient to interpret. *—Greg Blaney, MD*

Abnormal lab work or ECG tracing may reveal unacceptable "silent" immunopathology. In that case, monitor these signs regularly and use them as a guide to gauge pace of therapy.

Other Ways to Assess Immunopathology

Even for diseases that have ideal measures for tracking immunopathology, it is sometimes possible to have a flare in symptoms and not know why. This is particularly true for patients whose diseases have a strong mental component and have trouble thinking critically about their illness. Sometimes the onset of uncomfortable symptoms simply cannot be explained, only managed. Other times though, it is a factor within a patient's control. These questions might help patients gain insight into why they feel worse.

ORGANIZATION AND DEVELOPMENT OF THE IMMUNE SYSTEM

The immune system is a wonderful collaboration between cells and proteins that work together to provide defence against infection. These cells and proteins do not form a single organ like the heart or liver. Instead, the immune system is dispersed throughout the body to provide rapid responses to infection. Cells travel through the bloodstream or in specialized vessels called lymphatics. Lymph nodes and the spleen provide structures that facilitate cell-to-cell communication.

The bone marrow and thymus represent training grounds for two cells of the immune system (B-cells and T-cells, respectively). The development of all cells of the immune system begins in the bone marrow with a hematopoietic (blood-forming) stem cell. This cell is called a "stem" cell because all the other specialized cells arise from it. Because of its ability to generate an entire immune system, this is the cell that is most important in a bone marrow or hematopoietic stem cell transplant. It is related to embryonic stem cells, but is a distinct cell type. In most cases, development of one cell type is independent of the other cell types.

Primary immunodeficiencies can affect only a single component of the immune system or multiple cells and proteins. To better understand the immune deficiencies, this chapter will describe the organization and maturation of the immune system. Although all components of the immune system interact with each other, it is typical to consider two broad categories of immune responses: the innate immune system and the adaptive immune system.

Innate immune responses are those that rely on cells that require no additional "training" to do their jobs. These cells include neutrophils, monocytes, natural killer (NK) cells and a set of proteins termed the complement proteins. Innate responses to infection occur rapidly and reliably. Even infants have excellent innate immune responses.

Adaptive immune responses comprise the second category. These responses involve T-cells and B-cells, two cell types that require "training" or education to learn not to attack our own cells. The advantages of the adaptive responses are their long-lived memory and the ability to adapt to new germs.

Central to both categories of immune responses is the ability to distinguish foreign invaders (things that need to be attacked) from our own tissues, which need to be protected. Because of their ability to respond rapidly, the innate responses are usually the first to respond to an "invasion." This initial response serves to alert and trigger the adaptive response, which can take several days to fully activate. Early in life, the innate responses are most prominent. Newborn infants do have antibodies from their mother but do not make their own antibodies for several weeks.

The adaptive immune system is functional at birth, but it has not gained the experience necessary for optimal memory responses. Although this formation of memory occurs throughout life, the most rapid gain in immunologic experience is between birth and three years of age. Each infectious exposure leads to training of the cells so that a response to a second exposure to the same infection is more rapid and greater in magnitude.

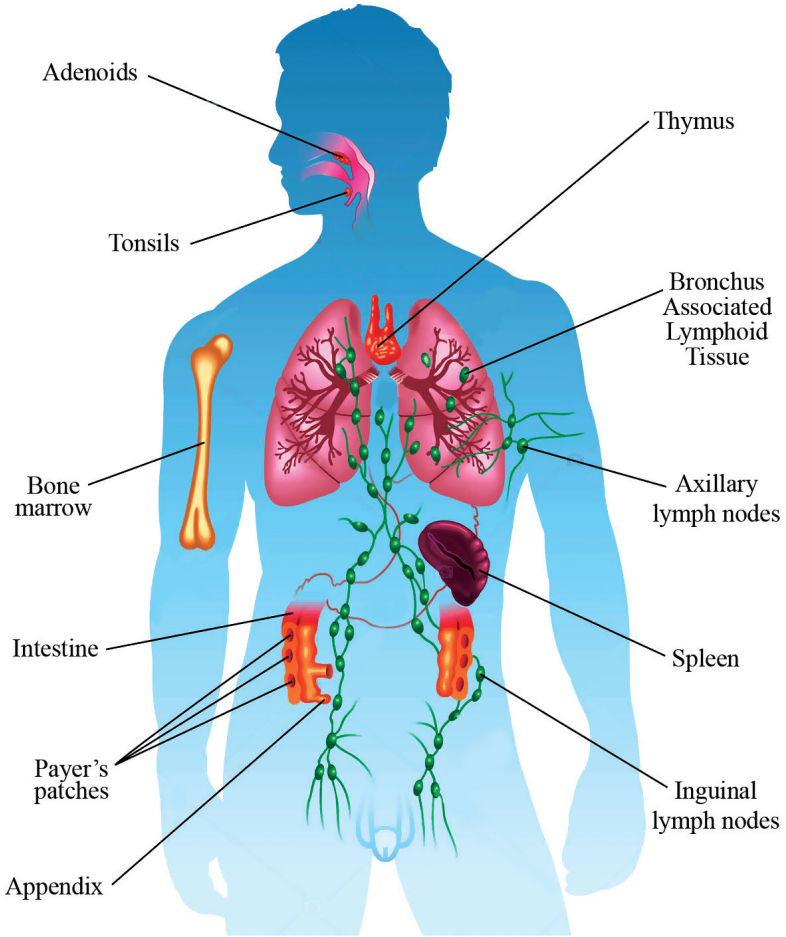


Fig. Major Organs of the Immune System.

Over the first few years of life, most children catch a wide variety of infections and produce antibodies directed at those specific infections. The cells producing the antibody "remember" the infection and provide long-lasting immunity to it. Similarly, T-cells can remember viruses that the body has encountered and can make a more vigous response when they encounter the same virus again. This rapid maturation of the adaptive immune system in early childhood makes testing young children a challenge since the expectations for what is normal change with age. In contrast to the adaptive immune system, the innate immune system is largely intact at birth.

A. *Thymus:* The thymus is an organ located in the upper chest. Immature lymphocytes leave the bone marrow and find their way to the thymus where they are "educated" to become mature T-lymphocytes.
B. *Liver:* The liver is the major organ responsible for synthesizing proteins of the complement system. In addition, it contains large numbers of phagocytic cells which ingest bacteria in the blood as it passes through the liver.
C. *Bone Marrow:* The bone marrow is the location where all cells of the immune system begin their development from primitive stem cells.
D. *Tonsils:* Tonsils are collections of lymphocytes in the throat.
E. *Lymph Nodes:* Lymph nodes are collections of B-lymphocytes and T-lymphocytes throughout the body. Cells congregate in lymph nodes to communicate with each other.
F. *Spleen:* The spleen is a collection of T-lymphocytes, B-lymphocytes and monocytes. It serves to filter the blood and provides a site for organisms and cells of the immune system to interact.
G. *Blood:* Blood is the circulatory system that carries cells and proteins of the immune system from one part of the body to another.

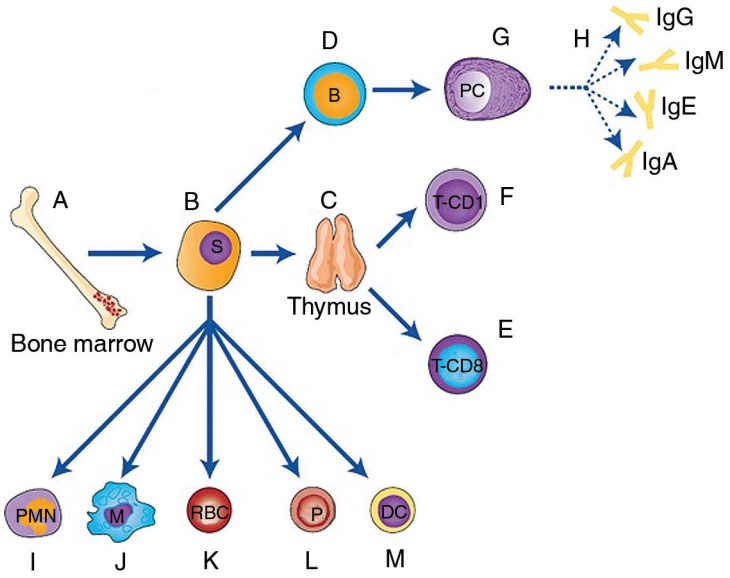


Fig. Cells of the Immune System.

A. *Bone Marrow:* The site in the body where most of the cells of the immune system are produced as immature or stem cells.
B. *Stem Cells:* These cells have the potential to differentiate and mature into the different cells of the immune system.
C. *Thymus:* An organ located in the chest which instructs immature lymphocytes to become mature T-lymphocytes.
D. *B-Cells:* These lymphocytes arise in the bone marrow and differentiate into plasma cells which in turn produce immunoglobulins (antibodies).

E. *Cytotoxic T-cells:* These lymphocytes mature in the thymus and are responsible for killing infected cells.
F. *Helper T-cells:* These specialized lymphocytes "help" other T-cells and B-cells to perform their functions.
G. *Plasma Cells:* These cells develop from B-cells and are the cells that make immunoglobulin for the serum and the secretions.
H. *Immunoglobulins:* These highly specialized protein molecules, also known as antibodies, fit foreign antigens, such as polio, like a lock and key. Their variety is so extensive that they can be produced to match all possible microorganisms in our environment.
I. *Neutrophils (Polymorphonuclear PMN Cell):* A type of cell found in the blood stream that rapidly ingests microorganisms and kills them.
J. *Monocytes:* A type of phagocytic cell found in the blood stream which develops into a macrophage when it migrates to tissues.
K. *Red Blood Cells:* The cells in the blood stream which carry oxygen from the lungs to the tissues.
L. *Platelets:* Small cells in the blood stream which are important in blood clotting.
M. *Dendritic Cells:* Important cells in presenting antigen to immune system cells.

COMPONENTS OF THE IMMUNE SYSTEM

Each major component of the immune system will be discussed separately below. Immune deficiencies can affect a single component or multiple components. The manifestations of immune deficiencies can be a single type of infection or a more global susceptibility to infection. Because of the many interactions between the cells and proteins of the immune system, some immune deficiencies can be associated with a very limited range of infections.

For these immune deficiencies, there are other elements that "take up the slack" and can compensate at least partly for the missing piece. In other cases, the ability to defend against infection is very weak over all and the person may have significant problems with infections.

The cells of the immune system can be categorized as lymphocytes (T-cells, B-cells and NK cells), neutrophils, and monocytes/macrophages. These are all types of white blood cells. The major proteins of the immune system are predominantly signaling proteins (often called cytokines), antibodies, and complement proteins.

CELLS OF THE IMMUNE SYSTEM

Macrophages are involved in both in vivo and in vitro immune responses, and have certain functional properties. In the process of Phagocytosis, macrophages function as effector cells as they recognize engulf, and destroy foreign (antigenic) substances. Macrophages are accessory cells in the immune response. They are the major antigen-presenting cells of the body that interact with antigen as a primary step in the induction of an immune response. B cells can also present antigen. Antigen presentation involved:

1. Binding and uptake of antigen by the macrophage surface membrane, which creates a tightly bound antigen that is more immunogenic than free antigen.
2. Processing and later re-expression of antigen on the antigen-presenting cell surface in association with MHC (class II)-encoded glycoproteins.
3. Release of soluble mediators, such as the monokine (macrophage-derived hormone) which stimulate the maturation and proliferation of T cells (the result of this sequence of events is the activation of antigen-specific B cells and T cells).

Lymphocytes are both precursor cells of immunologic function as well as regulators and effectors of immunity. Smaller lymphocytes (T cells) have a long life span of months or years, whereas larger lymphocytes (B cells)

have a shorter life span of 5 to 7 days. *A general method for detection and quantitation of T cells and B cells depends on the differential reactivity of the two cell types with appropriately prepared red blood cells.*

1. T cells accumulate sheep red blood cells (SRBCs) around their surfaces and form clusters referred to as erythrocyte (E) rosettes.
2. There is no such reaction between B cells and SRBCs, unless the red blood cells (indicated as E for erythrocytes) are coated with hemolysin-antibody (A) and special non-hemolytic preparations of guinea pig complement (C), thus called EAC rosettes.

T-LYMPHOCYTES

Surface Markers: CD1, CD3, and CD11 are found on most peripheral blood T cells. CD3 is associated with, but distinct from, the T-cell receptor for antigen; CD11, with the SRBC rosette receptor. CD4 is present on T helper cells, effector cells for delayed hypersensitivity, and CD2 cell inducers. CD8 is present on cytotoxic and T suppressor cells. CD10 is present on stem cells, some B cells, and activated peripheral blood T cells.

Subpopulations:

1. Effector T (Te) cells, also called T_{DTH} cells, are the peripheral lymphocytic cells responsible for delayed type hypersensitivity (DTH) reactions.
2. Cytotoxic T (Tc or CTL) cells are induced artificially by immunization with allogeneic tissue and naturally by tumors and virus. To be induced to the killer function, the precursor cells must be stimulated by antigen in association with class II MHC molecules.
3. Memory T (Tm) cells are induced during primary immunization; they recognize the specific antigen and participate in the anamnestic response.
4. Helper T (Th) cells are lymphocytes that recognize a specific antigen in association with a homologous class II MHC molecule and collaborate with B cells and macrophages in the induction of the humoral immune response. Similar cells collaborate with other T cells to facilitate the production of Te cells.
5. Suppressor T (Ts) cells are lymphocytes that recognize a specific antigen and interfere with the development of an immune response either directly or via suppressor factors. These cells may be involved in the prevention of Autoimmunity. Ts cell precursors are activated by antigens in association with a particular type of class II MHC molecule.

B-LYMPHOCYTES

Surface Markers

Surface immunoglobulin binds specific antigens and functions as an antigen recognition site that initiates the differentiation of the B cell, resulting in antibody synthesis. Contact between the antigen epitope and the immunoglobulin in the B-cell membrane triggers cell division. As this process continues, the B cell matures into a plasma cell with abundant rough endoplasmic reticulum, actively secreting large amounts of the antibody specifically reactive with its homologous epitope.

Subpopulations: B cells are divided into subpopulations according to the immunoglobulin class they synthesize: D, M, G, A, and E B-cells respectively.

IMMUNE CELLS ARE PRODUCED IN THE BONE MARROW

With regard to the cell cycle, tissues in higher animals can be divided into three types. The first type is tissue in which cells do not proliferate once the animal has reached maturity (*e.g.*, nerve cells). In the second type, the cells are normally in the G0 phase of the cell cycle and are resting but can proliferate if required (*e.g.*, hepatocytes).

The third type of tissue is that in which cells continue to replicate constantly (*e.g.*, epithelial cells). Cells involved in immune responses belong to the third group. They are produced in the bone marrow throughout an individual's life and are distributed within the body as they differentiate. Bone marrow cells that can differentiate into all types of blood and immune cells are called hematopoietic stem cells. These cells enter the circulation after differentiating into erythrocytes, platelets, leukocytesand other cells.

Leukocytes include neutrophils (whose main function is to ingest bacteria), eosinophils, and basophils. Eosinophils and basophils are related to the elimination of parasites. Together with macrophages, which are created through the differentiation of monocytes in the blood, all of these cells are involved in innate immunity and inflammation. However, they also play the role of effectors in acquired immune response. Natural killer cells, which are a type of lymphocyte lacking T cell receptors and immunoglobulins, also act as effectors in acquired immune response.

Table: Major Immune Cells.

Immune cell			Function
Leukocyte	Lymphocyte	T cell — Helper T cell	Acquired immune response regulation
		Killer T cell	Destruction of target cell (cell damage)
		B cell — Plasma cell	Production of immunoglobulin
		NK cell	Destruction of target cell (cell damage)
	Dendritic cell		Predation, antigen presentation
	Macrophage		Predation, antigen presentation
	Neutrophil		Bacteria predation
	Eosinophil		Elimination predation
	Basophil		Elimination predation
	Mast cell		Evocation of type I allergy

Dendritic cells sense and capture foreign microorganisms, allergens, and denatured self-components; they subsequently process these proteins and present them to T cells. Dendritic cells play a critical role in initiating the acquired immune response. Dendritic cells are a diverse group of cells derived from the bone marrow and are formed via multiple pathways.

Among lymphocytes, the T and B cells are mainly responsible for acquired immunity. These lymphocytes have T cell receptors and immunoglobulin respectively on their cell surfaces, which specifically bind to specific antigens. T cell receptor and immunoglobulin genes are recombined during proliferation and differentiation of these cells that take place in the thymus and bone marrow respectively. Through genetic recombination, these receptors can achieve almost infinitely diverse variations in the structure of the site that binds to antigens. This mechanism for recombining specific genes is a feature unique to the vertebrate immune system and cannot be seen in other cells. Furthermore, only one type of recombined receptor molecule exists in each lymphocyte clone. Consequently, when lymphocyte clones respond to antigens and proliferate, the number of lymphocyte subpopulations with T cell receptors or immunoglobulins that can bind to a specific antigen increases. This is the essence of the acquired immune responses.

IMMUNE CELL LINEAGE AND DIFFERENTIATION PHASE

The cells of the immune system not only circulate in the blood and lymphatic vessels as leukocytes but are also distributed across various tissues of the body. These cells, in their entire life, monitor foreign invasion and pathological changes in cells in the body while changing their positions and differentiating to change the state of genetic expression. The lineage of numerous immune system cells and their differentiation phase have conventionally been classified and defined according to morphologic and staining characteristics. However, modern molecular genetic methods allow them to be clearly distinguished according to clusters of differentiation (CDs). CDs are cell surface marker molecules that can be identified and defined using monoclonal antibodies. While not as detailed and complete as the lineage mapping of all the cells in nematodes, the lineage and

differentiation phases of immune system cells of higher animals have been well defined by combining over 300 CDs. The CDs are closely linked to the functional characteristics of various immune cells, and therefore the entire picture of the immune system in which diverse types of cells migrate from location to location while changing their characteristics is gradually being revealed.

PRIMARY AND SECONDARY LYMPHOID ORGANS: SITE OF IMMUNE CELL GROWTH

The lymphoid organs are sites at which immune cells exist in large numbers and where they proliferate, differentiate, and become activated. Cells destined to become T or B cells proliferate and undergo gene recombination of T cell receptor and immunoglobulin in the thymus and bone marrow, respectively, which are called primary lymphoid organs. Lymphocyte clones are cells responsible for acquired immunity and thus express only one type of receptor gene out of the diverse variations created through genetic recombination. Among the almost infinite variety of binding structures resulting from recombination, naturally, some receptors have recognition specificity for structures included in "self" components. Here, the primary lymphoid organs play an important role in the elimination of clones with such receptors to establish antigen-specific "immune tolerance."

Antigen-specific immune responses can be referred to as the proliferation and differentiation of cell clones that express receptor molecules with specificity for a certain antigen. It is in the lymph nodes, spleen and mucosa-associated lymphoid tissues (MALT), where T cells and antigen presenting cells such as dendritic cells and macrophages meet and initiate antigen-specific acquired immune responses, causing T cells to proliferate. Moreover, B cells also become activated at these sites to proliferate and differentiate into cells secreting immunoglobulin. These sites are called secondary lymphoid organs.

LUPUS

Lupus is a systemic autoimmune disease that occurs when your body's immune system attacks your own tissues and organs. Inflammation caused by lupus can affect many different body systems—including your joints, skin, kidneys, blood cells, brain, heart and lungs.

Lupus can be difficult to diagnose because its signs and symptoms often mimic those of other ailments. The most distinctive sign of lupus—a facial rash that resembles the wings of a butterfly unfolding across both cheeks—occurs in many but not all cases of lupus.

Some people are born with a tendency towards developing lupus, which may be triggered by infections, certain drugs or even sunlight. While there's no cure for lupus, treatments can help control symptoms.

SYMPTOMS

Lupus Facial Rash

No two cases of lupus are exactly alike. Signs and symptoms may come on suddenly or develop slowly, may be mild or severe, and may be temporary or permanent. Most people with lupus have mild disease characterized by episodes—called flares—when signs and symptoms get worse for a while, then improve or even disappear completely for a time. The signs and symptoms of lupus that you experience will depend on which body systems are affected by the disease.

The most common signs and symptoms include:

- Fatigue
- Fever

- Joint pain, stiffness and swelling
- Butterfly-shaped rash on the face that covers the cheeks and bridge of the nose or rashes elsewhere on the body
- Skin lesions that appear or worsen with sun exposure (photosensitivity)
- Fingers and toes that turn white or blue when exposed to cold or during stressful periods (Raynaud's phenomenon)
- Shortness of breath
- Chest pain
- Dry eyes
- Headaches, confusion and memory loss.

CAUSES

Lupus occurs when your immune system attacks healthy tissue in your body (autoimmune disease). It's likely that lupus results from a combination of your genetics and your environment. It appears that people with an inherited predisposition for lupus may develop the disease when they come into contact with something in the environment that can trigger lupus. The cause of lupus in most cases, however, is unknown.

Some potential triggers include:

- *Sunlight:* Exposure to the sun may bring on lupus skin lesions or trigger an internal response in susceptible people.
- *Infections*: Having an infection can initiate lupus or cause a relapse in some people.
- *Medications:* Lupus can be triggered by certain types of blood pressure medications, anti-seizure medications and antibiotics. People who have drug-induced lupus usually get better when they stop taking the medication. Rarely, symptoms may persist even after the drug is stopped.

RISK FACTORS

Factors that may increase your risk of lupus include:

- *Your sex:* Lupus is more common in women.
- *Age:* Although lupus affects people of all ages, it's most often diagnosed between the ages of 15 and 45.
- *Race:* Lupus is more common in African-Americans, Hispanics and Asian-Americans.

COMPLICATIONS

Inflammation caused by lupus can affect many areas of your body, including your:

- *Kidneys:* Lupus can cause serious kidney damage, and kidney failure is one of the leading causes of death among people with lupus.
- *Brain and Central Nervous System*: If your brain is affected by lupus, you may experience headaches, dizziness, behaviour changes, vision problems, and even strokes or seizures. Many people with lupus experience memory problems and may have difficulty expressing their thoughts.
- *Blood and Blood Vessels*: Lupus may lead to blood problems, including anemia and increased risk of bleeding or blood clotting. It can also cause inflammation of the blood vessels (vasculitis).
- *Lungs:* Having lupus increases your chances of developing an inflammation of the chest cavity lining (pleurisy), which can make breathing painful. Bleeding into lungs and pneumonia also are possible.
- *Heart:* Lupus can cause inflammation of your heart muscle, your arteries or heart membrane (pericarditis). The risk of cardiovascular disease and heart attacks increases greatly as well.

OTHER TYPES OF COMPLICATIONS

Having lupus also increases your risk of:

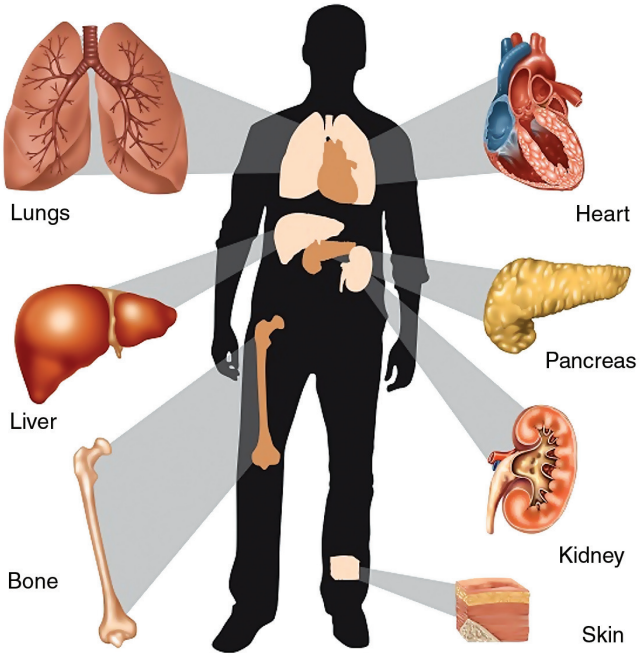
- *Infection:* People with lupus are more vulnerable to infection because both the disease and its treatments can weaken the immune system.
- *Cancer:* Having lupus appears to increase your risk of cancer; however the risk is small.
- *Bone tissue death (avascular necrosis):* This occurs when the blood supply to a bone diminishes, often leading to tiny breaks in the bone and eventually to the bone's collapse.
- *Pregnancy complications*: Women with lupus have an increased risk of miscarriage. Lupus increases the risk of high blood pressure during pregnancy (preeclampsia) and preterm birth. To reduce the risk of these complications, doctors often recommend delaying pregnancy until your disease has been under control for at least six months.

ORGAN TRANSPLANTS

Organ transplantation involves removing organs from a donor and transplanting them into someone who may be very ill or dying from organ failure. It can save the life of the person who receives the organ.

TYPES OF ORGAN AND TISSUE TRANSPLANTS

Organs that can be transplanted in Australia include the heart, kidneys, liver, lungs, intestine and pancreas. Tissue can also be transplanted, including heart valves, skin, bone and parts of the eye.



Organ Transplants

You may need an organ transplant if you have an organ that is not working any more (end-stage organ failure). An organ transplant is usually considered after other possible treatments have been tried. It may be an option if specialists think the transplant can save your life. A transplant can also be used to improve someone's quality of life – for example, a kidney transplant for a person who has experienced kidney failure. And a tissue transplant may, for example, help someone who has suffered severe burns to a sensitive area of skin, such as the face.

Donate Organs and Tissue

People can donate organs when they die (deceased donor) or they can donate a kidney or part of their liver while they are still alive (live donor). A living donor is usually a relative or close friend of the person who needs the kidney or liver transplant.

IMPORTANT ISSUES TO CONSIDER

Whether or not you have an organ transplant is for you, your family and loved ones, and your health care team to decide. It is important to understand your condition and the potential benefits and risks of organ transplant, as with any medical treatment.

IMPACT ON YOUR EMOTIONS

An organ transplant can affect not just your body but how you feel. Some people experience stress from possible organ rejection or side effects from medicines. Others find it difficult to adapt to their new situation. It may help to speak with your health care team about how you feel following the procedure. You may also want to contact patient support groups to hear from people who have also had an organ transplant.

Life After an Organ Transplant

If you have had an organ transplant, you will probably need to take medications and have regular medical appointments for the rest of your life. Rejection occurs when your body treats the transplanted organ as foreign and attacks it. Anti-rejection medications work on the immune system to stop this from happening. However, anti-rejection medicines may bring a higher risk of side effects such as infection. You and your health care team will usually need to work together to balance the risk of organ rejection with the risk of side effects.

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Infectious Diseases

Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the diseases can be spread, directly or indirectly, from one person to another. Zoonotic diseases are infectious diseases of animals that can cause disease when transmitted to humans.

Germs, or microbes, are found everywhere in the air, soil, and water. There are also germs on your skin and in your body. Many of them are harmless, and some can even be helpful. But some of them can make you sick. Infectious diseases are diseases that are caused by germs.

There are many different ways that you can get an infectious disease:

- Through direct contact with a person who is sick. This includes kissing, touching, sneezing, coughing, and sexual contact. Pregnant mothers can also pass some germs along to their babies.
- Through indirect contact, when you touch something that has germs on it. For example, you could get germs if someone who is sick touched a door handle, and then you touch it.
- Through insect or animal bites.
- Through contaminated food, water, soil, or plants.

There are four main kinds of germs:

- *Bacteria:* One-celled germs that multiply quickly. They may give off toxins, which are harmful chemicals that can make you sick. Strep throat and urinary tract infections are common bacterial infections.
- *Viruses:* Tiny capsules that contain genetic material. They invade your cells so that they can multiply. This can kill, damage, or change the cells and make you sick. Viral infections include HIV/AIDS and the common cold.
- *Fungi:* Primitive plant-like organisms such as mushrooms, mold, mildew, and yeasts. Athlete's foot is a common fungal infection.
- *Parasites:* Animals or plants that survive by living on or in other living things. Malaria is an infection caused by a parasite.

INFECTIONS – BACTERIAL AND VIRAL

Many human infections are caused by either bacteria or viruses. Bacteria are tiny single-celled organisms, thought by some researchers to be related to plants. They are among the most successful life forms on the planet, and range in habitat from ice slopes to deserts.

Bacteria can be beneficial – for instance, gut bacteria help us to digest food – but some are responsible for a range of infections. These disease-causing varieties are called pathogenic bacteria. Many bacterial infections can be treated successfully with appropriate antibiotics, although antibiotic-resistant strains are beginning to emerge. Immunisation is available to prevent many important bacterial diseases. A virus is an even smaller micro-organism that can only reproduce inside a host's living cell. It is very difficult to kill a virus. That's why some of the most serious communicable diseases known to medical science are viral in origin.

BACTERIA AND VIRUSES ENTER THE BODY

To cause disease, pathogenic bacteria must gain access into the body. The range of access routes for bacteria includes:

- Cuts
- Contaminated food or water
- Close contact with an infected person
- Contact with the faeces of an infected person
- Breathing in the exhaled droplets when an infected person coughs or sneezes
- Indirectly, by touching contaminated surfaces – such as taps, toilet handles, toys and nappies.

Viruses are spread from one person to another by:

- Coughs
- Sneezes
- Vomits
- Bites from infected animals or insects
- Exposure to infected bodily fluids through activities such as sexual intercourse or sharing hypodermic needles.

Forgetting to wash your hands after handling pets and animals is another way for germs to be taken in by mouth.

BACTERIA TYPES

Bacteria that cause disease are broadly classified according to their shape. *The four main groups include:*

- *Bacilli:* Shaped like a rod with a length of around 0.03mm. Illnesses such as typhoid and cystitis are caused by bacilli strains.
- *Cocci:* Shaped like a sphere with a diameter of around 0.001mm. Depending on the sort, cocci bacteria group themselves in a range of ways, such as in pairs, long lines or tight clusters. Examples include *Staphylococci* (which cause a host of infections including boils) and *Gonococci* (which cause the sexually transmissible infection gonorrhoea).
- *Spirochaetes:* As the name suggests, these bacteria are shaped like tiny spirals. Spirochaetes bacteria are responsible for a range of diseases, including the sexually transmissible infection syphilis.
- *Vibrio:* Shaped like a comma. The tropical disease cholera, characterised by severe diarrhoea and dehydration, is caused by the vibrio bacteria.

CHARACTERISTICS OF THE BACTERIUM

Most bacteria, apart from the cocci variety, move around with the aid of small lashing tails (flagella) or by whipping their bodies from side to side. Under the right conditions, a bacterium reproduces by dividing in two. Each 'daughter' cell then divides in two and so on, so that a single bacterium can bloom into a population of some 500,000 or more within just eight hours.

If the environmental conditions don't suit the bacteria, some varieties morph into a dormant state. They develop a tough outer coating and await the appropriate change of conditions. These hibernating bacteria are called spores. Spores are harder to kill than active bacteria because of their outer coating.

CURING A BACTERIAL INFECTION

The body reacts to disease-causing bacteria by increasing local blood flow (inflammation) and sending in cells from the immune system to attack and destroy the bacteria. Antibodies produced by the immune system

attach to the bacteria and help in their destruction. They may also inactivate toxins produced by particular pathogens, for example tetanus and diphtheria. Serious infections can be treated with antibiotics, which work by disrupting the bacterium's metabolic processes, although antibiotic-resistant strains are starting to emerge. Immunisation is available to prevent many important bacterial diseases such as Hemophilus influenza Type b (Hib), tetanus and whooping cough..

VIRUS TYPES

A virus is a miniscule pocket of protein that contains genetic material. If you placed a virus next to a bacterium, the virus would be dwarfed. For example, the polio virus is around 50 times smaller than a *Streptococci*bacterium, which itself is only 0.003mm long. Viruses can be described as either RNA or DNA viruses, according to which type of nucleic acid forms their core.

The four main types of virus include:

- *Icosahedral:* The outer shell (capsid) is made from 20 flat sides, which gives a spherical shape. Most viruses are icosahedral.
- *Helical:* The capsid is shaped like a rod.
- *Enveloped:* The capsid is encased in a baggy membrane, which can change shape but often appears spherical.
- *Complex:* The genetic material is coated, but without a capsid.

THE BODY'S RESPONSE TO VIRAL INFECTION

Viruses pose a considerable challenge to the body's immune system because they hide inside cells. This makes it difficult for antibodies to reach them. Some special immune system cells, called T-lymphocytes, canrecognise and kill cells containing viruses, since the surface of infected cells is changed when the virus begins to multiply.

Many viruses, when released from infected cells, will be effectively knocked out by antibodies that have been produced in response to infection or previous immunisation.

CURING A VIRAL INFECTION

Antibiotics are useless against viral infections. This is because viruses are so simple that they use their host cells to perform their activities for them. So antiviral drugs work differently to antibiotics, by interfering with the viral enzymes instead.

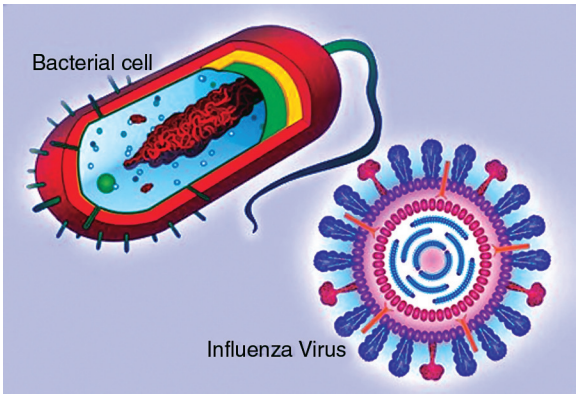
Antiviral drugs are currently only effective against a few viral diseases, such as influenza, herpes, hepatitis B and C and HIV – but research is ongoing. A naturally occurring protein, called interferon (which the body produces to help fight viral infections), can now be produced in the laboratory and is used to treat hepatitis C infections.

IMMUNISATION AGAINST VIRAL INFECTION IS NOT ALWAYS POSSIBLE

It is possible to vaccinate against many serious viral infections such as measles, mumps, hepatitis A and hepatitis B. An aggressive worldwide vaccination campaign, headed by the World Health Organization (WHO), managed to wipe out smallpox.

However, some viruses – such as those that cause the common cold – are capable of mutating from one person to the next. This is how an infection with essentially the same virus can keep dodging the immune system. Vaccination for these kinds of viruses is difficult, because the viruses have already changed their format by the time vaccines are developed.

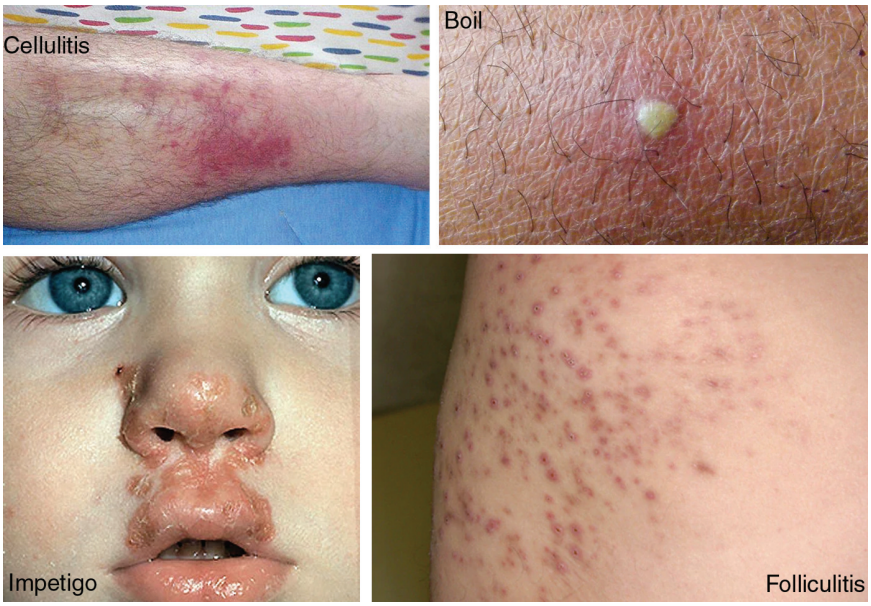
BACTERIA VS VIRUS



Bacteria and viruses are different types of pathogens, organisms that can cause disease. Bacteria are larger than viruses and are capable of reproducing on their own. Viruses are much smaller than bacteria and cannot reproduce on their own. Instead, viruses reproduce by infecting a host and using the host's DNA repair and replication systems to make copies of itself.

The symptoms of a bacterial or viral infection depend on the area of the body that is affected. Sometimes the symptoms of the two can be very similar. For example, runny nose, cough, headache, and fatigue can occur with the common cold (virus) and with a sinus infection (bacteria). A doctor may use the presence of other symptoms (such as fever or body aches), the length of the illness, and certain lab tests to determine if an illness is due to a virus, bacteria, or some other pathogen or disease process.

BACTERIAL SKIN INFECTIONS



Bacterial skin infections are usually caused by gram-positive strains of Staphylococcus and Streptococcus or other organisms. *Common bacterial skin infections include:*

- Cellulitis causes a painful, red infection that is usually warm to the touch. Cellulitis occurs most often on the legs, but it can appear anywhere on the body.
- Folliculitis is an infection of the hair follicles that causes red, swollen bumps that look like pimples. Improperly treated pools or hot tubs can harbour bacteria that cause folliculitis.

- Impetigo causes oozing sores, usually in preschool-aged children. The bullous form of impetigo causes large blisters while the non-bullous form has a yellow, crusted appearance.
- Boils are deep skin infections that start in hair follicles. Boils are firm, red, tender bumps that progress until pus accumulates underneath the skin.

Bacterial skin infections are treated with oral or topical antibiotics depending on the strain causing the infection.

FOODBORNE BACTERIAL INFECTIONS

Bacterial infections are one cause of foodborne illness. Nausea, vomiting, diarrhea, fever, chills, and abdominal pain are common symptoms of food poisoning. Raw meat, fish, eggs, poultry, and unpasteurized dairy may harbour harmful bacteria that can cause illness. Unsanitary food preparation and handling can also encourage bacterial growth.

Bacteria that cause food poisoning include:

- Campylobacter jejuni (C. jejuni) is a diarrheal illness often accompanied by cramps and fever.
- Clostridium botulinum (C. botulinum) is a potentially life-threatening bacterium that produces powerful neurotoxins.
- Escherichia coli (E. coli) O157:H7 is a diarrheal (often bloody) illness that may be accompanied by nausea, vomiting, fever, and abdominal cramps.
- Listeria monocytogenes (L. monocytogenes) causes fever, muscle aches, and diarrhea. Pregnant women, elderly individuals, infants, and those with weakened immune systems are most at risk for acquiring this infection.
- Salmonella causes fever, diarrhea, and abdominal cramps. Symptoms typically last between 4 and 7 days.
- Vibrio causes diarrhea when ingested, but it can also cause severe skin infections when it comes in contact with an open wound.

SEXUALLY TRANSMITTED BACTERIAL INFECTIONS

Many sexually transmitted diseases (STDs) are caused by harmful bacteria. Sometimes, these infections aren't associated with any symptoms but can still cause serious damage to the reproductive system.

Common STDs caused by bacterial infections include:

- Chlamydia is an infection in men and women caused by an organism called Chlamydia trachomatis. Chlamydia increases the risk of pelvic inflammatory disease (PID) in women.
- Gonorrhea, also known as "clap" and "the drip," is caused by Neisseria gonorrhoeae. Men and women can be infected. Gonorrhea also increases the risk of pelvic inflammatory disease (PID) in women.
- Syphilis can affect men and women and is caused by the bacteria Treponema pallidum. Untreated, syphilis is potentially very dangerous and can even be fatal.
- Bacterial vaginosis, which causes an overgrowth of pathogenic bacteria in the vagina (the CDC does not consider this a STD).

OTHER BACTERIAL INFECTIONS

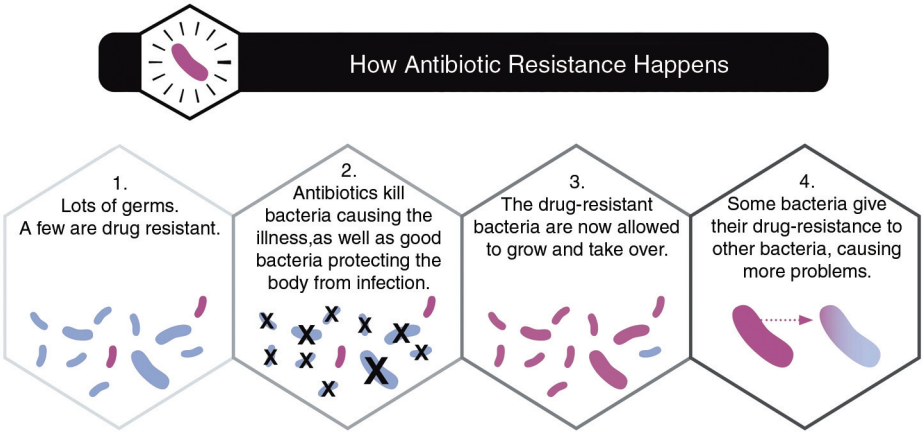
Harmful bacteria can affect almost any area of the body. *Other types of bacterial infections include:*

- Bacterial meningitis is a severe infection of the meninges, the lining of the brain.
- Otitis media is the official name for an infection or inflammation of the middle ear. Both bacteria and viruses can cause ear infections, which commonly occur in babies and small children.
- Urinary tract infection (UTI) is a bacterial infection of the bladder, urethra, kidneys, or ureters.
- Respiratory tract infections include sore throat, bronchitis, sinusitis, and pneumonia. Bacteria or viruses may be responsible for respiratory tract infections. Tuberculosis is a type of bacterial lower respiratory tract infection.

ANTIBIOTICS

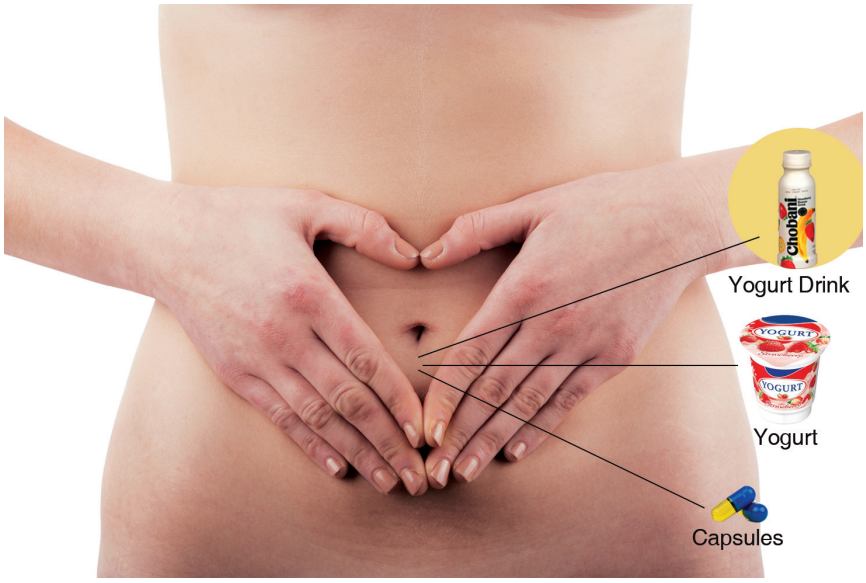
Antibiotics are medications that fight bacterial infections. They work by disrupting the processes necessary for bacterial cell growth and proliferation. It's important to take antibiotics exactly as prescribed. Failure to do so could make a bacterial infection worse. Antibiotics don't treat viruses, but they're sometimes prescribed in viral illnesses to help prevent a "secondary bacterial infection." Secondary infections occur when someone is in a weakened or compromised state due to an existing illness.

ANTIBIOTIC RESISTANCE



Overuse and misuse of antibiotics has led to a rise in antibiotic resistance. Antibiotic resistance occurs when bacteria are no longer sensitive to a medication that should eliminate an infection. Antibiotic-resistant bacterial infections are potentially very dangerous and increase the risk of death. About 2 million people in the U.S. suffer from antibiotic resistant infections each year and 23,000 die due to the condition. The CDC estimates 14,000 deaths alone are due to Clostridium difficile (C. difficile) infections that occur because of antibiotic suppression of other bacteria allow C.difficile to proliferate. Most deaths due to antibiotic resistant infections occur in hospitalized patients and those who are in nursing homes.

GOOD BACTERIA AND PROBIOTICS



Beneficial bacteria live in the human gastrointestinal (GI) tract and play an important role in digestion and immunity. Most people know it's smart to eat yogurt after completing a course of antibiotics to repopulate the GI tract with helpful bacteria that were wiped out from the antibiotics.

Some studies have shown probiotics can shorten the duration of infectious diarrhea. They may also reduce the risk of developing diarrheal illness due to antibiotic use. Probiotics seem to reduce gas, bloating, and abdominal pain associated with irritable bowel syndrome (IBS). Ongoing research seeks to determine the types and dosages of bacteria that are most beneficial to human health.

NEUROTROPIC VIRUS

A neurotropic virus is a virus that is capable of infecting nerve cells.

TERMINOLOGY

A neurotropic virus is said to be neuroinvasive if it is capable of accessing or entering the nervous system and neurovirulent if it is capable of causing disease within the nervous system. Both terms are often applied to central nervous system infections, although some neurotropic viruses are highly neuroinvasive for the peripheral nervous system (*i.e.* herpes simplex virus). Important neuroinvasive viruses include poliovirus, which is highly neurovirulent but weakly neuroinvasive, and rabies virus, which is highly neurovirulent but requires tissue trauma (often resulting from an animal bite) to become neuroinvasive. Using these definitions, herpes simplex virus is highly neuroinvasive for the peripheral nervous system and rarely neuroinvasive for the central nervous system, but in the latter case may cause herpesviral encephalitis and is therefore considered highly neurovirulent. Many arthropod-borne neurotropic viruses, like West Nile virus, spread to the brain primarily via the blood system by crossing the blood-brain barrier in what is called hematogenous dissemination.

Examples

Neurotropic viruses that cause infection include Japanese Encephalitis, Venezuelan Equine Encephalitis, and California encephalitis viruses; polio, coxsackie, echo, mumps, measles, influenza and rabies, as well as diseases caused by members of the family Herpesviridae such as herpes simplex, varicella-zoster, Epstein–Barr, cytomegalo and HHV-6viruses. Those causing latent infection include herpes simplex and varicella-zoster viruses. Those causing slow virus infection include measles virus, rubella and JC viruses, and retrovirusessuch as human T-lymphotropic virus 1 and human immunodeficiency virus.

RESEARCH USE

Neurotropic viruses are increasingly being exploited as research tools, and for their potential use in treatment. In particular, they are being used to improve the understanding of the nervous systems circuits.

OTHER NEUROTROPIC INFECTIONS

Several diseases, including transmissible spongiform encephalopathy, kuru, and Creutzfeldt–Jakob disease resemble a slow neurotropic virus infection—but are, in fact, caused by the infectious proteins known as prions.

FUNGAL INFECTIONS

Fungal infections are often classified as either:

- Opportunistic
- Primary

Opportunistic infections are those that develop mainly in immunocompromised hosts; primary infections can develop in immunocompetent hosts.

Fungal infections can be:

- Systemic
- Local

Local fungal infections typically involve the skin, mouth (causing stomatitis), and/or vagina (causing candidal vaginitis) and may occur in normal or immunocompromised hosts.

OPPORTUNISTIC FUNGAL INFECTIONS

Many fungi are opportunists and are usually not pathogenic except in an immunocompromised host. Causes of immunocompromise include AIDS, azotemia, diabetes mellitus, lymphoma, leukemia, other hematologic cancers, burns, and therapy with corticosteroids, immunosuppressants, or antimetabolites. Patients who spend more than several days in an ICU can become compromised because of medical procedures, underlying disorders, and/or undernutrition.

Typical opportunistic systemic fungal infections (mycoses) include:

- Candidiasis
- Aspergillosis
- Mucormycosis (zygomycosis)
- Fusariosis

Systemic mycoses affecting severely immunocompromised patients often manifest acutely with rapidly progressive pneumonia, fungemia, or manifestations of extrapulmonary dissemination.

PRIMARY FUNGAL INFECTIONS

Primary fungal infections usually result from inhalation of fungal spores, which can cause a localized pneumonia as the primary manifestation of infection. In immunocompetent patients, systemic mycoses typically have a chronic course; disseminated mycoses with pneumonia and septicemia are rare and, if lung lesions develop, usually progress slowly. Months may elapse before medical attention is sought or a diagnosis is made. Symptoms are rarely intense in such chronic mycoses, but fever, chills, night sweats, anorexia, weight loss, malaise, and depression may occur. Various organs may be infected, causing symptoms and dysfunction. Primary fungal infections may have a characteristic geographic distribution, which is especially true for the endemic mycoses caused by certain dimorphic fungi. For example,

- *Coccidioidomycosis:* Confined primarily to the southwestern US, Washington, northern Mexico, and Central and South America.
- *Histoplasmosis:* Occurring primarily in the eastern and Midwestern US and parts of Central and South America, Africa, Asia, and Australia.
- *Blastomycosis:* Confined to North America and Africa.
- *Paracoccidioidomycosis (formerly, South American blastomycosis):* Confined to that continent.

However, travelers can manifest disease any time after returning from endemic areas. *When fungi disseminate from a primary focus in the lung, the manifestations may be characteristic, as for the following:*

- *Cryptococcosis:* Usually, chronic meningitis.
- *Progressive Disseminated Histoplasmosis:* Generalized involvement of the reticuloendothelial system (liver, spleen, bone marrow).
- *Blastomycosis:* Single or multiple skin lesions or involvement of the prostate.
- *Coccidioidomycosis:* Bone and joint infections, skin lesions, and meningitis.

DIAGNOSIS

- Cultures and stains.
- Histopathology.
- Serologic tests (mainly for *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus,* and *Histoplasma*).

If clinicians suspect an acute or a chronic primary fungal infection, they should obtain a detailed travel and residential history to determine whether patients may have been exposed to certain endemic mycoses, perhaps years previously.

Pulmonary fungal infections must be distinguished from tumors and chronic pneumonias caused by non-fungal organisms such as mycobacteria (including TB). Specimens are obtained for fungal and mycobacterial culture and histopathology. Sputum samples may be adequate, but occasionally bronchoalveolar lavage, transthoracic needle biopsy, or even surgery may be required to obtain an acceptable specimen.

Fungi that cause primary systemic infections are readily recognized by their histopathologic appearance. However, identifying the specific fungus may be difficult and usually requires fungal culture. The clinical significance of positive sputum cultures may be unclear if they show commensal organisms (eg, *Candida albicans*) or fungi ubiquitous in the environment (eg, *Aspergillus* sp). Therefore, other evidence (eg, host factors such as immunosuppression, serologic evidence, tissue invasion) may be required to help establish a diagnosis.

Serologic tests may be used to check for many systemic mycoses if culture and histopathology are unavailable or unrevealing, although few provide definitive diagnoses.

Particularly useful tests include the following:

- Measurement of organism-specific antigens, most notably from *Cryptococcus neoformans*, *Histoplasma capsulatum*, and*Aspergillus* sp (occasional cross-reactivity with other fungi has been noted with each of these serologic tests).
- Serum beta-glucan, which is often positive in invasive candidiasis as well as *Pneumocystis jirovecii* infections.
- Complement fixation assays and newer enzyme immunoassays for anticoccidioidal antibodies, which are satisfactorily specific and do not require proof of rising levels (high titers confirm the diagnosis and indicate high risk of extrapulmonary dissemination).

Most other tests for antifungal antibodies have low sensitivity, specificity, or both and, because measurement of acute and convalescent titers is required, cannot be used to guide initial therapy.

EXPLAINING HIV AND AIDS

HIV is a virus that targets and alters the immune system, increasing the risk and impact of other infections and diseases. Without treatment, the infection might progress to an advanced disease stage called AIDS. However, modern advances in treatment mean that people living with HIV in countries with good access to health care very rarely develop AIDS once they are receiving treatment. The life expectancy of a person who carries the HIV virus is now approaching that of a person that tests negative for the virus, as long as they adhere to a combination of medications called antiretroviral therapy (ART) on an ongoing basis.

A *Kaiser Permanente* study in 2016 suggested that between 1996 and 2016, the gap in life expectancy between people who are HIV positive and HIV negative closed from 44 years to 12 years. The World Health Organization (WHO) also advises that a person living with HIV can resume a high quality of life with treatment, and that 20.9 million people worldwide were receiving ART as of mid-2017. We explain HIV and AIDS, their symptoms, causes, and treatments.

HIV

Human immunodeficiency virus (HIV) is a virus that attacks immune cells called CD4 cells, which are a type of T cell. These are white blood cells that move around the body, detecting faults and anomalies in cells as well as infections. When HIV targets and infiltrates these cells, it reduces the body's ability to combat other diseases. This increases the risk and impact of opportunistic infections and cancers. However, a person can carry HIV without experiencing symptoms for a long time. HIV is a lifelong infection.

However, receiving treatment and managing the disease effectively can prevent HIV from reaching a severe level and reduce the risk of a person passing on the virus.

AIDS

AIDS is the most advanced stage of HIV infection. Once HIV infection develops into AIDS, infections and cancer pose a greater risk. Without treatment, HIV infection is likely to develop into AIDS as the immune system gradually wears down. However, advances in ART mean than an ever-decreasing number of people progress to this stage. By the close of 2015, around 1,122,900 people were HIV-positive. To compare, figures from 2016 show that medical professionals diagnosed AIDS in an estimated 18,160 people.

CAUSES

People transmit HIV in bodily fluids, including:

- Blood
- Semen
- Vaginal secretions
- Anal fluids
- Breast milk.

In the United States, the main causes of this transfer of fluids are:

- Anal or vaginal intercourse with a person who has HIV while not using a condom or PrEP, a preventive HIV medication for people at high risk of infection.
- Sharing equipment for injectable illicit drugs, hormones, and steroids with a person who has HIV.

A woman living with HIV who is pregnant or has recently given birth might transfer the disease to her child during pregnancy, childbirth, or breastfeeding. The risk of HIV transmitting through blood transfusions is extremely low in countries that have effective screening procedures in place for blood donations.

Undetectable = Untransmittable

To transmit HIV, these fluids must contain enough of the virus. If a person has 'undetectable' HIV, they will not transmit HIV to another person, even if after a transfer of fluids. Undetectable HIV is when the amount of HIV in the body is so low that a blood test cannot detect it. People may be able to achieve undetectable levels of HIV by closely following the prescribed course of treatment. Confirming and regularly monitoring undetectable status using a blood test is important, as this does not mean that the person no longer has HIV. Undetectable HIV relies on the person adhering to their treatment, as well as the effectiveness of the treatment itself.

PROGRESSION TO AIDS

The risk of HIV progressing to AIDS varies widely between individuals and depends on many factors, including:

- The age of the individual
- The body's ability to defend against HIV
- Access to high-quality, sanitary health care
- The presence of other infections
- The individual's genetic inheritance resistance to certain strains of HIV
- Drug-resistant strains of HIV.

SYMPTOMS

For the most part, infections by other bacteria, viruses, fungi, or parasites cause the more severe symptoms of HIV. These conditions tend to progress further in people who live with HIV than in individuals with healthy immune systems. A correctly functioning immune system would protect the body against the more advanced effects of infections, and HIV disrupts this process.

EARLY SYMPTOMS OF HIV INFECTION

Some people with HIV do not show symptoms until months or even years after contracting the virus. However, around 80 percent of people may develop a set of flu-like symptoms known as acute retroviral syndrome around 2–6 weeks after the virus enters the body. *The early symptoms of HIV infection may include:*

- Fever
- Chills
- Joint pain
- Muscle aches
- Sore throat
- Sweats. particularly at night
- Enlarged glands
- A red rash
- Tiredness
- Weakness
- Unintentional weight loss
- Thrush

These symptoms might also result from the immune system fighting off many types of viruses. However, people who experience several of these symptoms and know of any reason they might have been at risk of contracting HIV over the last 6 weeks should take a test.

ASYMPTOMATIC HIV

In many cases, after the symptoms of acute retroviral syndrome, symptoms might not occur for many years. During this time, the virus continues to develop and cause immune system and organ damage. Without medication that prevents the replication of the virus, this slow process can continue for an average of around 10 years. A person living with HIV often experiences no symptoms, feels well, and appears healthy. Complying rigidly to a course of ART can disrupt this phase and suppress the virus completely. Taking effective antiretroviral medications for life can halt on-going damage to the immune system.

LATE-STAGE HIV INFECTION

Without medication, HIV weakens the ability to fight infection. The person becomes vulnerable to serious illnesses. This stage is known as AIDS or stage 3 HIV. *Symptoms of late-stage HIV infection may include:*

- Blurred vision
- Diarrhea, which is usually persistent or chronic
- Dry cough
- A fever of over 100°F (37°C) lasting for weeks
- Night sweats
- Permanent tiredness
- Shortness of breath, or dyspnea
- Swollen glands lasting for weeks
- Unintentional weight loss
- White spots on the tongue or mouth.

During late-stage HIV infection, the risk of developing a life-threatening illness increases greatly. A person with late-stage HIV can control, prevent and treat serious conditions by taking other medications alongside HIV treatment.

OPPORTUNISTIC INFECTIONS

HIV treatment is nowadays often effective enough to keep many infections at bay. In reducing the activity of the immune system, late-stage HIV reduces the ability of the body to combat a range of infections, diseases, and cancers. Infections that caused minimal or no health problems before the development of AIDS might pose a serious health risk once the condition has weakened the immune system. Medical professionals refer to these as opportunistic infections (OIs). Once any of these infections occur, a doctor will diagnose AIDS.

These include:

Candidiasis of the Bronchi, Trachea, Esophagus, and Lungs: As a fungal infection that normally occurs in the skin and nails, this frequently causes serious problems in the esophagus and lower respiratory tract for people with AIDS.

Invasive Cervical Cancer: This type of cancer begins in the cervix and spreads to other areas in the body. Regular checks with a cancer care team can help prevent the cancer or limit the spread.

Coccidioidomycosis: People sometimes refer to the self-limited version of this disease in healthy individuals as valley fever. Inhalation of the fungus *Coccidioides immitis* causes this infection.

Cryptococcosis: Cryptococcus neoformans is a fungus that can infect any part of the body, but most often enters the lungs to trigger pneumonia or the brain to cause swelling.

Cryptosporidiosis: The protozoan parasite *Cryptosporidium* causes this infection that leads to severe abdominal cramps and watery diarrhea.

Cytomegalovirus Disease (CMV): CMV can cause a range of diseases in the body, including pneumonia, gastroenteritis, and encephalitis, a brain infection. However, CMV retinitis is of particular concern in people with late-stage HIV, and it can infect the retina at the back of the eye, permanently removing sight. CMV retinitis is a medical emergency.

HIV-related Encephalopathy: An acute or chronic HIV infection can trigger this brain disorder. While doctors do not fully understand the cause, they consider it to be linked to post-infection inflammation in the brain.

Herpes Simplex (HSV): This virus, usually sexually transmitted or passed on in childbirth, is extremely common and rarely causes health issues or causes self-limiting recurrences in people with healthy immune systems. However, it can reactivate in people with HIV, causing painful cold sores around the mouth and ulcers on the genitals and anus that do not resolve. The sores, rather than a herpesdiagnosis, are an indicator of AIDS. HSV can also infect the breathing tube, lungs, or esophagus of people with AIDS.

Histoplasmosis: The fungus *Histoplasma capsulatum* causes extremely severe, pneumonia-like symptoms in people with advanced HIV. This condition can become progressive disseminated histoplasmosis and can impact on organs outside of the respiratory system.

Chronic Intestinal Isosporiasis: The parasite *Isospora belli* can infect the body through contaminated food and water, causing diarrhea, fever, vomiting, weight loss, headaches, and abdominal pain.

Kaposi's Sarcoma (KS): Kaposi's sarcoma herpesvirus (KSHV), also known as *human herpesvirus 8* (HHV-8), causes a cancer that leads to the growth of abnormal blood vessels anywhere in the body. If KS reaches organs, such as the intestines or lymph nodes, it can be extremely dangerous. KS appears as solid purple or pink spots on the surface of the skin. They might be flat or raised.

Lymphoma: People refer to cancer of the lymph nodes and lymphoid tissues as lymphoma, and many different types might occur. However, Hodgkin and non-Hodgkin lymphoma have strong links to HIV infection.

Tuberculosis (TB): The bacteria *Mycobacterium tuberculosis* causes this disease and can transfer in droplets if a person with an active form of the bacteria sneezes, coughs, or speaks. TB causes a severe lung infection as well as weight loss, fever, and tiredness, and can also infect the brain, lymph nodes, bones, or kidneys.

Mycobacteria, Including Mycobacterium Avium and Mycobacterium Kansasii: These bacteria occur naturally in the environment and pose few problems for people with fully-functioning immune systems. However, they can spread throughout the body and cause life-threatening health issues for people with HIV, especially in its later stages.

Pneumocystis Jirovecii Pneumonia (PJP): A fungus called *Pneumocystis jirovecii*causes breathlessness, dry cough, and high fever in people with suppressed immune systems, including those with HIV.

Recurrent Pneumonia: Many different infections can cause pneumonia, but a bacteria called Streptococcus pneumoniae is one of its most dangerous causes in people with HIV. Vaccines are available for this bacteria, and every person who has HIV should receive vaccination for *Streptococcus pneumoniae*.

Progressive Multifocal Encephalopathy (PML): The John Cunningham (JC) virus occurs in a vast number of people, usually lying dormant in the kidneys. However, in people with compromised immune systems, either due to HIV or medications, such as those for multiple sclerosis (MS), the JC virus attacks the brain, leading to a dangerous conditon called progressive multifocal leukoencephalopathy (PML). PML can be life-threatening, causing paralysis and cognitive difficulties.

Recurrent Salmonella Septicemia: This type of bacteria often enters the body in contaminated food and water, circulates the entire body, and overpowers the immune system, causing nausea, diarrhea, and vomiting.

Toxoplasmosis (Toxo): Toxoplasma gondii is a parasite that inhabits warm-blooded animals, including cats and rodents, and leaves the body in their feces. Humans contract the diseases by inhaling contaminated dust or eating contaminated food, but it can also occur in commercial meats. *T. gondii* causes severe infection in the lungs, retina, heart, liver, pancreas, brain, testes, and colon. Take care to wear protective gloves while changing cat litter and thoroughly wash the hands afterwards.

Wasting Syndrome: This occurs when a person involuntarily loses 10 percent of their muscle mass through diarrhea, weakness, or fever. Part of the weight loss may also consist of fat loss.

PREVENTION

Preventing OIs is key to extending life expectancy with late-stage HIV. *Aside from managing HIV viral load with medications, a person who lives with the disease must take precautions, including the following steps:*

- Wear condoms to prevent other STIs.
- Receive vaccinations for potential OIs. Discuss these with your primary care physician.
- Understand the germs in your surrounding environment that could lead to an OI. A pet cat, for example, could be a source of toxoplasmosis. Limit exposure and take precautions, such as wearing protective gloves while changing litter
- Avoid foods that are at risk of contamination, such as undercooked eggs, unpasteurized dairy and fruit juice, or raw seed sprouts.
- Do not drink water straight from a lake or river or tap water in certain foreign countries. Drink bottled water or use water filters.
- Ask your doctor about work, home, and vacation activities to limit exposure to potential OIs.

Antibiotic, antifungal, or antiparasitic drugs can help treat an OI.

HIV AND AIDS MYTHS AND FACTS

Many misconceptions circulate about HIV that are harmful and stigmatizing for people with the virus.

The following cannot transmit the virus:

- Shaking hands
- Hugging
- Kissing

- Sneezing
- Touching unbroken skin
- Using the same toilet
- Sharing towels
- Sharing cutlery
- Mouth-to-mouth resuscitation or other forms of "casual contact"
- The saliva, tears, feces, and urine of a person with HIV.

DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) estimates that about 1 in every 7 HIV-positive Americans is unaware of their HIV status. Becoming aware of HIV status is vital for commencing treatment and preventing the development of more severe immune difficulties and subsequent infections.

HIV BLOOD TESTS AND RESULTS

A doctor can test for HIV using a specific blood test. A positive result means that they have detected HIV antibody in the bloodstream. The blood is re-tested before a positive result is given. After potential exposure to the virus, early testing and diagnosis is crucial and greatly improves the chances of successful treatment. Home testing kits are also available. HIV might take 3 - 6 months to show up in testing, and re-testing may be necessary for a definitive diagnosis. People at risk of infection within the last 6 months can have an immediate test. The test provider will normally recommend another test within a few weeks.

TREATMENT

No cure is currently available for HIV or AIDS. However, treatments can stop the progression of the condition and allow most people living with HIV the opportunity to live a long and relatively healthy life. Starting ART early in the progression of the virus is crucial. This improves quality of life, extends life expectancy, and reduces the risk of transmission, according to the WHO's guidelines from June 2013. More effective and better-tolerated treatments have evolved that can improve general health and quality of life by taking as little as one pill per day. A person living with HIV can reduce their viral load to such a degree that it is no longer detectable in a blood test. After assessing a number of large studies, the CDC concluded that individuals who have no detectable viral load "have effectively no risk of sexually transmitting the virus to an HIV-negative partner." Medical professionals refer to this as undetectable = untransmittable (U=U).

Emergency HIV pills, or Post-exposure Prophylaxis

If an individual believes they have been exposed to the virus within the last 3 days, anti-HIV medications, called post-exposure prophylaxis (PEP), may be able to stop infection. Take PEP as soon as possible after potential contact with the virus. PEP is a treatment lasting a total of 28 days, and physicians will continue to monitor for HIV after the completion of the treatment.

Antiretroviral Drugs

The treatment of HIV involves antiretroviral medications that fight the HIV infection and slows down the spread of the virus in the body. People living with HIV generally take a combination of medications called highly active antiretroviral therapy (HAART) or combination antiretroviral therapy (cART). There are a number of subgroups of antiretrovirals, such as:

Protease Inhibitors

Protease is an enzyme that HIV needs to replicate. These medications bind to the enzyme and inhibit its action, preventing HIV from making copies of itself.

These include:

- Atazanavir/cobicistat (Evotaz)
- Lopinavir/ritonavir (Kaletra)
- Darunavir/cobicistat (Prezcobix).

Integrase Inhibitors

HIV needs integrase, another enzyme, to infect T cells. This drug blocks integrase. These are often the first line of treatment due to their effectiveness and limited side effects for many people.

Integrase Inhibitors include:

- Elvitegravir (Vitekta)
- Dolutegravir (Tivicay)
- Raltegravir (Isentress).

Nucleoside/nucleotide Reverse Transcriptase Inhibitors (NRTIs)

These drugs, also referred to as "nukes," interfere with HIV as it tries to replicate.

This class of drugs includes:

- Abacavir (Ziagen)
- Lamivudine/zidovudine (Combivir)
- Emtricitabine (Emtriva)
- Tenofovir disproxil (Viread).

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs work in a similar way to NRTIs, making it more difficult for HIV to replicate.

Chemokine Co-receptor Antagonists

These drugs block HIV from entering cells. However, doctors in the U.S. do not often prescribe these because other drugs are more effective.

Entry Inhibitors

Entry inhibitors prevent HIV from entering T cells. Without access to these cells, HIV cannot replicate. As with chemokine co-receptor antagonists, they are not common in the United States. People will often use a combination of these drugs to suppress HIV. A medical team will adapt the exact mix of drugs to each individual. HIV treatment is usually permanent, lifelong, and based on routine dosage. A person living with HIV must take pills on a regular schedule.

Each class of ARVs has different side effects, but possible common side effects include:

- Nausea
- Fatigue
- Diarrhea
- Headache
- Skin rashes.

COMPLEMENTARY OR ALTERNATIVE MEDICINE

Although many people who have HIV try complementary, alternative, or herbal options, such as herbal remedies, no evidence confirms them to be effective. According to some limited studies, mineral or vitamin supplements may provide some benefits in overall health. It is important to discuss these options with a health care provider because some of these options, even vitamin supplements, may interact with ARVs.

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Cardiovascular Pathology

Diseases of the heart fit into several general categories: congenital heart disease, ischemic heart disease, valvular diseases, and diseases of the myocardium (*i.e.*, cardiomyopathies). Pericardial diseases and cardiac tumors are an additional small subset of conditions affecting the heart. A common manifestation of many different forms of heart disease is congestive heart failure (CHF). In general terms, congestive heart failure is the inability of the heart to pump enough blood to supply the body's oxygen requirements. It can represent failure of cellular adaptation (*e.g.*, decompensated hypertrophy due to hypertension or chamber dilation due to regurgitant valves) or the outcome of myocardial damage caused by other diseases (*e.g.*, scarring due to ischemic injury, inflammation, or accumulation of iron in hemochromatosis).

Classic symptoms of heart disease are chest pain or discomfort, dyspnea (including orthopnea and paroxysmal nocturnal dyspnea), palpitations, syncope, and edema. Dyspnea is an uncomfortable awareness of breathing. Orthopnea is dyspnea when in the recumbent position due to increased venous return and increased pulmonary venous pressure. Patients with orthopnea sleep upright on pillows to avoid becoming short of breath. Paroxysmal nocturnal dyspnea is when patients awaken with dyspnea 2–4 hours after falling asleep (due to central redistribution of peripheral edema).

An understanding of heart sounds is important in the clinical evaluation of heart disease. The S_1 sound is caused by closing of the mitral and tricuspid valves, and the S_2 sound is caused by closing of the aortic and pulmonary valves. In a patient with hypertension (systemic or pulmonary), closing of the associated valve (aortic or pulmonic) is accentuated (louder); in a patient with stenosis, the closing is diminished in strength (softer sound). S_2 is physiologically split during inspiration (aortic, A_2, first and pulmonic, P_2 second)—increased venous return to the right side of the heart delays closure of the pulmonic valve and decreased return to the left side speeds closure of the aortic valve. Wide splitting of S_2 is caused by a greater than normal delay in pulmonic closure (*e.g.*, right bundle branch block, pulmonic stenosis) or earlier aortic valve closure due to decreased left ventricular volume (*e.g.*, mitral regurgitation, ventricular septal defect). Paradoxical splitting (P_2 first and A_2second) occurs with delayed closure of the aortic valve (*e.g.*, left bundle branch block, aortic stenosis). A pathologic S_3 occurs with ventricular systolic dysfunction during the rapid filling phase of diastole or from impact of the left ventricle against the chest wall. It is particularly common in the setting of CHF. S_4 is from ejection of blood from the atrium into a non-compliant ventricle, as might be encountered in the setting of ventricular hypertrophy related to systemic hypertension, or in the setting of an acute myocardial infarct.

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Rheumatic fever is an inflammatory disorder caused by a Group A strep throat infection. It affects the connective tissue of the body, causing temporary, painful arthritis and other symptoms. In some cases rheumatic fever causes long-term damage to the heart and its valves. This is called rheumatic heart disease.

CAUSES OF RHEUMATIC FEVER

Rheumatic fever occurs as a result of a rare strain of strep throat that isn't treated with antibiotics quickly enough or at all. Doctors aren't sure why this rare strain of strep triggers this inflammatory disorder. It's probably because antibodies (special proteins in the blood that attack strep) mistakenly also attack healthy cells, such as the heart muscle and valve cells, as well as joint, brain and skin tissue, causing a reaction that results in inflammation.

Strep throat is most common in school-aged children, and so is rheumatic fever. Rheumatic fever was a leading cause of disability and death in children in the United States before 1960. Today, rheumatic fever is not common in the United States because most people have access to penicillin and other antibiotics. However, it does still occur in this country and remains a leading cause of early death in countries with less-developed health care systems. There is also a genetic factor in rheumatic fever. The members of some families are much more likely to develop it, and researchers are currently looking to understand why.

SIGNS AND SYMPTOMS OF RHEUMATIC FEVER

Rheumatic fever can cause:

- *Carditis:* Inflammation of the heart muscle and heart tissue. Carditis can cause a rapid heart rate, fatigue, shortness of breath and exercise intolerance. This is the most serious of the symptoms and may have long-term effects on health. Carditis occurs in approximately 50 percent of those who have rheumatic fever
- *Arthritis:* Swelling, redness and pain in the joints, especially knees, ankles, elbows and wrists. This is a common symptom and occurs in approximately 70 percent of people who have rheumatic fever
- Splotchy rash that doesn't itch
- *Subcutaneous Nodules:* tiny, hard lumps under the skin
- Fever
- *Chorea:* Involuntary movement of the extremities. This is more common in females.

TESTING AND DIAGNOSIS FOR RHEUMATIC FEVER

There is no single test to diagnose rheumatic fever. Your child's doctor may use the modified Jones criteria to determine if your child has rheumatic fever. A child must show evidence of a prior strep infection through throat culture or blood work, as well as labs that show inflammation in the body. These tests, combined with other physical findings and signs of heart involvement, help doctors make the diagnosis.

Your child's doctor may also order an electrocardiogram (ECG) and/or an echocardiogram (ultrasound of the heart). An ECG is done to look for abnormal electrical conduction through the heart; an echocardiogram is done to look for leaking heart valves, fluid in the sac around the heart or poor heart muscle function.

TREATMENTS FOR RHEUMATIC FEVER

Penicillin, aspirin and other medicines are used to treat rheumatic fever. Children will also have to stay on a low dose of penicillin for years to reduce the risk of recurrence. It's very important to prevent a recurrence because of the risk of more damage to the heart.

OUTLOOK FOR RHEUMATIC FEVER

Carditis, or inflammation of the heart muscle and tissue, is the most serious result of rheumatic fever. Some children don't develop carditis while others develop mild carditis that may not cause problems in the future.

For children who do develop severe carditis, the inflammation leads to scarring and permanent damage to the heart, and particularly to the heart valves. The mitral valve, which controls the flow of blood between the upper left chamber and the lower left chamber of the heart, is most often damaged. The aortic valve, which sends the blood from the left lower chamber out to the body, is the next most commonly affected heart valve. Leakage of the heart valves is the most common finding.

In later years, blockage of the mitral valve can occur due to scarring. If either valve starts to leak severely, surgery to repair or replace it may be necessary. Usually this isn't necessary before adulthood, but in severe cases, surgery during youth is necessary.

FOLLOW-UP CARE FOR RHEUMATIC FEVER

Children and teens who have serious rheumatic heart disease will need to see a cardiologist regularly for the rest of their lives. The doctor will monitor heart function so that if problems develop, they can be addressed as quickly as possible.

INFECTIVE ENDOCARDITIS

Infective endocarditis is an infection of the inner surface of the heart, usually the valves. Symptoms may include fever, small areas of bleeding into the skin, heart murmur, feeling tired, and low red blood cell count. Complications may include valvular insufficiency, heart failure, stroke, and kidney failure. The cause is typically a bacterial infection and less commonly a fungal infection. Risk factors include valvular heart diseaseincluding rheumatic disease, congenital heart disease, artificial valves, hemodialysis, intravenous drug use, and electronic pacemakers. The bacteria most commonly involved are streptococci or staphylococci. Diagnosis is suspected based on symptoms and supported by blood cultures or ultrasound. There is also a non-infective form of endocarditis.

The usefulness of antibiotics following dental procedures for prevention is unclear. Some recommend them in those at high risk. Treatment is generally with intravenous antibiotics. The choice of antibiotics is based on results of blood cultures. Occasionally heart surgery is required. The number of people affected is about 5 per 100,000 per year. Rates, however, vary between regions of the world. Males are affected more often than females. The risk of death among those infected is about 25%. Without treatment it is almost universally fatal.

SIGNS AND SYMPTOMS

- Fever occurs in 97% of people; malaise and endurance fatigue in 90% of people.
- A new or changing heart murmur, weight loss, and coughing occurs in 35% of people.
- Vascular phenomena: septic embolism (causing thromboembolic problems such as stroke or gangrene of fingers), Janeway lesions (painless hemorrhagic cutaneous lesions on the palms and soles), intracranial hemorrhage, conjunctival hemorrhage, splinter hemorrhages, kidney infarcts, and splenic infarcts.
- Immunologic phenomena: glomerulonephritis which allows for blood and albumin to enter the urine, Osler's nodes (painful subcutaneous lesions in the distal fingers), Roth's spots on the retina, positive serum rheumatoid factor
- Other signs may include night sweats, rigors, anemia, spleen enlargement.

CAUSE

Many microorganisms can cause infective endocarditis. These are generally isolated by blood culture, where the patient's blood is drawn and any growth is noted and identified. The term bacterial endocarditis (BE) commonly is used, reflecting the fact that most cases of IE are due to bacteria; however, infective endocarditis (IE) has become the preferred term.

Bacterial

Staphylococcus aureus followed by *Streptococci* of the viridans group and coagulase negative Staphylococci are the three most common organisms responsible for infective endocarditis. Other *Streptococci* and *Enterococci* are also a frequent cause of infective endocarditis. HACEK group of microorganisms and fungi are seen less frequently in North America.

The viridians group include S. oralis, S. mitis, S. sanguis, S. gordonii and S. parasanguis. The primary habitats for these organisms are oral cavity and upper respiratory tract. These bacteria are present in the normal oral flora and enter the bloodstream usually by dental surgical procedures (tooth extractions) or genitourinary manipulation; as such, dental surgeons must fully carry out protective and preventive measures. In some countries *e.g.* the USA, high risk patients may be given prophylactic antibiotics such as penicillin or clindamycin for penicillin allergic patients prior to dental procedures. Prophylactics should be bactericidal rather than bacteriostatic. Such measures are not taken in certain countries *e.g.* Scotland due to the fear of antibiotic resistance.

Because bacteria is the most common cause of infective endocarditis (especially Streptococci), antibiotics such as penicillin and amoxycillin (for beta lactamase bacteria) are used in prophylaxis. Micriobiological culture could also be used to identify the infecting organism and testing its sensivitiy to different types of antibiotics.

Viridans alpha-hemolytic *streptococci*, that are present in the mouth, are the most frequently isolated microorganisms when the infection is acquired in a community setting. In contrast, *Staphylococcus* blood stream infections are frequently acquired in a health care setting where they can enter the blood stream through procedures that cause break in the integrity of skin, such as surgery, catheterisation, or during access of long term indwelling catheters or secondary to intravenous injection of recreational drugs. *Enterococcus* can enter the bloodstream as a consequence of abnormalities in the gastrointestinal or genitourinary tracts.

Some organisms, when isolated, give valuable clues to the cause, as they tend to be specific.

- *Pseudomonas* species, which are very resilient organisms that thrive in water, may contaminate street drugs that have been contaminated with drinking water. *P. aeruginosa* can infect a child through foot punctures, and can cause both endocarditis and septic arthritis.
- *S. bovis* and *Clostridium septicum*, which are part of the natural flora of the bowel, are associated with colonic malignancies. When they present as the causative agent in endocarditis, it usually calls for a colonoscopy to be done immediately due to concerns regarding hematogenous spread of bacteria from the colon due to the neoplasm breaking down the barrier between the gut lumen and the blood vessels which drain the bowel.
- *HACEK* organisms are a group of bacteria that live on the dental gums, and can be seen with IV drug users who contaminate their needles with saliva. Patients may also have a history of poor dental hygiene, or pre-existing valvular disease.
- Less commonly reported bacteria responsible for so called "culture negative endocarditis" include *Bartonella*, *Chlamydia psittaci*, and *Coxiella*. Such bacteria can be identified by serology, culture of the excised valve tissue, sputum, pleural fluid, and emboli, and by polymerase chain reaction or sequencing of bacterial 16S ribosomal RNA.

Multiple case reports of infective endocarditis caused by unusual organisms have been published. *Propionibacterium* sp., which are normal skin flora, have been responsible for infective endocarditis sometimes leading to deaths due to the indolent course of this abscess producing infection. *Tropheryma whipplei* has caused endocarditis without gastrointestinal involvement. *Citrobacter koseri* was found in an immunocompetent adult. *Neisseria bacilliformis* was found in a patient with a bicuspid aortic valve.

Fungal

Fungal endocarditis (FE) is an often fatal and one of the most serious forms of infective endocarditis. *The types of fungi most seen associated with this disease are:*

Candida albicans is found as a spherical or oval budding yeast. It is associated with endocarditis in IV drug users, patients with prosthetic valves, and immunocompromised patients. It forms biofilms around thick-walled resting structures like prosthetic heart valves and additionally colonizes and penetrates endothelial walls. C. albicans is responsible for 24-46% of all the cases of FE, and its mortality rate is 46.6–50%.

Other fungi demonstrated to cause endocarditis are *Histoplasma capsulatum* and Aspergillus. Aspergillus contributes to roughly 25% of FE cases. Endocarditis with *Tricosporon asahii* has also been reported in a case report.

Risk Factors

Risk factors for infective endocarditis are based on the premise that in a healthy individual, bacteremia (bacteria entering the blood stream) is cleared quickly with no adverse consequences. However, if a heart valve is damaged, the bacteria can attach themselves to the valve, resulting in infective endocarditis. Additionally, in individuals with weakened immune systems, the concentration of bacteria in the blood can reach levels high enough to increase the probability that some will attach to the valve.

Some significant risk factors are listed here:

- Artificial heart valves
- Intracardiac devices, such as implantable cardioverter-defibrillators
- Unrepaired cyanotic congenital heart defects
- History of infective endocarditis
- Chronic rheumatic heart disease, which is an autoimmune response to repeated *Streptococcus pyogenes* infection
- Age-related degenerative valvular lesions
- Hemodialysis, a medical procedure that filters the blood of individuals with kidney failure
- Coexisting conditions, especially ones that suppress immunity. Diabetes mellitus, alcohol abuse, HIV/AIDS, and intravenous drug use all fall in this category.

Other conditions that result in large numbers of bacteria entering into the bloodstream include colorectal cancer (mostly *Streptococcus bovis*), serious urinary tract infections(mostly enterococci), and drug injection (*Staphylococcus aureus*). With a large number of bacteria, even a normal heart valve may become infected. A more virulent organism (such as *Staphylococcus aureus*) can cause infective endocarditis by infecting even a normal heart valve.

Intravenous drug users tend to get their right-sided heart valves infected because the veins that are injected drain into the right side of the heart. In rheumatic heart disease, infection occurs on the aortic and the mitral valves on the left side of the heart. Other factors that increase the risk of developing infective endocarditis are low levels of white blood cells, immunodeficiency or immunosuppression, malignancy, diabetes mellitus, and alcohol abuse.

Dental Operations

In the past, one in eight cases of infective endocarditis were because of bacteremia caused by dental procedures (in most cases due to *Streptococcus viridans*, which reside in the oral cavity), such as a cleaning or extraction of a tooth; this was thought to be more clinically significant than it actually was. However, it is important that a dentist or a dental hygienist be told of any heart problems before commencing treatment. Antibiotics are

administered to patients with certain heart conditions as a precaution, although this practice has changed in the US, with new American Heart Association guidelines released in 2007, and in the UK as of March 2008 due to new NICE guidelines. Everyday tooth brushing and flossing will similarly cause bacteremia, so a high standard of oral health should be adhered to at all times. Although there is little evidence to support antibiotic prophylaxis for dental treatment, the current American Heart Association guidelines are highly accepted by clinicians and patients.

PATHOGENESIS

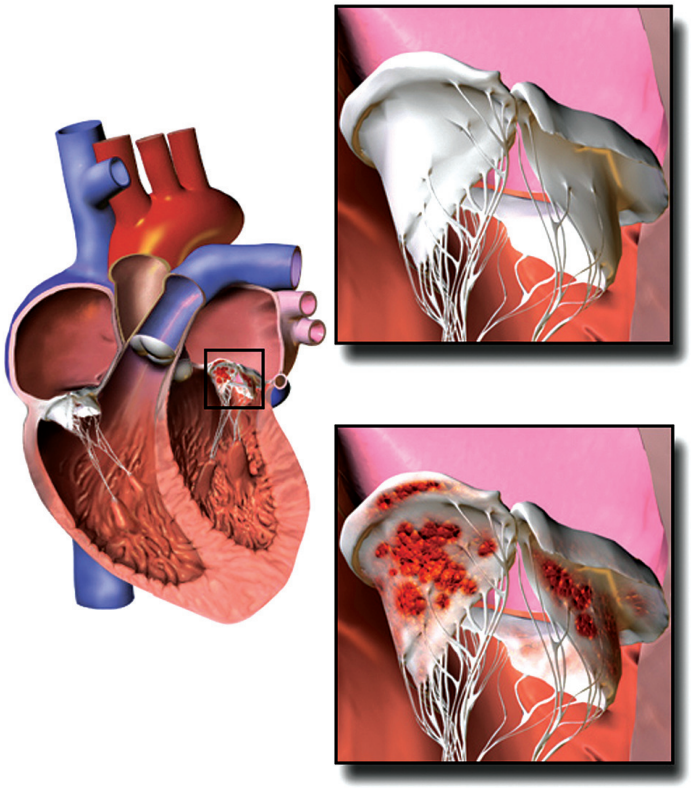


Fig. Drawing of Endocarditis.

Damaged valves and endocardium contribute to the development of infective endocarditis. Specifically, the damaged part of a heart valveforms a local blood clot, a condition known as non-bacterial thrombotic endocarditis (NBTE). The platelet and fibrin deposits that form as part of the blood clotting process allow bacteria to take hold and form vegetations. As previously mentioned, the body has no direct methods of combating valvular vegetations because the valves do not have a dedicated blood supply. This combination of damaged valves, bacterial growth, and lack of a strong immune response results in infective endocarditis.

Damage to the valves and endocardium can be caused by:

- Altered, turbulent blood flow, The areas that fibrose, clot, or roughen as a result of this altered flow are known as jet lesions. Altered blood flow is more likely in high pressure areas, so ventricular septal defects or patent ductus arteriosus can create more susceptibility than atrial septal defects.
- Catheters, electrodes, and other intracardiac prosthetic devices.
- Solid particles from repeated intravenous injections.
- *Chronic Inflammation:* Examples include auto-immune mechanisms and degenerative valvular lesions.

The risk factors for infective endocarditis provide a more extensive list of conditions that can damage the heart.

DIAGNOSIS

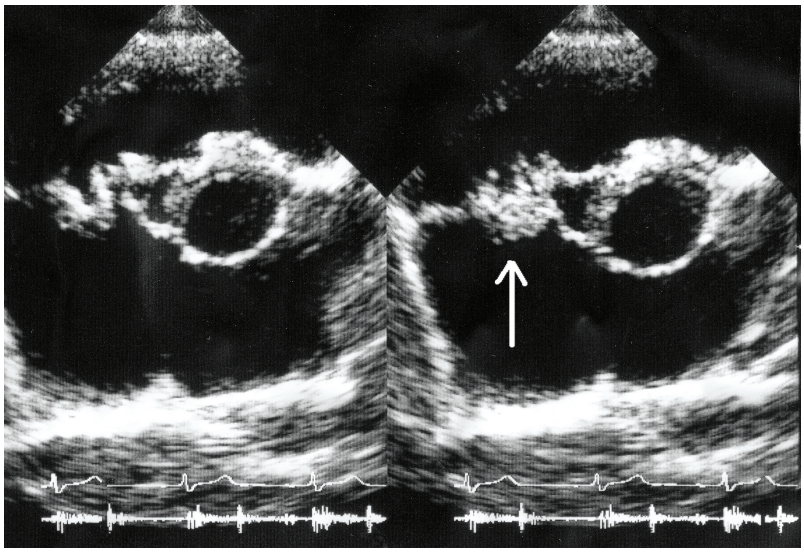


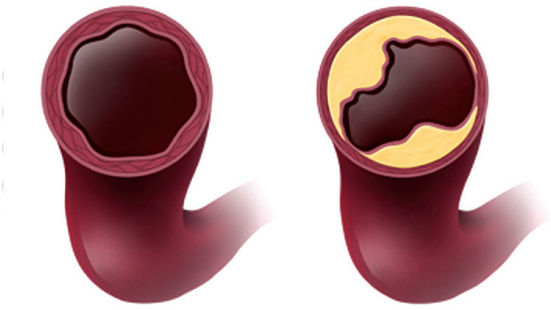
Fig. Vegetation on the Tricuspid valve by Echocardiography. Arrow Denotes the Vegetation.

In general, the Duke criteria should be fulfilled in order to establish the diagnosis of endocarditis. The blood tests C reactive protein (CRP) and procalcitonin have not been found to be particularly useful in helping make or rule out the diagnosis. As the Duke criteria rely heavily on the results of echocardiography, research has addressed when to order an echocardiogram by using signs and symptoms to predict occult endocarditis among patients with intravenous drug abuse and among non drug-abusing patients. However, this research is over twenty years old and it is possible that changes in the epidemiology of endocarditis and bacteria such as staphylococci make the following estimates incorrect.

Ultrasound

The transthoracic echocardiogram has a sensitivity and specificity of approximately 65% and 95% if the echocardiographer believes there is 'probable' or 'almost certain' evidence of endocarditis.

CORONARY ARTERY DISEASE (ATHEROSCLEROSIS)



Coronary artery disease (CAD) is a condition which affects the arteries that supply the heart with blood. It is usually caused by atherosclerosis which is a buildup of plaque inside the artery walls. This buildup causes the inside of the arteries to become narrower and slows down the flow of blood.

There are many risk factors for CAD, Some are not controllable, but others can be modified. CAD develops over a long period of time and eventually progresses to the point where you may feel symptoms such as chest pain. Diagnosis is made using various tests such as an electrocardiogram (ECG) or a stress test. Treatment for CAD includes lifestyle changes, medications, and sometimes, cardiac procedures or surgery.

ABOUT CORONARY ARTERY DISEASE

The heart is a muscle which pumps blood around the body through a network of blood vessels called arteries. The left side of the heart receives fresh, oxygen-rich blood from the lungs and then pumps it out through a large artery called the aorta. The aorta branches into smaller arteries that go to all parts of the body. The various parts of the body take the oxygen out of the blood. The now stale, oxygen-poor blood is returned to the right side of the heart through blood vessel called veins. The right side of the heart pumps this stale blood to the lungs where it picks up more oxygen and the cycle begins again.

The Coronary Arteries

The heart muscle, like every other part of the body, needs its own oxygen-rich blood supply. Arteries branch off the aorta and spread over the outside surface of the heart feeding oxygen to the muscle. The right coronary artery (RCA) supplies the bottom part of the heart. The short left main (LM) artery branches into the left anterior descending (LAD) artery that supplies the front of the heart and the circumflex (Cx) artery which supplies the back of the heart. In coronary artery disease, there is a blockage in the arteries that supply blood and oxygen to the heart. The most common cause is atherosclerosis which is a buildup of plaque inside the walls of the arteries. Plaque is made of several substances including cholesterol. Plaque buildup can start at an early age and is caused by a combination of genetic and lifestyle factors that are called risk factors. As plaque builds up over time, the arteries become increasingly narrow. Eventually, blood flow to parts of the heart is slowed or blocked. Poor blood flow to the heart can cause angina. Blood clots are more likely to form in arteries which have reduced blood flow, which then further block the arteries. CAD can eventually lead to unstable angina or a heart attack.

ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

Atherosclerosis: Sometimes called hardening of the arteries—can slowly narrow the arteriesthroughout your body. When atherosclerosis affects arteries that carry blood to the heart muscle, it's called coronary artery disease. That's the No. 1 killer of Americans. Most of those deaths are from heart attacks caused by blood clots. Atherosclerosis can create life-threatening blockages—without you ever feeling a thing. Since we're all at risk for coronary artery disease, it's worth learning more about atherosclerosis.

COLD FACTS ABOUT HARD ARTERIES

- More than 90,000,000 Americans have known cardiovascular disease.
- Almost 800,000 people in the U.S. have a heart attack each year.
- Around 500,000 people will die Almost 800,000 people in the US have a of coronary artery disease this year. More than a million will have a heart attack about 115,000 of them will die from it.
- About one in 7 deaths in the US is caused by Coronary Heart Disease. About 360,000 people will die from it each year.
- Half of all men who have severe atherosclerosis with no symptoms.
- More men than women die from coronary artery disease. The rates for women go up after menopause, but they never catch up with men's.
- Heart disease is the No. 1 killer in women, just as in men.

CAUSES

Many of us have heard that clogged arteries lead to heart attacks. But how does atherosclerosis cause coronary artery disease? First, the coronary arteries' smooth interior surface is damaged. High blood pressure, abnormal cholesterol levels, cigarette smoking, and diabetes are the most common reasons why. LDL—or "bad" cholesterol—then starts to build up in the coronary artery's wall. The body sends a "clean-up crew" of white blood cells and other cells to the toxic site. Over years, continuing buildup of cholesterol and the body's response to it create a plaque. That's a bump on the artery wall that can obstruct bloodflow.

Plaques' Sneak Attacks

Atherosclerosis plaques in the coronary arteries can behave in several ways:

They can grow slowly, Never blocking the artery or causing clots.

They can expand and block blood flow in a coronary artery. This may cause no symptoms, even when the artery is very blocked.

Other Times, A blockage does Cause Symptoms: Called "stable angina," this is most commonly chest pain with activity. It goes away with rest. It's not a heart attack.

A Plaque can Rupture: That causes blood to clot quickly inside the coronary artery.

*A Plaque Rupture is as Terrible as it Sounds*L The result is a blood clot that makes your chest hurt.

Two Things can Happen then:

- *Unstable Angina:* The clot doesn't totally block the blood vessel. It then dissolves without causing a heart attack.
- *Heart Attack (Myocardial Infarction):* The coronary artery is blocked by the clot. Heart muscle, starved for nutrients and oxygen, dies.
- Blood clots can form in any of the arteries of the heart, even those with only minor blockages.

REDUCE YOUR RISK OF CORONARY ARTERY DISEASE

No one can predict who will have a heart attack. But coronary artery disease isn't random. Most people with coronary artery disease have one or more controllable risk factors. Most people who have a heart attack will have at least one or more of the following risk factors. These all can contribute to atherosclerosis and coronary artery disease.

They are also the causes of Coronary Artery Disease:

- Cigarette smoking
- High cholesterol
- Obesity
- Lack of physical activity
- High blood pressure
- Diabetes
- Low fruit and vegetable consumption
- Poor socioeconomic status.

Most of us have plenty of room for improvement. The best way to determine your risk level is to see your doctor. But you can start to reduce your risk today. Eat right, don't smoke, and exercise. Remember to check with your doctor before starting a new exercise plan. Some people may also need to take medicine to keep their cholesterol and blood pressure in a healthy range.

VASCULAR DISEASE

As the heart beats, it pumps blood through a system of blood vessels, called the circulatory system. *The vessels are elastic tubes that carry blood to every part of the body:*

- Arteries carry blood away from the heart.
- Veins return blood back to the heart.

Vascular Disease includes any condition that affects your circulatory system, such as peripheral artery disease. This ranges from diseases of your arteries, veins and lymph vessels to blood disorders that affect circulation.

ARTERIAL DISEASE

Peripheral Artery Disease

Like the blood vessels of the heart (coronary arteries), your peripheral arteries (blood vessels outside your heart) also may develop atherosclerosis, the build-up of fat and cholesterol deposits, called plaque, on the inside walls. Over time, the build-up narrows the artery. Eventually the narrowed artery causes less blood to flow, and a condition called ischemia can occur. Ischemia is inadequate blood flow to the body's tissue. *Types of peripheral arterial disease include:*

- *Peripheral Artery Disease:* A blockage in the legs can lead to leg pain or cramps with activity (claudication), changes in skin colour, sores or ulcers and feeling tired in the legs. Total loss of circulation can lead to gangrene and loss of a limb.
- *Intestinal ischemic Syndrome:* A blockage in the blood vessels leading to the gastrointestinal system
- *Renal Artery Disease:* A blockage in the renal arteries can cause renal artery disease (stenosis). The symptoms include uncontrolled hypertension (high blood pressure), congestive heart failure, and abnormal kidney function.
- *Popliteal Entrapment Syndrome:* a rare vascular disease that affects the legs of some young athletes. The muscle and tendons near the knee compress the popliteal artery, restricting blood flow to the lower leg and possibly damaging the artery.
- Raynaud's Phenomenon consists of spasms of the small arteries of the fingers, and sometimes, the toes, brought on by exposure to cold or excitement.
- Buerger's Disease most commonly affects the small and medium sized arteries, veins, and nerves. Although the cause is unknown, there is a strong association with tobacco use or exposure. The arteries of the arms and legs become narrowed or blocked, causing lack of blood supply (ischemia) to the fingers, hands, toes and feet. Pain occurs in the arms, hands, and more frequently the legs and feet, even at rest. With severe blockages, the tissue may die (gangrene), requiring amputation of the fingers and toes. Superficial vein inflammation and symptoms of Raynaud's occur commonly in patients with Buerger's Disease.

Carotid Artery Disease

- Carotid artery disease is a blockage or narrowing in the arteries supplying the brain, and can lead to a transient ischemic attack (TIA) or stroke
- Carotid artery dissection begins as a tear in one layer of the artery wall. Blood leaks through this tear and spreads between the layers of the wall.
- Carotid body tumors are growths within the nervous tissue around the carotid artery
- Carotid artery aneurysm.

VENOUS DISEASE

Veins are flexible, hollow tubes with flaps inside, called valves. When your muscles contract, the valves open, and blood moves through the veins. When your muscles relax, the valves close, keeping blood flowing in one direction through the veins. If the valves inside your veins become damaged, the valves may not close completely. This allows blood to flow in both directions. When your muscles relax, the valves inside the damaged vein(s) will not be able to hold the blood. This can cause pooling of blood or swelling in the veins. The veins bulge and appear as ropes under the skin. The blood begins to move more slowly through the veins, it may stick to the sides of the vessel walls and blood clots can form.

- Varicose veins are bulging, swollen, purple, ropy veins, seen just under your skin, caused by damaged valves within the veins.
- Spider veins are small red or purple bursts on your knees, calves, or thighs, caused by swollen capillaries (small blood vessels)
- Klippel-Trenaunay syndrome (KTS), a rare congenital vascular disorder
- May-Thurner syndrome (MTS) is caused when the left iliac vein is compressed by the right iliac artery, which increases the risk of deep vein thrombosis (DVT) in the left extremity.
- Thoracic outlet syndrome (TOS) is a group of disorders that occur when there is compression, injury, or irritation of the nerves and/or blood vessels (arteries and veins) in the lower neck and upper chest area
- Chronic venous insufficiency (CVI) is a condition that occurs when the venous wall and/or valves in the leg veins are not working effectively, making it difficult for blood to return to the heart from the legs.

BLOOD CLOTS

A clot forms when clotting factors in the blood cause it to coagulate or become a solid, jelly-like mass. When a blood clot forms inside a blood vessel (a thrombus), it can dislodge and travel through the blood stream, causing a deep vein thrombosis, pulmonary embolis, heart attack or stroke.

Blood clots in the arteries can increase the risk for stroke, heart attack, severe leg pain, difficulty walking, or even the loss of a limb.usually caused by:

- Hypercoagulable states are conditions that put people at increased risk for developing blood clots.
- Deep vein thrombosis (DVT) is a blood clot occurring in a deep vein.
- Pulmonary embolism is a blood clot that breaks loose from a vein and travels to the lungs.
- Axillo-subclavian vein thrombosis, also called Paget-Schroetter Syndrome, is a most common vascular conditions to affect young, competitive athletes. The condition develops when a vein in the armpit (the axilla) or in the front of the shoulder (the subclavian vein) is compressed by the collarbone (clavicle), the first rib, or the surrounding muscle, increasing risk for blood clots.
- Superficial thrombophlebitis is a blood clot in a vein just under the skin.

AORTIC ANEURYSM

An aneurysm is an abnormal bulge in the wall of a blood vessel. Aneurysms can form in any blood vessel, but they occur most commonly in the aorta (aortic aneurysm) which is the main blood vessel leaving the heart:

- Thoracic aortic aneurysm (part of aorta in the chest).

FIBROMUSCULAR DYSPLASIA (FMD)

Fibromuscular dysplasia (FMD) is a rare medical condition. Patients with FMD have abnormal cellular growth in the walls of their medium and large arteries. This can cause the arteries with the abnormal growth to look beaded. The arteries may also become narrow (stenosis).

BLOOD CLOTTING DISORDERS

Blood clotting disorders are disorders that make the blood more likely to form blood clots (hypercoagulable) in the arteries and veins. *These conditions may be inherited (congenital, occurring at birth) or acquired during life and include:*

- Elevated levels of factors in the blood which cause blood to clot (fibrinogen, factor 8, prothrombin)
- Deficiency of natural anticoagulant (blood-thinning) proteins (antithrombin, protein C, protein S
- Elevated blood counts
- Abnormal Fibrinolysis (the breakdown of fibrin)
- Abnormal changes in the lining of the blood vessels (endothelium).

LYMPHEDEMA

The lymphatic system is a circulatory system that includes an extensive network of lymph vessels and lymph nodes. The lymphatic system helps coordinate the immune system's function to protect the body from foreign substances. Lymphedema is an abnormal build-up of fluid that causes swelling, most often in the arms or legs. Lymphedema develops when lymph vessels or lymph nodes are missing, impaired, damaged or removed.

Primary lymphedema is rare and is caused by the absence of certain lymph vessels at birth, or it may be caused by abnormalities in the lymphatic vessels. Secondary lymphedema occurs as a result of a blockage or interruption that alters the lymphatic system.

Secondary lymphedema can develop from an infection, malignancy, surgery, scar tissue formation, trauma, deep vein thrombosis (DVT), radiation or other cancer treatment. Doctors vary in quality due to differences in training and experience; hospitals differ in the number of services available. The more complex your medical problem, the greater these differences in quality become and the more they matter.

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