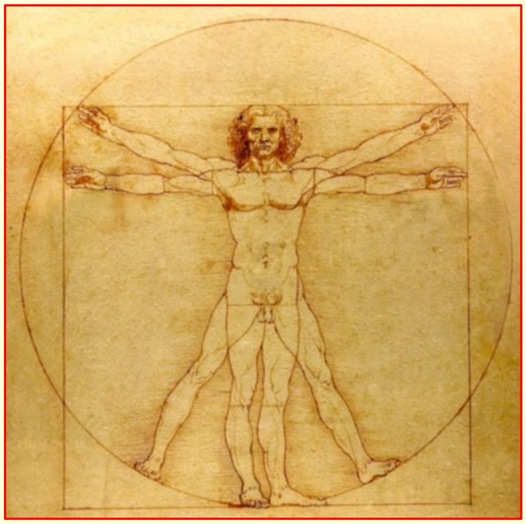
Physiology

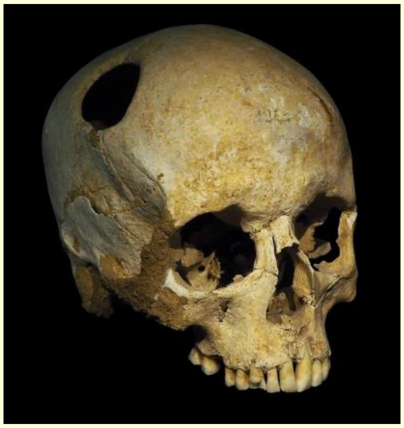


Vitruvian Man
Leonardo da Vinci
~1490 CE

This presentation deals with the workings of the human body in health and in disease. The word physiology comes from the Greek *physis* which means nature and which also led to "physics." One of the most important aspects of nature is our own body.

This is Leonardo's representation of the normal proportions of the human body as given by the Roman Architect Vitruvius (~75 BCE – 15 CE) in his *De Architectura*

Among the proportions proposed by Vitruvius
- the length of the outspread arms is equal to the height of a man
- from below the chin to the top of the head is one-eighth of the height of a man
- the maximum width of the shoulders is a quarter of the height of a man.
- from the breasts to the top of the head is a quarter of the height of a man.
- the distance from the elbow to the tip of the hand is a quarter of the height of a man.
- the distance from the elbow to the armpit is one-eighth of the height of a man.
- the length of the hand is one-tenth of the height of a man.
- the root of the penis is at half the height of a man.



Trepanated skull, showing healing, from Corseaux, Switzerland, ~3500 BCE

Early Surgery

Prehistoric humans learned to take care of trauma – fractures were fixated with wood or clay splints, severe wounds were sewn up. The first record of these techniques is the Edwin Smith Papyrus from Egypt which dates to 1600 BCE.

In many regions of the world trepanation occurred. This may have been an attempt to release malevolent spirits causing headache or epilepsy. Healing of the bone showed that some of the patients survived.

Ancient Medicines

Human beings slowly learned that certain plants were medicinal. Opium poppies were cultivated in Mesopotamia and Egypt. Castor beans and Senna tea were used as laxatives. Belladonna could be used against diarrhea. The bark of the willow tree was helpful for fever. Most ancient herbal remedies turned out to be more magical than medicinal.

Two modern drugs that were originally of natural origin are **digoxin** from foxglove which William Withering discovered in 1785, and **curare** which came from the poisoned darts of South American natives.

Seed pod of opium poppy

Belladonna contains atropine which inhibits intestinal motility.
Willow bark contains salicylates. Acetyl salicylic acid (ASA) was initially synthesized in 1853 and marketed by the firm Bayer (founded by Friedrich Bayer in 1863) as aspirin in 1899

The extract of foxglove (digitalis) was used to treat congestive heart failure.
Curare was obtained from natives in Guyana by Sir Walter Rayleigh in 1595. It is used as a muscle relaxant in anesthesia, and as a treatment for the muscle spasms in tetanus and strychnine poisoning. Both strychnine and curare come from trees of the genus Strychnos. The mode of action of curare – blocking transmission at the neuromuscular junction - was demonstrated by Claude Bernard in 1844.

Many ancient civilizations had their lists of medicines. Clay tablets in Mesopotamia contain prescriptions. The *Sushruta Samhita* which serves as the basis for Ayurveda medicine in India dates to about 600 BCE. The *Yellow Emperor's Canon of Internal Medicine* dates to ~200 BCE.

Of the thousands of medicines listed in these early texts, few have been found to be effective beyond what might be expected as a placebo. The healing power of placebo is great, and not to be dismissed. Nevertheless modern pharmacology is not much indebted to ancient herbalists.

Brass, ivory, ebony and pewter enema (clyster) syringes, Wellcome Collection

Enemas and Emetics

Since the dawn of time human beings appear to have been afraid of intestinal putrefaction. Diseases were attributed to the retention of rotting food within the bowel. According to Herodotus (5th Century BCE), the Ancient Egyptians set aside three days of each month for cleansing the intestines with enemas, purgatives, and emetics. In Europe from the 16th to the 20th centuries, clysters were considered an appropriate treatment for almost any disorder. Today's high colonics are the residual of this strange human fascination with cleansing our bowels.

Some of the fear of putrefaction from the intestines may have been related to the procedures that were used to prevent the decay of the body after death. The most important was to remove the intestines.

The Mummification Process

Physicians in Egypt were perhaps more concerned with (and more successful at) preserving the body after death than preventing the death of a living person. The patients themselves were perhaps also more concerned with the afterlife than the present life.

The video is from the J. Paul Getty Museum
https://www.youtube.com/watch?v=-MQ5dL9cQX0

Soap

Early soap was made by mixing fat or oils with lye (obtained from ashes). Soap acts as a surfactant allowing oil and dirt to be suspended in water and washed away. Soap was used for cleaning in the Middle East by 2800 BCE. The Egyptians used soap extensively. The Ancient Greeks also used soap. Indeed the word 'soap" is sometimes (incorrectly) related the to the poet Sappho.

The illustration shows a late 19th Century ad for Pears' soap.

Interestingly, while the barbarians used soap, the Romans did not. They applied oil to the skin and then removed the oil (and the dirt) with a *strigil* (scraper).

One of the myths about soap is that it was discovered when rain fell on the ashes of a sacrifice, formed lye (potassium or sodium hydroxide)

Asklepios at Epidaurus

Ancient Greek Medicine

Asklepios, son of Apollo was the Greek god of healing. His symbol was a rod with an entwined serpent. Sick people visited his shrines – asklepieions – in various locations to be cured. The main procedure at the shrine was to bathe and sleep the night. In the morning dreams were interpreted to provide instruction as to how to change one's life.

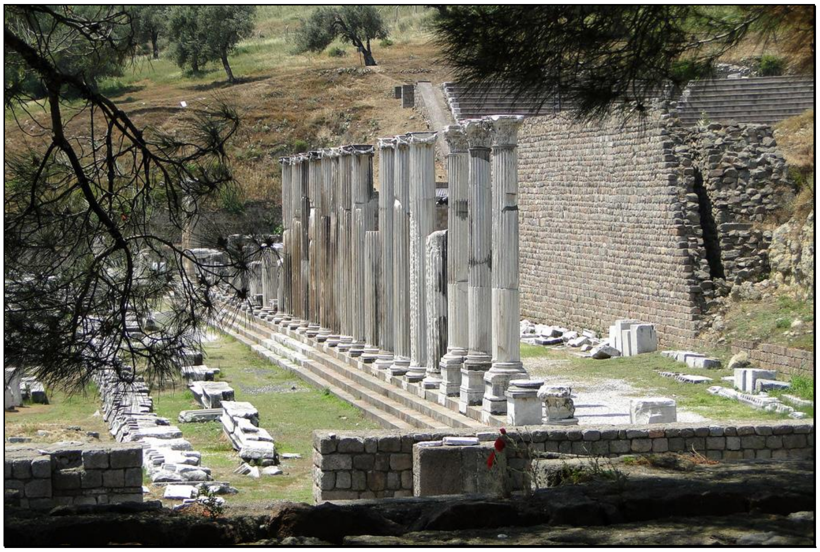
Hippocrates (460-370 BCE) worked at the asklepieion on the island of Kos in the Southern Aegean Sea. He proposed that diseases are not caused by the malevolence of the gods but by natural causes. This was true even for the sacred disease of epilepsy. He promoted healthy behavior. He is famous for the Hippocratic Oath.

Epidaurus is in the Peloponnesus in Southern Greece. Its ruins which date from the 4th Century BCE include a theatre and a sanctuary of Asklepios.

The rod of Asklepios should be distinguished from the Caduceus of Hermes (the messenger god) which has two intertwined snakes

Among the daughters of Asklepios were Hygeia (cleanliness) and Panacea (health).

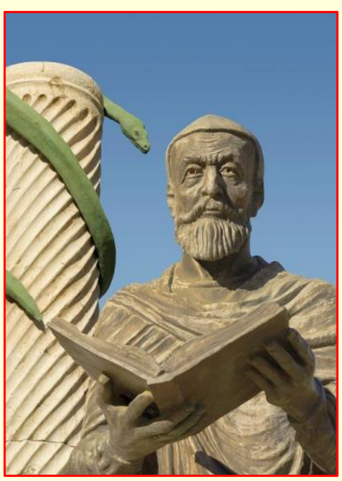
The Hippocratic Oath (translated by Joseph Loeb):
I swear by Apollo the Healer, by Asclepius, by Hygeia, by Panacea, and by all the gods and goddesses, making them my witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture.
To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art, if they want to learn it, without fee or indenture; to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the physician's oath, but to nobody else.
I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrong-doing. Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course. Similarly I will not give to a woman a pessary to cause abortion. But I will keep pure and holy both my life and my art. I will not use the knife, not even, verily, on sufferers from stone, but I will give place to such as are craftsmen therein.
Into whatsoever houses I enter, I will enter to help the sick, and I will abstain from all intentional wrong-doing and harm, especially from abusing the bodies of man or woman, bond or free. And whatsoever I shall see or hear in the course of my profession, as well as outside my profession in my intercourse with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets.
Now if I carry out this oath, and break it not, may I gain for ever reputation among all men for my life and for my art; but if I break it and forswear myself, may the opposite befall me.



This is a photograph by Adam Jones of the Asklepion at Pergamon on the East Coast of the Aegean in Modern Turkey. .
https://visionpubl.com/en/cities/pergamon/asklepieion/
http://www.ntimages.net/Pergamum-asclepion-theater-stoa-tns.htm

The columns show the portico of the shrine. Inside the shrine were areas for bathing, sleeping and consultation.

Pergamon was where the Roman physician Galen first practiced.



Modern statue of Galen, Pergamon

Galen of Pergamon (129-216 CE)

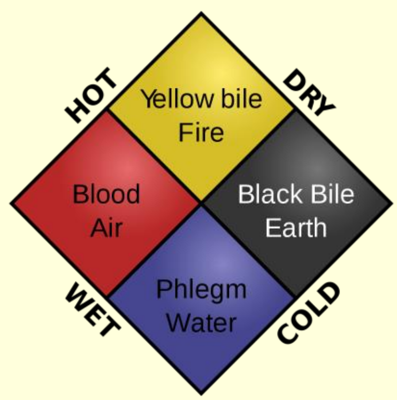
Galen was trained in medicine at the Asklepieion in Pergamon. There he studied anatomy and physiology in animals and wrote extensively. In 162 he travelled to Rome. The Emperor Marcus Aurelius was impressed by Galen who correctly diagnosed him as suffering from indigestion rather than some fatal disease He called him *Primum sane medicorum esse, philosophorum autem solum (*first among doctors and unique among philosophers). In 169 CE Galen described the Antonine Plague (probably Smallpox) which scourged the Roman Empire.

Galen learned much of his human anatomy from treating gladiators in Pergamon. Roman law did not allow the dissection of cadavers and so Galen extrapolated from animal anatomy to human. Thus he assumed that there was a *rete mirabile* at the base of the human brain just like in sheep,

and that this served to produce animal spirits. This was shown not to be the case by Vesalius in 1543.
Nevertheless Galen did demonstrate that the voice came from the larynx and showed how this was controlled by the recurrent laryngeal nerves. His dissections allowed him to become a proficient surgeon, and he reported a case wherein he removed an infected sternum revealing the beating heart and the patient survived.
Medicine in Rome was very competitive. With his ability to diagnose and to prognose Galen easily surpassed the other physicians. For example he was familiar with the recurrent spells of malaria ("quartan fever") and impressed patients by predicting the next paroxysm.
He assumed a character and a bearing that was imitated by physicians for centuries – aloof, taciturn, confident. Never let the patient know you have no idea what is going on.
Galen distinguished between arterial and venous blood but had no understanding of its circulation. He thought that the venous blood was created in the liver and the arterial blood created in the heart. Both were then distributed to the body and consumed by its organs.

Humoral Medicine

The Human body contains blood, phlegm, yellow bile and black bile. These are the things that make up its constitution and cause its pains and health. Health is primarily that state in which these constituent substances are in the correct proportion to each other, both in strength and quantity, and are well mixed. Pain occurs when one of the substances presents either a deficiency or an excess, or is separated in the body and not mixed with others. (Hippocrates, *On the Nature of Man*).



In his treatment of patients Galen followed the ideas of the Hippocratic school concerning the "humors." The basic theory of the humors likely originated in the Middle East or India. Present Ayurveda medicine has roots that go back to 600 BCE. Ayurveda posits five basic elements, adding ether to the four earthly elements.

Of the four basic fluids, blood is the only one that really exists. The theoretical bile fluids do not really equate to those produced in the gall bladder, and phlegm is not the same as the mucosy secretions of the respiratory system.

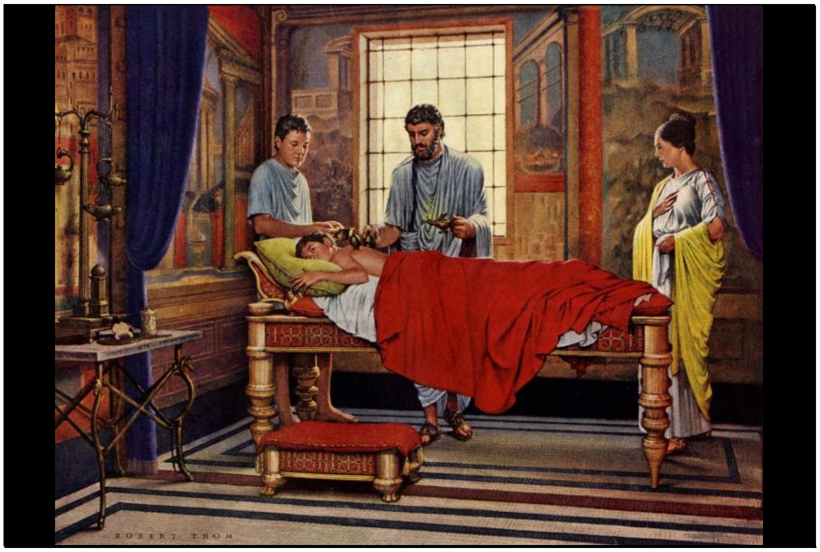
Fåhræus (1921) suggested that the four humours were based upon how blood clots. When blood is drawn in a glass container and left undisturbed for about an hour, four different layers can be seen. A dark clot forms at the bottom (the "black bile"). Above the clot is a layer of red blood

cells (the "blood"). Above this is a layer of white blood cells (the "phlegm"). The top layer is clear yellow serum (the "yellow bile").
https://en.wikipedia.org/wiki/Humorism

As well as their relations to the elements, the four humors were also associated with differences in personality or "temperament." The four temperaments were sanguine (enthusiastic, social, active), choleric (ambitious, decisive, angry), melancholic (thoughtful, reserved, anxious) and phlegmatic (relaxed, sympathetic, easy-going). These traits can be mapped into modern personality research such as the two factor theory of Eysenck which proposes the two dimensions of extraversion and neurosis. Thus sanguine is high E and low N, choleric is high E and high N, melancholic is low E and high N and phlegmatic is low E and low N. The Big Five Factor Theory – openness to experience, conscientiousness, extraversion, agreeableness and neuroticism (OCEAN) – is less easy to fit with the four temperaments.

Marble relief of bloodletting tools from the Asclepieion in Athens, 400 BCE

Bloodletting was a major part of ancient Greek and Roman medicine. The blood could be obtained by either venesection (cutting into a vein) or by cupping.



Humoral medicine is based on the idea of maintaining a proper balance between the different bodily fluids. Blood is the one that tends to run to excess, causing fever and inflammation. Thus bloodletting became a way to restore balance.

The theory behind bloodletting varied over the ages. As the years went by the idea became not so much to remove excess blood as to remove tainted blood.

Painting by Robert Thom (1957) of Galen applying cups. The skin was scratched or scarified and the heated cup drew out blood as it cooled and the pressure inside the cup decreased. This was a gentle mode of bloodletting. Galen also practiced bloodletting by venesection (phlebotomy). The vein was incised with a sharp knife or lancet and the blood dripped into a bowl.

In the 19th century leeches became widely used to remove blood from sick patients.

Bloodletting

Tintype photograph 1858

The treatment of disease by removing blood persisted from the time of Galen into the early years of the 20th Century. There was never any evidence that it helped. However, it was something to do when faced by diseases that one did not understand.

George Washington suffered from what was likely acute epiglottitis (cynanche) in December 1799. His doctors withdrew about 40% of his blood during their treatment of the president. Though the disease was dire, the bloodletting certainly did not help. Washington died.

Photograph is from the Burns Archive
http://www.burnsarchive.com/therapy---treatments.html

A history of bloodletting is available at
https://www.rcpe.ac.uk/sites/default/files/thomas_0.pdf

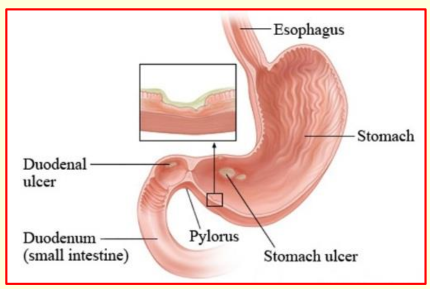
The death of Washington is described in
https://www.pbs.org/newshour/health/dec-14-1799-excruciating-final-hours-president-george-Washington

Although bloodletting was the accepted therapy for infections, several have accused Washington's physicians of killing their patient.

Evidence that bloodletting was detrimental accumulated in the 19th Century. Yet many physicians still defended its use. It is even mentioned as a treatment for pneumonia in the 20th Century textbook of William Osler.

One bizarre convergence of humoral theory with Christianity was the transfusion of a mentally ill man Arthur Coga with the blood of a sheep. The idea was to substitute the gentleness of the lamb for his tempestuous character. The patient did not die. His personality did not change. Other patients died and transfusion quickly went out of fashion.

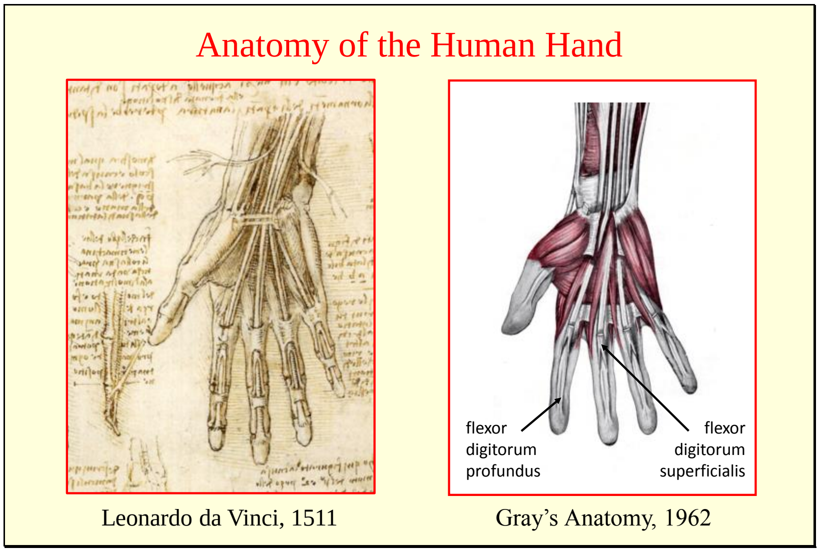
Evidence and Doctrine



Physicians are properly skeptical of new treatments. The recent idea that multiple sclerosis is caused by the congestion of veins draining from the brain was found incorrect after extensive testing. However, we do have a tendency to follow the teachings of our teachers. I remember being taught that peptic ulcer disease was caused by increased secretion of acid in the stomach and should be treated by bland diets, antacids and psychotherapy. Three decades ago, Robin Warren and Barry Marshall showed that an infection with *Helicobacter pylori* was the main cause of peptic ulcers, and that antibiotics were the best therapy.

Molière satirized the tendency of doctors to follow blindly the precepts of their teachers in *Le Malade Imaginaire* (1673). The foolish young doctor Thomas Dafouris is lauded because il s'attache aveuglément aux opinions de nos anciens, et que jamais il n'a voulu comprendre, ni écouter les raisons, et les expériences des prétendues découvertes de notre siècle, touchant la circulation du sang, et autres opinions de même farine. (He is blindly devoted to the ideas of our elders and has never wished to understand or hear about the experiments and supposed discoveries of our century about the circulation of the the blood and other ideas of the same ilk.)

Marshall and Warren received the 2005 Nobel Prize in Physiology and Medicine for their work on peptic ulcer.



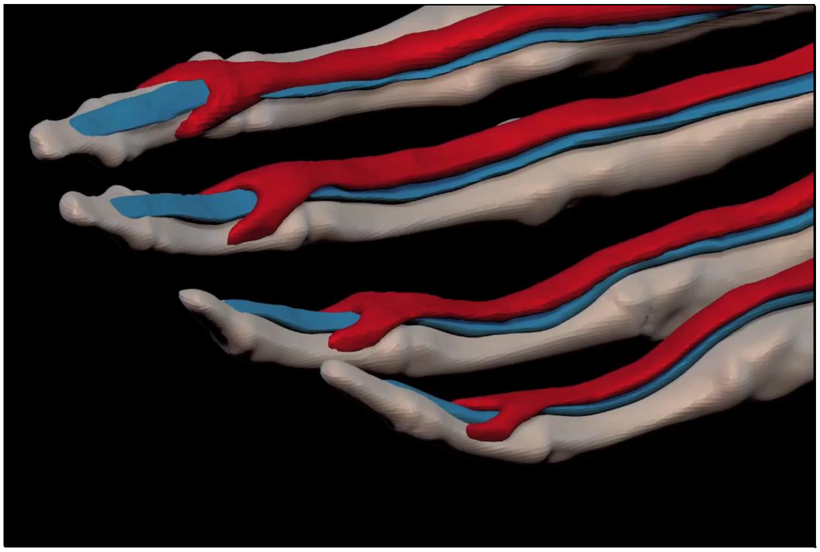
One of the greatest anatomists of the Renaissance was Leonardo da Vinci. He studied anatomy to satisfy his curiosity and to help him portray the human body in his paintings. He never published any of this work. The drawings are in his notebooks. He made his notes using mirror-writing.

Leonardo's sketches of the dissected hand are among the best anatomical drawings ever made. His drawing shows the attachments of both the flexor digitorum superficialis and the flexor digitorum profundus. The tendon of the superficial flexor divides to let the deep tendon pass through it to the distal phalanx. Leonardo's use of cutaway dissections to demonstrate these tendons is masterful. He also made a small sketch (on the left) to show the different attachments viewed from the side. The division in the tendon of the superficial tendon is often named "Camper's chiasm" after the anatomist Peter Camper who reported it in 1762 – a century and a half after Leonardo.

Leonardo performed many examinations of the human cadaver, sometimes in search of information to support his paintings, sometimes curious about life and death. The following is his description of an autopsy of an old man:

This old man, a few hours before his death, told me that he was over a hundred years old, and that he felt nothing wrong with his body other than weakness. And thus, while sitting on a bed in the hospital of Santa Maria Nuova in Florence, without any movement or other sign of any mishap, he passed from this life. And I dissected him to see the cause of so sweet a death. This I found to be a fainting away through lack of blood to the artery which nourished the heart and the other parts below it, which I found very dry, thin and withered. This anatomy I described very diligently and with great ease because of the absence of fat and humours which greatly hinder the recognition of the parts.

From Clayton, M. & Philo, R. (2010). *Leonardo da Vinci: The Mechanics of Man*, Royal Collection Trust., 2010.
Available at:
https://www.rct.uk/sites/default/files/file-downloads/9781909686834_High%20Res..pdf



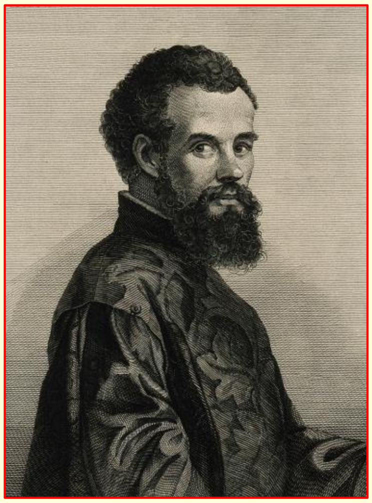
Anatomy of flexor digitorum muscles from Jake Hebbert's video
https://www.youtube.com/watch?v=ZpgOmn244gw

He uses tiny plasticine models of the different anatomical structures.

Manual Muscle Testing (MMT) from Russ Hoff's video
https://www.youtube.com/watch?v=-IlfWZqo-Mk

DIP is the distal interphalangeal joint, PIP is proximal interphalangeal joint. The phalanges are the three bones of the each of the fingers.

Once the fingers other than the one being flexed are extended it is impossible to flex the distal interphalangeal joint. This is because the tendons of the flexor and extensor muscles are linked between the fingers. The fingers often tend to move together rather than independently. Musicians need extensive training to use the fingers independently. In the nineteenth century pianists used various mechanical finger exercises to improve this independence. Schumann began to have problems with his fingers and ultimately gave up playing. This was once attributed to the effect of such exercises, but was more likely related to his syphilis or its treatment.



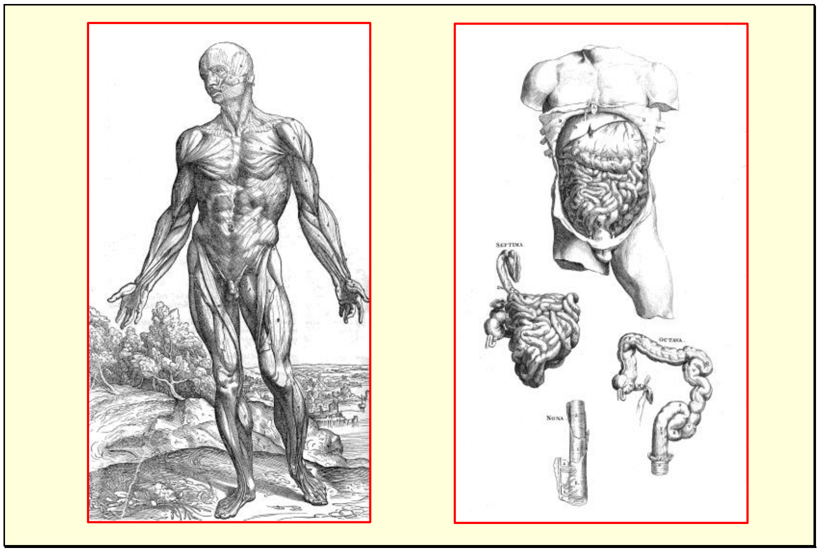
Andreas Vesalius (1514–1564)

Born in Brussels, Vesalius studied at the University of Leuven and then obtained his doctorate at the University of Padua in 1537. He published his *De Humani Corporis Fabrica* (On the fabric of the human body) in 1543. The wood-engravings of his dissections were probably the work of Johannes Stephanus Calcar or some other students of Titian. His work disproved claims by Galen about the brain's blood vessels, the origin of the venous blood vessels in the liver and the two-part mandibular bone.

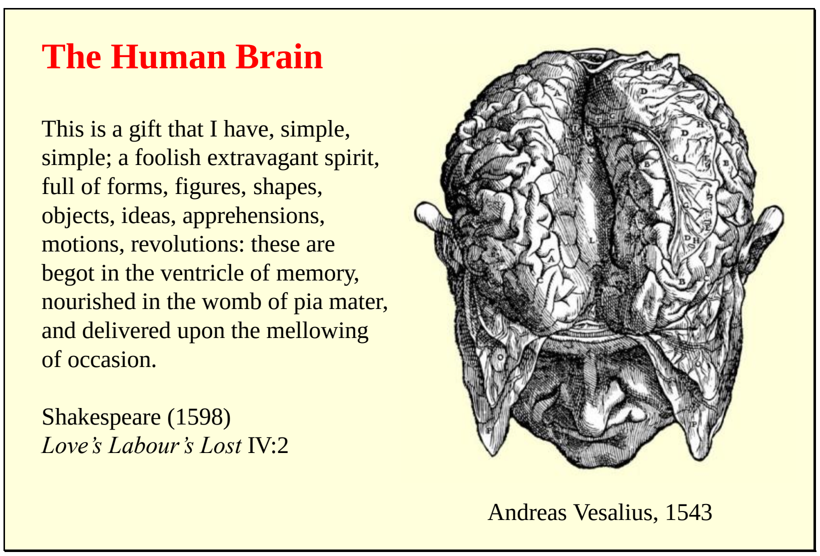
Galen's anatomical mistakes were partly due to his not having access to human cadavers. He based his ideas of human anatomy on dissections of animals. No one sought to question the authority of Galen for hundreds of years. This was partly due to the Church's edict against dissecting human cadavers.

Even Vesalius could not bring himself to state that the foramen ovale between right and left atria of the heart was not patent (open) in adult human beings (as it is in the fetus). He thought that there must be tiny holes that allowed the blood to pass.
Vesalius also published a brief letter on where to take blood during bloodletting. Galen had recommended a vein near the disease, but later Islamic authors had suggested different locations. Vesalius favored Galen's approach.

Vesalius dedicated his *Fabrica* to Charles V, the Holy Roman Emperor. The emperor appointed him his court physician and Vesalius served the emperor and his son Phillip II until 1564 when he decided to resume his studies in Padua. However while on a pilgrimage to Jerusalem he was shipwrecked and died. Some attributed this to God's vengeance for his desecration of the dead.



Other selected images from the book are available at
https://www.nlm.nih.gov/exhibition/historicalanatomies/vesalius_home.html



This is a speech by the school-teacher Holofernes in Shakespeare's *Love's Labour's Lost*. He is describing his ability to spout ideas.
He says that his fantastical notions are begot in the ventricles and nourished in the womb of the pia mater.
Holofernes was aware of the anatomy of Vesalius. Shakespeare had read widely.
As had Rembrandt in his painting of the *Anatomy Lesson of Dr. Deijman*.

Slide 21

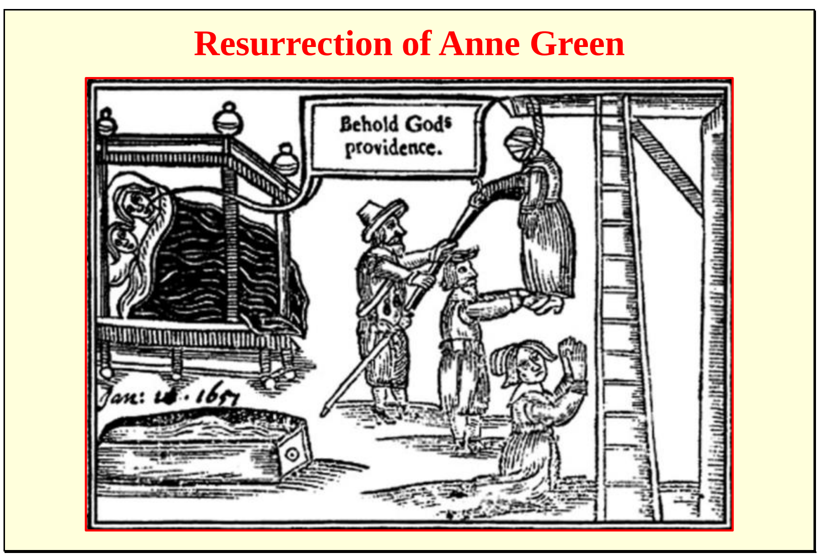
The Anatomy Lesson of Doctor Deijman
Rembrandt van Rijn
1656

The illustration on this slide is *The Anatomy Lesson of Dr. Deijman* (pronunciation: dee-eye-man). It is only a fragment of a larger painting that was severely damaged in a fire. The professor demonstrates the membranes surrounding the brain of the thief Joris Fontejn, who had been executed by hanging. The view of the brain derives from Vesalius.

The original painting showed the professor dissecting the brain and an assembly of students observing his work. The fellow on the left is a simple assistant. He is holding the calvarium – the top of the skull that has been removed

Short Talk on the Anatomy Lesson of Dr. Deyman by Anne Carson (1992), a Canadian poet:
A winter so cold that, walking on the Breestraat and you passed from sun to shadow you could feel the difference run down your skull like water. It was the hunger winter of 1656 when Black Jan took up with a whore named Elsje Ottje and for a time they prospered. But one icy January day Black Jan was observed robbing a cloth merchant's house. He ran, fell, knifed a man and was hanged on the twenty-seventh of January. How he fared then is no doubt known to you: the cold weather permitted Dr. Deyman to turn the true eye of medicine on Black Jan for three days. One wonders if Elsje ever saw Rembrandt's painting, which shows her love thief in violent frontal foreshortening, so that his pure soles seem almost to touch the chopped open cerebrum. Cut and cut deep to find the source of the problem, Dr. Deyman is saying, as he parts the brain to either side like hair. Sadness comes groping out of it.

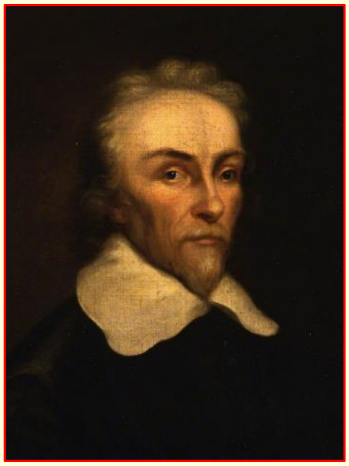
This is the Anatomical Theatre in Padua, built in 1595. Here several hundred students could watch an anatomical dissection by professors who had trained with Vesalius.



The need for cadavers for the new anatomy led to various official regulations.
In 1636 the charter granted by Charles II to the University of Oxford allowed the university anatomist to demand, for the purpose of anatomical dissection, the body of any person executed within 21 miles of Oxford.
Anne Green was a servant in the house of Sir Thomas Read. She was raped by her master’s grandson and gave birth to a stillborn child. Suspected of murdering her child, she was condemned to death and executed by hanging on December 14, 1650. Declared dead, her body was taken to the house of William Petty, Reader in Anatomy at the University of Oxford. He was to be assisted in the dissection by Thomas Willis and several other Oxford physicians. However,

before the dissection could begin she took an audible breath. The doctors gave her a cordial, bled some blood from her, and put her in bed with female servant to warm her up. She returned to full health, and went on to have three children and to live for another 15 years.
This incident is considered in Iain Pears' 1997 novel *An Instance of the Finger Post*.

An article about this event is
https://www.bmj.com/content/bmj/285/6357/1792.full.pdf



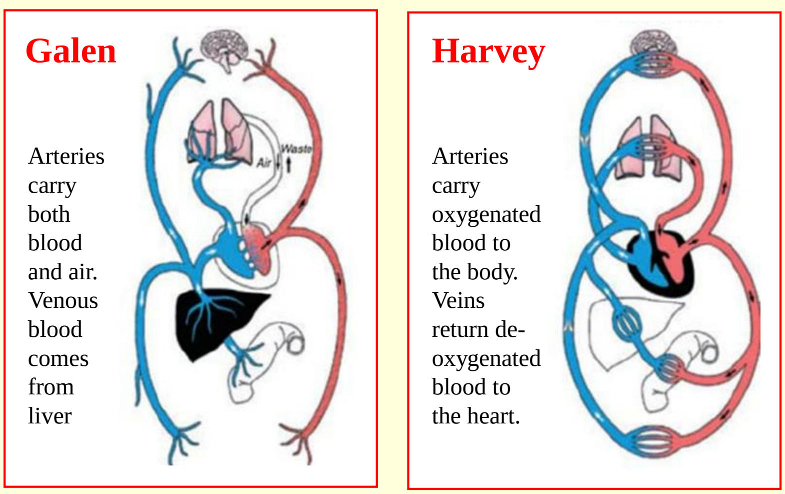
Anonymous Portrait, Royal College of Physicians, London

William Harvey (1578-1657)

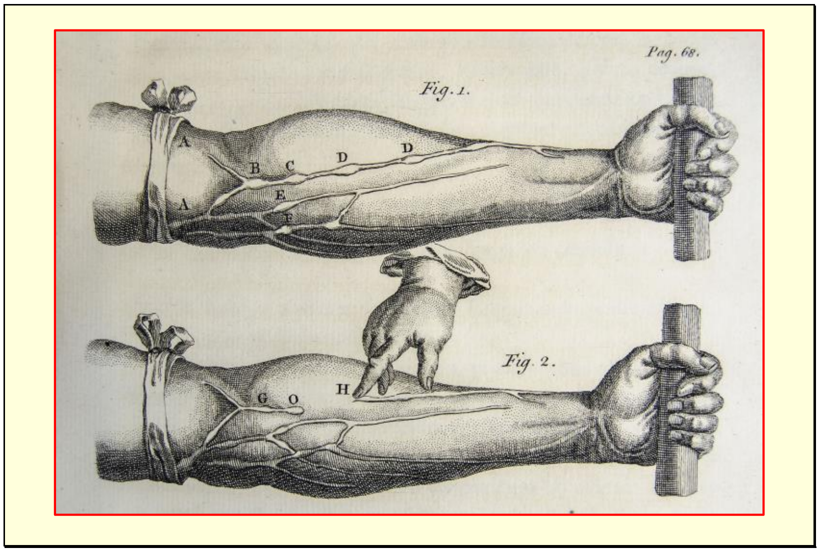
William Harvey matriculated at the University of Cambridge, and then studied medicine at the University of Padua. In 1609 he became the Physician in charge of Saint Bartholomew's Hospital in London. In 1618 he was appointed Physician Extraordinary to James I. In 1628 he published *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings)

Harvey's work on the circulation of the blood was supported by the Lumleian lectures (endowed by Baron Lumley and continuing to this day).

Harvey was a vocal skeptic about witchcraft and was instrumental in saving several women from execution as witches.



Although the diagram for Harvey illustrates how we now know the circulation works, Harvey did not actually know about oxygen which was not demonstrated until the next century by Joseph Priestley. Nor did he know about capillaries. These were first seen by Marcello Malpighi and Antonie van Leuwenhoek later in the 17th Century.

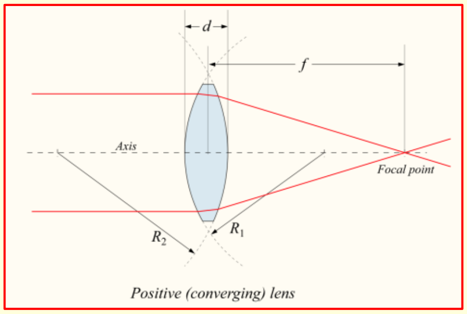


One of the advantages of growing old is that it is easy to see our veins and to demonstrate how blood flows only toward the heart and is prevented from flowing in the opposite direction by valves.
Harvey's discussion of the valves in the veins:

They are so constituted that they can never permit blood to move in the veins from the heart upwards to the head, downwards toward the feet, or sidewise to the arms. They oppose any movement of blood from the larger veins toward the smaller ones, but they favor and facilitate a free and open route starting from the small veins and ending in the larger ones.
This fact may be more clearly shown by tying off an arm of a subject as if for blood-letting A, A, fig. 1). There will appear at intervals (especially in rustics) knots, or swellings, like nodules (B, C, D, E, F), not only where there is branching (E, F), but also where none occurs (C, D), These are caused by the valves, appearing thus on the surface of the hand and arm. If you will clear the blood away from a nodule or valve by pressing a thumb or finger below it (H, fig. 2), you will see that nothing can flow back, being entirely prevented by the valve, and that the part of the vein between the swelling and the finger (H, O, fig. 2), disappears, while above the swelling or valve it is well distended (O, G).

Lenses

The first lenses for reading originated in Northern Italy in the late 13th Century CE. Over the next two centuries the process of grinding and polishing lenses was further developed, particularly in the Netherlands.



Microscopes were developed in Holland by the late 16th Century and the first telescopes soon thereafter. Descartes published a study of the science of optics in 1637, but it was not until Isaac Newton's *Opticks* (1704) that we had a clear an understanding of refraction.

In an article on *The 50 Greatest Breakthroughs since the Wheel* in the Atlantic Magazine (2013), the creation of optical lens is listed the 5th greatest discovery (after the printing press, electricity, penicillin and semiconductor electronics). Reading lenses allowed more people to read. Microscopes and telescopes extended the reach of our vision.
https://www.theatlantic.com/magazine/archive/2013/11/innovations-list/309536/

One of our greatest philosophers – Benedict Spinoza – made his living by grinding and polishing lenses.

Antonie van Leeuwenhoek (1632-1723)

Van Leeuwenhoek operated a draper's shop in Delft and later became a chamberlain in the city assembly. He initially used lenses to see the quality of the thread in his cloth, but soon became interested in whatever his microscopes could show him. He communicated his findings to the Royal Society in London, and after his death his daughter sent the society many of his microscopes and specimens.

Portrait by Jan Verkolje (~1680)

Van Leeuwenhoek served as an executor of the will of the painter Johannes Vermeer.

Replica of a microscope of van Leeuwenhoek

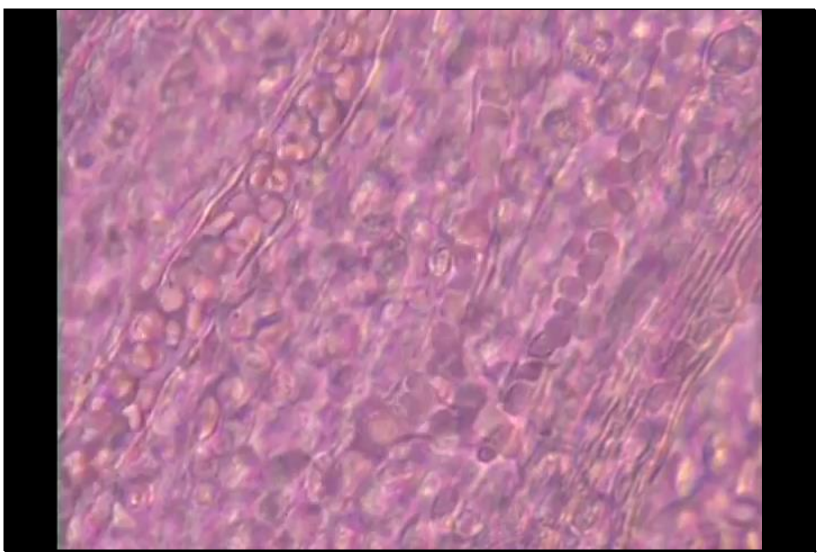
The Microscope

Van Leeuwenhoek's microscope was a simple magnifying lens. A tiny spherical lens provided a magnification of up to 300X. Others (e.g. Galileo, Robert Hooke) had made compound (2-lens) microscopes by the mid 17th century but these were not as powerful as Van Leeuwenhoek's.

Van Leeuwenhoek described:

- protozoa (1674)
- spermatozoa (1677)
- muscle fibers (1682)
- bacteria (1683)
- blood cells flowing in capillaries (1688)

Van Leeuwenhoek was unaware that Marcello Malpighi (1628–1694), and Italian anatomist, had also observed the microscopic flow of blood in capillaries in the frog lung in 1661. He hypothesized that capillaries were the link between the arterial and venous systems.



video showing blood flow through the caudal fin of a goldfish:
https://www.youtube.com/watch?v=wu01vlf4ORM

Capillaries allow only a single red blood cell at a time. Arterioles and venules are bigger.

From van Leeuwenhoek's description of the blood flowing in a tadpole's tale:
I discovered more than fifty circulations of the blood, in different places, while the animal lay quiet in the water, and I could bring it before the microscope to my wish. For I saw, not only that

the blood in many places was conveyed through exceedingly minute vessels, from the middle of the tail towards the edges, but that each of these vessels had a curve, or turning, and carried the blood back towards the middle of the tail, in order to be again conveyed to the heart. Hereby it plainly appeared to me, that the blood-vessels I now saw in this animal, and which bear the names of arteries and veins, are, in fact, one and the same, that is to say, that they are properly termed arteries so long as they convey the blood to the farthest extremities of its vessels, and veins when they bring it back towards the heart.

From Select Works Volume I, p 92
https://ia600200.us.archive.org/8/items/b24991016_0001/b24991016_0001.pdf

The demonstration of capillary blood-flow was the final explanation of Harvey's concept of the circulation of the blood.

Micrographia, 1665

Hooke's microscope

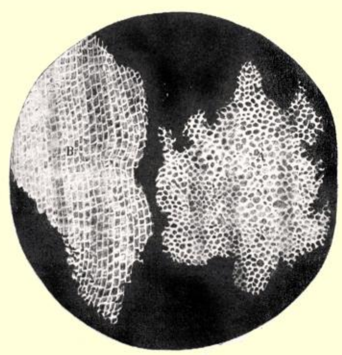


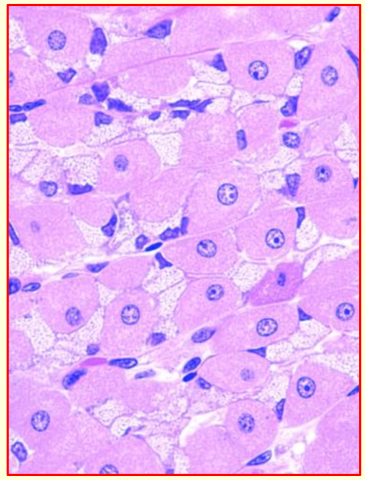
Illustration of the "cells" in cork

Robert Hooke (1635-1703) began as a chorister at Oxford but soon developed a passion for science. He worked as an assistant to Robert Boyle. His book *Micrographia* published his work with the microscope. Hooke was the first to describe the cellular structure of tissue in his description of a thin slice of cork. Hooke was the first to use the term "cells."

Cell Theory

After Hooke's initial recognition of cells, scientists found cells in many different tissues when looked at under the microscope. Theodor Schwann (1810-1882) was the first to clearly state cell theory in 1839.

1. All living organisms are composed of cells
2. The structure of organisms is determined by interactions between cells of different kinds
3. All cells arise from pre-existing cells (in the terms of Rudolf Virchow *omnis cellula e cellula*)



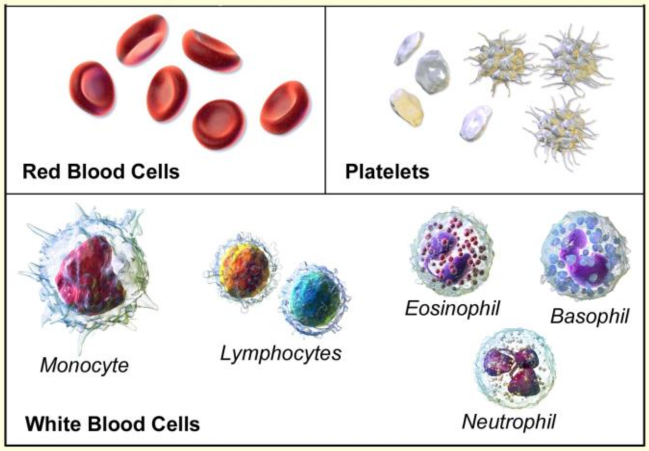
Matthias Schleiden (1804-1881) proposed plants were all made up of cells. Schwann clearly showed that animal tissues were similar to plants in that they also were composed of cells.

Schwann studied in Bonn under Johannes Müller (1801-1858). Many of Müller's students went on to become famous scientists: Rudolf Virchow (the father of pathology), Hermann von Helmholtz (who studied the velocity of nerve conduction and the mechanisms of hearing), Emil du Bois Reymond (who studied the electrical activity of nerves), and Ernst Haeckel (who studied embryology).

The slide shows parietal cells in the lining of the stomach. These cells look like fried eggs with the nucleus appearing as the yolk and the cytoplasm as the white. Most of the nuclei show a small blue dot – the nucleolus. Parietal cells produce the acid that is secreted into the stomach. The other cells in the section with more irregular shapes and nuclei are supporting cells and blood vessels.

This slide has been stained with Hematoxylin and Eosin (HE). This is the most widely used of all histological stains. The dark blue hematoxylin binds to the nuclei. The light red eosin binds to the cytoplasm.

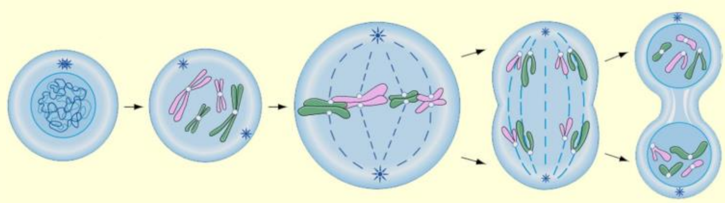
Cells of the Blood



Under the light microscope many different types of cells could be recognized. All had a cell membrane which separated the material inside the cell – the cytoplasm – from the outside. Most cells contained a single nucleus though some did not (e.g., red blood cells, platelets) and some were multinuclear (e.g. muscle cells). Typically the nucleus was spheroid though in some cells (e.g. neutrophils, basophils and eosinophils) the nucleus had multiple lobules. The light microscope could also indicate some of the material in the cytoplasm (e.g. the red granules in the eosinophil). However, it was impossible to resolve the structure of this material until the electron microscope.

However, light microscopes could show the changes in the nucleus when a cell underwent division.

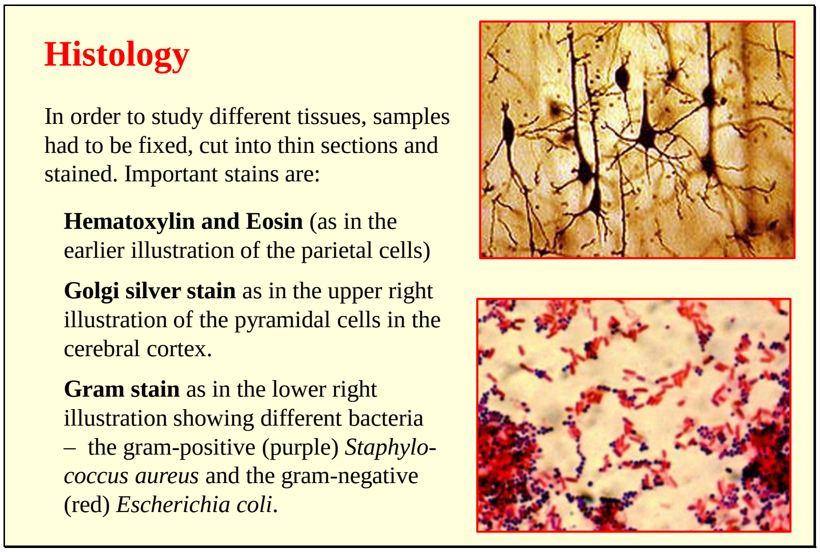
Omnis cellula e cellula



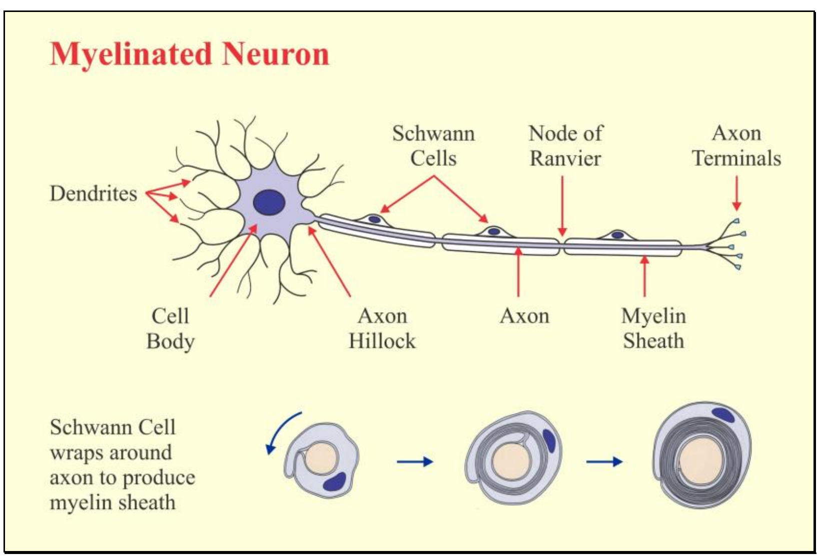
Early histologists observed evidence for cell division in the nuclei of cells in growing tissues. Mitosis is the process whereby the nucleus duplicates its chromosomes in the nucleus and divides into two separate cells each with a nucleus containing the same chromosomes as the original. At first the chromosomes separate and duplicate themselves. Then they line up and the centromeres in the cytoplasm pull them apart. Finally, two separate nuclei. are formed and the cell divides.

The word mitosis comes from the Greek *mitos*, thread, because the stained material in the cell nucleus appears as long threads in the first stages.

Chromosome comes from the Greek *chroma*, color, and *soma*, body. In the initial studies, chromosomes were just the darkly stained parts of cell nuclei. Later it would be determined that these were long strands of deoxyribonucleic acid (DNA).



Histology is the study of tissues

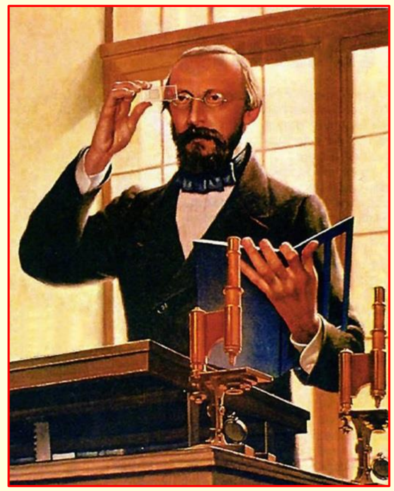


As well as making the first clear statement of cell theory, Schwann also described the cells that wrapped themselves around the axons of neurons to form the myelin sheath. The myelin serves as an insulator and causes nervous impulses to move more rapidly along the axon. How the Schwann cells made the myelin sheath (illustrated in the bottom of the slide) was not recognized until the electron microscope.

In addition Schwann was the first to recognize yeast cells as living. Van Leeuwenhoek had observed yeast cells but had not realized that they were alive.

Rudolf Virchow (1821-1902)

After studying with Johannes Müller, Virchow joined the staff at the Charité Hospital in Berlin, later also becoming the Professor of Pathology at the University of Berlin. He promoted the cell theory, standardized the procedures of autopsy, explained the process of thromboembolism, made the first diagnosis of leukemia, identified Trichinella spiralis and showed that the human roundworm comes from contaminated pork.



The illustration is modified from Robert Thom’s series of paintings on the History of Medicine (1957):
https://imgur.com/gallery/qXSrn

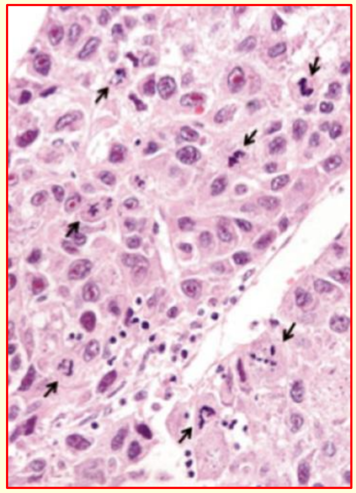
cf the illustration used earlier for Galen.

The Charité Hospital in Berlin was a very prominent center for medicine in the late 19th Century. Among its staff wereEmil von Behring, Robert Koch, and Paul Ehrlich, the future Nobel Prize winners in Physiology or Medicine.

Despite his numerous accomplishments, Virchow was obstinately wrong in several areas. He argued against the germ theory of infectious disease, arguing that germs proliferate in diseased tissue rather than cause the disease. He also argued against evolution, arguing that it was an untestable hypothesis, and insisting that man did not descend from the apes. He proposed that the bones of the Neanderthal Man, discovered in 1856, came from a diseased and injured human and did not indicate a separate species.

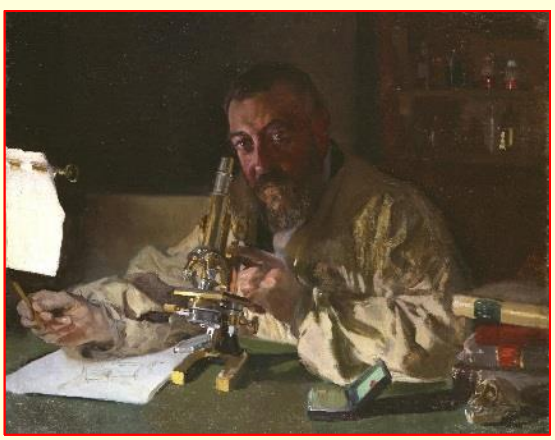
Pathology

Anatomical pathology – dissecting the cadaver to ascertain the cause of death – became common in the 17th and 18th Centuries. Giovanni Battista Morgagni (1682- 1771) published his *De Sedibus et causis morborum per anatomem indagatis* (Of the seats and causes of diseases investigated through anatomy) in 1761. During the 19th Century under the influence of Virchow, microscopic studies provided access to cellular pathology. Pathology could then begin to categorize the different diseases and their causes.



The slide shows a section of a liver cancer. The cells show characteristic pleomorphism (many different shapes rather than all the same) and multiple mitoses (indicated by arrows).

The histological diagnosis of cancer – often from a biopsy specimen – depends on a series of findings;
(i) anaplasia – the cells are no longer differentiated into the form they normally have
(ii) pleomorphism – the degree of de-differentiation varies among the cells
(iii) proliferation – the number of mitotic figures in a section is increased
(iv) invasion – the abnormal cells extend beyond their normal tissue limits



Physiology

Portrait of Doctor Luis Simarro
Joaquin Sorolla, 1897

From this time forth, the microscope became the symbol of the new science of medicine. The painting shows Dr Simarro, who had trained with Charcot in Paris, studying histological sections. The painting is a masterpiece in its portrayal of light. The physician’s face is illuminated by the light that shines through the microscope and onto the paper where he draws what he observes.