WE ARE SURVIVAL
MACHINES

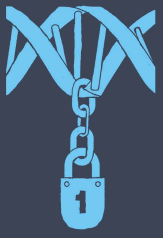
DK

A WINDOW INTO
THE BODY

RELICS OF A PRIMEVAL WORLD

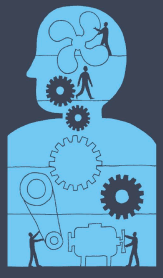
THE VIRTUES
OF ORANGES
AND LEMONS

ONE GENE–ONE
ENZYME



THE BIOLOGY BOOK

BIG IDEAS SIMPLY EXPLAINED



SICKNESS
IS NOT SENT BY
THE GODS

OILS
UPON THE
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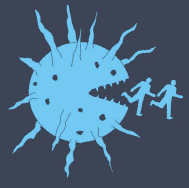
MACHINERY
OF LIFE



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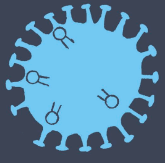

THE SEQUENCE OF
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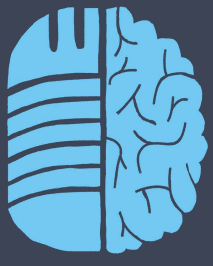

WE SPEAK
WITH THE
LEFT
HEMISPHERE

A BETTER ELEMENT DOES NOT EXIST
ON WHICH TO BASE LIFE

BIG IDEAS

THE ART BOOK
THE ASTRONOMY BOOK
THE BIBLE BOOK
THE BUSINESS BOOK
THE CLASSICAL MUSIC BOOK
THE CRIME BOOK
THE ECOLOGY BOOK
THE ECONOMICS BOOK
THE FEMINISM BOOK
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THE SOCIOLOGY BOOK

SIMPLY EXPLAINED

THE BIOLOGY BOOK

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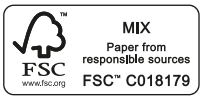

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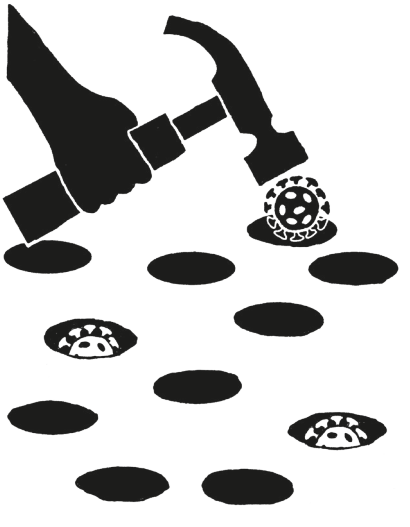

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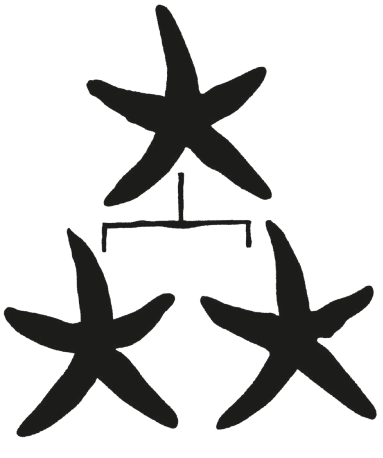

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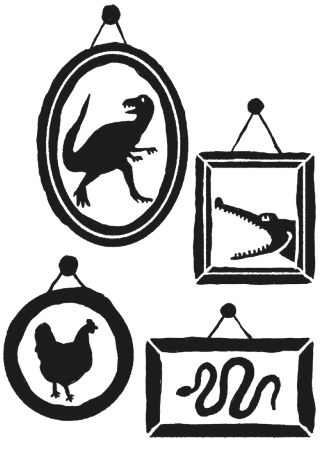
DIVERSITY OF LIFE AND EVOLUTION



ECOLOGY

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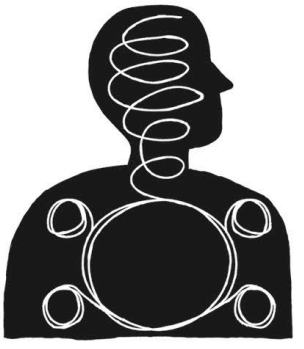


Biology, in the simplest terms, can be defined as the study of all life and living things. Along with physics, chemistry, Earth sciences, and astronomy, it is one of the divisions of the so-called natural sciences, all of which emerged from human curiosity about the composition and workings of the world around us and a deeply instilled desire to find rational explanations for natural phenomena.

Like the other natural sciences, biology has its beginnings in the ancient civilizations, and probably even earlier, as people built up a body of knowledge about their surroundings in order to survive:

> I like to define biology as the history of the Earth and all its life—past, present, and future.
> **Rachel Carson**

knowledge of the plants that are good to eat—or deadly—and where they can be found, and of the behavior of animals to help hunt—or avoid—them. Observation formed the basis for more detailed studies as societies developed and became more sophisticated, and in the civilizations of ancient China, Egypt, and especially Greece, a methodical approach to studying the natural world developed.

The world around us

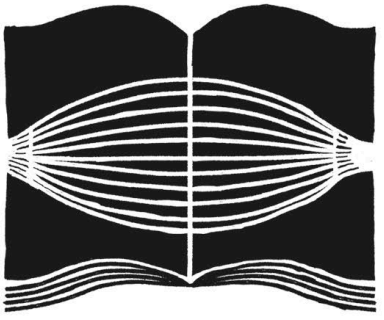
In the 4th century BCE, the Greek philosopher Aristotle began a systematic study of the world of living things by describing and classifying them. The Greek physician Hippocrates established some basic principles of medicine from his studies of the human body. Although more descriptive than analytic—and to modern thinking often erroneous—their discoveries and the theories that they inferred from their investigations provided the foundations of the study of all life for almost 2,000 years.

Then, in the late Middle Ages (1250–1500), Islamic scholars who worked to preserve and build on the knowledge of ancient thinkers, developed a sophisticated scientific approach to their research. This new method inspired the scientific revolution of the European Renaissance and the Enlightenment period. It was at this time that the sciences as we know them today emerged, with biology as a distinct division.

Branches of biology

What distinguished the modern scientific approach to the study of living things was that it was no longer simply descriptive, but actively investigated the ways in which things worked. In biology, this meant that there was a shift in emphasis from studying anatomy—the physical structure of organisms—to physiology, which is more focused on explaining the way that organisms work and the process of life itself. Given the abundance and diversity of life on our planet, it is not surprising that different branches of the subject began to evolve.

The most obvious division is determined by which particular living things are the subject of study. This has resulted in three distinct branches: zoology, the study of animals; botany, of plants; and microbiology, which examines microscopic organisms. Various subdivisions, such as biochemistry, cell biology, and genetics, have also been recognized as studies became



more advanced and specialized. There is also a myriad of practical applications of biological sciences in medicine and healthcare, agriculture and food production, and more recently—and pressingly—in understanding and mitigating environmental damage caused by human activity.

Core principles

Today, four underlying strands of thinking in modern biology can be identified, giving a better insight into the basic principles of the fields of study. These are: cell theory—the principle that all living things are composed of fundamental units known as cells; evolution—the principle that living things can and do change in order to survive; genetics—the principle that deoxyribonucleic acid (DNA) in all living things codes cell structure and is also passed to subsequent generations; and homeostasis—the principle that living things regulate their internal environment to maintain equilibrium.

Of course, there is a degree of overlap between these areas, as well as a number of subdivisions within each one. For the purposes of this book, however, these four divisions of biology are subdivided into nine chapters, each covering an aspect of biology, an underlying principle, or a specific branch. This helps to build a picture of the main ideas and their significance, and also to put them into their historical context to show how strands of thought developed over time.

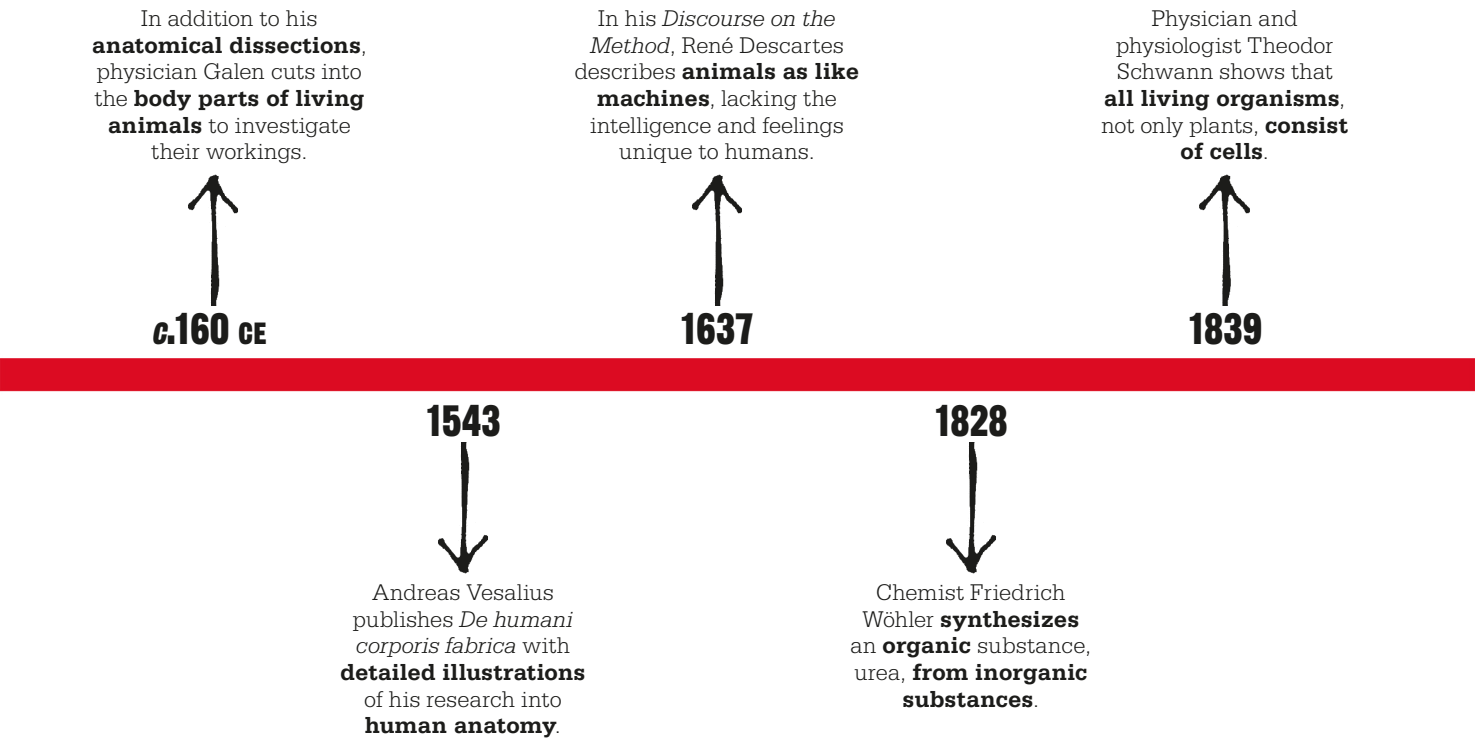
> “…the more we learn about living creatures, especially ourselves, the stranger life becomes.”
> **Lewis Thomas**

When reading this book, it is worth remembering that many of the most significant discoveries and insights in biology were made by amateurs, especially when the science was in its infancy. Today, the specialized world of biology is all too often seen as the province of academics and experts in white coats, and beyond the understanding of the ordinary person. The big ideas of biology are, however, like those of many other disciplines, often obscured by technical terms, or hampered by a lack of knowledge of the basic principles of the subject. This book aims to present those ideas in plain, jargon-free language, to satisfy the desire most of us have for a better understanding, and perhaps also to stimulate a thirst for further knowledge.

The fascination with the world of living things has been a human characteristic since prehistoric times, and can be seen today in the popularity of films and television series documenting the huge variety of life on our planet. As part of that world, we are also often in awe at the mystery of life itself, and wonder about our place in the natural order.

Biology is a result of our attempts to explore that world, and to explain its processes. But as well as providing the satisfaction of knowledge, it can also offer practical solutions to some of the problems we face as a species: providing food for an ever-growing population; combating illnesses in the face of virulent diseases; and even preventing catastrophic environmental damage. It is the hope that this book provides an insight into the ideas that have shaped our understanding of this vibrant and important subject. ■

LIFE



As biology is, broadly speaking, the science of living things, a major field of enquiry is that of exploring what constitutes life: what distinguishes living organisms from non-organic substances. Central to this are the two related disciplines of anatomy (the study of the structures of organisms) and physiology (how these structures work and behave).

Methodical examination

Historically, human anatomy and physiology evolved alongside medical sciences, but one of the first to conduct a methodical study of plants and animals was the philosopher Aristotle, in the 4th century BCE. His findings were, however, simply descriptive and involved little detailed anatomy. It was not until *c.*160 CE, when the physician Galen experimented on the organs of live animals, that any insight was gained into the ways they worked. Galen's work laid the foundations for experimental biology and physiology, and his findings were accepted until the Renaissance, when physicians and surgeons discovered and corrected errors that came from extrapolating evidence from animal dissection. Anatomy, especially human anatomy, in this period was a popular science, and publications such as Andreas Vesalius's *De humani corporis fabrica* and the anatomical drawings of Leonardo da Vinci were hugely influential.

The Age of Reason

The emphasis on human anatomy and physiology continued into the Enlightenment, the so-called Age of Reason, leading to an erroneous distinction being drawn between animal and human life. The workings of the Universe, and of plant and animal life, were understood in mechanistic terms, subject to the newly formulated laws of physics. Scientists and philosophers such as René Descartes argued that animals are incapable of reason or feelings, so are in effect simply machines—a view that held sway until the 19th century, when Darwin's writings proposed that humans are not distinct from other animals.

There remained, however, a lingering feeling that living organisms could not be entirely explained mechanistically, and that there is a mysterious "life force" in organic matter. The prevailing view was that organic

1850

The idea of **spontaneous generation** of cells is **refuted** by Rudolf Virchow's theory of the **reproduction of cells by division**.

1952

Stanley Miller and Harold Urey conduct **experiments replicating** conditions that created the **first organic molecules** on Earth from inorganic substances.

1967

Lynn Margulis develops the theory that complex, **eukaryotic cells evolved** in a process of **endosymbiosis**.

1972

The **fluid mosaic model** of **cell membrane structure** is proposed by Seymour Singer and Garth Nicholson.

2010

Biotechnologist Craig Venter leads the team that produces the **first synthetic lifeform**, a bacterium called *Mycoplasma laboratorium* (or **Synthia 1.0**).

matter could only be produced by living organisms. This was disproved by the production of an organic substance from inorganic ingredients by Friedrich Wöhler.

Investigation of the structure of organisms was greatly helped by the development of the microscope in the 17th century, and led to the discovery by Robert Hooke in 1665 of what he called "cells" in plants, which were later also noticed by Antonie van Leeuwenhoek and others. This led to the idea that these cells are the basic "building blocks" of organisms, the smallest units of living things. Matthias Schleiden and Theodor Schwann both independently concluded that all organisms, not just plants, are composed of cells, and organisms can be single- or multi-celled. Subsequent research into the structure and behavior of cells led Rudolf Virchow to the conclusion in 1850 that cells reproduce by division, and that new cells only emerge naturally from existing cells—disproving the long-held idea of spontaneous generation.

Cellular structures

Building on the discoveries of the cellular nature of organisms, scientists discovered that there are a multitude of different cellular forms, from single-celled organisms to multi-celled animals and plants, and that cells themselves ranged from the simple to the complex. According to the theory developed by Lynn Margulis, these complex, eukaryotic cells evolved billions of years ago from simpler prokaryotic cells engulfing others, absorbing some of their characteristics and developing a more complex structure. In the 1970s, biologists such as Seymour Singer and Garth Nicholson examined the structure of cells, in particular the membrane surrounding each cell, leading to the theory that it is the membrane that controls the movement of substances in and out of cells.

With the increase in knowledge and understanding of cellular structures came the idea of being able to create living matter from non-living substances in order to better understand how life first emerged from non-living matter billions of years ago. The first experiments in this field were conducted by Stanley Miller and Harold Urey in 1952, and were followed by the creation of the first synthetic life form, a bacterium, by a team of biotechnologists in 2010. ■

A WINDOW INTO THE BODY

EXPERIMENTAL PHYSIOLOGY

Cutting one pair of the **laryngeal nerves** of a living pig causes it to **stop squealing**.

Disabling other nerves emanating from a pig's brain **does not have the same effect**.

Experimental disabling of body parts shows what they do.

IN CONTEXT

KEY FIGURE
Galen of Pergamon
(129–*c.* 216 CE)

BEFORE
***c.* 500 BCE** In ancient Greece, the physician and vivisectionist Alcmaeon of Croton discovers that the optic nerve is essential for vision.

***c.* 350 BCE** The philosopher Aristotle performs dissections to investigate how parts of animals are interconnected.

***c.* 300–260 BCE** The physicians Herophilus and Erasistratus dissect human cadavers and perform vivisections on criminals.

AFTER
***c.* 1530–64** Andreas Vesalius's dissections of human corpses challenge Galen's ideas.

1628 English physician William Harvey publishes his account of the circulation of blood, debunking many of Galen's beliefs.

Some of the earliest advances in biology occurred within the fields of what are now known as anatomy (the study of the structure of living organisms) and physiology (the study of how living organisms function). In the Mediterranean, Greek physicians and natural philosophers began enquiries into these fields from about 500 BCE. Their investigations included dissections of dead human and animal bodies, and animal vivisections (the cutting open of live animals). For a limited period, they also included some human vivisections. However, due to religious teachings and taboos, all experimental cutting open of humans, whether alive or dead, ceased from about 250 BCE.

Galen's experiments

Although the Greeks achieved some progress in understanding anatomy and physiology from their dissections and vivisections, the most significant medical advances in classical antiquity occurred during the 2nd century CE, with the

See also: Anatomy 20–25 ▪ Circulation of the blood 76–79 ▪ Kidneys and excretion 98–99 ▪ The brain controls behavior 109 ▪ Speech and the brain 114–15

experiments carried out by Galen of Pergamon, physician to Emperor Marcus Aurelius in Rome.

Unlike those of his predecessors, Galen's experiments were carried out exclusively on animals—mainly monkeys, but also pigs, goats, dogs, oxen, and even an elephant—though he also treated people who had suffered deep wounds, which taught him much about human anatomy.

One way in which Galen sought to establish aspects of how the body functioned was by cutting away or disabling certain body parts of animals and then observing the effects. In one vivisection—carried out on a strapped-down, squealing pig—he cut two of the laryngeal nerves that carry signals from the brain to the larynx, or voice box. The pig continued to struggle but now did so noiselessly. The cutting of other nerves coming from the pig's brain did not have the same effect. This proved the function of these laryngeal nerves. Since it showed that the brain used nerves to control muscles involved in speech, the experiment supported Galen's opinion that the brain is the seat of voluntary action, including the choice of words (in humans) and other vocalizations (in animals).

> How many things have been accepted on the word of Galen?
>
> **Andreas Vesalius**
> **Flemish anatomist (1514–64)**

Galen went on to show that cutting the laryngeal nerves in some other animals also eliminated vocalization. Further vivisections included tying off an animal's ureters—the tubes that connect the kidneys to the bladder. The results proved that urine is formed in the kidneys—not in the bladder, as previously thought—and is then carried via the ureters to the bladder. Among other advances, Galen was also the first to recognize that blood moves through blood vessels, although he did not fully understand the workings of the circulatory system.

Questioning Galen's work

Galen is generally considered the greatest experimental anatomist and physiologist of the classical era, and his ideas about biology and medicine were influential in Europe for more than 1,400 years. However, many of his observations based on animal dissections were wrongly applied to humans. His account of the arrangement of blood vessels in the human brain, for example (based solely on the dissection of ox brains), was proved wrong by Arab scholar Ibn al-Nafis in 1242. Yet the unquestioning adherence to Galen's beliefs persisted for generations of physicians and hindered medical progress in Europe right up to the time of the Flemish anatomist Vesalius in the 16th century. ■

Galen

Claudius Galenus, better known as Galen, was born in 129 CE, in Pergamon, in what is now western Turkey. Originally a student of philosophy, at the age of 16 he switched to a medical career, studying first at a school of medicine in Pergamon and later at Alexandria in Egypt. At 28, he returned home and became chief surgeon to a troupe of gladiators, gaining much experience treating wounds. In 161 CE, he moved to Rome, where he won renown as an outstanding healer. In about 168 CE, Galen became personal physician to the emperor Marcus Aurelius. During this time, he wrote many treatises on various subjects, including philosophy, physiology, and anatomy, but less than a third have survived, in translations and commentaries by Islamic scholars.

Some sources suggest Galen died in Rome in 199 CE, but others state Sicily in *c.* 216 CE.

Key works

On the Uses of Parts of the Human Body
On the Natural Faculties
On the Use of the Pulse

HOW FEEBLY MEN HAVE LABORED IN THE FIELD OF ANATOMY FROM THE TIMES OF GALEN

ANATOMY

IN CONTEXT

KEY FIGURE
Andreas Vesalius
(1514–64)

BEFORE
***c.* 1600 BCE** Edwin Smith papyrus from Ancient Egypt identifies many organs of the human body.

2nd century CE Galen lays the foundations of anatomy by conducting detailed dissections of animals.

AFTER
1817 French naturalist Georges Cuvier groups animals according to their body structure.

1970s The invention of MRI (magnetic resonance imaging) and CAT (computerized axial tomography) scanners allows detailed, non-invasive analysis of the anatomy of living humans and animals.

People have probably known the basic features of the human and animal body since prehistoric times. And many physicians of ancient Greece and Rome were aware that a knowledge of human anatomy might be crucial to effective treatment. However, it was not until the 16th century that it became clear that the only way to get to know human anatomy in detail was by studying the human body itself.

This seems obvious now, but when Flemish physician Andreas Vesalius pioneered this approach in the 16th century, studying the body by dissecting human corpses, it was revolutionary. Physicians at the time did not believe in dissecting bodies. They thought they could get most of what they needed to know from the works of the ancient Roman physician Galen. But Vesalius, through his insistence on trusting only solid observations of the real thing, completely changed our knowledge of the human body.

Vesalius's detailed work also began to pin down how human anatomy differed from that of animals—and what they had in common. This focus on the details of variations in anatomy between species led to the development of the science of comparative anatomy, enabling the classification of animals into groups of related species. It eventually provided the basis for British naturalist Charles Darwin's theory of evolution.

> In our age, nothing has been so degraded and then wholly restored as anatomy.
> **Andreas Vesalius**

The dissection taboo

One of the problems for early human anatomists was the taboo on the dissection of corpses. The 5th-century-BCE Greek anatomist Alcmaeon tried to get around this by dissecting animals. In the following century, the city of Alexandria was

Andreas Vesalius

Vesalius was born Andries van Wesel in Brussels, then part of the Holy Roman Empire, in 1514. His grandfather was physician to Emperor Maximilian. Vesalius studied the arts at Leuven (now in Belgium) and medicine at Paris in France and Padua in Italy. He was made the chair of surgery and anatomy at the University of Padua on the day he graduated in 1537, aged just 23. There, his brilliant anatomy lectures soon became so famous that a local judge kept him supplied with the bodies of criminals from the gallows. He teamed up with some of the best artists in Italy to publish *De Fabrica*, his myth-busting seven-volume work on anatomy, in 1543. Soon after, he left teaching to become physician to Holy Roman Emperor Charles V and then King Philip II of Spain. In 1564, he died on the Greek island of Zakynthos on his way home from a trip to the Holy Land.

Key work

1543 *De Humani Corporis Fabrica* (*On the Structure of the Human Body*)

See also: Experimental physiology 18–19 ▪ The cellular nature of life 28–31 ▪ Circulation of the blood 76–79 ▪ Naming and classifying life 250–53 ▪ Extinct species 254–55 ▪ Natural selection 258–63

an exception; anatomists there were allowed to dissect human cadavers. One, Herophilus, made many key observations this way. He correctly asserted that the brain, rather than the heart, is the seat of human intelligence, and he identified the role of nerves. Herophilus went too far even for Alexandrians, however, when he conducted dissections on living criminals.

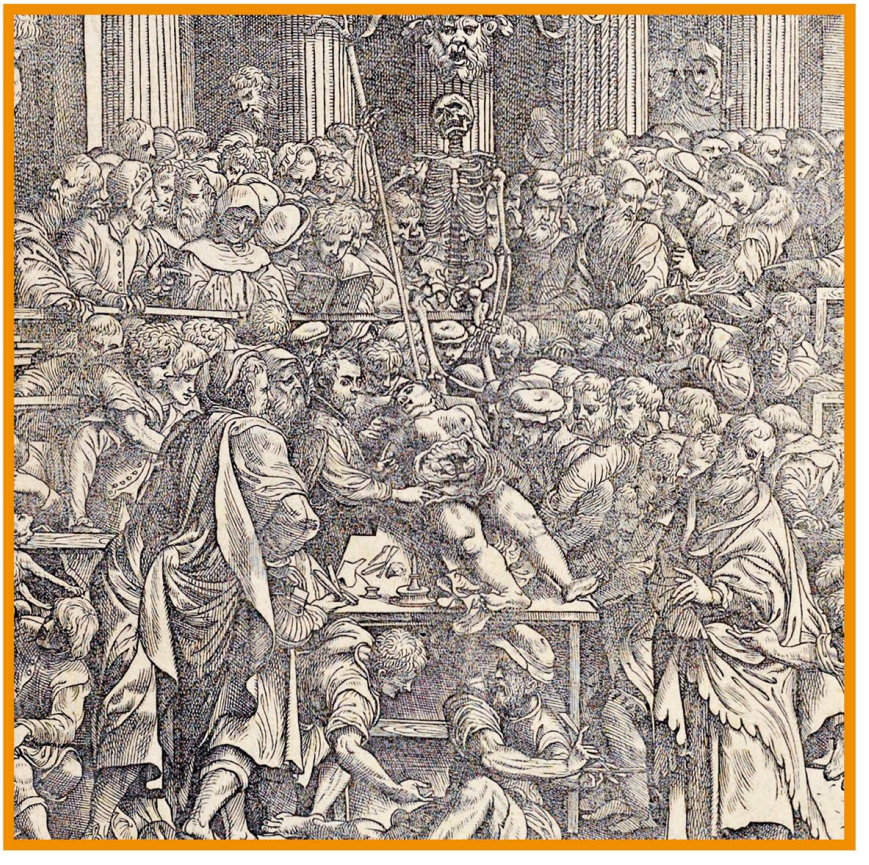
Received wisdom

Galen drew heavily on the work of Herophilus for his highly influential treatises *On Anatomical Procedure* and *On the Uses of the Parts of the Human Body*, which he compiled also using the results of his own dissections and vivisections of animals. One of his most important discoveries was that arteries are filled with flowing blood, not air as had previously been thought. He also learned much in his role as chief physician to the gladiators, which gave him a close-up view of some terrible combat wounds.

His work was so detailed and comprehensive that Galen's reputation was unassailable for the next 1,400 years. Even in Vesalius's time, lecturers would read from Galen's texts to instruct students, while in the background, barber surgeons dissected the bodies of executed criminals as instructed, and assistants pointed out the features that the lecturer was describing. It was always assumed that Galen was correct, even if the text did not appear to match what the students saw in the cadaver.

> … the most perfectly constructed of all creatures.
> **Andreas Vesalius**

Vesalius questioned Galen from the start of his career. He began his medical education in Paris under anatomists with full faith in Galen, and the lack of practical anatomy classes frustrated Vesalius. He completed his degree in Padua, where he began to dissect human corpses so he could learn anatomy first hand, rather than relying on Galen's texts. He had a sharp eye for detail and produced highly accurate anatomical drawings of the blood and nervous systems. His 1539 pamphlet showing the blood system in detail had instant practical benefits for physicians who needed to know where to take blood from—at the time, bloodletting was at the heart of medical practice. Vesalius's reputation soared, and he was »



This 16th-century image of Vesalius shows him dissecting the body of a woman at the University of Padua. His dissections often drew crowds of students and other onlookers.

made a professor of surgery and anatomy when he graduated. A Paduan judge guaranteed him a supply of cadavers—the bodies of hanged criminals. With these at his disposal, he was able to make repeated dissections for research and for student demonstrations.

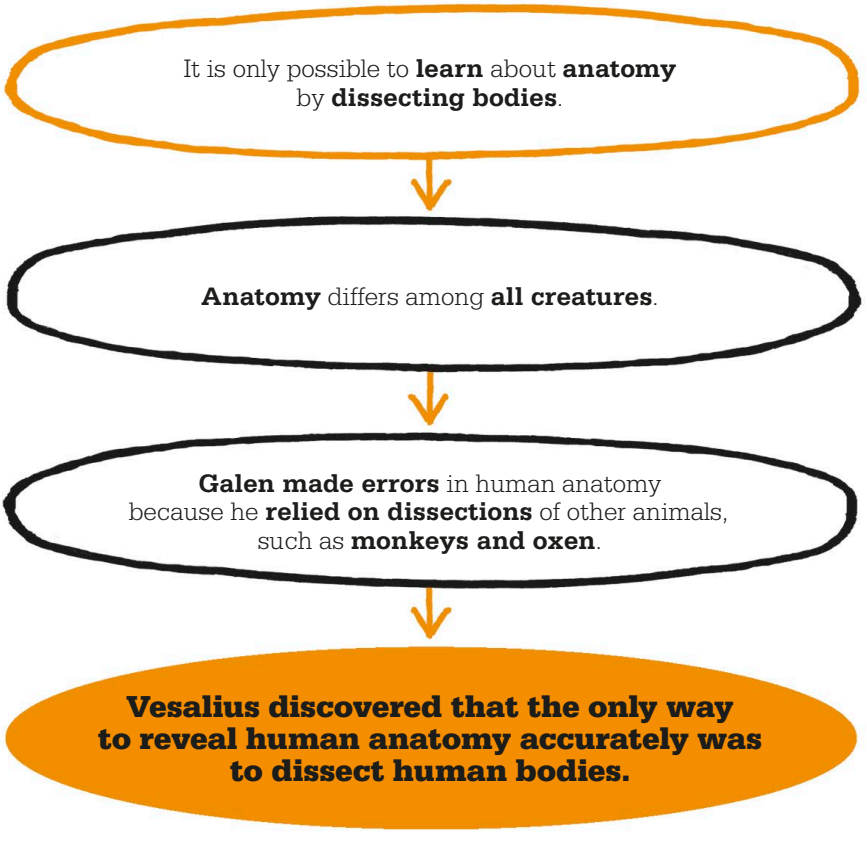
In all, Vesalius found more than 200 errors in Galen's texts, much to the outrage of those who regarded Galen's work as beyond criticism. He found, for instance, that the human sternum (breastbone) has three segments, not seven as Galen had claimed. Vesalius showed that the tibia and fibula bones of the lower leg are both longer than the humerus (upper arm bone), which Galen had asserted to be the body's second-longest bone (after the femur, or thighbone). And Vesalius also demonstrated that the lower jaw is a single bone, not two as Galen had written. Galen's errors were due not to shoddy work but to the fact that he had not been allowed to dissect human bodies. He had been forced to rely on dissections of animals such as oxen and macaque monkeys, and this explains most of his mistakes—for example, the humerus is indeed the macaque monkey's second-longest bone. Vesalius was so determined to alert his students to the difference that he hung up the skeletons of a human and a macaque in his lectures so that they could see the variation.

De Fabrica

In 1542, Vesalius gathered his discoveries into a detailed and comprehensive guide to human anatomy. Sometimes dissecting at home, sometimes in an artist's studio, he labored for a year in order that woodcut illustrations of every part of the human anatomy could be created. His dissections were detailed and precise, and he wanted the illustrations to be so, too. He made his cuts so that the features he wished to show could be seen clearly. Sometimes, this meant tying cords to corpses to ensure that they were held at the best angle while they were illustrated.

> From dissection of a living animal [we can] learn about the function of each part, or at least gain information that may lead us to deduce that function.
> **Andreas Vesalius**

No one knows who the artist or artists were, but the illustrations are masterful. Some of the initial sketches may have been made by Vesalius himself, since he was a talented artist. Historians once believed they were drawn by German-born Italian Jan Stephan van Calcar, but he probably only illustrated Vesalius's first pamphlet *Tabulae Anatomica* (1538). True masterpieces of Renaissance art, each anatomical figure poses gracefully like a classical statue in a classical landscape, as if a living person. Vesalius presented anatomy not as the product of crude butchery but as a noble science.



Anyone looking at these dissections would see the intricate beauty of the body's structure, not gore and savagery.

From the artists' drawings, a team of highly skilled craftsmen carved images in relief on blocks of pear wood from which to print the book. Vesalius carried these blocks across the Alps from Venice to Basel in Switzerland in 1543 to make ready for printing his great work *De Humani Corporis Fabrica* (*On the Structure of the Human Body*), often shortened to *De Fabrica*.

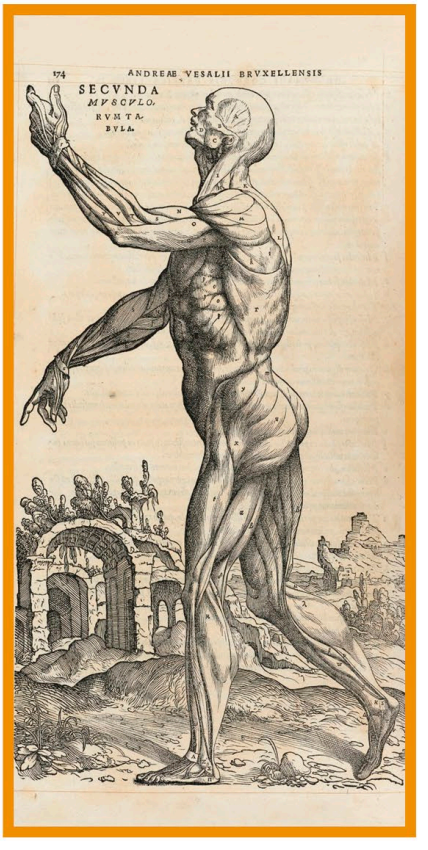
De Fabrica sparked a scientific revolution. It gave physicians a largely accurate and detailed picture of human anatomy for the first time. And it put direct observation, rather than book-learning and abstract thinking, at the very forefront of science. Moreover, it laid the foundations for medicine to become a science, not just a skill.

Vesalius's techniques and the detail of his observations showed later generations of anatomists a new way to find out how the bodies of humans and animals work—they contributed, for example, to English physician William Harvey's discovery of the circulatory system 80 years later. Harvey studied in Padua and drew inspiration not only from Vesalius's depictions of blood vessels but the idea of experimenting on real bodies. Harvey also drew on Italian veterinary physician Carlo Ruini's description of the one-way valves in a horse's heart, which appeared in Ruini's 1598 publication *Anatomia del Cavallo* (*Anatomy of the Horse*), a milestone in veterinary anatomy.

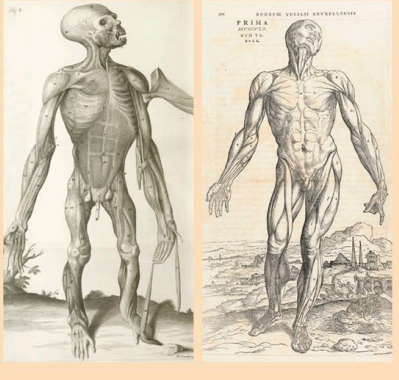
New ways of seeing

Over the centuries, new details of anatomy have been discovered, particularly with the invention of the microscope, which revealed tiny anatomical details. In 1661, Italian biologist Marcello Malpighi located capillaries, and around the same time, Danish physician Thomas Bartholin discovered the lymphatic system. Further advances have come with the development of scanning techniques that offer close anatomical study of living people.

Improvements in technology have gradually made the human body a territory that can be charted with the same eagerness shown by explorers arriving in new lands. ■



This illustration from Vesalius's *De Humani Corporis Fabrica* depicts the major external muscle groups of the human body. Such detail was only possible because he dissected human cadavers.

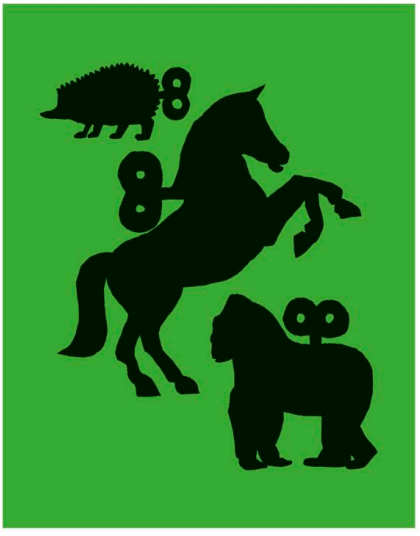


These anatomical drawings of an orangutan (left) and a human show the similar limb proportions of the two related species.

Comparative anatomy

Vesalius's insights into the differences and similarities between human and animal anatomies led to the development of comparative anatomy. This discipline would draw out unsuspected relationships between species. For example, English physician Edward Tyson (1651–1708), often considered the founder of comparative anatomy, showed that apes and humans have more in common anatomically than humans do with monkeys.

Comparative anatomy was used to classify animals into the groups we know today. In 1817, Georges Cuvier divided animals into four large groups – vertebrates, mollusks, articulates, and radiates—according to body plan. Four decades later, Charles Darwin showed how variations in anatomy revealed the gradual process of change that was central to his theory of evolution by natural selection. This confirmed humanity as just one part of a great spectrum of animal anatomy that has evolved over time.



ANIMALS ARE MACHINES

ANIMALS ARE NOT LIKE HUMANS

IN CONTEXT

KEY FIGURE
René Descartes (1596–1650)

BEFORE
***c.*350 BCE** Aristotle asserts in his book *History of Animals* that embryos arise from a kind of contagion.

AFTER
1739 Scottish philosopher David Hume claims that animals are endowed with thought and reason.

1802 British clergyman William Paley argues for the existence of God, saying that the intricate mechanism of animals, like a watch, implies there is a "watchmaker."

1962 Researchers provide evidence of procedural memory (long-term), used in performing tasks unconsciously.

1984 American philosopher Donald Davidson insists that since animals have neither speech nor beliefs, they cannot have thought.

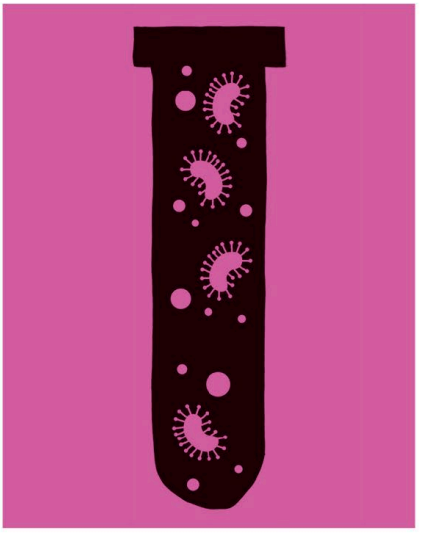
In the 17th century, the French aristocracy became fascinated by automata—ingeniously whirring, singing, mechanical toys. French philosopher René Descartes declared that animals are also a kind of automata. Descartes' key philosophical statement, known as Cartesian dualism, held that the human body is simply a machine that the mind directs. He went on to claim that humans have a mind and animals do not. In his 1637 treatise *Discourse on the Method*—best known for "I think, therefore I am"—Descartes argued that everything in nature, other than the human mind, can be explained with mechanics and mathematics. Animals, he stated, were no more than machines with physical parts and movements. His clinching argument was that since animals cannot speak, they have no soul.

> There is none that leads weak minds further from the straight path of virtue than that of imagining that the souls of beasts are of the same nature as our own
> **René Descartes**

Animal consciousness

The suggestion that there is a fundamental difference between humans and animals no longer bears the weight of scientific evidence. Tool-use was once thought to be uniquely human, but it has long been observed in animals such as chimpanzees and crows. Similarly, it was once thought that testing whether or not an animal can recognize itself in a mirror might prove or disprove consciousness; most species, but not all, fail the test. It is now acknowledged that there are many other ways in which animals might be self-aware. ■

See also: The brain controls behavior 109 ▪ Innate and learned behavior 118–23 ▪ Animals and tools 136–37



I CAN MAKE UREA WITHOUT KIDNEYS

BIOCHEMICALS CAN BE MADE

IN CONTEXT

KEY FIGURE
Friedrich Wöhler (1800–82)

BEFORE
***c.*200 CE** Galen suggests that life is created through pneuma, a subtle material in the air.

1807 Swedish chemist Jöns Jacob Berzelius suggests a fundamental difference between organic chemicals and inorganic chemicals.

AFTER
1858 German chemist Friedrich Kekulé proposes the theory of chemical structure when he suggests that carbon atoms have four bonds and can link together to form a chain.

1877 German physiologist Felix Hoppe-Seyler establishes biochemistry as an academic discipline with his book *Physiological Chemistry*.

1903 Finnish chemist Gustaf Komppa makes camphor—the first product synthesized organically.

In the 3rd century BCE, ancient Greek philosophers such as Aristotle held that plants and animals were imbued with a "vital force," which was an imperceptible component that gave them life. However, this theory of vitalism was disproved at a stroke with an accidental discovery made by German chemist Friedrich Wöhler.

Artificial synthesis

In 1828, Wöhler was attempting to make ammonium cyanate in his laboratory, and accidentally synthesized urea, a well-known organic substance found in urine. According to the prevailing theory of vitalism, organic compounds such as urea could only be made by living things through a "vital force"—yet Wöhler had created it from inorganic matter, in what is now called "the Wöhler synthesis."

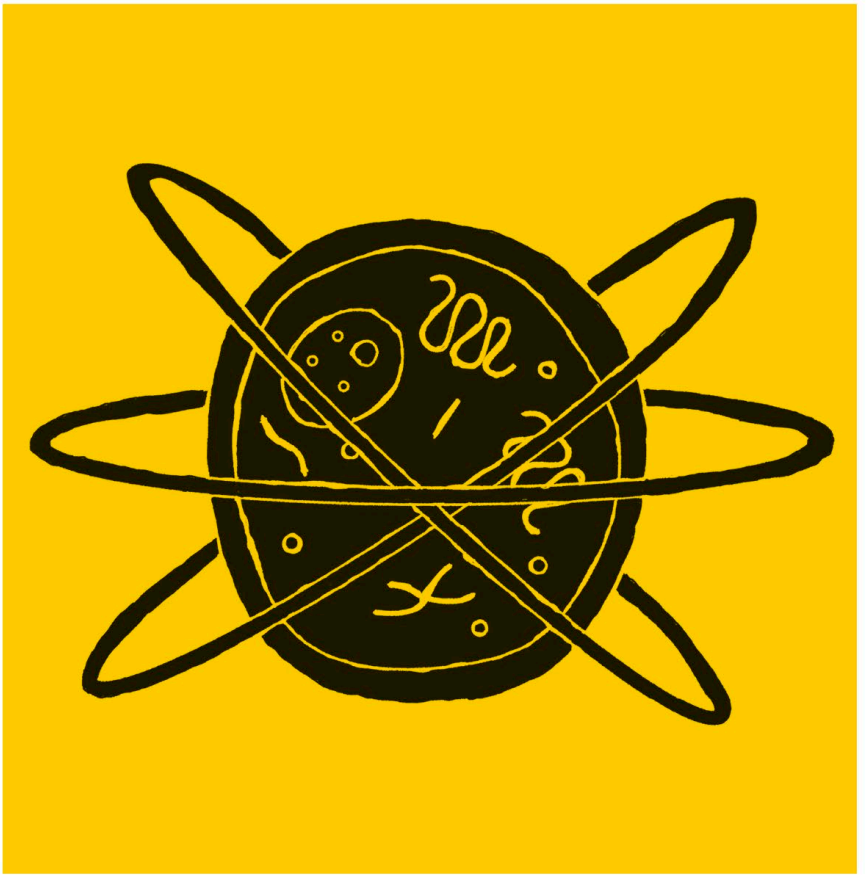
The importance of Wöhler's discovery not only refuted vitalism, but laid the foundation for modern organic chemistry. Up to the early 19th century, scientists had defined organic chemistry as the study of compounds derived from biological sources, as opposed to inorganic chemistry, which concerns inorganic compounds. Today, organic chemistry deals with all carbon-based compounds, even those with a non-biological origin, while the study of processes that occur in living organisms is covered by the field of biochemistry. ■

Friedrich Wöhler achieved the first artificial synthesis of a biological molecule when he created urea, announcing "I can make urea without thereby needing to have kidneys".

See also: Metabolism 48–49 ▪ Drugs and disease 143

THE TRUE BIOLOGICAL ATOM

THE CELLULAR NATURE OF LIFE



IN CONTEXT

KEY FIGURE
Theodor Schwann
(1810–82)

BEFORE
1665 Robert Hooke coins the term "cell" for tiny compartments he sees in cork bark under his microscope.

1832 Belgian botanist Barthélemy Dumortier records seeing cells divide in plants, calling it "binary fission."

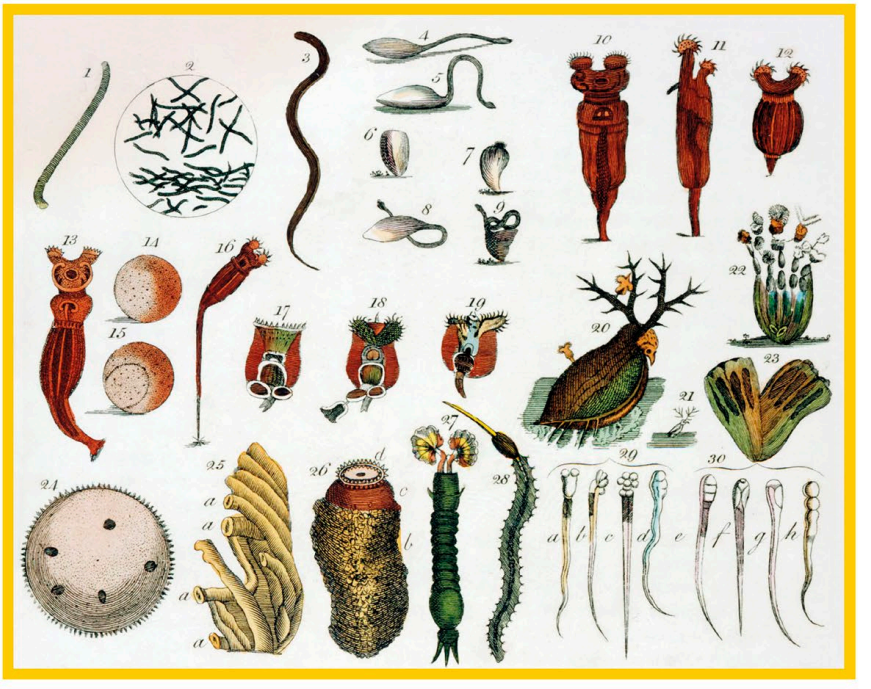
AFTER
1852 Polish-German physiologist Robert Remak publishes evidence that cells are derived from other cells as a result of cell division.

1876 Polish-German botanist Eduard Strasburger suggests that nuclei only arise from the division of existing nuclei, based on his studies of cells in flowering plants.

When English scientist, architect, and pioneer microscopist Robert Hooke coined the term "cell" in 1665, he was looking at greatly magnified, but dead and empty boxlike units in a sample of cork bark. Peering at what resembled a honeycomb under his instrument's lenses, he was struck by the similarity of the uniform, repeating components to rows of monks' rooms in a monastery, known as cellulae.

Other microscope users began to notice boxlike units in all kinds of living samples, from plant leaves and stems to pond water and animal blood. Notably, in the 1670s and 1680s, Dutch scientist Antonie

See also: How cells are produced 32–33 ▪ Making life 34–37 ▪ Complex cells 38–41 ▪ Cell membranes 42–43 ▪ Germ theory 144–151 ▪ Epigenesis 184–185 ▪ Mitosis 188–189



Leeuwenhoek's observations of "animalcules" were met with scepticism when he first wrote to the Royal Society in London about his discoveries in 1673.

van Leeuwenhoek described finding cells in saliva (some of which were bacteria), human blood, and semen. He then observed that pond water was teeming with living, moving, tiny life forms, which he called "animalcules." Leeuwenhoek became the first person to observe single-celled organisms under a microscope. However, he, along with Hooke and their 17th-century contemporaries, did not understand the significance of these tiny constituents of life.

A microscopic world

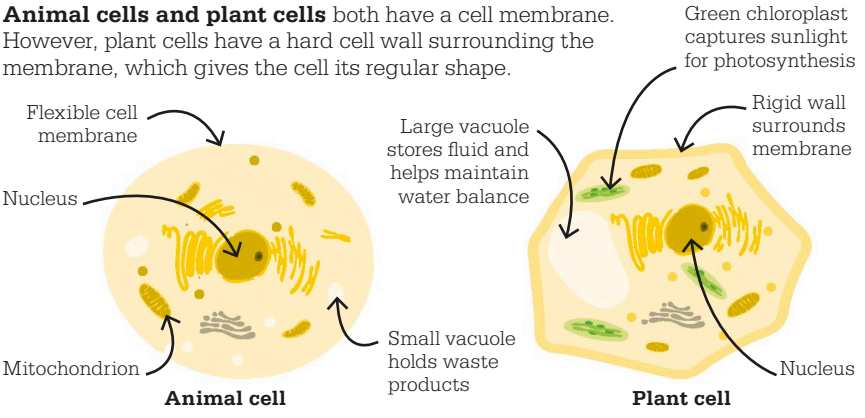
During the late 1790s, German botanist Johann Heinrich Friedrich Link was fascinated by the herbs that flourished in dry land during a trip to Portugal. He examined the herbs' microstructure and noticed that each cell had its own wall, which in dry conditions would pull away from the walls of adjacent cells. Until that time, it was suspected that cells shared walls. In the 1820s–30s, French physiologist Henri Dutrochet studied many samples from nature through his microscopes, some gathered from the weeds and ponds in his garden. He concluded that for both plants and animals, the cell is the ultimate unit in both anatomy or structure, and also in physiology, writing "everything is ultimately derived from the cell."

At the beginning of the 19th century, German biologist and physician Theodore Schwann, a university professor and expert in constructing experimental equipment, was intrigued by the discovery of cells in so many living organisms. As he examined samples from humans and other animals, he noted recurring cellular structures. At the same time, Matthias Schleiden, another scientist at Schwann's university in Berlin, Germany, was studying plant cells. Schleiden was professor of botany and, like Schwann, an able and serious investigator. The pair combined observations, with Schleiden telling Schwann about a prominent spherical dark body, or nucleus, which he had seen in the majority of his plant cell samples.

Schwann had not yet found clear evidence of nuclei, or even of widespread cellular structure, in his studies of animal tissues. This was understandable. The plant cell's nucleus is prominent, and the whole cell's outer layer has a relatively thick, semirigid cell wall, often giving a geometric shape that is easily noticed under a microscope—this is what Robert »

Hooke's drawing of cork cells, (from his landmark book *Micrographia*, 1665). The book contained illustrations of microscopic life with a level of detail not seen before.

Animal cells and plant cells both have a cell membrane. However, plant cells have a hard cell wall surrounding the membrane, which gives the cell its regular shape.



Hooke saw when he gave cells their name. Animal cells have less obvious nuclei and lack thick cell walls. Their outer cell membranes are thin and flexible, allowing more amorphous, changeable shapes that are microscopically less easily recognized.

The nucleus is usually the most prominent of a cell's organelles—the many specialized internal structures that carry out particular functions in the cell. In 1833, Scottish botanist Robert Brown fully described and named the nucleus, but it was Schleiden who was among the first to recognize that the nucleus has an important role in cell function. Schleiden theorized that new cells are created from the nuclei of existing cells. This was partly after viewing the small—and, as was discovered later, rapidly dividing—cells inside endosperm tissue—a plant seed's starchy food store. His suggestion was that the nucleus generated more nuclei, like a plant producing new buds, and a cell would then form around each one by some form of crystallization or spontaneous generation.

In 1838, Schleiden published his ideas in an article called "Contributions to Our Knowledge of Phytogenesis"—phytogenesis being the study of plant origins and development. He described how each part of a plant is composed of cells, and proposed that the first stages in the life of an organism, and its subsequent development, were all based on cells.

While discussing the role of the cell's nucleus in production of new cells over a meal with Schleiden in 1838, Schwann was struck by the similarity of animals to plants. In his experiments on animal subjects, which included toad larvae and embryos of pigs, he recalled seeing objects resembling cell nuclei in the notochord, a structure which forms early in a vertebrate embryo's development and becomes the animal's spine.

Schwann developed ways to distinguish animal cell membranes and nuclei under the microscope, and began to study animal tissues in early development, including the liver, kidneys, and pancreas. He came to the conclusion that cells are the basic units of life —in animals as well as plants. He also recognized that as an animal grows, early cells develop into specialized types with distinct functions, a process called differentiation.

James Smith constructed this microscope in 1826 using Lister's achromatic lens to limit the effects of optical aberrations.

Upgrading the microscope

In the early 17th century, the first compound microscope was developed by Dutch eyeglasses-makers. Later that century, Robert Hooke built his own microscope, and in 1665, he published his illustrated observations of the microscopic world in his book *Micrographia*.

In the late 1820s, frustrated at the quality of microscope images, British opticist and naturalist Joseph Jackson Lister (father of Joseph Lister, pioneer of antiseptic surgery) enlisted the help of James Smith, from the optical instrument-making firm William Tulley. By combining lenses made from different types of glass, such as flint and crown glasses, Lister and Smith could greatly reduce the optical aberrations (distortion and haziness). In 1830, Lister began grinding his own lenses and teaching his techniques to other optical instrument-makers. His new, improved microscopes stimulated rapid progress in the study of microscopic life.

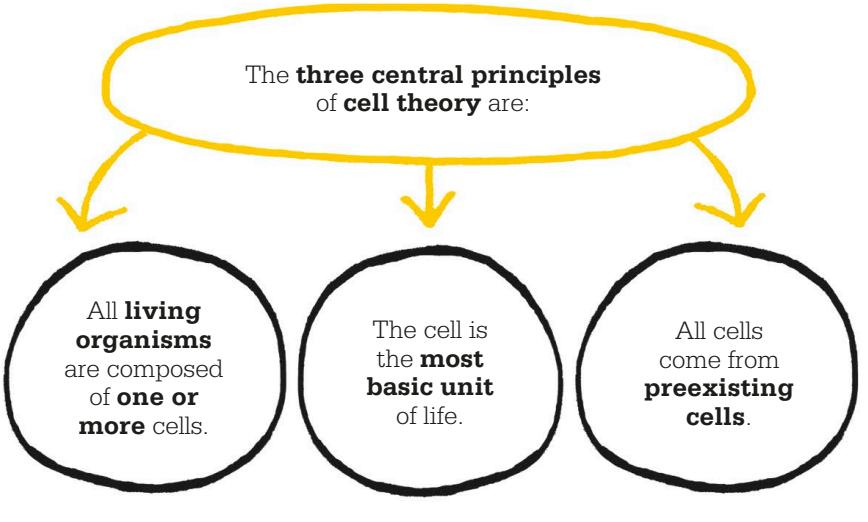
> The cause of nutrition and growth resides not in the organism as a whole but in the separate elementary parts—the cells.
> **Theodor Schwann**

Cell theory

In 1839, Schwann formulated his theories on animal and plant cells in his book, *Microscopic investigations on the similarity of structure and growth of animals and plants*. Schwann—giving full credit to Schleiden—proposed that all living things are made up of cells and that the cell is the fundamental unit of life—the two principles that became the basis of cell theory. Schwann was also recognized for classifying adult animal tissues into five distinct groups, describing the cellular structures of each category. The groups included: separate independent cells (such as blood); compacted independent cells (including fingernails, skin, and feathers); cells whose connecting walls have combined (such as bone, teeth, and cartilage); elongated cells that have formed fibers (such as fibrous tissue and ligaments); and cells formed by the fusion of walls and cavities (muscles, tendons, and nerves).

A third principle

The notion that cells are the basic structural and functional units of all living things was quickly accepted by other scientists. In 1858, a third principle of cell theory was put forward by prominent German physician and politician Rudolf Virchow, when he stated that "all living cells arise from preexisting living cells." He disputed the prevailing view that new cells and living material could form spontaneously by processes such as budding or crystalizing. Under the microscope, Virchow had observed entire living cells splitting to form new ones, a process now known as cell division. ■



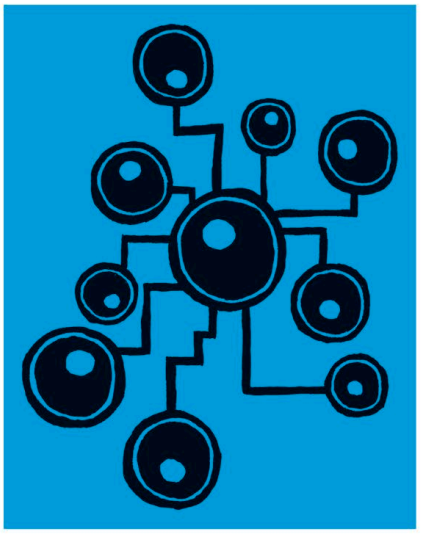
Theodor Schwann

Born in Neuss, Germany, in 1810, the fourth son of Leonard Schwann, who was a goldsmith and printer. He qualified as a physician in 1834, but chose instead to assist his professor, renowned German physiologist Johannes Müller, with his research.

Aided by the latest advances in microscopy, Schwann observed the role of yeast in fermentation, which contributed to the germ theory of disease developed by Louis Pasteur. Schwann's other studies included the involvement of enzymes in digestion, investigations of muscle and nerve function, and defining the basics of embryology. By the age of 30, Schwann had completed his landmark achievements. He continued as an experimental inventor and gifted lecturer, and was celebrated in later years for his thorough scientific methods. Schwann died in Cologne in 1882.

Key work

1839 *Microscopic investigations on the similarity of structure and growth of animals and plants*



ALL CELLS COME FROM CELLS

HOW CELLS ARE PRODUCED

IN CONTEXT

KEY FIGURE
Rudolf Virchow (1821–1902)

BEFORE
1665 English scientist Robert Hooke describes the microscopic chambers he sees in cork as "cells."

1838–39 Matthias Schleiden and Theodor Schwann declare that cells are the basic building blocks of plants and animals.

1852 Robert Remak questions the theory that cells arise from blastema.

AFTER
1858 In a series of lectures, Rudolf Virchow argues that all diseases can be traced back to cells.

1882 Walther Flemming uses the word "mitosis" to describe cell division and discovers chromosomes.

1911 American biologist Thomas Morgan shows that chromosomes carry genes.

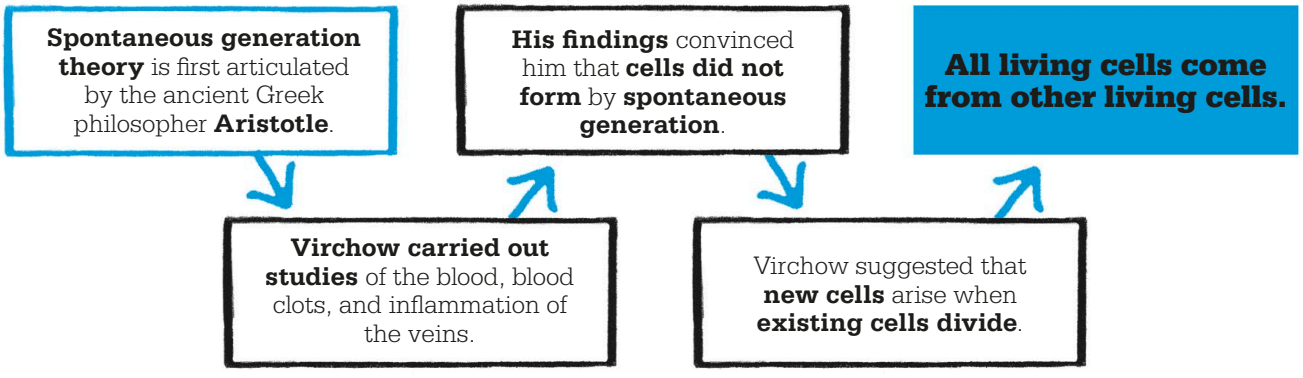
In 1855, Polish-German physiologist Rudolf Virchow challenged the generally held view of spontaneous generation, a theory stating that living organisms could arise from nonliving material. Virchow declared that all cells arise from pre-existing cells—or "omnis cellula e cellula," as he said in his Latin epigram. Subsequently proved to be true, though, it became the third principle of cell theory, revolutionizing the understanding of how the body functions and how disease occurs.

Rudolf Virchow's achievements included the first descriptions of many diseases and the development of the first systematic method of autopsy.

Today, scientists understand that cell reproduction takes place in all eukaryotic organisms—that is, animals, plants, and fungi. Most cells undergo division, called mitosis, whereby a parent cell divides into two daughter cells. This allows the total number of cells to increase, so an organism can grow, replace cells lost naturally (such as red blood cells), and create the new cells necessary to repair damage.

It took a long time for scientists to realize the true importance of cells for all living things. This was partly due to the slow development of microscope technology. Since the boundaries of plant cells are easier to observe than those of animals, the three principles of cell theory (living things are made from cells, cells are the basic units of life, and all cells come from cells) were advanced first in respect of plants. In 1835, German botanist Hugo von Mohl observed in green algae that new cells are formed by the division of cells. Three years later, German physiologist Matthias Schleiden generalized

See also: The cellular nature of life 28–31 ▪ Complex cells 38–41 ▪ Germ theory 144–51 ▪ Cancer metastasis 154–55 ▪ The discovery of gametes 176–77 ▪ Mitosis 188–89 ▪ Chromosomes 216–19



this for all plants, and then in 1839, fellow German Theodor Schwann extended it to animals.

Cell genesis

Schwann recognized the importance of cells for living organisms, but his explanation of how they were created was wrong. He suggested that new cells crystallized out of an "amorphous basic substance," the blastema. Effectively, this was a form of spontaneous generation, with new cells growing within a "nurturing fluid." Following this reasoning, Austrian pathologist Karl Rokitansky suggested that chemical imbalances in the blood sometimes caused the blastema to spawn abnormal cells and that these were the causes of disease.

From 1844, Virchow conducted microscopic studies of the blood, blood clots, and phlebitis (the inflammation of venous walls) at the Charité Hospital, Berlin. His observations convinced him that new cells did not crystallize in the way described by Schwann. Then, in 1852, fellow Polish-German physiologist Robert Remak, who worked in Virchow's laboratory, declared that he believed new cells arose from the division of pre-existing ones. This idea was revolutionary, and three years later Virchow articulated it himself in an essay—but he was accused of plagiarism for not crediting Remak.

Disease and cell structures

Virchow argued that all diseases can be traced back to cells—in other words, certain cells become sick rather than a whole body—and different diseases affect different cells. He was also the first to suggest that cancer might arise from the activation of previously dormant cells, and observed that a blood disease he named leukemia was connected to abnormal increases in white blood cells. His research and theories have led to him being known today as "the father of modern pathology."

The work done by Virchow, and advances in microscopy that enabled the discovery that cell nuclei contain threadlike structures we now know to be chromosomes, paved the way for scientists trying to understand DNA—a sequence of events that has had a profound impact on modern biology, genetics, and medicine. ■

Hayflick limit

In 1962, American anatomist Leonard Hayflick showed that normal cells are mortal, dividing 40 to 60 times before entering a state of aging, then death. Using human and animal cells, he disproved the established belief in cell immortality first advanced by French biologist Alexis Carrel in 1912.

The number of possible cell divisions is called the Hayflick limit, and it correlates with the length of the telomeres at each end of chromosomes. Telomeres are "caps" that protect the ends of chromosomes and prevent them from fusing with each other. In a normal cell, every time DNA replication takes place, small sections of the telomeres fail to copy and are lost. Eventually, this means the cell can no longer successfully divide. Most cancerous cells, however, are exceptions. They contain the enzyme telomerase, which prevents the telomeres from shortening. Scientists are researching ways to develop telomerase inhibitors, which may limit the life of cancer cells.

LIFE IS NOT A MIRACLE

MAKING LIFE

IN CONTEXT

KEY FIGURES
Stanley Miller (1930–2007), **Harold Urey** (1893–1981)

BEFORE
1828 Friedrich Wöhler makes urea, the first time an organic chemical (a chemical found in a living organism) has ever been synthesized.

1859 Louis Pasteur shows that life cannot generate spontaneously from the air or from non-living matter.

1924, 1929 Alexander Oparin and J.B.S. Haldane separately advocate abiogenesis.

AFTER
1968 Leslie Orgel suggests that life began with RNA.

1993 Michael Russell posits that life began metabolically around hydrothermal vents.

2010 Craig Venter's team creates a synthetic organism.

Life is Earth's, and perhaps the Universe's, greatest phenomenon. As far as we can tell, all life on Earth descends from a chance coupling of complex chemicals early in our planet's history—a union that created a remarkable organic structure that could not only grow but reproduce itself. Scientists have long puzzled how that accident happened and whether it could be reproduced in the laboratory, in order to create life from scratch.

In the 1920s, some scientists challenged Pasteur's refutation of the spontaneous generation of life. Soviet biochemist Alexander Oparin and British geneticist

See also: Biochemicals can be made 27 ▪ The cellular nature of life 28–31 ▪ Metabolism 48–49 ▪ The genetic code 232–33 ▪ The human genome project 242–43

Could **life** on Earth have arisen **spontaneously** out of **inorganic materials**?

↓

Ammonia, methane, and hydrogen exist in Jupiter's atmosphere and were probably **abundant** on **primordial Earth**.

↓

Miller's and Urey's experiment **created amino acids** by discharging **electricity** through a mix of **ammonia, methane**, and **hydrogen**.

↓

So, at least **organic chemicals** can be created spontaneously **from inorganic chemicals**.

J.B.S. Haldane separately proposed abiogenesis, the idea that life originated from non-living matter in an inorganic environment. A crucial question was whether the complex organic chemicals that are the basis of life could self-assemble.

Making organic material

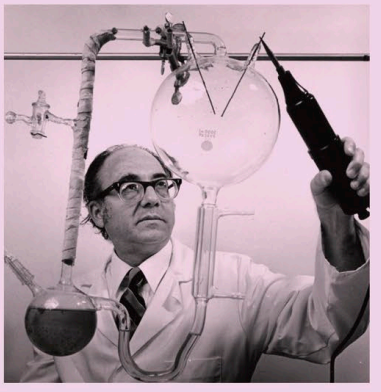
In a famous experiment of 1953, American chemists Stanley Miller and Harold Urey tested the Oparin–Haldane theory. They wanted to mimic the "primordial soup" that was believed to be Earth's atmosphere in its infancy, and test whether, as Oparin had suggested, frequent lightning flashes in such a thick atmosphere could have provided sufficient energy to bring the right molecules together.

Miller and Urey sealed inside a glass jar all the gases they believed might have been in primitive Earth's atmosphere—ammonia, methane, hydrogen—and added water vapor. They shot electric sparks repeatedly into the mixture.

After a day, the water in the jar turned pink. After a week, it turned into a deep red, thick brew. When he analyzed it, Miller found five amino acids—carbon-based building blocks of proteins and the basis of all known living organisms. In 2007, using modern techniques, further analysis of the equipment from the original experiment showed that Miller had actually made at least 13 amino acids.

Miller and Urey had proved that organic chemicals could be created inorganically. Similar experiments created carbohydrates and showed that simple chemical reactions can even string proteins together.

Therefore, creation of the basic chemicals needed for life is by no means special. It is probably going on right now in many places in »



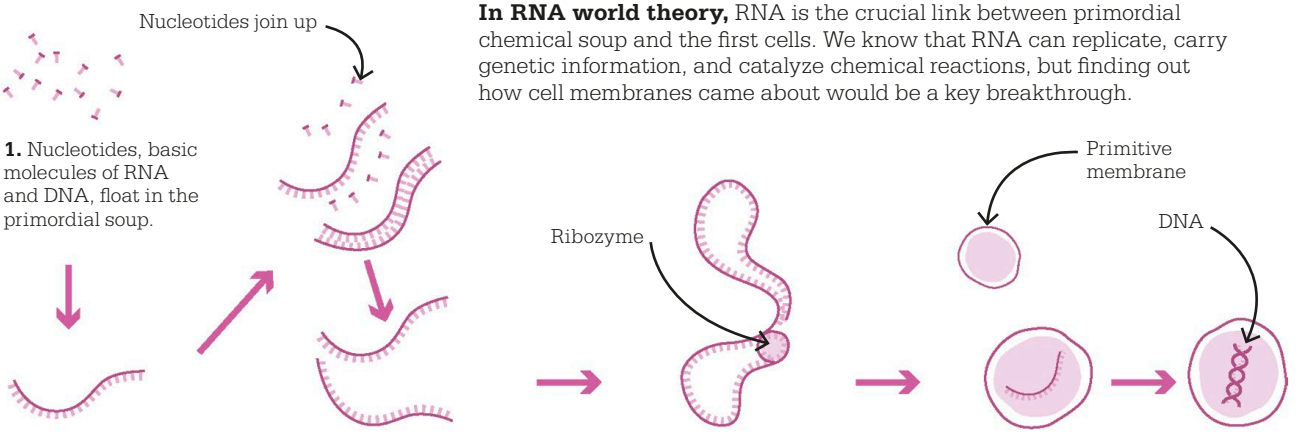
Stanley Miller

Born in 1930 in Oakland, California, Miller graduated in chemistry from Berkeley in 1951. That same year, he heard Nobel laureate Harold Urey lecture on the solar system's origins and on how organic chemicals might have formed on primitive Earth. Inspired, Miller persuaded Urey to embark with him on their famed 1953 experiment.

Miller taught chemistry at the California Institute of Technology (Caltech), Columbia University, and, from 1960, the University of California, San Diego. He continued studying synthesis of organic chemicals; in 1973, he made 33 amino acids in a repeat of his 1953 experiment. Miller pioneered exobiology (the study of biology in space) and was a key instigator of the search for life on Mars, which he hoped would confirm theories about origins of life on Earth. He died in 2007.

Key works

1953 "A Production of Amino Acids under Possible Primitive Earth Conditions"
1986 "Current Status of the Prebiotic Synthesis of Small Molecules"



In RNA world theory, RNA is the crucial link between primordial chemical soup and the first cells. We know that RNA can replicate, carry genetic information, and catalyze chemical reactions, but finding out how cell membranes came about would be a key breakthrough.

1. Nucleotides, basic molecules of RNA and DNA, float in the primordial soup.

2. Some nucleotides join up in random order to form chains of primitive RNA.

3. An RNA chain replicates when its nucleotides attract others: a double chain forms, then breaks into two copies.

4. Some chains fold into a structure called a ribozyme, which catalyze chemical reactions. Some ribozymes make nucleotides, so replicate better.

5. Super-replicating RNA chains wrap themselves in primitive membranes and twist to form the first DNA.

the Universe. Scientists estimate that comets dusted early Earth with millions of tons of organic chemicals. But it is a huge leap from proteins to a chemical that can reproduce itself, and a huge leap again to the first living cell, with chemicals wrapped in a self-contained, membrane-bound unit.

RNA and replication

DNA (deoxyribonucleic acid) is the chemical molecule inside cells that carries the genetic code for life. In 1953, the same year as the Miller–Urey experiment, molecular biologists James Watson from the US and Britain's Francis Crick discovered DNA's double-helix structure. The workings of its code were cracked over the next decade.

RNA (ribonucleic acid) is the single-strand version of DNA. It breaks off in small snippets copied from a single DNA strand to carry genetic instructions to one of the cell's ribosomes—factories for making proteins from amino acids.

In 1968, British chemist Leslie Orgel suggested that life on Earth could have begun with a simple molecule of RNA that could replicate itself. Orgel teamed up with Crick to pursue this idea by focusing on enzymes. Enzymes are essential proteins that speed up (catalyze) biochemical reactions in living organisms. If RNA could produce enzymes, it could use the enzymes to stimulate formation of molecules to build new RNA strands. In 1982, American biochemist Thomas Cech found some RNA enzymes, called ribozymes, which could snip themselves out of the RNA strand to perform their tasks.

In 1986, American physicist Walter Gilbert coined the term "RNA world" to describe the early world in which RNA molecules cut and pasted themselves together to form ever more useful sequences, or codes. In 2000, American molecular biologist Thomas Steitz confirmed that RNA activates and controls ribosomes. It seemed to confirm that life began with RNA, since the ribosome is an ancient component of cells and vital to making proteins. Yet there was still no evidence that RNA—or DNA—could reproduce by itself outside a living cell.

Scientists since the 1980s had been trying to create RNA that can replicate by itself. Gradually, they got RNA strands to copy bigger and bigger strands. By 2011, British molecular biologist Philipp Holliger had created an RNA strand that could copy 48 percent of its total

Interstellar clouds of gas and dust, such as these around the Orion Nebula, can contain organic chemicals, and several types have been found in meteorites that have landed on Earth.

length. Yet, after decades of effort, self-replicating RNA is still some way off. Some scientists have experimented with synthesizing simple nucleic acids, such as PNA (peptide nucleic acid), in case they could be the key to life's origin, but as yet these substances have not been found in nature.

Energy to create life

A rival school of thought is that metabolism, the ability to use energy, came first. This was helped by the discovery of hydrothermal vents in 1977. These volcanic chimneys on the seabed throw out a grocery store of minerals and lots of heat—perhaps similar to early Earth's volcanic environment. In 1993, British geologist Michael Russell suggested that the first complex organic molecules formed at these hot spots, inside little funnels of iron pyrite (iron sulfide, which may be crucial to enzyme function) around the vents.

Stanley Miller had pointed out in 1988 that hydrothermal vents were too hot for living organisms to survive. But in 2000, American oceanographer Deborah Kelley discovered vast numbers of cooler vents. The theory is that life began in places like these, where heat and energy can fire up the process of making organic molecules such as RNA inside rock pores. Eventually, the molecules could create their own membranes and escape from the porous rock into open water.

> The origin of life appears to be almost a miracle, so many are the conditions which would have to be satisfied to get it going.
> **Francis Crick**

Heat-loving bacteria thrive in waters around volcanic vents such as the Grand Prismatic Spring in Yellowstone National Park, US, so could have lived in similar habitats on early Earth.

Coding an organism

While scientists across the world in the 1990s engaged in the project to catalog the entire human genetic code, or genome, a team led by US biotechnologist Craig Venter explored if they could create not just organic chemicals, but living organisms. Their idea was to use genetic engineering techniques to strip away RNA, bit by bit, of every gene not vital for replication.

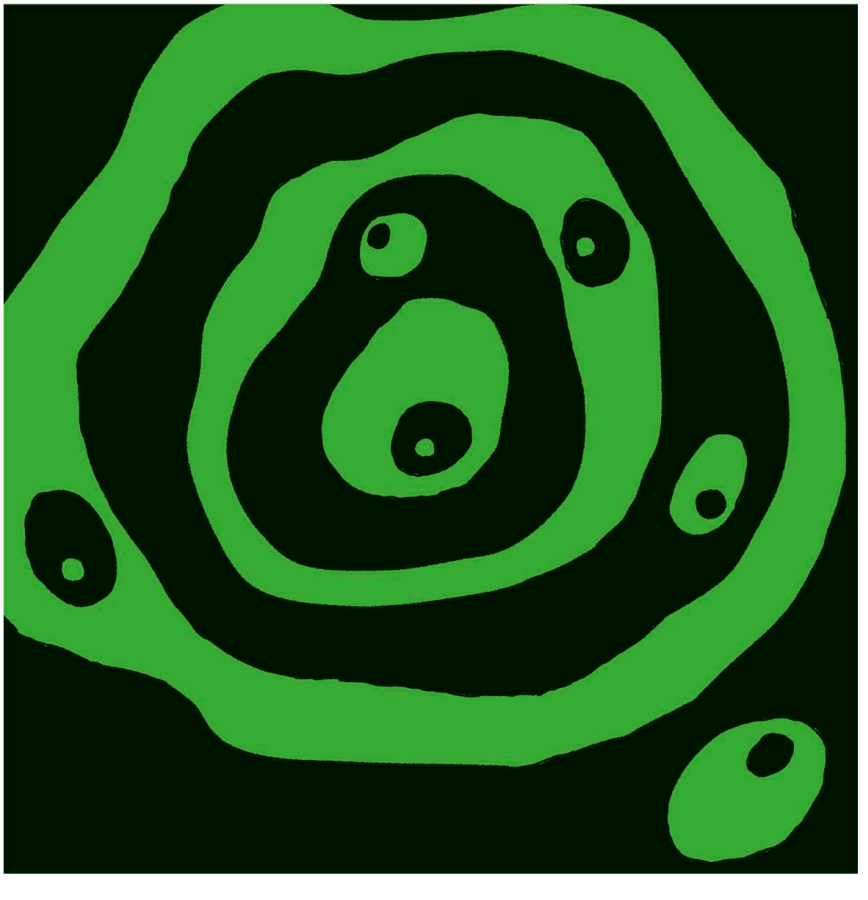
They started by artificially recreating the genome of a bacteria called *Mycoplasma mycoides*. In 2010, they successfully inserted the genome into a related bacterium in place of its own genetic material. This new bacterium reproduced to create many copies, just like other living bacteria. It was claimed that Venter's team had created the world's first synthetic life form. It was called Synthia 1.0, and had the names of the 46 team members and three famous quotations encoded into its RNA, to ensure it could always be identified as artificial.

In 2016, Venter's team stripped away even more genes to create Synthia 3.0, a bacterium with the smallest genome of any freely living organism. With just 473 genes, it not only survived but reproduced. However, Synthia 3.0 is not a truly synthetic life form since its genome had been replicated with the aid of living bacteria.

Nonetheless, Venter's project launched a "synthetic biology revolution," in which scientists seek ways to create entirely synthetic organisms: some look for ways to make artificial membranes; others to custom-design genes. Their vision is to create organisms that can do anything from cleaning up pollution to producing eco-friendly plastics. However, there is still a long way to go in understanding exactly how life started, let alone creating new life from scratch. ■

SMALLER CELLS RESIDE INSIDE THE LARGER CELLS

COMPLEX CELLS



IN CONTEXT

KEY FIGURE
Lynn Margulis (1938–2011)

BEFORE
1665 Robert Hooke coins the word "cell" to describe microscopic structures he sees in cork bark.

1838 Matthias Schleiden and Theodor Schwann propose that all life is made up of cells.

1937 French biologist Edouard Chatton first divides life into two groups of cell structures: prokaryotic and eukaryotic.

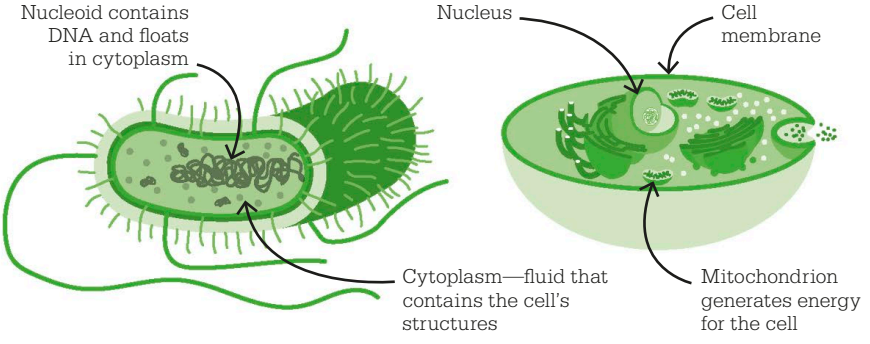
AFTER
1977 American biologists Carl Woese and George Fox propose a new, third, domain of organisms—the Archaea.

2015 Evidence emerges that shows that the ancestors of eukaryotes (organisms with complex cells) most likely developed from the Archaea.

Life, even in its simplest forms, is extraordinarily complex, and there will have been countless evolutionary steps from the first cells on Earth toward this complexity. Approximately 4 billion years ago, the first steps towards life may have been taken when simple organic molecules joined together to form long-chain macromolecules (large molecules). A primary characteristic of life is its ability to reproduce, and these first molecules would have reproduced by replicating through a series of naturally occurring chemical reactions. The molecules that were the most efficient replicators produced more copies of

See also: The cellular nature of life 28–31 ▪ How cells are produced 32–33 ▪ Cell membranes 42–43 ▪ Respiration 68–69 ▪ Food chains 284–85

Typical prokaryote and eukaryote cells



Prokaryotes are tiny, single-celled organisms such as bacteria. The cells have no membrane-bound organelles. Instead of a nucleus, DNA is found in a region called the nucleoid that floats freely in the cytoplasm.

Eukaryotes include organisms such as animals, plants, and fungi. Eukaryotic cells have membrane-bound organelles including a nucleus, which contains DNA. They are much larger than prokaryotic cells.

themselves and outcompeted less able systems. The evolution of a protective membrane surrounding the genetic material would have provided huge advantages and given rise to the first prokaryote cells (single-celled organisms that have no membrane-bound cell structures, or organelles), similar to a modern bacterium.

Earth's atmosphere contained little oxygen at this time. These first organisms were extremely simple, feeding on an abundance of organic molecules and producing energy through fermentation, a process that did not require oxygen.

Prokaryotes and oxygen

Early prokaryotic cells diverged into two distinct lineages called the eubacteria and the archaebacteria. Around 3.5 billion years ago, some eubacteria developed the ability to convert sunlight into chemical energy. These were the ancestors of today's cyanobacteria, a group of photosynthetic bacteria (formerly called blue-green algae). Over approximately the next billion years, these photosynthesizers increasingly dominated the living world, releasing oxygen as a waste product. Earth's atmosphere and its early shallow oceans experienced a spike in oxygen levels, which had a profound effect. Oxygen is highly reactive and can destroy delicate biological structures. Several prokaryotes evolved mechanisms to deal with this problem, the most successful of which was respiration—the process of producing energy while converting oxygen into water molecules.

Origin of the eukaryotes

The evolution of respiration around 2.5 billion years ago could have triggered the development of eukaryotic cells. All advanced life forms contain eukaryotic cells, with their more complex internal structure and the presence of »

The nucleus

The fundamental difference between prokaryotes and eukaryotes is that eukaryotic cells have membrane-bound organelles, including the nucleus, while prokaryotic cells do not. In fact, the defining characteristic of eukaryotic cells is the presence of a nucleus—the container for the cell's genes, encoded in molecules of DNA.

The origin of the nucleus is still a matter of dispute. Biologists disagree as to which came first, the nucleus or mitochondria. Some scientists suggest that gaining mitochondria, which are responsible for generating energy, would have been essential for the evolution of eukaryotes.

Lynn Margulis proposed that the nucleus in its present form evolved after the other organelles were acquired. Other theories contend that the nucleus evolved in prokaryotes first, and that this enabled their fusion with the bacterial ancestors that became mitochondria.

> Life is bacterial and those organisms that are not bacteria have evolved from organisms that were.
> **Lynn Margulis**

> I don't consider my ideas controversial. I consider them right.
> **Lynn Margulis**

membrane-bound organelles. These organelles include the cell nucleus, which houses the cell's genetic material; the mitochondria, where cellular respiration takes place; and the chloroplasts in plant cells, which are the sites of photosynthesis. Explaining the origin of eukaryotic cells is a major challenge for biologists. The complexity of the eukaryote cell greatly exceeds that of even the most sophisticated prokaryote, and a typical eukaryotic cell is about a thousand times bigger by volume.

Endosymbiotic theory

In 1883, French botanist Andreas Schimper observed that chloroplasts in green plants divided and reproduced in a way that closely resembles the reproduction of free-living cyanobacteria. He suggested that green plants had evolved from a close relationship, or symbiosis, between two organisms.

Russian biologist Konstantin Mereschkowski—who was one of the first to notice that there were structural similarities between plant chloroplasts and cyanobacteria—was familiar with Schimper's work. Inspired by his studies of the symbiotic relationship between fungi and algae in lichens, Mereschkowski developed the idea that complex organisms could arise from partnerships between less complex organisms. In 1905, he published his proposal that chloroplasts were descended from cyanobacteria that had been engulfed by a host cell and established a symbiotic relationship with it, and that plants owed their ability to photosynthesize to the cyanobacteria. This theory, that complex organisms arose from the joining of less complex organisms, is called endosymbiosis.

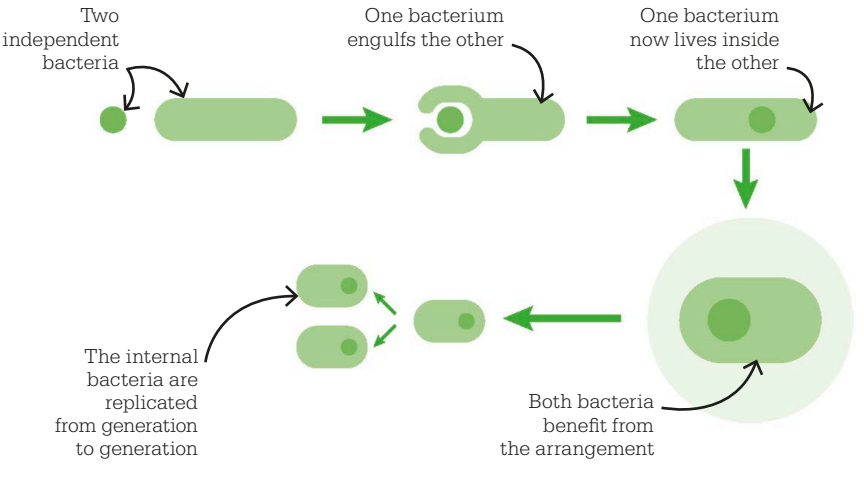
During the 1920s, American biologist Ivan Wallin suggested an endosymbiotic origin for mitochondria (the organelles responsible for generating energy). He suggested that mitochondria had originally been aerobic bacteria (requiring oxygen to survive).

These theories were largely rejected for the next few decades, but in 1959, American botanists Ralph Stocking and Ernest Gifford discovered that chloroplasts and mitochondria had their own DNA, different from that found in the nucleus of the cell. It was the first concrete evidence that the ancestors of these organelles might have existed as free-living cells.

Unorthodox ideas

DNA research was still a very new field in the early 1960s and the discovery of DNA in chloroplasts and mitochondria was disputed. In 1965, American biologist Lynn Margulis tackled the question for her Ph.D. dissertation and convincingly demonstrated the presence of DNA in the chloroplasts of a single-celled alga. She published an article in the *Journal of Theoretical Biology* in 1967, in which she laid out her idea that some of the fundamental organelles of eukaryotic cells, including mitochondria and chloroplasts, were once free-living prokaryotes. Margulis had not only formulated a theory for the origin of cell organelles, but for the evolution of eukaryotes.

When Margulis published her first book, *Origin of Eukaryotic Cells,* in 1970, endosymbiosis was still far from accepted. She had not



The theory of endosymbiosis suggests that eukaryotic cells evolved from early prokaryote cells being engulfed by other cells and developing a symbiotic relationship. Mitochondria formed when aerobic bacteria were ingested and chloroplasts formed when photosynthetic bacteria were ingested.

Lynn Margulis presented evidence for endosymbiosis theory, which biologist Richard Dawkins described as "one of the great achievements of 20th-century evolutionary biology."

yet overcome the assumption of the time that evolution occurred in small steps—endosymbiosis represented a great evolutionary leap forward. There were also many biologists who found the idea that DNA could be found outside the nucleus distinctly unorthodox, even though the evidence for DNA in chloroplasts and mitochondria was steadily gaining strength.

Serial endosymbiosis

Margulis's theory for the evolution of eukaryotic cells is often referred to as serial endosymbiotic theory, or SET. It proposes that eukaryotic cells came about through the merging of several different kinds of prokaryotic cells. According to Margulis, small bacteria capable of aerobic respiration parasitized larger, anaerobic (non-oxygen based) prokaryote cells by burrowing through their cell walls. In most cases this would result in the death of the invaded cell, but in just enough cases the two cells survived and coexisted. The parasite, with its ability to deal with oxygen, allowed its host to survive in previously uninhabitable environments. The host supplied the fuel for aerobic respiration and gained access to the bacteria's energy producing capabilities. As the two became more dependent on each other, the small respiratory parasites eventually evolved into the mitochondria—the first eukaryotic organelles.

Although almost all eukaryotic cells contain mitochondria, only those of plants and some unicellular organisms contain chloroplasts. This suggests that they evolved after mitochondria were already well established. Margulis hypothesized that some of the new mitochondrial partnerships consumed cyanobacteria, but some must have escaped being digested and evolved into chloroplasts.

Supporting evidence

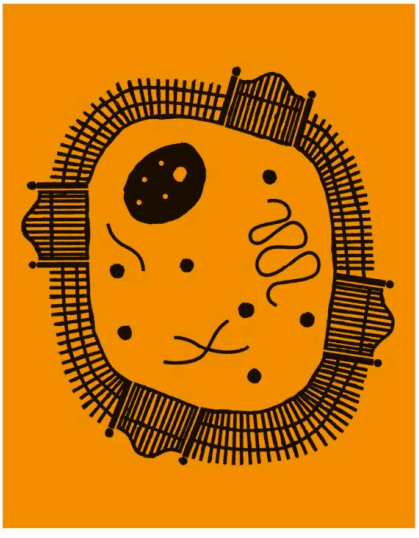
In 1967, a paper was published that supported Margulis's endosymbiotic theory. In 1966, Korean-American microbiologist Kwang Jeon was studying a colony of single-celled amoebae when they were struck by a bacterial infection that killed most of the amoeba cells. Several months later, he observed that the surviving amoebae remained healthy, with the bacteria still thriving inside them. More surprisingly, when he used antibiotics to kill the bacteria, the host amoeba died too—it had become dependent on the invading organism. Jeon discovered that this was because the bacteria were making a protein that the amoebae now needed to survive. The two species had formed a symbiotic relationship and evolved into a new species of amoeba. ■

Archaea ancestors

In 2015, a new group of Archaea—the single-celled organisms formerly known as archaebacteria—was discovered in deep-sea sediments in the Atlantic Ocean. Named *Lokiarchaeota*, or "Loki" for short, this new group appeared to be the closest relatives of eukaryotes—complex organisms whose cells have a membrane-bound nucleus—yet discovered. Loki's genome (genetic material) contains a multitude of genes previously known only to exist in eukaryotes. Among them are genes that play an essential role in eukaryotic functions, including those linked to the cytoskeleton, a structure that helps cells maintain their shape.

The role these eukaryote genes play in Loki is a mystery, but it could fit with a controversial theory that eukaryotes evolved from an Archaeal ancestor—Loki has been described by scientists as a "missing link" between eukaryotes and ancient prokaryotes.

Lokiarchaeota was discovered on the Mid-Atlantic Ridge, close to a hydrothermal vent system known as Loki's Castle.



A FLEXIBLE MOSAIC OF GATEKEEPERS

CELL MEMBRANES

IN CONTEXT

KEY FIGURES
Seymour Singer (1924–2017),
Garth Nicolson (1943–)

BEFORE
1839 Theodor Schwann and Matthias Schleiden suggest that all plants and animals are composed of cells.

1952 British physiologists Alan Hodgkin, Andrew Huxley, and Bernard Katz propose that pumps in a cell membrane pull sodium ions (electrically charged atoms) into a cell.

1959 J.D. Robertson, an American chemist, concludes that cell membranes consist of a lipid bilayer between two protein layers.

AFTER
2007 American biochemist Ken Jacobson explains that some phospholipids are bunched up into "rafts" that help transport materials through the cell membrane.

Every living cell is surrounded by a membrane that holds the cell's contents together. For a long while, cell membranes were believed to be proof against nearly every substance but water.

Discovery of lipids

In the 1880s, German self-taught physicist Agnes Pockels observed, while washing up, the way surface films, especially oily films, bind the water surface together. Each oily film possesses a hydrophobic (water-hating) side exposed to the air and a hydrophilic (water-liking) side that floats on the denser water. In the 1890s, British biologist Ernest Overton explored how a cell's membrane kept the contents from leaking out while letting in nutrients. Overton and German pharmacologist Hans Meyer proposed independently that the cell membrane was a binding, oily layer—hydrophilic outside and hydrophobic inside—called a lipid.

> A cell is a complex structure, with its investing membrane, nucleus, and nucleolus.
> **Charles Darwin**

In 1925, Dutch physiologists Evert Gorter and François Grendel revealed that dissolved membranes cover an area twice as large as undissolved ones, so the membrane had to be a double layer of lipids.

In fact, it turned out to be like a sandwich of two facing layers, each hydrophilic on the outside and hydrophobic on the inside, which keeps the cell waterproof. Each layer is made of tadpole-shaped phospholipids, with hydrophilic phosphate heads and hydrophobic lipid tails. In 1935, British physiologist Hugh Davson and biochemist James Danielli realized that there were also proteins in the membrane, but assumed they were only structural.

The fluid mosaic model

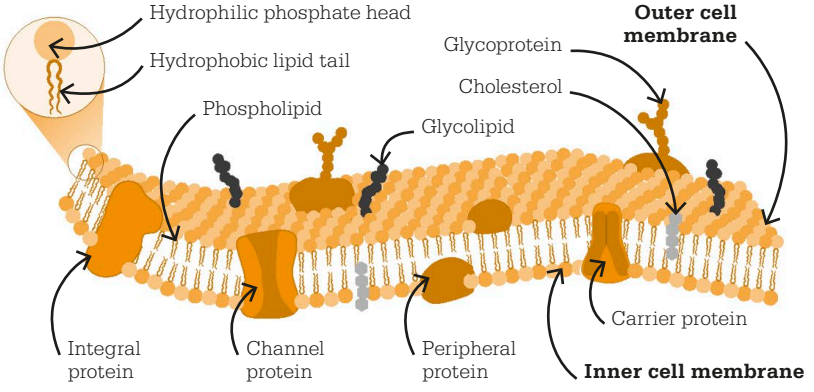
As American cell biologist Seymour Jonathan Singer and biochemist Garth Nicolson showed in 1972, the membrane is not simply a bag, but

See also: The cellular nature of life 28–31 ▪ Making life 34–37 ▪ Complex cells 38–41 ▪ Metabolism 48–49 ▪ Respiration 68–69 ▪ Reactions of photosynthesis 70–71 ▪ Plant transpiration 82–83 ▪ Plant translocation 102–103

a sophisticated, flexible border that controls how substances pass through to meet the cell's needs. Singer and Nicolson pieced earlier discoveries together to propose their fluid mosaic model of a cell membrane. The double lipid layers protecting and containing the cell form a dynamic fluid, dotted with a complex, moving mosaic of different structures. Its fluidity allows the membrane to bend, shift, and adapt to changing conditions.

In the membrane, cholesterol particles maintain fluidity by stopping phospholipids from breaking apart when it gets hot or sticking together when it gets cold. In Singer and Nicolson's model, glycoprotein chains project from the membrane; researchers later realized that these provide a cell's identity markers, or antigens. We now know that glycoproteins are complexes within the membrane, rather than single units. Lipids with a projecting carbohydrate tail, called glycolipids, stabilize the membrane and help identify the cell to the body's immune system. Proteins integrated within the membrane control which particles pass through it. Peripheral proteins on either side of the membrane help with processes such as cellular respiration, in which the cell uses oxygen to release energy.

The cell membrane is an oily fluid that flexes and shifts, with a mosaic of active components suspended within and on its surfaces—some help transport molecules across the membrane; some carry catalysts and sensors to control cellular processes.



Methods of transport

Molecules of oxygen and carbon dioxide can diffuse through the membrane because they are tiny with no electrical charge. They are needed in large amounts to provide the cell's energy. Some large and charged molecules pass along channel proteins by osmosis (see below). Carrier proteins pump molecules through the membrane against the concentration gradient, so the cell expends a little energy.

Singer's and Nicolson's model has since been modified, but still provides a clear picture of cell-membrane structure and function. ■

A plant depends on osmosis to fill its cells with water until they are rigid; the strong-walled cells cannot burst from taking in too much water, unlike animal cells. Loss of water makes cells shrink and plants wilt.

Osmosis

For a cell to survive, materials must move in and out through the cell membrane. They do this by simple diffusion, active transport by proteins, and osmosis.

Osmosis is the movement of water molecules, through a membrane, from an area of high water-molecule concentration to one with a low water-molecule concentration. The membrane must be permeable enough to allow water to pass through, but block any substance dissolved in it. So only the water moves through. A concentrated solution contains fewer water molecules than a dilute one; water always moves to concentrated solutions from dilute areas. This simple movement is vital to living cells.

When the concentration is the same both inside the cell and in the fluid around it, it is said to be isotonic and there is no movement. When the fluid outside the cell is more dilute (hypotonic), water is drawn into the cell and the cell swells. If the fluid outside a cell is more concentrated (hypertonic), water flows out and the cell shrinks.

FOOD AND ENE

RGY

1580s — Physiologist Santorio Santorio **weighs himself**, his food and drink, and his excretions **over a period of some 30 years**.

1600s — By measuring the **mass of a willow tree**, and amounts of soil and water, Jan van Helmont demonstrates that **plants gain mass** from **water**.

1747 — James Lind observes that certain **foodstuffs contain nutrients** essential to maintain good health.

1783 — Lazzaro Spallanzani explains that **digestion** is not merely a mechanical operation, but a **chemical process**.

1827 — The **three main food** groups (carbohydrates, fats, and proteins) are **identified** by William Prout.

1840 — Pioneering organic chemist Justus Liebig shows that food, as well as **living organisms**, is composed of organic **substances containing carbon**.

A particular focus of interest in the study of living organisms is the way in which life is sustained by nutrients, and how the organisms process these nutrients to provide energy for their necessary functions.

Understanding these processes involves more than a simple examination of the anatomy of the organisms, and requires a more experimental approach to studying their physiology—the way they function. A pioneer in this method of experimental biology was Santorio Santorio, who from the 1580s conducted an experiment that lasted some 30 years: he meticulously weighed himself, all his food and drink, and all the urine and feces he excreted, observing the difference between these amounts. He concluded that some "insensible perspiration" must account for the discrepancy. His experiment prompted further study of the way animals extract energy from food, a process that later was likened, by Antoine Lavoisier, to the burning of fuel in air.

Nutrition and growth

Early in the 17th century, Jan van Helmont took a similarly methodical approach to studying the processes of nutrition and growth in plants, measuring the mass of a willow tree and the soil and water it stood in, and observing that the tree grew by absorbing water. In the 1770s and 1780s, experiments by Jean Senebier showed that plants also use carbon dioxide (CO_2) to grow and Jan Ingenhousz and Joseph Priestley revealed that plants give off oxygen as a by-product. Most importantly, however, Ingenhousz demonstrated that sunlight is also a factor in the process, giving a foundation for the idea of photosynthesis.

Groundbreaking discoveries such as these were made during the 17th and 18th centuries, a period of unprecedented scientific advances. In 1747, having some understanding of the processes of nutrition and growth, James Lind went on to demonstrate that certain nutrients are essential to life and health, and that different components in foods have specific nutritional functions. Later, William Prout identified three distinct groups of necessary foods (fats, carbohydrates, and proteins), classified by their chemical properties. Justus Liebig built on this idea to show that all foods are

1850s

Louis Pasteur discovers that **yeast cells** can **cause fermentation** in the absence of oxygen.

1876

Wilhelm Kuhne explains that the chemical reactions of **metabolism require catalysts** produced by the organism, which he calls **enzymes**.

1894

The action of specific **enzymes** triggering different **chemical reactions** is described by Emil Fischer.

1937

Hans Krebs describes how **metabolic reactions** in an organism follow a chemical pathway, forming a **cyclical sequence of reactions**.

1960s

Photosynthesis in plants is shown by Mervin Calvin to involve a cycle of reactions that **take carbon dioxide** from the air **to produce nutrients**.

composed of organic substances, which are distinguished by their chemical composition, specifically a combination of carbon and hydrogen. This definition of organic substances marked the beginnings of organic chemistry.

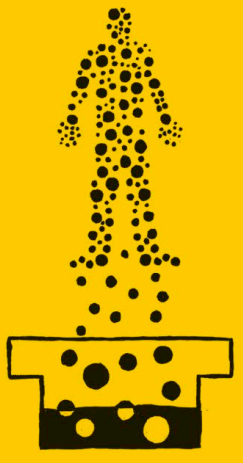
Metabolism

Chemical reactions came to be recognized as an important factor in the process of extracting energy from food. Digestion, the way food is broken down so that it can provide nutrition for the cells, was assumed to be a largely mechanical process until the late 18th century. In 1783, Lazzaro Spallanzani showed that the digestive tract in animals not only breaks the food down physically, but also releases digestive juices that chemically reduce food to molecules.

Food and drink became a particular focus for biologists in the 19th century, and it was problems in the wine industry that led Louis Pasteur to investigate the process of fermentation. He discovered that living yeast cells produce nutrients in a process of anaerobic respiration ("life without oxygen"), prompting a debate between himself and Liebig, who maintained that fermentation is a purely chemical reaction. The argument was settled, however, some years later, by Eduard Buchner, who explained that it is the enzymes of yeast—whether alive or not—that trigger the fermentation process.

The term "enzyme" had been coined by Wilhelm Kuhne, who had observed that the chemical reactions in cells, known as metabolism, can occur only in the presence of catalysts—chemicals that trigger the process but themselves remain unaltered. Organisms produce particular catalysts, which Kuhne dubbed enzymes, to speed up specific reactions. A later study of enzymes by Emil Fischer explained their action as a kind of lock-and-key process, with each enzyme a lock into which a specific substrate fits.

More in-depth insights into the workings of metabolism came from research in the 20th century. Hans Krebs developed the theory that metabolism is dependent on a chemical pathway between cells, forming a cycle of reactions. Mervin Calvin studied the process of photosynthesis, discovering a cyclical sequence of reactions in the cells of plants to make food substances. ■



LIFE IS A CHEMICAL PROCESS

METABOLISM

IN CONTEXT

KEY FIGURE
Santorio Santorio
(1561–1636)

BEFORE
4th century BCE Aristotle explains that heat is released when animals eat food.

13th century Ibn al-Nafis suggests that the body is in a state of constant change of energy and nourishment.

AFTER
1784 Antoine Lavoisier shows how much oxygen and carbon dioxide are consumed during human respiration.

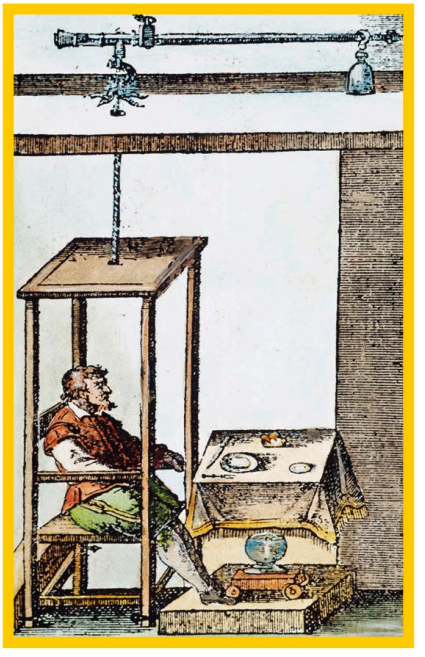
1837 German physiologist Heinrich Magnus demonstrates that respiration takes place throughout the body.

1937 German-born British biochemist Hans Krebs discovers the citric acid metabolic cycle (now called the Krebs cycle).

Metabolism is the chemistry that keeps organisms alive. It is both the entire sum of chemical reactions in an organism, and the way the organism converts food into energy and materials and eliminates waste. The statistical foundations for understanding metabolism were laid by Italian physician Santorio Santorio in the early 17th century.

Scientific measurement

Both Aristotle and 13th-century Arab physician Ibn al-Nafis had suggested a relationship between the body's food intake, energy, and production of heat. But Santorio realized that without measurement, this remained a vague notion, so in the 1580s, he began a study that he pursued for more than 30 years. He built a chair on which he could weigh himself, and he also weighed everything he ate, drank, and excreted through urine and feces. Santorio kept a precise record of every change in his body weight. He found that for every pound of food he ate, he excreted less than half a pound and concluded that the difference was "insensible perspiration." That is, perspiration that is intangible—weight lost as heat and moisture from the body surface or through the mouth during the act of breathing. He found that this varied according to environmental conditions, as



Santorio's weighing chair was suspended from the short arm of a steelyard—a device with a long graduated arm, along which a weight is moved until it balances.

See also: Experimental physiology 18–19 ▪ The cellular nature of life 28–31 ▪ Essential nutrients 56–57 ▪ Respiration 68–69 ▪ Hemoglobin 90–91

well as his health and what he ate. He conducted similar tests on others and, in 1614, summed up his research in *De Statica Medicina* (*On Medical Measurement*). In this, he stressed the need for a good balance between body intake and insensible perspiration for health. It was the first study of metabolism.

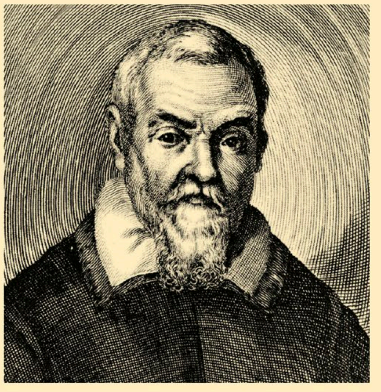
Chemical reactions

French chemist Antoine Lavoisier became convinced that the chemistry behind burning and breathing—combustion and respiration—are effectively the same. Experiments by himself and other scientists showed that when an animal breathes, it consumes oxygen and creates waste carbon dioxide—just as, he correctly believed, when things burn. In 1784, he created a device called an ice calorimeter to conduct an experiment. The amount of ice that melted in the calorimeter would reveal the amount of heat produced during combustion and respiration inside a sealed chamber. He placed glowing charcoal in the chamber, then a live guinea pig. Both coal and guinea pig consumed oxygen and produced heat. The burning coal created heat rapidly, the guinea pig more slowly—but it was clear that combustion and respiration generate heat in the same way.

Lavoisier wondered if the body's oxygen consumption varied, so he asked an assistant to wear a mask controlling the oxygen supply and measured the amount of gas that was inhaled. He found that the body uses more oxygen when exercising than when resting, and more when eating and when cold.

We now know that when animals inhale oxygen, a form of combustion called cellular respiration makes heat in their bodies, fueled by food. Oxygen arrives in body cells along with glucose from food. Cells burn the glucose and release its energy; its hydrogen joins with oxygen to produce water, and its carbon joins with oxygen to make toxic carbon dioxide—which has to be exhaled.

Interlinked chemical reactions are at the heart of metabolism and the way in which all living things break substances down and build them up in order to maintain life. Metabolism makes the difference between life and death. ■



Santorio Santorio

Born in 1561, Santorio studied medicine at the University of Padua in Italy, the leading medical school at that time. After graduating in 1582, he practiced as a physician for several years. He met Galileo in Venice and kept up a correspondence with him. Hugely inventive, Santorio created an early clinical thermometer and the pulsilogium, the first accurate clock for measuring the pulse. He also invented a wind gauge and a meter to calculate the speed of water currents.

Santorio is most famous for his pioneering research in experimental physiology, especially his experiments with his self-built weighing chair. He became professor of theoretical medicine at Padua in 1611 but resigned after students complained he was too absorbed in his research. He returned to medical practice in Venice, where he was made president of the Venetian College of Physicians. He died in 1636.

Key work

1614 *De Statica Medicina* (*On Medical Measurement*)

PLANTS HAVE A FACULTY TO CORRECT BAD AIR

PHOTOSYNTHESIS

IN CONTEXT

KEY FIGURE
Jan Baptista van Helmont (1580–1644)

BEFORE
1450 Nicholas of Cusa states that weighing a plant in a pot over time would show that its mass derives solely from water.

AFTER
1754 Joseph Black, a British chemist, isolates "fixed air," now called carbon dioxide.

1884 Polish-German plant cytologist Eduard Strasburger names chlorophyll-making bodies in leaves "chloroplasts."

1893 The term photosynthesis is coined by American botanist Charles Barnes.

1965 Egyptian Mabrouk El-Sharkawy and American John Hesketh, both plant physiologists, show that differences in leaf anatomy affect rates of photosynthesis.

Green plants, algae, and cyanobacteria use water, harness energy from the Sun, and gather carbon dioxide in order to grow. This process is called photosynthesis, a term derived from the Greek *phos*, meaning "light," and *sunthesis,* "putting together." The waste product of photosynthesis is oxygen, which plants release into the atmosphere.

Photosynthesizing organisms are called photoautotrophs because they use energy from light to make organic molecules from inorganic matter—mainly from carbon dioxide and water. The organic molecules are sugars, used as food. Plants also take nutrients from weathered rock and decomposing animals and plants in soil.

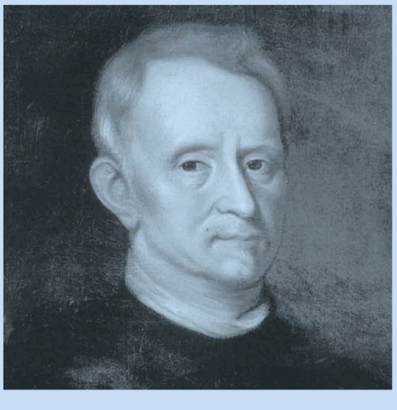
Photoautotrophs form the basis of every food chain, in which energy flows through feeding from one organism to another. Plants and other photoautotrophs feed almost all non-photosynthesizing organisms on the planet. Organisms that graze on photoautotrophs directly are herbivores; animals that eat herbivores or their immediate predators indirectly consume photoautotrophs. Without plants performing photosynthesis, life as we know it would not exist. Yet it was not until the 17th century that scientists began to investigate how plants fueled their growth.

> It is more than a figure of speech to say that plants create life out of thin air.
>
> **Michael Pollan**
> **American science writer**

Water

In the early 1600s, Dutch-Belgian physician and chemist Jan Baptista van Helmont was inspired by German scholar Nicholas of Cusa to set up an experiment. It was designed to test the conventional wisdom of the time: that a plant grows and gains mass from the soil in which it is planted. Helmont weighed and planted a small, 5 lb

Jan Baptista van Helmont



Born in Brussels in the Spanish Netherlands (today's Belgium) in 1580, van Helmont received a doctorate in medicine in 1599 from the Catholic University of Louvain. He became an acclaimed physician, traveling throughout Europe to refine his skills.

After marrying into nobility, Helmont dedicated his life to chemical research, believing that experimentation was crucial to understanding the natural world. He was a moderate supporter of Paracelsus and rejected Aristotle's theory of four essential elements in favor of two—air and water.

Helmont wrote about his research in many scientific treatises, but they were not all published until after his death in 1644; his son published his collected works in 1648. Helmont is regarded by some as the father of air chemistry, because of his investigations into chemical reactions of gases.

Key works

1613 *On the Magnetic Healing of Wounds*
1642 *A New Theory of Fevers*
1648 *Origin of Medicine*

See also: Complex cells 38–41 ▪ Metabolism 48–49 ▪ Essential nutrients 56–57 ▪ The beginnings of organic chemistry 61 ▪ Reactions of photosynthesis 70–71 ▪ Plant transpiration 82–83 ▪ Food chains 284–85 ▪ Recycling and natural cycles 294–97

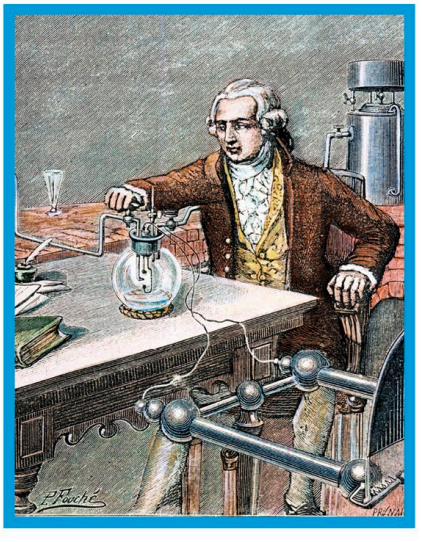
(2.2 kg) willow tree in a large pot, which also contained 200 lb (91 kg) of carefully weighed soil.

After consistently watering the tree for five years, Helmont weighed the tree and soil again. The willow tree gained 164 lbs (74 kg) and the soil lost only 2 oz (57 g). Helmont concluded that plants needed only water, not soil, to grow and gain mass, indeed, that all things were the product of simple water.

Helmont's conclusion was only partly correct: he was not aware of the role played by soil in supplying mineral nutrients for plant growth. He was the first to show that plants need water to grow, so finding the first reactant of photosynthesis. He also conducted many experiments into vapors given off by chemical reactions and coined the term "gas." One gas, which he named *gas sylvestre*, was later found to be "fixed air," or carbon dioxide.

Oxygen

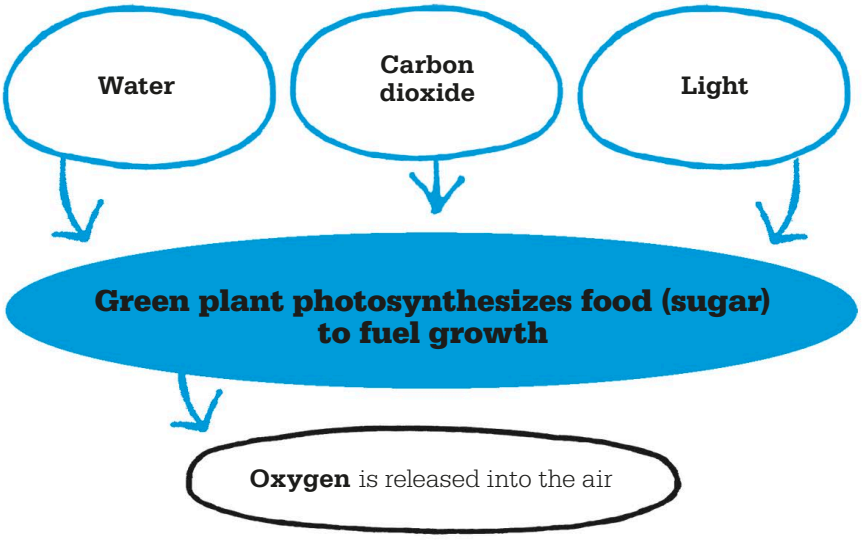
In the late 18th century, Joseph Priestley, a British naturalist, minister, chemist, and educator, studied "airs," or gases. He subscribed to the hypothesis of the time that air could be contaminated by something called phlogiston, a noxious, invisible substance that was released by combustion—burning flammable material.



Antoine Lavoisier demonstrated in 1778 that combustion involves reactions with oxygen (which he named in 1779), so disproving the phlogiston theory, but not all scientists agreed with him.

In one of his many experiments, described in several volumes called *Experiments and Observations on Different Kinds of Air* in the 1770s, Priestley found that air was not a single substance, but a mixture of gases. He isolated several of them, including one in 1774 he named "dephlogisticated air," as it seemed to cleanse air contaminated by phlogiston, for example air in a jar exhausted by burning a candle.

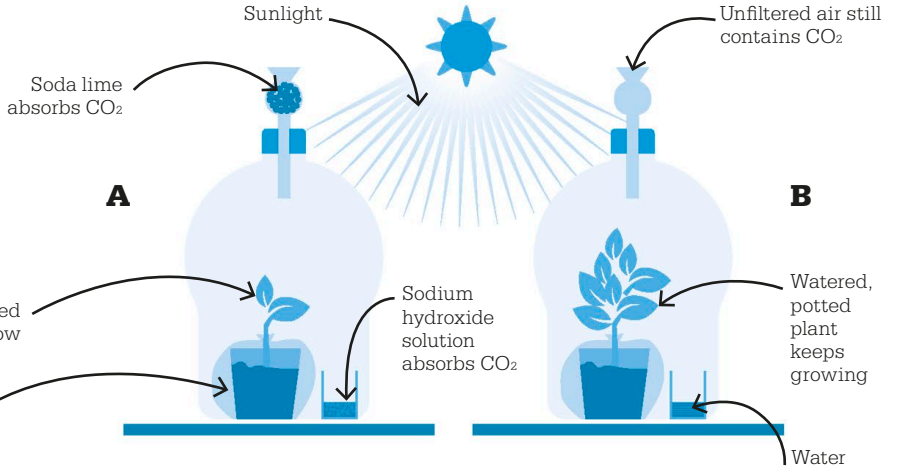
Priestley also observed in 1774 that a mouse placed alone under a sealed bell jar will die, but it will live if a sprig of mint is placed under the jar with the mouse. Priestley concluded that the plant gave off good air and "restored" the "injured" air under the bell jar, allowing the mouse to live. The fact that plants release oxygen was now established. Later that same year, French chemist Antoine Lavoisier repeated Priestley's experiment and isolated the same gas.



Light and green leaves

In 1779, inspired by Priestley's work, Dutch chemist Jan Ingenhousz investigated what plants require for growth, by testing their production of dephlogisticated air and the effect upon them of light.

Ingenhousz conducted more than 500 experiments, detailing them in his book *Experiments upon Vegetables* (1779). He used an aquatic plant, pondweed, so that he could easily observe any gas bubbles given off by the plant. To show that the gas in the bubbles was dephlogisticated air, he collected the bubbles and used the gas to light a flame. »



Sénébier's experiment to prove plants absorbed carbon dioxide (CO_2) used bell jars to control the air content around each plant. The plant in bell jar A does not grow if CO_2 is extracted from the air, but the air in bell jar B contains CO_2 and the plant keeps growing.

Ingenhousz demonstrated that the bubbles emerged only when the pondweed is exposed to light, not warmth. A plant's need for light was the next line of evidence in understanding photosynthesis.

He also described how only the green leaves and stalks gave off oxygen; that more oxygen is released in bright light; and that plants contaminate the air at night with "fixed air" (carbon dioxide).

Carbon dioxide

Jean Sénébier, a Swiss naturalist, botanist, and pastor, dispensed with the idea that plants took in bad air and absorbed phlogiston to give out good air (oxygen). In 1782, Sénébier described an elegant experiment, consisting of two bell jars each with a plant, a source of water, and sunlight (see above). One bell jar was left open to the surrounding air, and the other jar was sealed and emptied of fixed air (carbon dioxide). Both jars had a container with the same amount of water, but the water in the sealed jar contained sodium hydroxide, to absorb any carbon dioxide in the jar. The plant that had access to air containing carbon dioxide continued to grow, while the plant deprived of carbon dioxide did not.

A plant's ability to gather carbon in inorganic form as carbon dioxide gas and transform the carbon atoms into organic compounds is called "carbon fixation."

Sénébier concluded that green plants absorb carbon dioxide, in sunlight, to use it as food to fuel growth. He also confirmed that leaves give off oxygen, although he incorrectly assumed that this pure air "is the product of the transformation of fixed air."

Swiss chemist Théodore de Saussure suggested in 1804 that water must also contribute to increasing a plant's mass, after weighing and measuring plants in containers and the surrounding gases. He found that the amount of carbon dioxide a growing plant took in weighed less than the total weight of the organic mass plus oxygen it produced, so water must account for the difference.

> … this is a green world, with animals comparatively few and small, and dependent on the leaves. By leaves we live.
>
> **Patrick Geddes**
> **Scottish ecologist (1854–1932)**

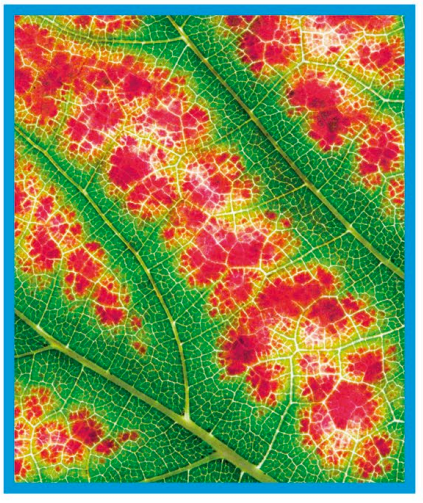
Green grains

Joseph-Bienaimé Caventou and Pierre-Joseph Pelletier were two French pharmacists who extracted and studied various alkaloids from vegetable plants. They discovered intriguing compounds such as caffeine, strychnine, and quinine. In 1817, they isolated the green pigment in plants. They named the substance chlorophyll, from the Greek *chloros*, meaning "green," and *phyllon*, or "leaf."

German botanist Hugo von Mohl studied the green plant cells through a microscope and, in 1837, described chlorophyll as grains (*chlorophyllkörnern*), although he did not realize their purpose.

Energy

By the mid-19th century, the basic ingredients and products of the process in which a plant increased its mass had been determined.



Fall foliage color is a result of the chloroplasts stopping making chlorophyll, which usually masks other pigments present in the leaf, such as orange, yellow, and red carotenoids.

Julius Robert von Mayer, a German physician and physicist, recognized that the process was actually one of energy conversion. He was one of several scientists whose work would contribute to the first law of thermodynamics: the law of the conservation of energy. Mayer described the law in 1841; it states that energy cannot be destroyed or created.

In 1845, Mayer proposed that plants convert light energy into chemical energy, or "difference." In photosynthesis, energy from the Sun initiates a series of chemical reactions that gathers carbon atoms from air and makes them into sugar molecules to fuel a plant.

The role of chlorophyll

The simple sugar produced by the process of photosynthesis is then converted by the plant into glucose for its immediate energy needs. Any leftover glucose molecules are strung together in large, branched chains to form starch. Starch is the plant's storage molecule and serves as an energy store. Both glucose and starch are different forms of carbohydrate.

> The plants take in one form of power, light; and produce another power, chemical difference.
> **Julius Robert von Mayer**

In 1862–64, German botanist Julius von Sachs used iodine to stain starch granules in leaves and show that starch was created only in light. In 1865, with the aid of the latest microscopes, he described how starch formed only inside the chlorophyll grains. This confirmed that the chlorophyll bodies must be the site of photosynthesis.

Chlorophyll bodies in plant cells were shown to give off oxygen, in an ingenious experiment by German physiologist Théodor Engelmann in 1882. He used a prism to project a spectrum of light onto a filament of green algae under the microscope. He added oxygen-loving bacteria to the slide, and they clustered at the algae parts under blue or red light, indicating that the chlorophyll was absorbing the red and blue light to produce oxygen. The green-light wavelength is not absorbed by chlorophyll, but is reflected back so our eyes see the green color.

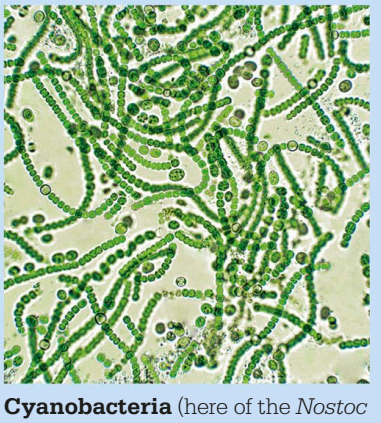
It was only in the 20th century that advances in molecular chemistry made possible the next step—to uncover the chemical reactions of photosynthesis. ■

Cyanobacteria

Photosynthesizing, single-celled cyanobacteria live in water and, like plants, contain chlorophyll and use carbon dioxide, water, and sunlight to produce oxygen, sugar, and other organic molecules.

About 3.5 billion years ago, Earth's primitive atmosphere had very little oxygen, but fossils exist of cyanobacteria from that age. It is thought that they introduced oxygen—the waste product of photosynthesis—into the atmosphere and changed the course of our planet's evolutionary trajectory. In an oxygenated atmosphere, organisms were able to use oxygen to harness more energy from food and power larger, multicellular bodies.

Cyanobacteria (previously called blue-green algae) are also nitrogen-fixers: they take nitrogen directly out of the air and incorporate it into organic molecules such as proteins and nucleic acids. This ability makes them highly nutritious photoautotrophs at the base of the food chain.



Cyanobacteria (here of the *Nostoc* genus) are common in fresh and marine waters and have fairly large cells compared to other bacteria.

THE VIRTUES OF ORANGES AND LEMONS

ESSENTIAL NUTRIENTS

Regular consumption of **citrus fruits** soon banishes the **symptoms of scurvy** in affected sailors.

Other **assumed remedies**, such as vinegar, do nothing to improve the condition of **scurvy-afflicted sailors**.

The body needs a substance found in citrus fruits to carry out a vital function—without it, scurvy develops.

IN CONTEXT

KEY FIGURE
James Lind (1716–94)

BEFORE
***c.* 3800 BCE** The skeleton of an infant with abnormal bone formation indicates that scurvy existed in Egypt at this time.

***c.* 1550 BCE** Scurvy is described for the first time in Ebers papyrus of Egypt.

1500 CE Sailors in Portuguese explorer Pedro Cabral's fleet are given oranges and lemons, and some are cured of scurvy.

1614 English military surgeon John Woodall notes that eating citrus fruits can cure scurvy.

AFTER
1912 Polish biochemist Casimir Funk lists four vital "vitamines" in food that can prevent certain diseases.

1928 Hungarian biochemist Albert Szent-Gyorgyi isolates the chemical ascorbic acid (vitamin C).

During the time of the crusades in Europe, from the 11th to 13th centuries, physicians and military commanders became aware of a debilitating disease that seemed to strike armies on long overland journeys. The disease came to be called scurvy and was characterized by fatigue, bleeding gums, porous bones, and abnormal bone formation. Ultimately, it could kill. Later, between the 14th and 18th centuries, the Renaissance and the age of exploration saw an expansion of trade and the rise of great maritime powers. Scurvy was the largest cause of illness and death among sailors on long sea voyages lasting several months or even years.

The causes of scurvy

Although the scientific basis of scurvy was yet to be established, various seafarers and physicians realized that it was related to the sailors' inadequate diet. This was limited to those provisions taken on board at the start of a voyage, such as biscuits and salt beef.

See also: Food groups 60 ▪ Enzymes as biological catalysts 64–65 ▪ How enzymes work 66–67 ▪ Respiration 68–69

In the 18th century, ports such as Moorea in French Polynesia, allowed British explorer James Cook to restock his fleet with fresh produce—including citrus fruit—to help combat scurvy.

Sailors had no access to fresh food. While some people came to realize that scurvy could be prevented by eating vegetables and fresh fruit, especially citrus fruits, the naval and medical establishments ignored this advice, partly because many doctors had other (mistaken) ideas. One such theory proposed that scurvy was a digestive disorder and that it could be prevented by drinking laxatives.

Scurvy experiments

In 1747, Scottish naval surgeon James Lind carried out the first serious investigation into various cures that had been suggested for scurvy. Working on HMS *Salisbury*, Lind picked out 12 sailors with scurvy, separated them into six pairs, and gave each pair a daily dose of one of six alleged remedies. These were cider, dilute sulfuric acid, vinegar, seawater, two oranges and a lemon, and a laxative made up of a spicy paste. Within a few days, the sailors who had eaten the oranges and lemons were showing an improvement, while the rest remained sick. Lind concluded that a specific substance in citrus fruits could cure scurvy and perhaps prevent it from occurring.

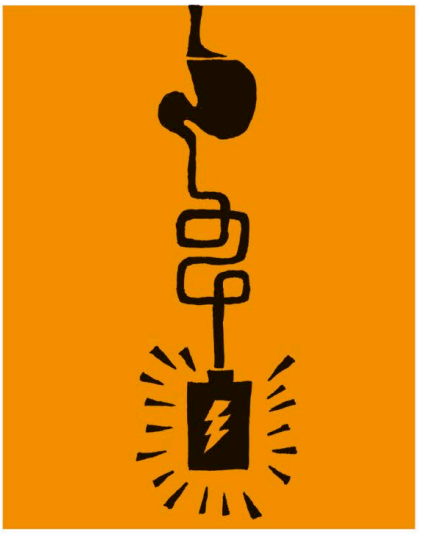
Lind's experiment was one of the first clinical trials in modern medicine, and it led to the idea of essential nutrients. These are substances that the body needs to function normally—but since they cannot be made by the body itself, they must be included in our diet.

We now know that the essential nutrient we need to prevent scurvy is vitamin C—several metabolic enzymes require it in order to function properly. Vitamin C was first isolated as a specific molecule in 1928. By then, the connection was understood between several other illnesses and the nutrients whose absence causes them. Together, these came to be called nutritional deficiency diseases. Today, around 40 essential nutrients are known, including 13 vitamins (small organic molecules) and 16 minerals—elements such as calcium and iron.

Although Lind's experiment proved that eating citrus fruits could cure and prevent scurvy, four decades passed before Britain's Royal Navy acted on his advice. In 1795, it began to issue lemon juice to crews on long journeys to prevent scurvy. ■

Nutritional deficiency diseases

Other than scurvy, two classic nutritional deficiency diseases are beriberi, caused by lack of thiamine (vitamin B1), and rickets, most commonly caused by vitamin D deficiency. Wheat flour and rice contain naturally occurring thiamine, but this is lost through milling and other processing. Beriberi is more widespread in regions where processed white rice, lacking in thiamine, forms a big part of the diet. Vitamin D deficiency is a risk to anyone whose diet lacks foods rich in vitamin D, which include fatty fish, egg yolks, and fortified breakfast cereals, particularly if they get little exposure to sunlight: the Sun's rays hitting the skin allows the body to make some vitamin D. Other well-known deficiency diseases include vitamin B12 deficiency anemia, a risk to vegans, since vitamin B12 is found only in animal products, and iodine deficiency, which can cause an enlarged thyroid gland among other health problems.



THE CONVERSION OF VICTUALS INTO VIRTUES

DIGESTION

IN CONTEXT

KEY FIGURE
Lazzaro Spallanzani
(1729–99)

BEFORE
***c.*180 CE** Galen concludes from animal dissections that food is "assimilated" in the stomach and is converted into blood in the liver.

1543 Andreas Vesalius publishes *On the Structure of the Human Body*, which includes a detailed anatomy of the gastrointestinal tract.

1648 Flemish physician Jan Baptist van Helmont describes chemical processes in the body and probable roles in digestion.

AFTER
1823 British chemist William Prout finds that gastric fluids contain hydrochloric acid.

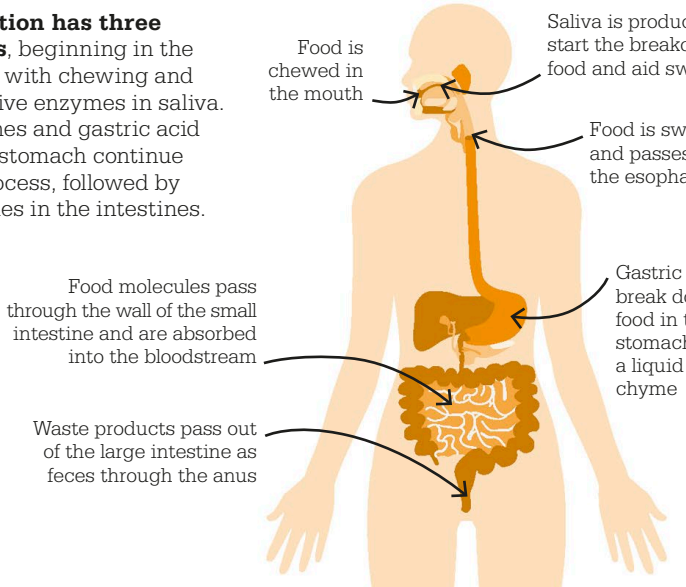
1836 German physician Theodor Schwann isolates and names the digestive enzyme pepsin.

The process of digestion, whereby food is broken down into molecules that can be transported around the body by the bloodstream and absorbed by cells, was largely a mystery until the 18th century. The breakthrough in understanding came when Italian biologist Lazzaro Spallanzani found that gastric fluids contain specific chemicals that are crucial to the decomposition of food.

Before Spallanzani, physicians held competing theories about the process. Some considered that heat within the body "cooked" food to produce energy. One school of thought likened digestion to fermentation, while another argued that food pieces were simply ground up in a mechanical process, known as trituration.

Vitalism was an even older theory that dated back to the ancient world, was championed by Aristotle, and persisted into the 19th century. It held that bodily processes were driven by a spiritual life force and argued that something as miraculous as digestion could not be explained in just physical terms.

Digestion has three stages, beginning in the mouth with chewing and digestive enzymes in saliva. Enzymes and gastric acid in the stomach continue the process, followed by enzymes in the intestines.



See also: Anatomy 20–25 ▪ Metabolism 48–49 ▪ Essential nutrients 56–57 ▪ Food groups 60 ▪ The beginnings of organic chemistry 61 ▪ Fermentation 62–63 ▪ Respiration 68–69 ▪ Circulation of the blood 76–79

In the 16th and 17th centuries, Flemish and English physicians Andreas Vesalius and William Harvey made groundbreaking advances in anatomy, and by the early 18th century, physicians knew more about the gastrointestinal tract from dissecting animal and even human cadavers. They became aware of digestive juices, known to be acidic, but most still believed digestion was a mechanical process rather than a chemical one.

Gastric juices

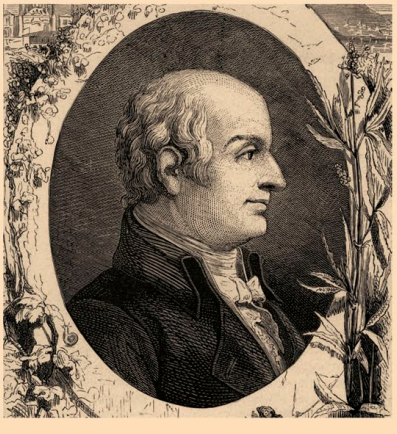
In the late 1770s, Spallanzani conducted meticulous and rigorous experiments that proved that digestion is a chemical process. He improved on the experimental design of French entomologist René Antoine Ferchault de Réaumur, who had attempted to establish that digestion could take place in vitro—in an artificial environment outside the body—as would be expected if it just purely chemical. Spallanzani's methods included feeding crows with food that was placed in tiny perforated cylinders attached to long lengths of twine. After a certain amount of time, the cylinders were retrieved, and the food inside was found to have been partly digested.

> If I set out to prove something, I am no real scientist. I have to learn to follow where the facts lead me. I have to learn to whip my prejudices.
> **Lazzaro Spallanzani**

Spallanzani also extracted gastric fluid (which he called gastric juices) from animals' stomachs to experiment with digestion in vitro. Carefully maintaining the fluid at body temperature, he was able to observe directly the chemical decomposition of different foods. He noted that vegetable matter, fruit, and bread were digested more quickly than meat, and that the process in vitro took longer than it did within the stomach. This suggests that gastric juices are renewed from the stomach wall when needed, which increases the efficiency of the process. He also highlighted the importance of mastication (chewing) and saliva in the mouth: breaking food into smaller pieces increases the surface area exposed to gastric juices, and saliva itself contains digestive chemicals.

Spallanzani's findings paved the way for further discoveries about digestion in the 19th century, including evidence from US Army surgeon William Beaumont in 1833, when he observed, experimented on, and isolated gastric juices from a patient with a gunshot wound to the stomach. In 1897, Russian physiologist Ivan Pavlov published his findings on the nervous-system mechanism that triggers the secretion of gastric fluids, leading to his famous work on conditioned reflexes in animals. ■

Lazzaro Spallanzani



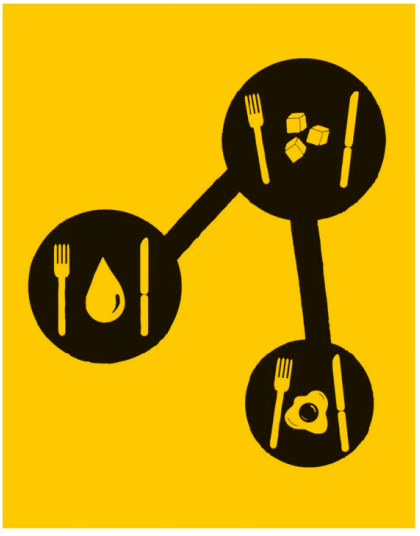
Born in 1729 into a distinguished family in Scandiano, northeast Italy, Lazzaro Spallanzani was initially persuaded by his father to pursue a career in law. However, at college he abandoned his legal studies in favor of other interests, including physics and natural science.

By his early 30s, Spallanzani was both an ordained Catholic priest and a professor at the University of Modena. In 1769, he accepted a post at the University of Pavia, where he remained until his death in 1799. His achievements made him well known across Europe, earning him membership in prestigious scientific societies.

In addition to his work on digestion, Spallanzani conducted important research into animal reproduction: he was the first to perform in vitro fertilization, using frogs. His experiments on bats anticipated the discovery of echolocation in the 1930s.

Key work

1780 *Dissertation on the Physiology of Animals and Vegetables*



THE SACCHARINE, THE OILY, AND THE ALBUMINOUS

FOOD GROUPS

IN CONTEXT

KEY FIGURE
William Prout (1785–1850)

BEFORE
1753 James Lind demonstrates that eating citrus fruit can prevent scurvy.

1816 French physiologist François Magendie shows that nitrogen in food is essential for good health.

AFTER
1842 Justus von Liebig identifies the importance of proteins.

1895 Dutch physician Christiaan Eijkman discovers that what is later called vitamin B protects against the disease beriberi.

1912 Polish biochemist Casimir Funk discovers vitamins.

1950s Physiologists and nutritionists begin to explain how excess fat and sugar can cause heart disease.

By the early 19th century, it was clear that life depends on chemical processes and that certain chemicals in food play a key role in health. In the 1820s, British physician William Prout's investigations of the chemistry of digestion led to his discovery of the main food groups.

Analyzing the gut contents of animals such as rabbits and pigeons, Prout saw that they contained just a few basic substances, made from carbon, hydrogen, and oxygen. And when he discovered hydrochloric acid in the stomach of several animals, he became convinced of the chemical nature of digestion.

In 1827, Prout published the first of three papers on chemicals in food, which he called "alimentary substances." He divided foods into three "principles": saccharine (carbohydrates), oily (fats), and albuminous (proteins). This was the first clear exposition of the three main food groups.

Nowadays, it is understood that carbohydrates are sugars and starches made from carbon, hydrogen, and oxygen; they provide the basic energy for cells. Fats and oils (lipids)—also made from carbon, hydrogen, and oxygen—are used by the body for backup energy, vitamin storage, the production of hormones, and as protection for organs. Proteins perform many roles—from building muscles, to defense against infections. They are made from 20 or so amino acids, which in turn are built from carbon, hydrogen, nitrogen, oxygen, or sulfur. ■

Red meat, fish, eggs, cheese, nuts, and broccoli are all foods that are rich in protein, which is essential for the growth and repair of animals' bodies.

See also: Biochemicals can be made 27 ▪ Making life 34–37 ▪ Essential nutrients 56–57 ▪ Digestion 58–59 ▪ The beginnings of organic chemistry 61

A BETTER ELEMENT DOES NOT EXIST ON WHICH TO BASE LIFE

THE BEGINNINGS OF ORGANIC CHEMISTRY

IN CONTEXT

KEY FIGURE
Justus von Liebig (1803–73)

BEFORE
1756 British chemist Joseph Black discovers "fixed air" (now known to be carbon dioxide).

1803 British chemist John Dalton proposes that "fixed air"—produced by respiring animals and absorbed by plants—contains one carbon atom and two oxygen atoms.

AFTER
1858 Scottish chemist Archibald Couper and German chemist August Kekulé suggest that every carbon atom can form chemical bonds with up to four other carbon atoms.

Late 1940s American chemist Robert Woodward synthesizes natural food substances and other organic compounds from simple, inorganic precursors, showing that natural products can indeed be synthesized.

Natural substances fall into two main groups: inorganic materials, like the minerals in rocks; and organic substances—those found in, or derived from, living things, such as food.

After German chemist Friedrich Wöhler had shown, in 1828, that urea—an organic component of mammalian urine—could be made in the laboratory by reacting inorganic chemicals, there was a surge of research into the nature of organic matter.

Advances in research

In 1831, Justus von Liebig, a German chemist, perfected techniques that enabled the accurate determination of how much carbon, oxygen, and hydrogen are contained in organic compounds. Subsequently, he went on to conduct research into areas such as the chemistry of food, plant and animal nutrition, and respiration. Through this work, it became clear that the chemistry of both food substances and living organisms is largely based on molecules containing carbon atoms.

> Carbon [is] in more kinds of molecules than … all other kinds of molecules combined.
>
> **Neil deGrasse Tyson**
> **American astrophysicist**

Later, chemists discovered that the huge diversity of organic substances is due to a unique property of carbon atoms: they can form bonds with up to four other atoms, including other carbon atoms. This allows large, complicated macromolecules based on chain- and ring-like carbon structures to be built in living organisms. They make up four main groups: proteins, carbohydrates, lipids, and nucleic acids. Put simply, life as it exists on Earth could never have developed without carbon. ■

See also: Biochemicals can be made 27 ▪ Making life 34–37 ▪ Photosynthesis 50–55 ▪ Food groups 60 ▪ Fermentation 62–63 ▪ Reactions of photosynthesis 70–71

LIFE WITHOUT FREE OXYGEN

FERMENTATION

IN CONTEXT

KEY FIGURE
Louis Pasteur (1822–95)

BEFORE
1680 Antonie van Leeuwenhoek is the first to observe single-celled microorganisms in pond water under the microscope.

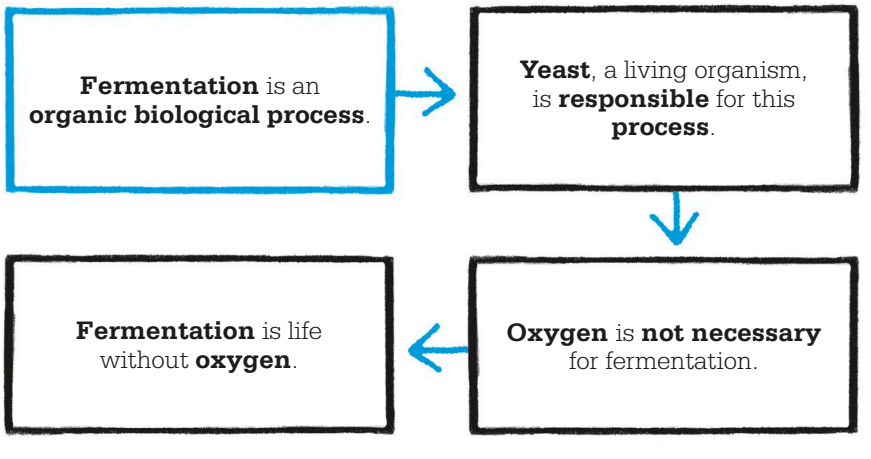
1837 Theodor Schwann, French engineer Charles Cagniard de la Tour, and German pharmacist Friedrich Traugott Kützing independently discover that yeast is a living organism and reproduces by budding.

AFTER
1881 German physician and and bacteriologist Robert Koch isolates microorganisms that cause infectious diseases.

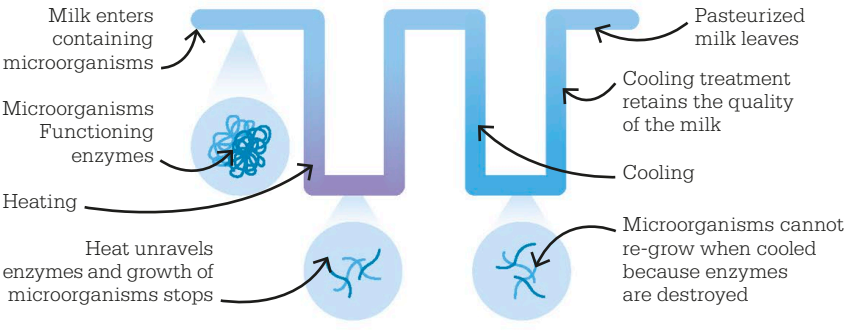
1897 Eduard Buchner demonstrates that it is the action of enzymes in yeast that causes fermentation to occur, and not the yeast cell itself.

Louis Pasteur originally made his name as a chemist, and when he was appointed Dean of Science at the University of Lille, France, he was approached by a local wine producer to investigate the problem of souring during the process of fermentation. At that time, in the 1850s, fermentation was widely believed to be a purely chemical, rather than a biological, process. Some, however, disagreed.

Several scientists, notably Theodor Schwann, observed that yeast is an intrinsic component of the fermentation process that converts sugar into alcohol, and that yeast is a living organism, which usually reproduces through a form of cell division called budding. Schwann also showed that just as yeast is essential to start fermentation, the process stops when yeast ceases to reproduce. The inference was clear: the conversion of sugar into alcohol during fermentation is part of a biological process dependent on the action of a living organism. With this in mind, Pasteur set out to identify the cause of spoiling in wine, beer, and vinegar production. His experiments confirmed Schwann's thesis, and further showed that in this organic process, the cells of living yeast derive energy from nutrients such as



See also: The beginnings of organic chemistry 61 ▪ Enzymes as biological catalysts 64–65 ▪ How enzymes work 66–67 ▪ Germ theory 144–51



Pasteurization of milk was first used commercially in 1882. It involves heating milk to destroy harmful microorganisms, increasing storage time and preventing the outbreak of diseases such as typhoid and tuberculosis.

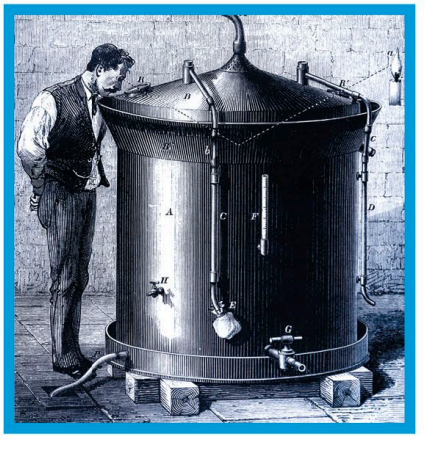
sugar, while converting them into alcohol and carbon dioxide. Pasteur also showed that fermentation can occur in the absence of oxygen, or as he defined it, "life without air."

Pasteurization

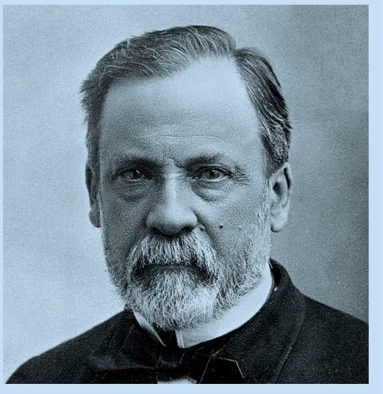
Having established the organic nature of fermentation, Pasteur became fascinated by the world of microorganisms. Importantly for the wine and beer industries, his research into fermentation revealed that different types of microorganisms cause different kinds of fermentation, not all of which are desirable. Specific types of yeast are responsible for the production of alcohol in wine, for example, but the presence of other yeasts are the cause of souring.

To prevent further unwanted fermentation in wines and beers, or the fermentation that causes milk to sour, Pasteur suggested a rapid heating and cooling of the liquids to kill the microorganisms responsible and prevent their reproduction, a process that became known as pasteurization.

Despite Pasteur's discoveries, German scientist Justus von Liebig opposed the idea that microorganisms were involved in fermentation and insisted that it was purely inorganic. The "Liebig–Pasteur dispute" was only resolved in 1897, when German chemist Eduard Buchner found that yeast extract with no living cells was capable of causing the conversion of glucose to ethanol. He concluded that the enzymes in the yeast cells, rather than the living yeast itself, cause fermentation. ■



The apparatus used by Louis Pasteur for cooling and fermenting during his time working with beer. Pasteur's later work on microorganisms led him to the invention of pasteurization.



Louis Pasteur

Born in 1822 and the son of a tanner, Pasteur was and brought up in the Jura region of France. After studying in Besançon, he enrolled at the École Normale Supérieure in Paris, and left with a doctorate in physics and chemistry in 1847. Pasteur was appointed professor of chemistry at the University of Strasbourg in 1848, and subsequently held posts at the University of Lille, the École Normale Supérieure, and Sorbonne University. At Lille, he began the research into fermentation that sparked his interest in microorganisms, and led to pasteurization of milk and the first vaccines. In 1859, Pasteur entered a contest for the best experiment to disprove the theory of spontaneous generation. In his winning entry, he boiled meat broth in a swan-necked flask, blocking the entrance of airborne microbes. After his death in 1895, Pasteur was honored with a state funeral at Notre-Dame Cathedral.

Key work

1878 *Microbes Organized, their role in Fermentation, Putrefaction and Contagion*

CELLS ARE CHEMICAL FACTORIES

ENZYMES AS BIOLOGICAL CATALYSTS

IN CONTEXT

KEY FIGURE
Wilhelm Kühne (1837–1900)

BEFORE
1752 French scientist René-Antoine Ferchault de Réaumur investigates the role of gastric juices in digesting food.

1857 Louis Pasteur introduces the germ theory of fermentation, associating the process with living organisms.

AFTER
1893 German chemist Wilhelm Ostwald classifies enzymes as catalysts.

1894 Emil Fischer, a German chemist, proposes the lock-and-key model to explain how enzymes interact with their target molecules.

1926 American chemist James Sumner obtains crystals of the enzyme urease and demonstrates that it is a protein.

An enormous amount of biochemical activity takes place in living cells as they obtain the energy they need to maintain themselves. This activity is called metabolism. It is the process of chemical and physical change involved in sustaining life and includes repairing and renewing tissues, obtaining energy from food, and breaking down waste materials. Most of these reactions do not occur spontaneously. They are only made possible by catalysis—the action of catalysts. These substances change the rate of a reaction without being changed themselves, enabling them to catalyze further reactions.

> [Catalysts] form new compounds into the composition of which they do not enter.
> **Jöns Jakob Berzelius**

Enzymes are now known to be biological catalysts, facilitating the essential chemical reactions that sustain all living things. Without enzymes, the reactions that life depends on would take place at a rate far too slow to sustain it.

In 1833, French chemists Anselme Payen and Jean François Persoz were the first to isolate an enzyme (which they called a "ferment"). They conducted an experiment in which they obtained a substance that had the ability to convert starch into sugar. They derived this substance from germinating barley and called it diastase, although it is now known as amylase. Two years later, in 1835, Swedish chemist Jöns Jakob Berzelius coined the term catalyst to describe substances that promoted chemical reactions without being altered themselves. The following year, German physiologist Theodor Schwann discovered pepsin while he was investigating digestive processes; this was the first enzyme to be derived from animal tissue. Over the next few years, other chemists discovered more enzymes.

The production of alcoholic drinks by fermentation has been practiced for millennia, but it was

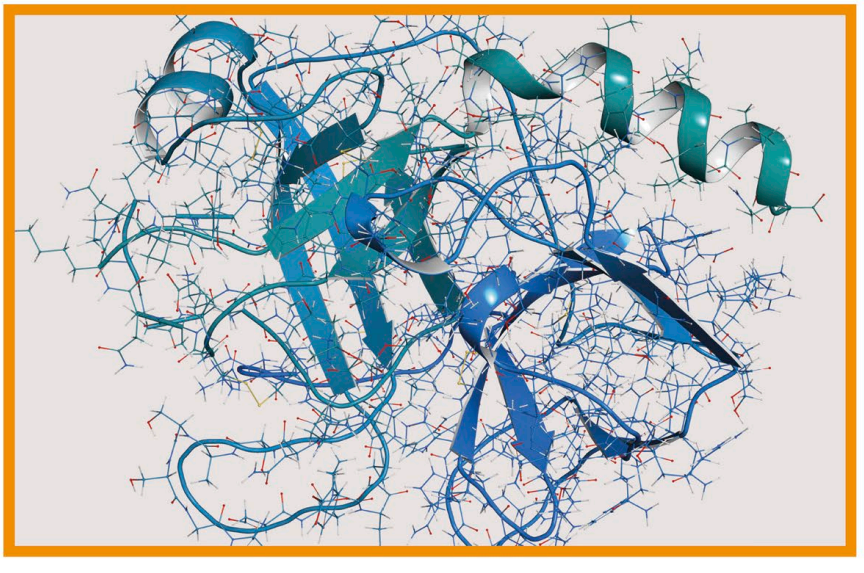
See also: Metabolism 48–49 ▪ Digestion 58–59 ▪ The beginnings of organic chemistry 61 ▪ Fermentation 62–63 ▪ How enzymes work 66–67

not until the 19th century that the process was found to be caused by living organisms. In the late 1850s, Louis Pasteur, who was studying the fermentation of sugar to alcohol by yeast, came to the conclusion that it was caused by "ferments" within the yeast cells. He believed that these substances could only function within living organisms. German biochemist Justus von Liebig challenged Pasteur's view, believing that fermentation was a purely chemical process that did not require the involvement of microorganisms.

Non-living substances

In 1876, Wilhelm Kühne discovered trypsin, which is produced in the pancreas and breaks down proteins in the small intestine. He was the first scientist to use the word "enzyme"; this came to be used to refer to non-living substances such as pepsin and amylase, while "ferment" referred to the chemical activity associated with living organisms. Then, in a series of experiments carried out in 1897, German chemist Eduard Buchner investigated the ability of yeast extracts, rather than of living yeast cells, to ferment sugar. He discovered that fermentation took place even when no living yeast cells were present, effectively putting an end to the argument that fermentation required a living organism. He named the enzyme that enabled fermentation zymase. (It is now known that this is, in fact, a set of several enzymes.)

Enzymes are usually named according to the molecule they act upon, with the suffix -ase added to the name of the substrate. For example, lactase breaks down lactose, the sugar in milk. This system of naming was suggested by French microbiologist Emile Duclaux in 1899. ■



The enzyme trypsin (seen here in model form) binds to molecules of the amino acids arginine and lysine to break down proteins in the gut and aid digestion.

Wilhelm Kühne

Born into a wealthy family in Hamburg, Germany, in 1837, Wilhelm Kühne went to the University of Göttingen at the age of 17 to study chemistry, anatomy, and neurology. After he graduated, he was awarded a doctorate for a thesis on induced diabetes in frogs. He then went on to study physiology at various universities around Europe, before succeeding Hermann von Helmholtz as chair of physiology at the University of Heidelberg, Germany, in 1871.

While he was there, Kühne focused his research mostly on the physiology of muscles and nerves (particularly the optic nerve), as well as on the chemistry of digestion. Notably, he discovered the protein-digesting enzyme trypsin. Kühne remained at Heidelberg until his retirement in 1899, and he died in that city the following year.

Key work

1877 "Über das Verhalten Verschiedener Organisirter und sog. Ungeformter Fermente" ("On the Behavior of Various Organized and So-Called Unformed Ferments")

THEY MUST FIT TOGETHER LIKE LOCK AND KEY

HOW ENZYMES WORK

IN CONTEXT

KEY FIGURE
Emil Fischer (1852–1919)

BEFORE
1828 German chemist Friedrich Wohler demonstrates that organic chemicals can be made in the laboratory.

1857 French microbiologist Louis Pasteur publishes the results of his investigations into the role of yeast in alcoholic fermentation.

AFTER
1897 German chemist Eduard Buchner demonstrates that enzymes will work without living cells being present.

1965 David Chilton Phillips, a British biologist, uses X-ray crystallography to work out the structure of lysozyme.

1968 Swiss biologist Werner Arber and American postdoctoral student Stuart Linn isolate the first restriction enzyme, a powerful tool for genetic engineering.

By the end of the 19th century, the existence of enzymes as biological catalysts was firmly established. But how did they work? A particular enzyme will generally only interact with a certain substance, called a substrate. German chemist Emil Fischer was one of the first people to investigate this phenomenon. His research into the structure of different types of sugar molecule and the enzymes that cause their fermentation led him to observe famously that "enzyme and glucoside [the natural precursor of glucose] must fit together like a lock and key".

> Essentially, every protein undergoes some kind of a change when it binds another protein; most of the time a fairly major change.
> **Daniel Koshland**

Enzymes are large molecules, and the substrates they interact with are usually much smaller. This difference in size means that the enzyme and substrate are only in contact at a very specific part of the enzyme, called the active site—but a single enzyme may have more than one active site. Fischer's model of 1894 proposed that the substrate fits into the active site in a similar manner to a key fitting into a lock, resulting in the formation of an enzyme substrate complex where the reaction takes place. After this, the complex breaks apart, releasing the end products of the reaction and leaving the enzyme as it was before.

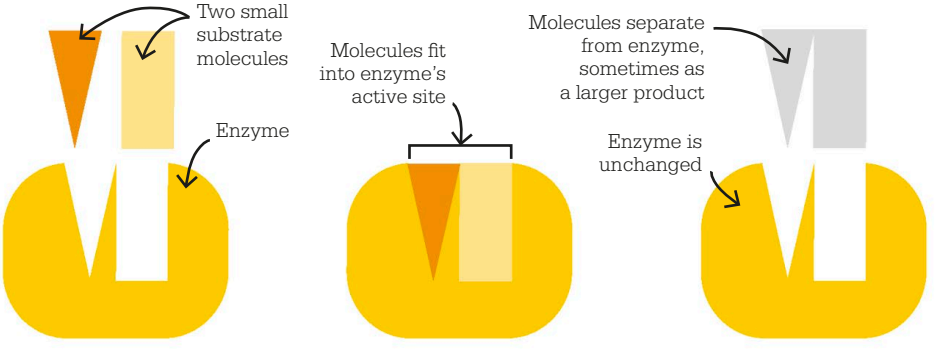
Enzymes as proteins

Fischer's explanation of why enzymes were so specific in their actions proved to be a useful and enduring one. Later discoveries, however, began to show that its portrayal of the enzyme as a rigid lock waiting for a specific substrate key could not be the whole story.

In 1926, American biochemist James Sumner obtained pure crystals of the enzyme urease, which breaks down urine into ammonia and carbon dioxide, and

See also: Biochemicals can be made 27 ▪ Metabolism 48–49 ▪ Fermentation 62–63 ▪ Enzymes as biological catalysts 64–65 ▪ Genetic engineering 234–39

The lock-and-key model, introduced by Fischer, shows that enzymes and substrate molecules have complementary shapes. They bond at the enzyme's active site and a reaction takes place, leaving the enzyme unchanged at the end of the reaction.



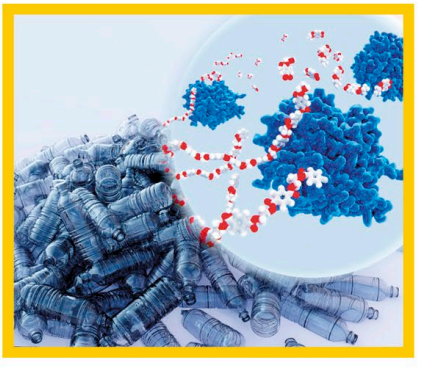
found that they consisted entirely of protein. He speculated that all enzymes were proteins. Sumner's theory provoked controversy at first but was accepted in 1930, when fellow American biochemist John Northrop was able to crystalize the digestive enzymes pepsin and trypsin, discovering that they, too, were proteins.

Also around this time, British geneticist J.B.S. Haldane suggested that bonds that formed between an enzyme and its substrate distorted the substrate and so catalyzed the reaction. He wrote, "The key does not fit the lock perfectly but exercises a certain strain on it." In 1946, American chemist Linus Pauling said that the catalytic activity of enzymes involved an active region of the surface of the enzyme that was complementary in structure not to the substrate molecule as it was normally, but to the substrate molecule under strain.

Induced-fit theory

In 1958, American biochemist Daniel Koshland developed the lock-and-key hypothesis with his theory of induced fit. He suggested that the active site of an enzyme was not an exact template for the substrate, like a rigid lock into which a specific shaped key fits. When the substrate comes into contact with the active site, it produces a structural change in the enzyme, bringing the catalytic groups of the enzyme into alignment with those of the substrate, so that the reaction takes place. Koshland's model was more akin to a hand slipping into a glove that stretches to fit, rather than a key into a lock.

Enzymes only function if pH and temperature conditions are right. In humans, they work best at pH2 in the stomach and pH7.5 in the intestines and usually at normal body temperature (98.6°F / 37°C). ■

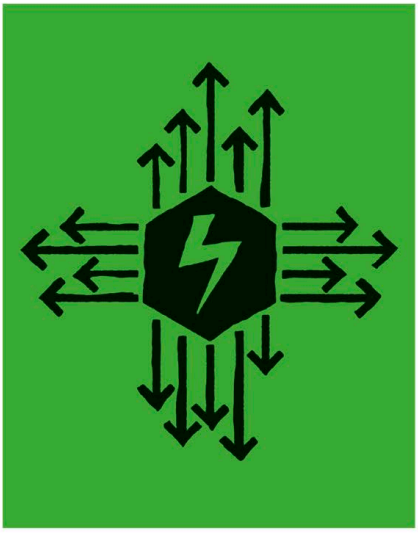


PETase (shown in blue in this image) is a bacterial enzyme that breaks down PET (polyethylene terephthalate) plastics. Its use could be important in the fight against plastic pollution.

Enzyme inhibitors

Enzyme inhibitors are molecules that can slow down or stop the catalytic action of an enzyme. Two common types of enzyme inhibitor are competitive and non-competitive inhibitors.

Competitive inhibitors resemble the substrate and compete with it for a place in the enzyme's active site. If active sites are occupied by inhibitors and unavailable to the substrate, the reaction is slowed. Non-competitive inhibitors, by contrast, alter the enzyme in a way that prevents it from accepting the substrate. A non-competitive inhibitor interacts with the enyzme but usually not at the active site. The effect of this is to change the shape of the enzyme, and thus the active site, so that the substrate can no longer interact with the enzyme to form the enzyme-substrate complex. This prevents the reaction from taking place.



THE METABOLIC PATHWAY THAT RELEASES ENERGY FROM FOOD

RESPIRATION

IN CONTEXT

KEY FIGURE
Hans Adolf Krebs
(1900–81)

BEFORE
1784 French chemist Antoine Lavoisier shows that the body's heat is linked to the inhalation of oxygen and exhalation of carbon dioxide in a chemical process that he calls respiration.

1929 German biochemist Karl Lohmann discovers adenosine triphosphate (ATP), the energy carrier in cells.

AFTER
1946 German-American biochemist Fritz Lipmann discovers coenzyme A, which feeds the citric acid cycle.

1948 Mitochondria (tiny specialized subunits within cells) are found to be the site of the respiration reactions by American biochemists Eugene Kennedy and Albert Lehninger.

The biochemical process of respiration takes place in all living cells. With the help of oxygen, it is the way in which energy is extracted from food to drive all other chemical processes needed for life.

The term respiration was coined in the 18th century by chemists who first discovered and investigated gases in the air. They found that animals breathed out more carbon dioxide and less oxygen than they breathed in—and at night, so did plants. The assumption was that glucose (or sugar) from food was the fuel for this change in gases. During the first half of the 1930s, it was revealed how glucose was broken down into a simpler substance known as pyruvate. This process, called glycolysis, releases a small amount of energy and requires no oxygen. Today, it is recognized by scientists as fermentation, an ancient metabolic process that was used by early organisms even before Earth had an oxygen-rich atmosphere.

> Without ATP, even the smallest piece of action in our bodies would slow down and stop.
> **Jonathan Weiner**
> **American author**

A metabolic pathway

In 1937, Hans Krebs, a German chemist working in Sheffield, UK, published the steps by which pyruvate, the product of glycolysis, is oxidized. In respiration, oxidation is the loss of electrons and the release of energy. This energy can then be harvested by other molecules in the cell. Krebs had worked this out over a number of years by allowing muscle and liver tissue from pigeons to take in oxygen, then analyzing the organic chemicals present. He had predicted that a number of organic compounds containing either four or six carbon atoms—known as four- and six-carbon organic acids—could be made by the gradual oxidation of pyruvate. He found that some of these

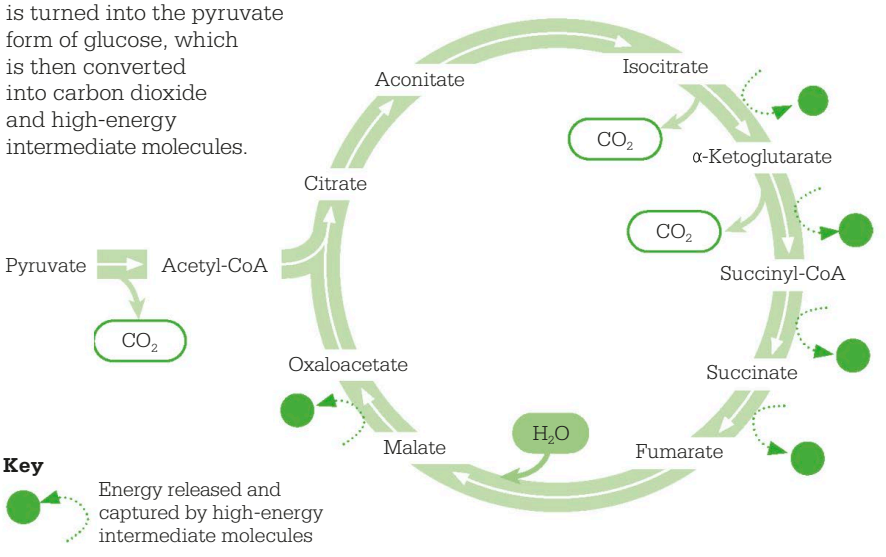
See also: Animals are not like humans 26 ▪ Biochemicals can be made 27 ▪ The cellular nature of life 28–31 ▪ Enzymes as biological catalysts 64–65 ▪ How enzymes work 66–67 ▪ Reactions of photosynthesis 70–71

chemicals were present in varying amounts, and their proportions changed according to how much oxygen was absorbed by the tissue. Krebs used this fact to build a metabolic pathway that was a loop, beginning and ending with citric acid; this is why the process is often called the citric acid cycle.

The citric acid cycle is central to cellular respiration. Pyruvate enters the cycle as acetyl-CoA. CoA is short for coenzyme A, which is a chemical that reduces pyruvate into an acetyl group and carbon dioxide. This acetyl group, which has two-carbon molecules, enters the cycle, where it reacts with the four-carbon molecule, oxaloacetate, to make a six-carbon molecule called citrate.

The cycle then follows a series of oxidation reactions that release electrons and energy. The electrons and energy are captured in a series of reduction reactions by other molecules. After eight steps, the cycle is back at oxaloacetate, and the molecules in the pathway have been changed from six carbon atoms to four, plus two molecules of carbon dioxide. The energy that is released by these reactions is then captured by high-energy intermediate molecules. These molecules, like a recharged battery, will then be kept as stored energy for use by the cell in later steps of respiration. Enzymes that catalyze the citric acid cycle's reactions also speed it up or slow it down based on the cell's energy needs. Krebs's work on the cycle is crucial to our understanding of metabolism and energy production. ■

The citric acid cycle (CAC)—or Krebs cycle—is a series of chemical reactions that is responsible for generating the energy needed by complex organisms. Fuel for this cycle is food that is turned into the pyruvate form of glucose, which is then converted into carbon dioxide and high-energy intermediate molecules.



Hans Adolf Krebs

Born in 1900 in Hildesheim, Germany, Hans Adolf Krebs qualified as a doctor at the age of 25. Keen to work in research, he took a post as a biochemist in Berlin. In 1932, while working at the University of Freiburg, he published his discovery of the metabolic pathway for urea formation, which established his scientific reputation. Krebs had Jewish ancestry and left Germany in 1933 to escape the Nazis. He took a job at the University of Sheffield, in the UK, and it was there that he discovered the citric acid cycle (CAC). Recognition took time, but in 1947 he was elected to Britain's Royal Society, and in 1953 he received the Nobel Prize in Physiology or Medicine, along with Fritz Lipmann. Working with British-American biochemist Hans Kornberg, Krebs went on to discover the glyoxylate cycle in 1957. He died in Oxford, UK, in 1981.

Key works

1937 *Metabolism of Ketonic Acids in Animal Tissues*
1957 *Energy Transformations in Living Matter: A Survey*

PHOTOSYNTHESIS IS THE ABSOLUTE PREREQUISITE FOR ALL LIFE

REACTIONS OF PHOTOSYNTHESIS

IN CONTEXT

KEY FIGURE
Melvin Calvin (1911–97)

BEFORE
1905 British plant physiologist Frederick Blackman explains that factors such as light and temperature affect the rate of photosynthesis.

AFTER
1958 Robert Emerson, an American botanist, describes the specific short and long wavelengths of light that, in light-dependent photosynthesis, activate two different centers of energy conversion.

1966 Biochemists Marshall Hatch and Roger Slack in Australia find an alternate, 4-carbon pathway during the dark reaction in some plants, including sugar cane.

1992 Rudolph Marcus wins the Nobel Prize in Chemistry for having discovered the electron transport chain.

By the late 19th century, green plant cells were known to harness energy from light in photosynthesis. But which chemical processes employed water, carbon dioxide, and sunlight to create chemical energy in the form of sugar and oxygen as a waste product? It was long believed that carbon dioxide and water combined to produce sugar, with carbon dioxide giving off oxygen.

In 1931, Cornelis van Niel, a Dutch-American microbiologist, proposed that oxygen in fact derived from the splitting of water molecules and that the reaction depended on light. In 1939, British biochemist Robert Hill confirmed Niel's theory and showed carbon dioxide must be broken down, or reduced, to sugar in a separate reaction—a process now known as carbon fixation.

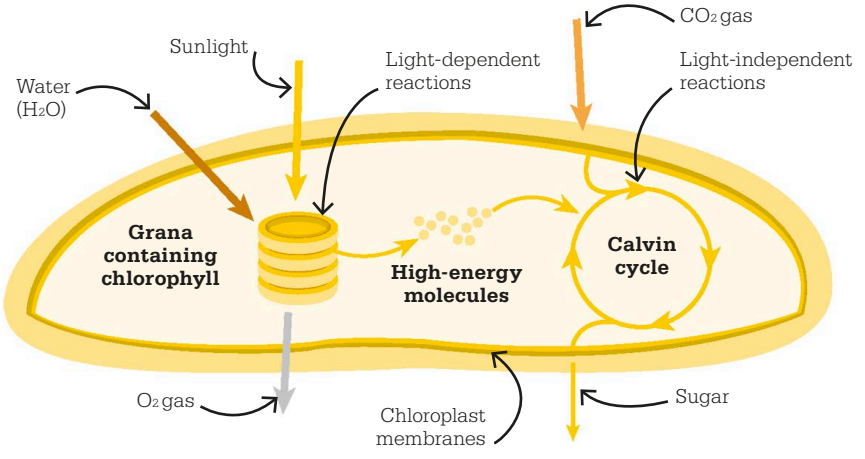
The Calvin cycle

From 1945, American biochemist Melvin Calvin led a team that pioneered the use of radioactive carbon-14 to track carbon's entire

The chloroplast is an organelle in plant cells. It contains green chlorophyll within stacks, called grana, formed from the folded, inner cell membrane.

See also: Complex cells 38–41 ▪ Photosynthesis 50–55 ▪ The beginnings of organic chemistry 61 ▪ Enzymes as biological catalysts 64–65 ▪ Plant transpiration 82–83 ▪ Plant translocation 102–103 ▪ Recycling and natural cycles 294–97

In the chloroplast, light-dependent reactions use chlorophyll to harness solar energy. The result is the splitting of water into hydrogen and oxygen gas (O_2), and the creation of high-energy molecules. These power the Calvin cycle in the chloroplast's liquid matrix, generating sugar after multiple carbon dioxide (CO_2) molecules are broken down.



route through a plant during photosynthesis, in groundbreaking research. He proved that carbon fixation occurs in a "dark reaction" (a reaction not dependent on light), which is actually a cascade of reactions. His discovery is called the Calvin cycle, or Calvin-Benson cycle, after one of his collaborators, American biologist Andrew Benson.

The process of producing sugar from carbon dioxide is called a cycle because it involves a series of complex chemical reactions, in which the last molecule formed in the cycle initiates production of the cycle's first molecule, and so on.

The first reactions (carbon fixation stage) in the Calvin cycle remove, or fix, carbon atoms, one at a time, from carbon dioxide in the air. It takes six turns of the cycle, each taking in one carbon atom, to harness enough carbon to create a sugar molecule that can be used by the plant. Once six carbon atoms are fixed, they undergo more reactions (carbon reduction stage) to form 3-carbon sugar molecules; one molecule leaves the chloroplast to feed the plant. The other sugar molecules continue in the cycle to the carbon regeneration stage, and re-form into 6-carbon molecules. They provide energy to fix another carbon atom from the air.

The Calvin cycle is a very energy-intensive process; Calvin showed that it must be powered by high-energy molecules produced in the light-dependent stage of photosynthesis. However, when accepting his 1961 Nobel Prize in Chemistry, Calvin acknowledged that precisely what happens after sunlight excites chlorophyll was still unknown, suggesting it might be an "electron transfer process."

Light-dependent reactions

In 1956–65, Canadian-American theoretical chemist Rudolph Marcus described the electron transport chain, a series of protein molecules that readily transfers electrons, during the light-dependent stage of photosynthesis, to release energy.

When light reaches chloroplasts in plant cells, each chlorophyll molecule behaves like an antenna, absorbing light energy, and sheds electrons (negatively charged subatomic particles). The loose electrons flow from protein to protein in the electron transport chain and, combined with the activity of nearby enzymes, create high-energy molecules. The high-energy molecules then move deeper into the chloroplast's liquid space, or matrix, to power the Calvin cycle's light-independent reactions.

Once they shed electrons in the light-dependent stage, chlorophyll molecules each need a fresh set of electrons to function again. Robert Hill's research helped show that, in the chloroplast, water molecules donate electrons to chlorophyll and break apart into hydrogen ions (electrically charged atoms) and oxygen atoms. Hydrogen ions are used to make high-energy molecules and oxygen atoms escape as waste gas through leaf stomata (pores). ■

> By blending water and minerals from below with sunlight and CO_2 from above, green plants link the earth to the sky.
>
> **Fritjof Capra**
> **Austrian-American physicist**

TRANSP
AND
REGULA

ORT

TION

William Harvey demonstrates that a fixed volume of **blood circulates** around the human body.

1628

Nicolas Steno's demonstration of the muscular nature of the **heart** confirms the theory that it **pumps blood around the body**.

1660s

From Arnold Berthold's discovery that a chemical from the testes is responsible for masculinity, it is found that **hormones** secreted by other glands also **trigger certain responses**.

1849

1661

Using a microscope, Marcello Malpighi observes a **branching network** of minute **blood vessels**, the capillaries.

1727

Stephen Hales describes the linear **flow of water** and **nutrients in plants**, with water flowing from their roots to their leaves and the air.

1850s

Organisms are found by Claude Bernard to regulate **internal conditions** to **compensate** for changes in **external conditions**.

During the scientific revolution of the 17th and the 18th centuries, there were significant advances in the understanding of how organisms process the nutrients essential to life (see pp.46–73). At the same time, scientists were investigating the ways in which these nutrients are transported to the parts where they are needed within the organism.

Perhaps the most obvious of these is the blood system flowing within the bodies of animals. It was generally assumed that this was a one-way flow, with blood being produced and then used up by the organs, but this was challenged by William Harvey's demonstration in 1628 that in fact a fixed volume of blood circulates in a closed system around the body.

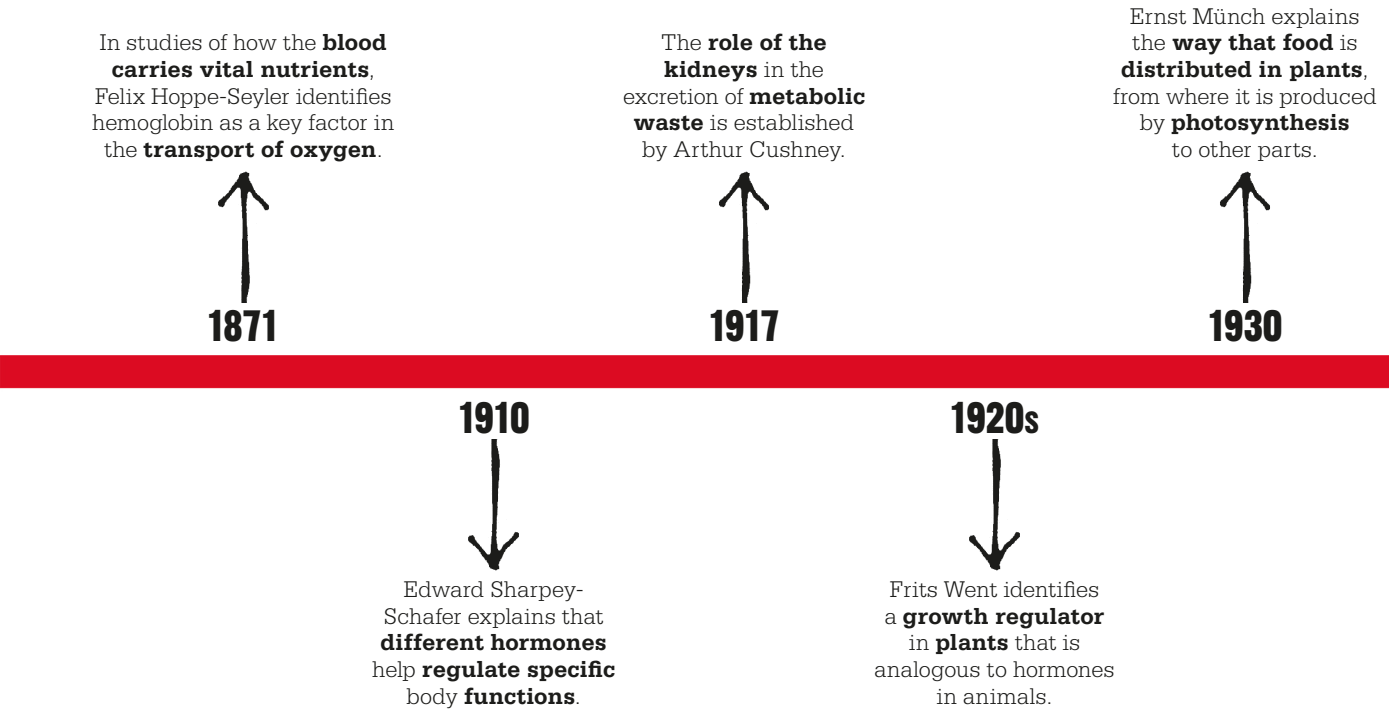
The discovery of microscopic blood vessels, called capillaries, by Marcello Malpighi in 1661 led to the idea that it was through their thin walls that vital substances can be absorbed by neighboring cells. In that same decade, Nicolas Steno demonstrated that the heart is an organ composed of muscle and that its function is to pump blood around the body.

The purpose of blood

Through these studies, it became established that the purpose of the circulation of the blood was to transport essential nutrients to all parts of the body. The question that then inevitably needed to be investigated was how exactly these nutrients are carried in the blood. One of the breakthroughs in this research was the discovery that hemoglobin, which is found in the red blood cells, plays a vital role in carrying oxygen from the lungs to where it is needed in the body. Felix Hoppe-Seyler's studies of the chemical composition of hemoglobin in the 1860s and early 1870s revealed that it contains iron, which absorbs oxygen in a process of oxidation.

Related to this research into the transport of nutrients was the question of how the waste products of metabolism are removed from the body. It was not until 1917, however, that Arthur Cushney pinpointed the role of the kidneys in filtering blood to remove the waste, which can then be excreted in the form of urine.

Nutrients, however, were found to be not the only substances that are transported around the bodies



of humans and animals. Other substances are secreted by certain organs, triggering chemical reactions as a response. One of the first to be identified, in 1849, was testosterone—produced by the testes—which Arnold Berthold discovered to be responsible for physical and behavioral masculinity. These substances, known as hormones, are produced by various glands, and each hormone has a different chemical composition that triggers a specific response in the body.

Internal regulation

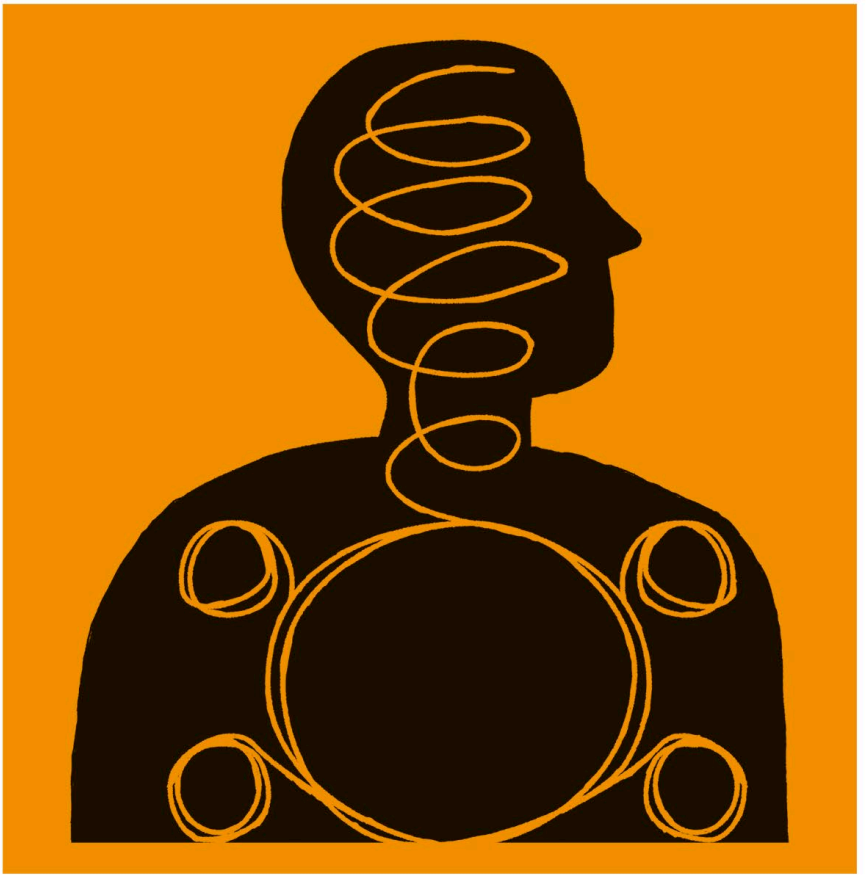
In the 1850s, a theory seemingly unrelated to Berthold's research into hormones emerged. Claude Bernard observed that bodies tend to maintain a stable internal environment (such as temperature), despite changes in external conditions, in a process called homeostasis. This suggested that there is some mechanism of self-regulation to ensure the optimal conditions for life. It was not until some 50 years later, in 1910, that Edward Sharpey-Schafer explained that this regulation is controlled by hormones, which act as chemical communicators that trigger the necessary responses of the organs to maintain stability.

Similar investigations into the transport systems of plants began in the 18th century, showing a fundamental difference from those of animals. While blood in animals flows in circulation, Stephen Hales found that the analogous flow is linear in plants: water flows through the plant from the roots to the leaves, where it evaporates. And—just as in animals—the flow carrying nutrients through plants also transports other substances. These include the chemical discovered by Frits Went in the 1920s that has a similar function to hormones in animals, triggering chemical responses that regulate plant growth.

This flow of water and nutrients is essentially a one-way system, but does not explain how food produced by photosynthesis makes its way to parts of plants, such as the roots, which are not capable of photosynthesis. Ernst Münch eventually solved this conundrum, by showing that sugars and other products of photosynthesis are carried in the sap, which flows through a system of phloem vessels to the parts of the plant where the food is needed. ■

IT HAD A MOVEMENT, AS IT WERE, IN A CIRCLE

CIRCULATION OF THE BLOOD



IN CONTEXT

KEY FIGURE
William Harvey
(1578–1657)

BEFORE
2nd century BCE Galen believes blood travels out from the heart and liver and is consumed by the body.

13th century CE Ibn al-Nafis suggests that blood circulates between the lungs and heart.

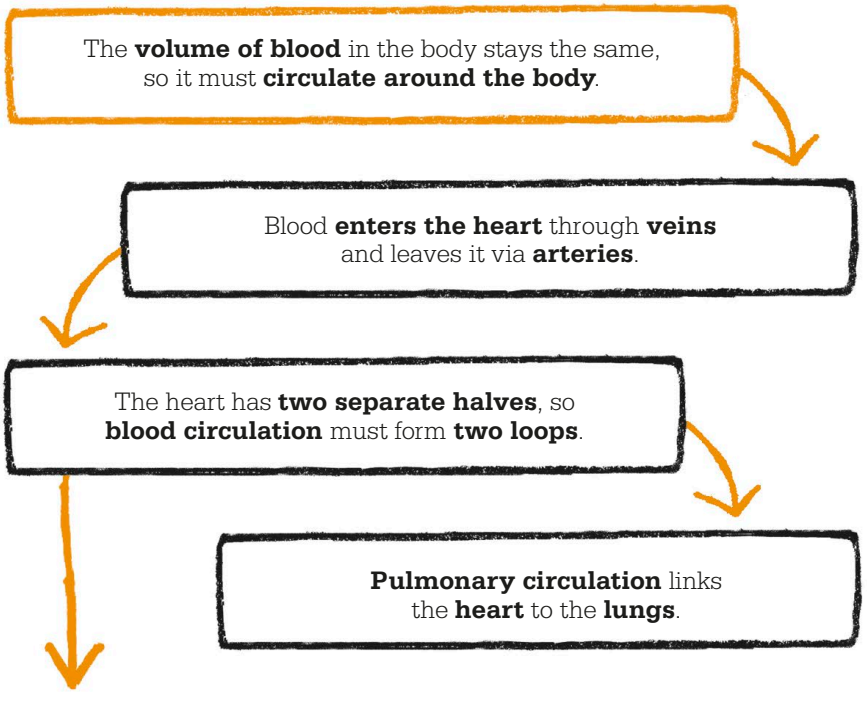
AFTER
1658 Jan Swammerdam discovers red blood cells using a microscope.

1840 Hemoglobin is discovered to be the oxygen carrier in blood.

1967 The first successful human-to-human heart transplant is carried out in South Africa by surgeon Christiaan Barnard.

In 1628, English doctor William Harvey was able to confirm the way that blood circulates, flowing in a double loop from the heart to the lungs, back to the heart, and around the rest of the body. This significant feature of human—and animal—anatomy had been misconstrued for centuries. The scientific examination of cadavers was considered taboo, and so the form and function of human organs were something of a mystery. The best research came from the dissection of animals and from glimpses of the interior of the living body seen by surgeons tending to critical wounds. Inevitably, these sources of evidence provided

See also: Experimental physiology 18–19 ▪ Anatomy 20–25 ▪ Capillaries 80 ▪ The heart muscle 81 ▪ Haemoglobin 90–91



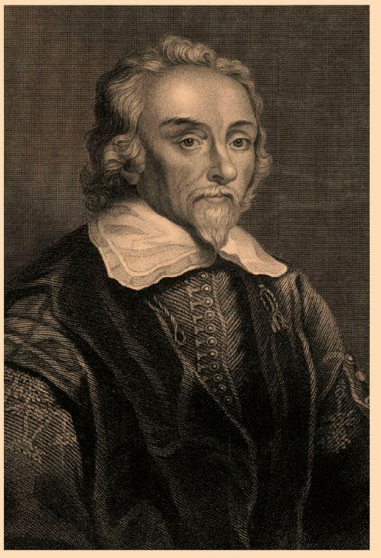
Systemic circulation carries blood around the body.

incomplete information and, in some cases, led to significant misconceptions.

Veins and arteries

In the 1600s, Western medicine was still largely based on the work of Galen, a Greek doctor working in Rome in the 2nd century CE. Galen had been a gladiators' surgeon and was able to observe internal human anatomy when he treated his patients for serious injuries they had received in the arena.

Early medical thought in ancient Egypt considered the network of vessels in the body to be channels for air; it was believed that blood filled these vessels only when they were damaged. Galen dismissed this view, saying that the vessels always contained blood. He identified the difference between the veins and arteries from their different characteristics: arteries are firmer and located deeper in the body, while veins are flimsier and generally closer to the surface. Galen argued that venous blood was generated in the liver and fed the body, allowing it to grow and heal itself, while arterial blood was filled with pneuma, a "vital spirit" that was obtained from the air. Pneuma, he reasoned, passed from the arterial blood to the venous supply through tiny pores in the intraventricular septum—the »



William Harvey

Born in 1578 in Kent, England, William Harvey graduated from Cambridge University at the age of 15. He then studied abroad, most significantly in Padua, Italy, where he was taught medicine by Italian anatomist Hieronymus Fabricius. In 1609, aged just 31, Harvey was made chief physician at St. Bartholomew's Hospital in London. Six years later, he was appointed Lumleian lecturer at the Royal College of Physicians, and in 1618 he became physician to King James I. After the publication of his most famous work in 1628, his popularity waned, because the medical establishment was reluctant to accept his radical theory of the heart. He was vindicated in 1661, four years after his death.

Key works

1628 *An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings*
1651 *On the Generation of Animals*

muscular wall between the left and right sides of the heart. Arterial blood was created in the heart and transferred in the opposite direction; it contained waste products, which were expelled when breathing out.

The 11th-century Persian polymath Ibn Sina (known in the West as Avicenna) wrote important works on medicine, but his discussion of circulation restated the inaccuracies in Galen's model. Then, in 1242, Syrian doctor Ibn al-Nafis authored a commentary on Ibn Sina's writings on anatomy and gave the first accurate description of pulmonary circulation, asserting that blood from the right side of the heart flowed through the lungs and then back to the heart.

Overturning old ideas

Four centuries after Ibn al-Nafis, William Harvey published his book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (*An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings*), commonly known as *De Motu Cordis*. This was inspired by the findings of his medical school teacher, Italian anatomist Hieronymus Fabricius, who had described the valves in veins: pairs of flaps at an angle to the walls of the vein, which allowed blood to flow in only one direction, toward the heart. To Harvey, this directional flow strongly indicated blood circulation.

One of the central premises of Galen's theory was that blood is consumed by the body, but Harvey rejected this. He calculated that the heart, which he understood to be a muscular pump, pushes out about 2 fl oz (57 ml) of blood as it contracts with every heartbeat. At around 72 heartbeats per minute, if Galen was correct, the body would have to be producing—and consuming—up to 144 fl oz (4 liters) every minute. This did not seem possible. In fact, Harvey's calculations were an underestimate: the heart pumps the entire volume of blood—about 1 gallon (5 liters)—every minute.

A system of two parts

Harvey further investigated the anatomy of blood vessels and performed vivisections on eels and other fish to watch how their hearts pumped in the last few moments of life. He also tied the veins and arteries of vivisected animals to prove how the blood entered and exited the heart. Tying arteries made the organ swell up with blood, while closing off the veins emptied the heart.

> The heart of animals is the foundation of their life, the sovereign of everything within them … that upon which all growth depends.
>
> **William Harvey**
> ***On the Motion of the Heart and Blood*, 1628**

Ultimately, Harvey concluded that the blood's volume is constant and that it travels around the body in a closed system made up of two sections, with arteries carrying blood away from the heart, and veins bringing it back. The section we now call pulmonary circulation is a loop that connects the heart to the lungs. Harvey was unaware that the blood carried gases, but by the 19th century it was understood that the body takes in oxygen from the air and transports it in the bloodstream, while the carbon dioxide the blood accrues on its circuit of the body is expelled. These processes take place in the lungs and are called gas exchange.

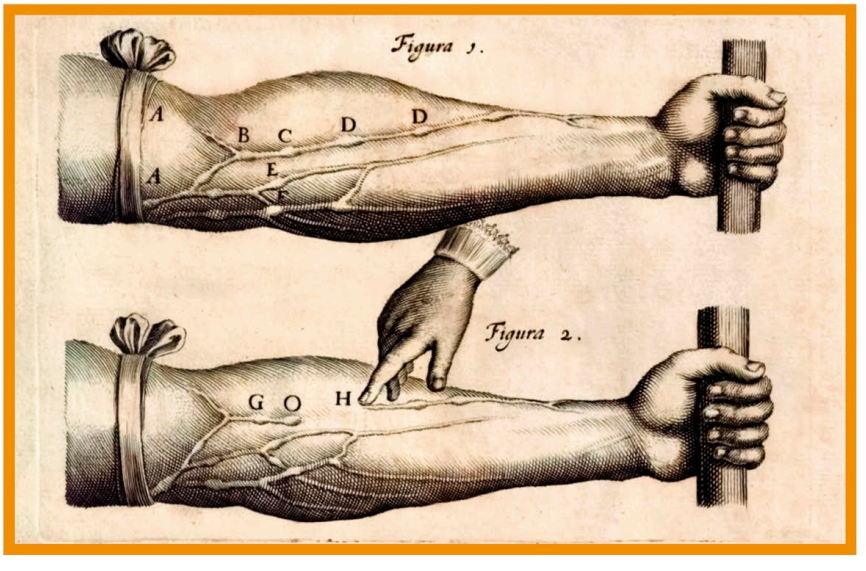


Plate 1 of Harvey's *On the Motion of the Heart and Blood* illustrates the network of veins in the forearm. Figure 2, at the bottom, shows how blood will empty from a vein if it is blocked from its journey toward the heart.

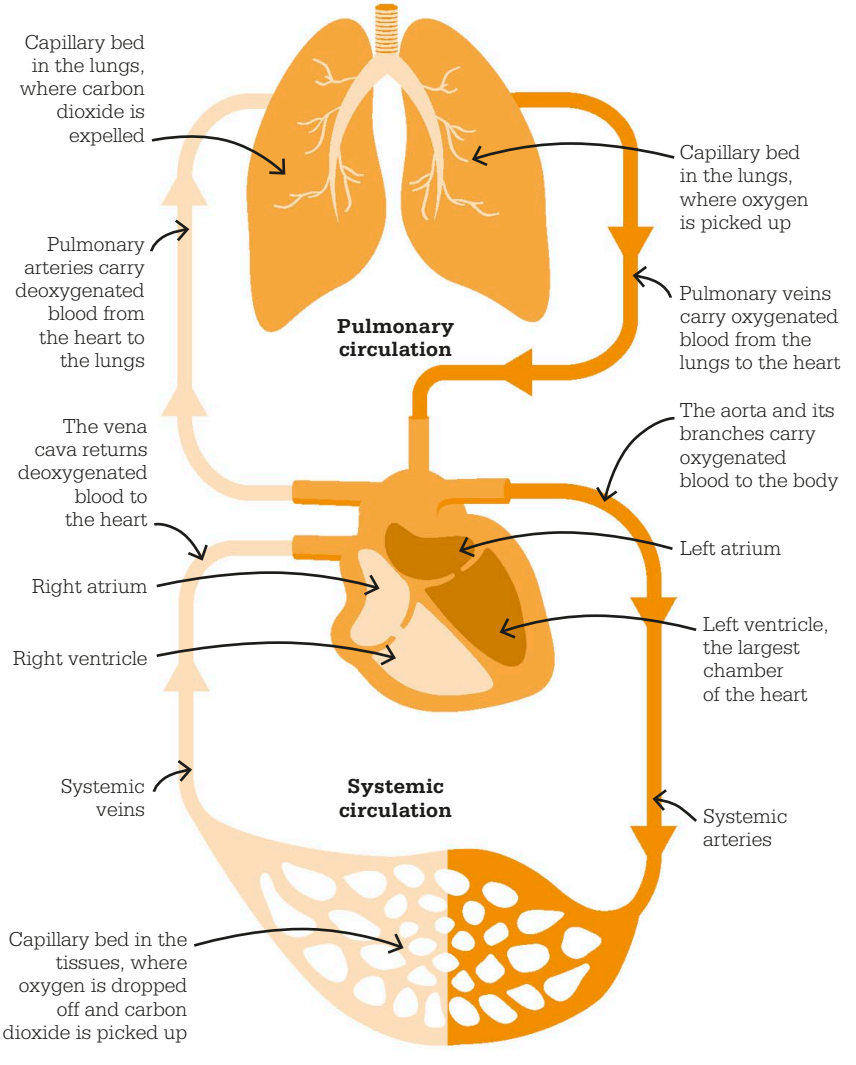
Back at the heart, the oxygenated blood then travels through the rest of the body via what is now called systemic circulation. The blood is expelled by the contraction of the left ventricle, the largest chamber in the heart, and pushed into the aorta, the largest artery. Arteries (with the exception of pulmonary arteries) always carry oxygenated blood. They have a rigid structure that includes a layer of smooth muscle so they can withstand the high pressures required to push 1 gallon (5 liters) of liquid around the whole body via its 62,100 miles (100,000 km) of vessels.

Harvey described how the arteries fed blood directly into the tissues of the body and how, from there, it was collected by the veins and returned to the right side of the heart, where it enters the pulmonary loop. However, he was unable to explain how blood was transferred from the arterial to the venous system. In 1661, using the newly invented microscope, Italian biologist Marcello Malpighi observed intricate networks of microscopic vessels—capillaries, which form the connection between arteries and veins. Each network is known as a capillary bed.

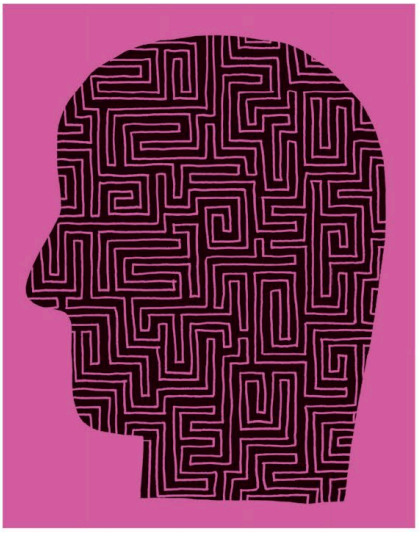
> [Blood] moves in a circle from the center to the extremities and back from the extremities to the center.
>
> **William Harvey**
> ***On the Motion of the Heart and Blood*, 1628**

Veins are flimsier vessels than arteries, and the blood inside them is at a lower pressure. While arterial blood is forced along by the pulsing heartbeat, the passage of venous blood back to the heart is aided by the contraction of skeletal muscles during normal movement of the body, which squeezes the vessels.

Harvey's description of the double-looped circulatory system had far-reaching effects. Not only did it aid medical interventions such as the use of ligatures to stem bleeding, but it also demonstrated that scientists could change medical doctrine—something that had remained in stasis for centuries. ■



Pulmonary circulation moves oxygenated and deoxygenated blood between the heart and the lungs. Systemic circulation moves oxygen-rich blood from the heart around the body and oxygen-depleted (carbon dioxide-rich) blood back to the heart.



BLOOD PASSES THROUGH MANY WINDINGS

CAPILLARIES

IN CONTEXT

KEY FIGURE
Marcello Malpighi
(1628–94)

BEFORE
1559 Italian physician Matteo Colombo observes that the pulmonary vein carries blood from the lungs to the heart, and not air as previously believed.

1658 Dutch biologist Jan Swammerdam is the first to write about observing red blood cells.

AFTER
1696 Dutch anatomist Frederik Ruysch shows that blood vessels are present in almost all tissues and organs.

1839 Theodor Schwann demonstrates that capillaries have walls made of thin cells.

1922 Danish professor August Krogh describes how oxygen, nutrients, and other substances pass from capillaries to supply the surrounding tissues.

In 1628, English physician William Harvey produced the first thorough account of the heart and circulatory system. He described how blood moves away from the heart in arteries and returns to the heart in veins, but his ideas were not quite complete. Without powerful enough microscopes, Harvey could not explain how or where blood passes from arteries into veins.

Harvey died in 1657. Soon after, in 1660–61, the missing link was discovered by Italian professor of medicine Marcello Malpighi. He detected the tiniest blood vessels —capillaries—while studying frog lungs and bladders with the latest model of microscope. Malpighi followed the frog's arteries as they repeatedly divided to become "tubules," conveying blood toward tiny veins. He wrote: "I could clearly see that the blood is divided and flows through tortuous vessels and that it is not poured out into spaces, but is always driven through tubules and distributed by the manifold bendings of the vessels."

In 1666, Malpighi was one of the earliest microscopists to observe red blood cells. However, it would be many years before scientists showed that it is hemoglobin in the red blood cells that carries oxygen and that capillaries act as the body's exchange vessels. The capillaries permeate all body tissues—nutrients, gases (oxygen and carbon dioxide), and wastes pass back and forth between the blood and tissues, across thin capillary walls composed of a single layer of endothelial cells. ■

> "… these elude even the keenest sight because of their small size."
> **Marcello Malpighi**

See also: Experimental physiology 18–19 ▪ Anatomy 20–25 ▪ Circulation of the blood 76–79 ▪ The heart muscle 81

THE HEART IS SIMPLY A MUSCLE

THE HEART MUSCLE

IN CONTEXT

KEY FIGURE
Nicolas Steno (1638–86)

BEFORE
***c.* 180 CE** Galen states that blood is made in the liver.

1628 William Harvey pronounces that the heart's primary function is to circulate the blood around the body.

AFTER
1881 Czech-Austrian physician Samuel Siegfried Karl von Basch invents an early form of the blood pressure monitor.

1900 Dutch physician William Einthoven begins work on the electrocardiogram (ECG).

1958 Swedish cardiac surgeon Ake Senning and Swedish engineer Rune Elmqvist develop the first fully implantable heart pacemaker.

1967 South African surgeon Christiaan Barnard carries out the first full heart transplant.

Humans feel a quickened heartbeat not only when physically active, but also in times of high emotion. From these experiences came ideas that the heart harbored the essence of a person. Danish biologist-geologist Niels Stensen (Nicolas Steno in Latin), made a career of challenging such old doctrines.

During the early 1660s, Steno was especially fascinated by muscle actions. He contended that when a muscle contracts, it changes its shape but not its volume, and devised geometric descriptions for muscle motions. He then decided to test the age-old notion that the heart was the source of an intangible life force, or "vital spirit."

Steno studied animal hearts and was already familiar with various muscles in the body, their fibers, and their associated blood vessels and nerves. He found that the heart, too, contained these parts—and little more. In 1662, he announced that the heart is an ordinary muscle, not the body's center of vital power and warmth as previously believed. In 1651, William Harvey thought the beating heart was "excited by the blood." Steno's observations on the structure and function of muscles challenged such beliefs and was seen as a turning point in understanding muscle contraction and how the heart beats. ■

Nicolas Steno was not only the first scientist to discover that the heart is a muscle, but he also showed that it consists of two separate pumps.

See also: Experimental physiology 18–19 ▪ Anatomy 20–25 ▪ Circulation of the blood 76–79 ▪ Capillaries 80

PLANTS IMBIBE AND PERSPIRE

PLANT TRANSPIRATION

IN CONTEXT

KEY FIGURE
Stephen Hales (1677–1761)

BEFORE
1583 Andrea Cesalpino, an Italian physician and botanist, determines that plants draw up water by absorption.

1675 Marcello Malpighi first observes and illustrates xylem vessels, which he names *tracheae*, because they remind him of the airways in insects.

AFTER
1891 Polish-German botanist Eduard Strasburger shows that the upward movement of water is a physical process occurring in non-living xylem vessels.

1898 British naturalist Francis Darwin, a son of Charles Darwin, describes how loss of water by transpiration is controlled by stomata (in most plants) closing at night.

The evaporation of water from plants had been observed by naturalists for centuries, but English clergyman Stephen Hales was the first to provide evidence of the process now called transpiration. He had already studied human blood pressure and carried out a series of meticulous and ingenious experiments over several years to test whether plants also had a circulatory system.

Hales described his experiments and conclusions in 1727 in *Vegetable Staticks*, a groundbreaking book on air chemistry and plant physiology.

> … a plant on the edge of a desert is said to struggle for life against the drought, though more properly it should be said to be dependent on the moisture.
>
> **Charles Darwin**
> ***On the Origin of Species*** **(1859)**

Hales proved that water "perspires," or evaporates, from the leaves and pulls water, or sap, upward from the roots, after it is absorbed from the soil, in a linear direction rather than circulating around the plant.

Water enters the roots

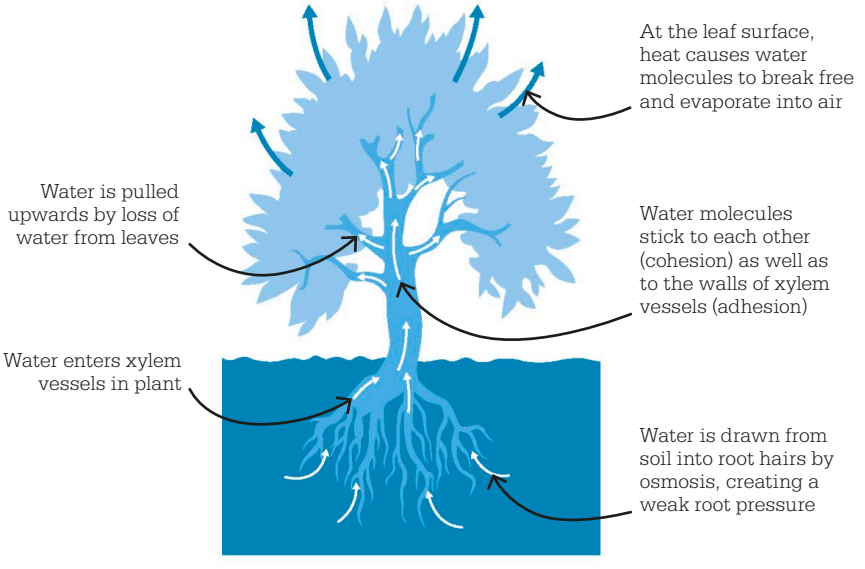
In one experiment, Hales placed a glass tube on a severed grapevine trunk and observed how "the force of sap"—now known as the root pressure—drove sap upward as the roots "imbibed" water from the soil after a shower of rain. It was not until the 1830s that French physiologist Henri Dutrochet described the process of osmosis (from the Greek *ŏsmos*, meaning "push"), by which water moves into the root from the surrounding soil.

In osmosis, water moves to a solution with a high concentration of dissolved substances (solutes) through a semipermeable membrane in order to balance the concentration of solutes on both sides of the membrane.

Plant roots have hairs with semipermeable walls that are one cell thick. Chemical reactions in the root hairs draw mineral ions (positively charged atoms) from the soil, concentrating them in roots.

See also: Cell membranes 42–43 ▪ Photosynthesis 50–55 ▪ Capillaries 80 ▪ Plant translocation 102–03

Transpiration, or evaporation of water through the stomata (pores) of leaves, acts in the same way as sucking water through a straw, pulling sap upward against the pull of gravity. It happens only in daylight, when stomata open.



Water follows the minerals into the roots by osmosis. Once in the roots, water enters what Hales termed "capillary sap vessels"—named xylem in the 19th century and consisting of long, dead, strawlike cells—to travel up the plant.

Water moves to the leaves

Hales had described "the strong attraction" of the xylem vessels, but was unaware of the forces that enable water to hold together as it moves up the plant. The "cohesion-tension theory" was explained by Henry Dixon and John Joly in 1894 and refined by several others in the early 20th century.

Like a magnet, a positive end of one water molecule is attracted to the negative end of another, nearby water molecule. So water molecules are cohesive, or sticky, creating a chain of water molecules. Water molecules also prefer to stick to the sides of a vessel—a state known as adhesion. (If you hold a glass of water in your hand and tip it slightly, the water will run down the side of the glass.) The adhesive quality of water aids the upward movement of water in a plant stem.

Hales realized that the "plentiful perspiration of the leaves" pulled water up the stem and that sap flow varies according to the light level, weather, and number of leaves.

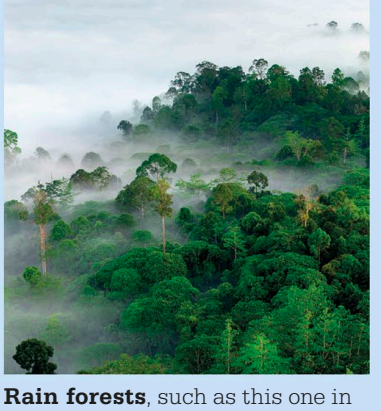
According to cohesion-tension theory, as the chains of water molecules arrive at a leaf, each molecule in the chain is drawn toward a stoma (leaf pore) and evaporates. This creates a negative pressure (tension), pulling the next water molecule up, in a continuous process called transpiration pull. ■

Plants create rain

On land, about 90 percent of water in the atmosphere passes through plants. Trees, shrubs, and herbaceous plants take up water from the soil through their roots. Some water is broken down in photosynthesis, but most is used to help with transport of mineral nutrients, to keep plant cells turgid, and to cool the plant by evaporation.

At the leaf surface, the warmth of daylight causes the chemical bonds of the water molecule chains to break and evaporate into the air as gas, or water vapor. As the vapor rises and cools in the atmosphere, it condenses back into water droplets to form clouds. When droplets get large enough, they fall as rain (precipitation). So plants are an essential part of Earth's water cycle.

Like sweat evaporating from skin, transpiration carries heat from the tree tops, as the water converts from a liquid to a gaseous form, and so also cools the local climate.



Rain forests, such as this one in Borneo, show the result of many large trees transpiring: low mists form and release water back to the soil in a continuous cycle.

CHEMICAL MESSENGERS CARRIED BY THE BLOODSTREAM

HORMONES TRIGGER RESPONSES

IN CONTEXT

KEY FIGURE
Arnold Berthold (1803–61)

BEFORE
1637 French philosopher René Descartes suggests that animals work like machines, subject to the laws of physics.

1815 Jean Pierre Flourens, a French physiologist, shows the role of different parts of the brain in controlling behavior.

AFTER
1901 Japanese-American chemist Takamine Jokichi isolates the hormone adrenaline (although the term hormone is not coined until four years later).

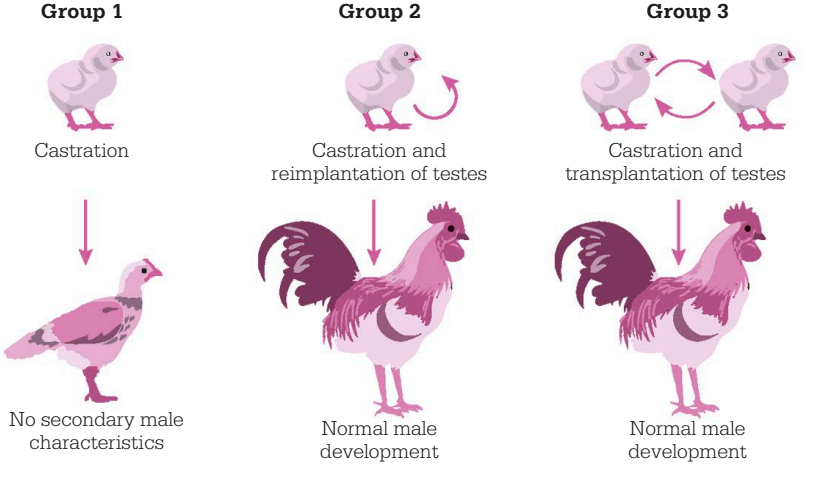
1910 Edward Sharpey-Schafer demonstrates that hormones play a vital role in regulating body functions.

1921 Canadian physician Frederick Banting isolates the hormone insulin and uses it to treat diabetes.

Hormones are the body's chemical messengers. Released into the bloodstream by the endocrine glands—which include the pituitary, pineal, and adrenal glands and the pancreas, thyroid, testes, and ovaries—they are carried to other parts of the body, where each triggers an effect. Hormones are found in all multicelled organisms—plants, fungi, and animals—and they influence or control many physiological activities, including growth, development, puberty, the regulation of blood sugar levels, and appetite. The endocrine system, and the nervous system in animals, is one of the major methods of internal communication in living things.

At the beginning of the 19th century, biologists believed that the development of sexual characteristics was controlled via the nervous system. In 1849,

Arnold Berthold's experiment involved removing the male sex organs (testes) from six chicks. In Group 1, he did nothing more. In Group 2, he grafted one of each chick's testes into its abdomen. In Group 3, he transplanted one of each chick's testes into the other castrated chick.



See also: Digestion 58–59 ▪ Circulation of the blood 76–79 ▪ Homeostasis 86–89 ▪ Hormones help regulate the body 92–97 ▪ Electrical nerve impulses 116–17

> These chemical messengers, or hormones as we might call them, have to be carried … to the organ which they affect by means of the bloodstream.
> **Ernest Starling, 1905**

German physiologist and curator of the University of Göttingen's zoological collection Arnold Berthold conducted an experiment in which he removed the testes from six male chickens. As a result, they failed to develop male secondary sexual characteristics. However, when he transplanted testes from another bird into the abdomens of two of his castrated birds, the birds did develop male secondary sexual characteristics as normal.

When Berthold dissected his chickens, he found that the transplanted testes had formed no nerve connections. His conclusion was that whatever triggered sexual development had to travel via the bloodstream and not via the nerves.

Starling and Bayliss

Despite Berthold's findings, the belief that communication between organs occurred by means of electrical signals from the nervous system persisted. In 1902, however, British physiologist Ernest Starling and his brother-in-law William Bayliss, working together in their laboratories in London, investigated the nerves of the pancreas and small intestine. They were testing the theory of Russian physiologist Ivan Pavlov that secretions from the pancreas were controlled by nerve signals traveling from the wall of the small intestine to the brain and back to the pancreas.

Having cut away all the nerves linked to the vessels supplying the pancreas and small intestine, Starling and Bayliss introduced acid into the small intestine and discovered that the pancreas produced its secretions as normal. Next, they tested their hypothesis that the acid triggered the small intestine's release of a certain substance into the bloodstream. They scraped some material from the lining of the small intestine, added acid to it, filtered off the resulting fluid, and injected it into an anesthetized dog. Within just a few seconds, they detected secretions from the pancreas, proving that the triggering link between the small intestine and the pancreas was not carried by the nervous system.

The first hormone

The chemical messenger released by the small intestine was named secretin, the first substance to be called a hormone. Starling and Bayliss found that secretin is released from the lining of the small intestine into the bloodstream in response to the arrival of acidic fluid from the stomach. It travels through the bloodstream to the pancreas, where it stimulates the secretion of bicarbonate, which neutralizes stomach acid. They found secretin to be a universal stimulant—the secretin from one species stimulates the pancreas of any other species. ■

Arnold Berthold

The second youngest of six children in Soest, in Germany, in 1803, Berthold studied medicine at the University of Göttingen, presenting his doctoral thesis in 1823. He did a tour of several European universities before returning to Göttingen as professor of medicine in 1835 and becoming curator of its zoological collection five years later. Berthold's areas of research were varied. In addition to his revolutionary experiments with chickens, he discovered an antidote for arsenic poisoning and studied myopia, pregnancy, and the formation of fingernails. He died in Göttingen in 1861. Since 1980, the German Society for Endocrinology has awarded the Berthold Medal in his honor.

Key work

1849 *Transplantation der Hoden* (*Transplant of the Testicles*)

THE CONSTANT CONDITIONS MIGHT BE TERMED EQUILIBRIA

HOMEOSTASIS

IN CONTEXT

KEY FIGURE
Claude Bernard (1813–78)

BEFORE
1614 Santorio Santorio investigates the chemical processes that underpin life.

1849 Arnold Berthold discovers that not all body activities are controlled by the nervous system.

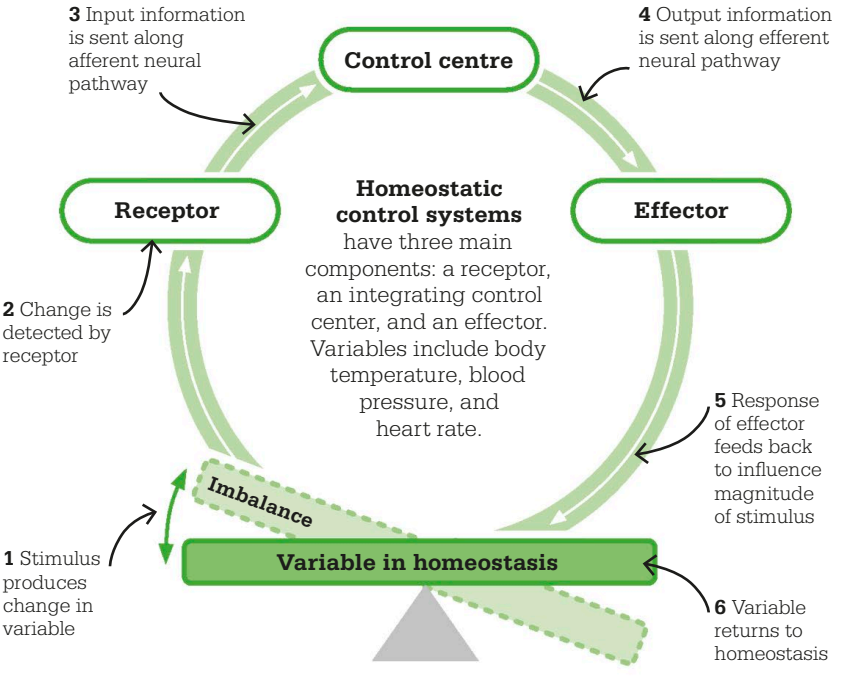
AFTER
1910 Edward Sharpey-Schaffer demonstrates the crucial role played by hormones in regulating body functions.

1926 Walter Cannon is the first physiologist to use the term homeostasis.

To maintain life, the cells that make up an organism are bathed in a fluid that supplies nutrients and carries away waste. Whether an animal is simple or complex, its body works to maintain the stability of the fluid environment that all of its cells need to survive. The processes that together maintain and regulate a stable internal environment within living organisms are known as homeostasis.

Homeostasis is one of biology's key concepts. The structure and function of animals is geared toward maintaining homeostasis. Individual cells engage in activities that ensure their survival, and the cells making up the tissues in complex organisms contribute to the survival of the organism. The combined contributions of cells, tissues, and organ systems

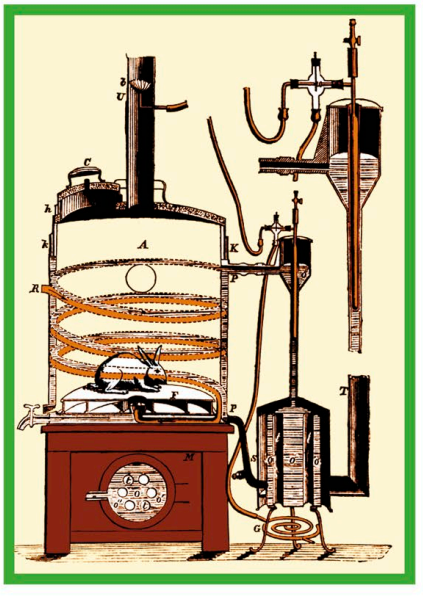
See also: Circulation of the blood 76–79 ▪ Hormones trigger responses 84–85 ▪ Hormones help regulate the body 92–97 ▪ Muscle contraction 132–33



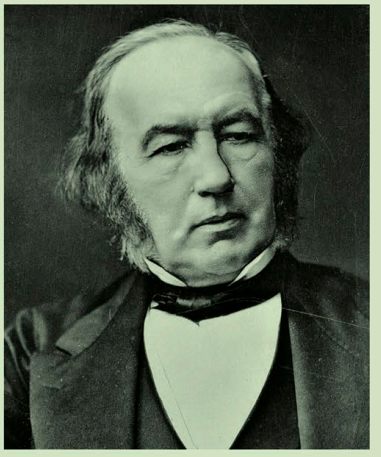
ensure the essential maintenance of a stable internal environment in which the cells can thrive.

French physiologist Claude Bernard was one of the principal investigators who established the importance of experimentation in the life sciences. He embraced Theodor Schwann's cell theory, calling the cell "a vital atom," and saw the relationship between cells and their environment as being fundamental to the understanding of physiology. In 1854, Bernard introduced the concept of the *milieu intérieur* (the internal environment) to describe the mechanisms that keep an animal's internal environment in equilibrium even while its external environment is constantly changing.

To begin with, the internal environment as far as Bernard was concerned meant the blood, but »



This apparatus was designed and used by Claude Bernard in experiments to study the effects of heat on animals – just one aspect of Bernard's many investigations of homeostasis.



Claude Bernard

Born in 1813 near Villefranche, France, as a boy Bernard helped his father tend his vineyards. After studying medicine in Paris between 1834 and 1843, he began working with François Magendie, the leading experimental physiologist of the day. In 1854, Bernard was elected to the French Academy of Sciences. When Magendie died the following year, Bernard succeeded him as full professor at the Collège de France in Paris. Emperor Napoleon III had a laboratory built for him at the Museum of Natural History in 1864. Bernard separated from his wife in 1869 because she strongly disapproved of his practice of vivisection.

Following his death in 1878, Bernard's funeral was financed by the French government, the first time a scientist in France had been honored in this way.

Key work

1865 *An Introduction to the Study of Experimental Medicine*

he later extended this to include the interstitial fluid that surrounds cells. Bernard was aware that the temperature of the blood was actively regulated. He speculated that this might be at least partly controlled through altering the diameter of blood vessels, noting that the skin's blood vessels constricted in cold conditions and dilated when it was hot. He also discovered that blood sugar levels were maintained by the storage and release of glycogen in and from the liver, and he investigated the role of the pancreas in digestion.

Toward the end of his life, Bernard drew his research together into a proposal that the purpose of the body's processes was to maintain a constant internal environment. It did this by means of myriad interlinked reactions that compensated for changes in the outside environment. He wrote, "The living organism does not really exist in the *milieu extérieur* but in the liquid *milieu intérieur*."

Bernard's concept of the *milieu intérieur* regulated by physiological mechanisms was in opposition to the then still widely held belief in a "vital force" operating beyond the bounds of physics and chemistry.

> The living body, though it has need of the surrounding environment, is nevertheless relatively independent of it.
> **Claude Bernard**

Humans and other animals can thrive in a wide range of environmental conditions due to their ability to regulate their internal temperature.

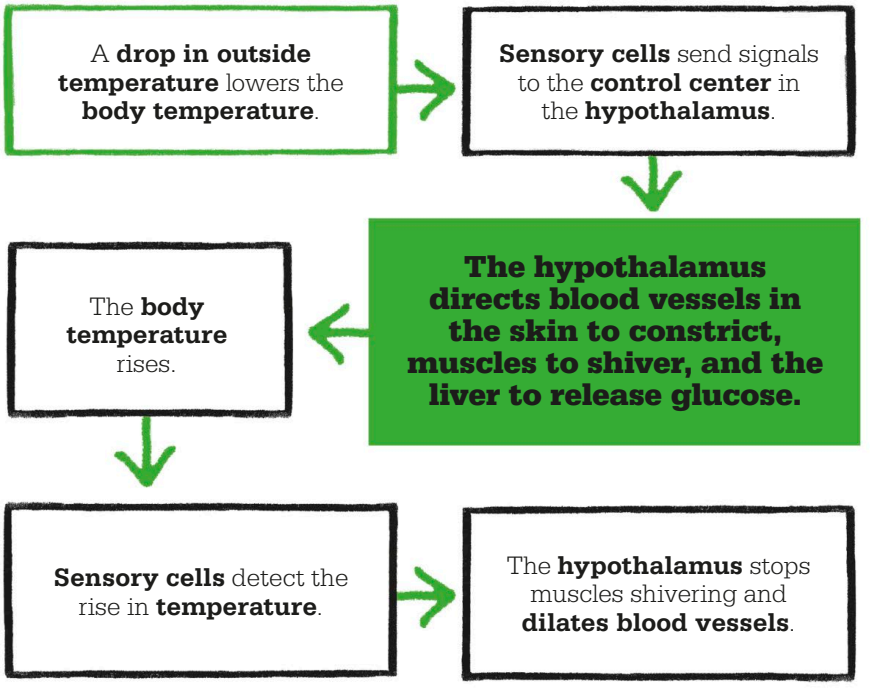
Bernard declared that the principles underpinning biological science were no different from those of physics and chemistry. Despite the fact that Bernard was, at the time, the most famous scientist in France, his hypothesis that the internal environment remained stable independent of external conditions was largely ignored for the next 50 years.

Self-regulation

In the first years of the 20th century, Bernard's concept of the internal environment was at last taken up by physiologists such as William Bayliss and Ernest Starling, the discoverers of secretin, the first hormone to be identified. Starling described the regulation of the internal environment as "the wisdom of the body." The endocrine system, which produces hormones, is now known to be a crucial driver of homeostasis. The pancreas, for example, produces the hormone insulin, which is essential in regulating blood sugar levels.

American physiologist Walter Cannon developed Bernard's ideas further. In 1926, Cannon coined the term homeostasis to describe the process of self-regulation by which an organism keeps its body temperature steady and controls other vital conditions, such as the blood's levels of oxygen, water, salt, sugar, protein, and fat. The prefix *homeo*, meaning "similar"—rather than *homo*, "the same"—reflected Bernard's understanding that internal conditions may vary within certain limits.

One of Cannon's most important discoveries was the role played by the sympathetic nervous system—that part of the system involved in involuntary responses—in maintaining homeostasis. He correctly theorized that the sympathetic nervous system works in concert with the adrenal glands to maintain homeostasis in emergencies. Cannon originated the phrase "fight or flight" to describe the body's reaction to stressful situations, which cause the adrenal glands to release the



hormone adrenaline into the bloodstream. Adrenaline release triggers several effects. In the skeletal muscle of the limbs, it brings about increased blood flow by relaxing blood vessels. This ensures that energy-giving blood sugars arrive, and waste products are removed, much more efficiently. At the same time, adrenaline causes blood vessels in the skin to contract and promotes clotting, both effects designed to minimize loss of blood from injury. Adrenaline also triggers the breakdown of glycogen and the release of glucose from the liver into the bloodstream, and it stimulates respiration, maximizing the delivery of oxygen from the lungs to the bloodstream.

In 1946, Swedish physiologist Ulf von Euler identified the key neurotransmitter (or impulse carrier) of the sympathetic nervous system in mammals as norepinephrine, not adrenaline as Cannon had believed.

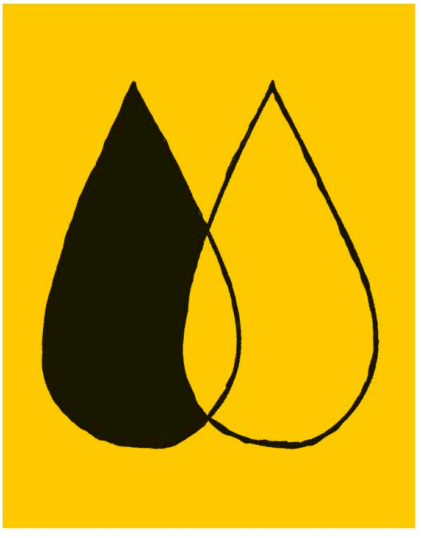
Three-component system

Maintaining the stable conditions of homeostasis requires a system with three components: a receptor, a control center, and an effector. These work together in a negative feedback loop, which works to oppose or reset the stimulus that triggers action. This idea was first introduced by Cannon, who described the body's adjustments that keep disturbances within narrow limits.

Sensory receptors are cells that are stimulated by changes in the environment—for example, nerve cells that detect variations in temperature, or cells in the blood vessels that detect changes in blood pressure. A stimulus triggers the sending of a signal from the receptor to a control center, which determines an appropriate response. One of the most important control centers is the hypothalamus, a region of the brain that oversees everything from body temperature to heart rate, blood pressure, and sleep and wake cycles. If it is appropriate, the control center signals an effector, which brings about the changes needed to restore balance. This effector might be the muscles that make you shiver when you are cold, or a gland in the endocrine system that releases a hormone to regulate calcium levels in the blood. Once balance has been restored, the sensory cells signal the change to the hypothalamus, which will deactivate the effectors.

The regulation of blood sugar levels discovered by Bernard is a good example of a negative feedback loop. The presence of glucose in the bloodstream stimulates the pancreas to produce insulin, which signals the liver to store excess glucose in the form of glycogen. As glucose concentrations in the blood are reduced, the pancreas stops producing insulin and the liver stops producing glycogen. Glucose levels in the blood are thus maintained within the specific range necessary for the body's requirements. The body's negative feedback mechanism is triggered by high glucose levels, and it shuts off when they fall to lower levels. ■

> What happens in our bodies is directed toward a useful end.
> **Walter Cannon**



AIR COMBINING WITH THE BLOOD

HEMOGLOBIN

IN CONTEXT

KEY FIGURE
Felix Hoppe-Seyler (1825–95)

BEFORE
2nd century CE Galen describes how a vital component of the air, called pneuma, enters the lungs and mixes with the blood.

1628 William Harvey shows that blood moves in a double circulatory system, one loop connecting to the lungs and the other to the body.

AFTER
1946 An abnormal structure of hemoglobin is found to be the cause of thalassemia.

1959 Max Perutz discovers the molecular structure of hemoglobin, using X-ray crystallography.

Present day By 2013, more than 1,000 variants of the hemoglobin molecule are known to exist within the human population.

Blood gets its **red color** from an iron-rich **protein called hemoglobin**.

Oxygen molecules entering the blood **bond to the iron** in the hemoglobin.

Hemoglobin can carry **70 times more oxygen** than if the gas were **dissolved in blood plasma**.

Hemoglobin carries oxygen around the body to where it is needed.

Blood is the body's primary transport system, carrying hormones, nutrients, and waste materials—but its most significant function is to transport oxygen. Just how blood does this first began to be understood in the 19th century, thanks to the work of scientists like German physiologist and biochemist Felix Hoppe-Seyler.

In humans, 55 percent of the blood's volume is made up of a yellowish liquid called plasma, which is mostly water. Many of the contents carried in the blood are dissolved in this plasma. However, oxygen does not dissolve well in water. Platelets and white blood cells, important for immune function, make up 2 percent.

Red blood cells (erythrocytes) account for the remaining volume of blood and move oxygen from the lungs to wherever it is needed. A clue to the method by which these cells perform this task is their red

See also: Biochemicals can be made 27 ▪ Circulation of the blood 76–79 ▪ Capillaries 80 ▪ Blood groups 156–57

color, caused by hemoglobin, a large protein packed inside them. As Hoppe-Seyler and others discovered, it is hemoglobin that is the body's real oxygen carrier. This particular ability was first revealed in 1840 by German chemist Friedrich Ludwig Hünefeld. When another German, physiologist, Otto Funke, created a crystalline form of hemoglobin in the 1850s, Hoppe-Seyler was able to show that this crystalline material could both take in and give out oxygen, demonstrating its function in the blood.

How hemoglobin works

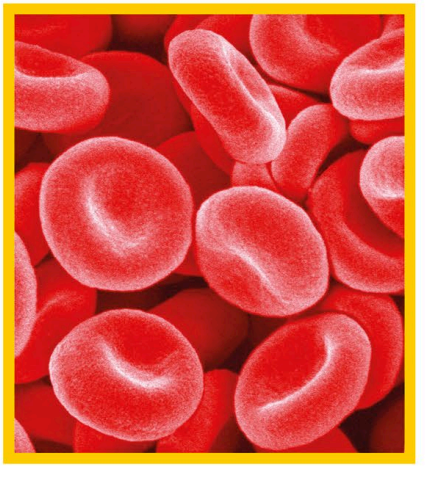
Before hemoglobin can begin to work, air is breathed into the body and is eventually channeled into tiny air sacs in the lungs, called alveoli. Here, oxygen (O_2) passes across the thin lining of the air sacs into blood and the red blood cells.

The hemoglobin in red blood cells is a large bundle of protein globules arranged into four subunits. Each of the subunits harbors an iron ion at its center. (It is actually this ion that gives blood its red color.) Inside the cells, each hemoglobin molecule picks up four oxygen molecules—one bonded to each iron ion—and each red blood cell has around 270 million hemoglobin molecules within it.

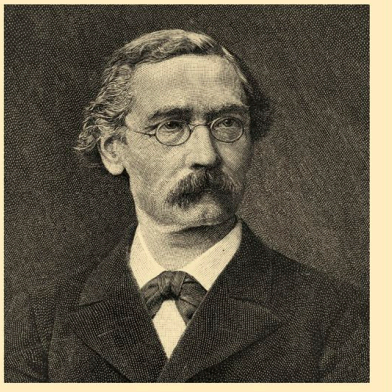
We now know that hemoglobin can carry about 70 times more oxygen than could be dissolved in blood plasma and that a typical 1-gallon (5-liter) human blood volume carries 1.8 pints (1 liter) of oxygen at any one time. Oxyhemoglobin, which is the fully saturated form of hemoglobin, gives the oxygenated blood that flows through the arteries a bright strawberry-red color. Deoxygenated blood in veins is darker, partly due to carbaminohemoglobin being present. This compound helps the body get rid of the carbon dioxide (CO_2) waste produced by cells, but only a quarter of the CO_2 is carried back to the lungs this way, where it diffuses into the air and is exhaled. Most of the body's CO_2 is dissolved in the blood's plasma as bicarbonate ions.

In 1959, Austrian molecular biologist Max Perutz showed the four-unit structure of hemoglobin using X-ray techniques, for which he received the Nobel Prize in Chemistry in 1962.

There are now known to be in excess of 1,000 different human hemoglobin variants, some of which cause conditions such as sickle cell disease and thalassemia. These often cause anemia, which is a harmful decrease in the total amount of red blood cells or hemoglobin in the blood. ■



Human red blood cells, seen here in a microscopy photograph, circulate in the body for about 100–120 days. They are then broken down, and the iron is reused to make new red blood cells.



Felix Hoppe-Seyler

Considered one of the founding figures in biochemistry and molecular biology, Felix Hoppe-Seyler was born in Freyburg, Germany, in 1825 as Ernst Felix Hoppe. Orphaned at the age of nine, he was adopted by his brother-in-law Georg Seyler, a member of a powerful family with links to the Bavarian Illuminati (a secretive society of philanthropists). After he had qualified as a doctor, Hoppe-Seyler pursued his research in Tübingen and then Strasbourg. As well as his hemoglobin work, he carried out important studies into chlorophyll, the green plant chemical responsible for capturing solar energy during the process of photosynthesis. Hoppe-Seyler is also credited with the isolation of various complex proteins (which he called proteids at the time). In 1877, he founded the *Journal for Physiological Chemistry* and was its editor until his death in 1895.

Key work

1858 *Manual of Physiological and Pathological-Chemical Analysis*

OILS UPON THE CREAKY MACHINERY OF LIFE

HORMONES HELP REGULATE THE BODY

IN CONTEXT

KEY FIGURE
Edward Sharpey-Schafer (1850–1935)

BEFORE
1849 Arnold Berthold's experiment with castrated roosters points to the existence of an unknown regulatory mechanism in the body.

1850s Claude Bernard introduces the idea of the *milieu intérieur*, the stable internal environment of an organism.

AFTER
1915 American neurologist Walter Cannon demonstrates a link between the endocrine glands and emotional responses.

1950 Philip Hench, Edward Kendall, and Tadeusz Reichstein are awarded the Nobel Prize in Physiology or Medicine for the discovery of cortisone, a hormone treatment for rheumatoid arthritis.

1980s Synthetic human insulin is mass-produced for the treatment of diabetes.

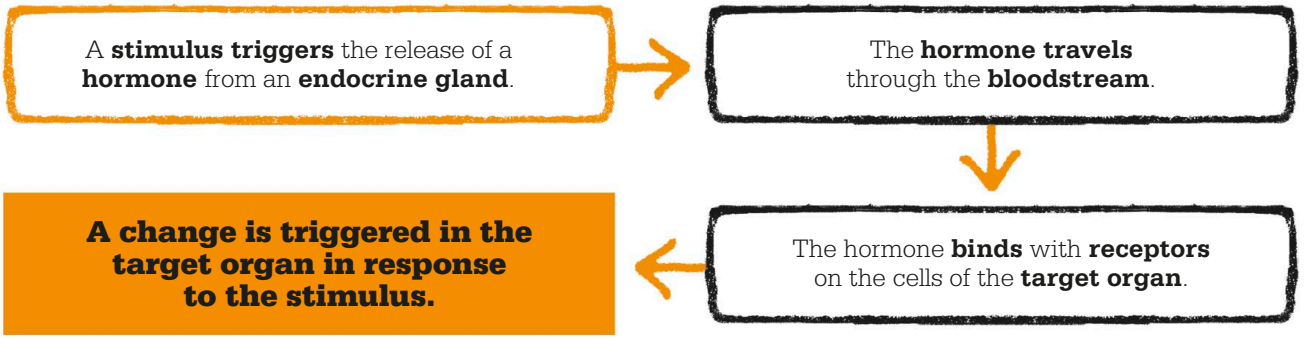
The ability of an organism to maintain a relatively stable internal state despite environmental changes is called homeostasis. It requires reliable communication between cells and tissues in different parts of the body. This is accomplished through the release of chemicals called hormones; these are carried through the bloodstream to their target cells, which respond appropriately. The word "hormone" was first used in June 1905 by British physiologist Ernest Starling. He defined hormones as "the chemical messengers that, speeding from cell to cell along the bloodstream, may coordinate the activities and growth of different parts of the body." The cells, tissues, and organs that secrete hormones together make up the body's endocrine system.

Identifying hormones

Experimental work by 19th-century scientists such as Arnold Berthold and Claude Bernard had already established that some kind of chemical communication takes place between different organs in an animal. However, when Starling introduced his new term, very little was known about the nature of hormones or how they worked.

Later in the 19th century, doctors described successfully treating patients with certain disorders by administering extracts of animal tissues, such as the thyroid and adrenal glands and the pancreas. It would later become apparent that these disorders were the result of hormone deficiencies. In 1889, Mauritian neurologist Charles Edouard Brown-Séquard informed the Academy of Sciences in Paris that he had injected himself with a concoction made up from veins, semen, and other fluids from the testicles of dogs and guinea pigs. The results were, he reported, a marked improvement in his strength, stamina, and ability to concentrate. He later suggested, in 1891, that all tissues produced secretions that might be extracted and used to treat disease; this

> Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates so that proteins and fats may be added to the diet.
> **Frederick Banting**



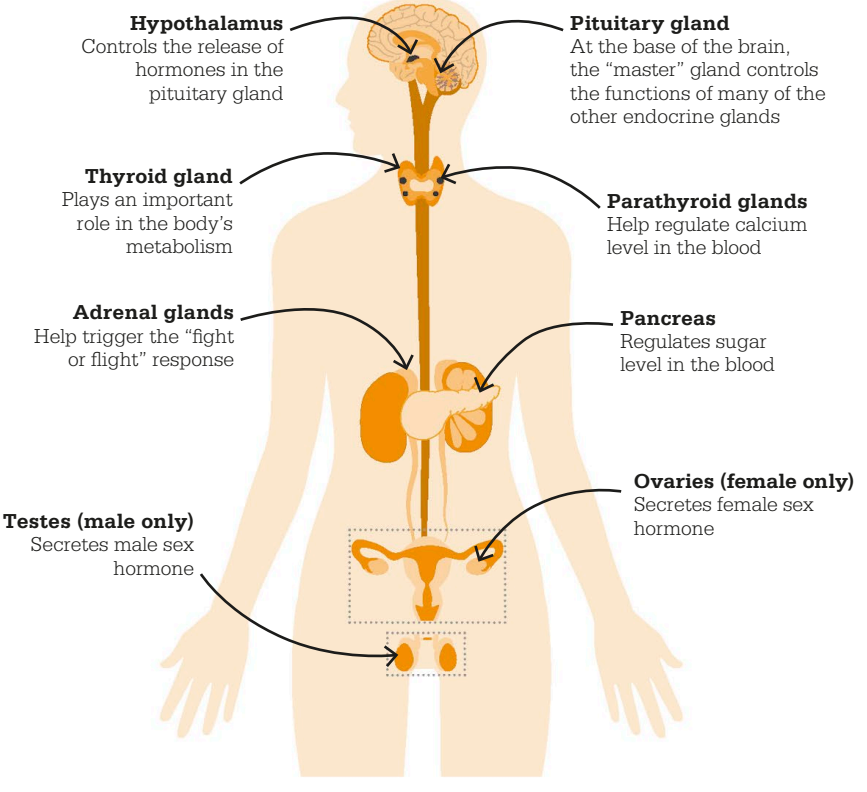
See also: Metabolism 48–49 ▪ Digestion 58–59 ▪ Circulation of the blood 76–79 ▪ Hormones trigger responses 84–85 ▪ Homeostasis 86–89

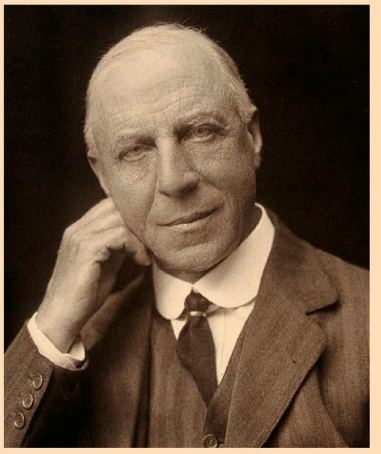
may be the first suggestion of what would become known as hormone replacement therapy.

Also in 1889, German physicians Joseph von Mering and Oskar Minkowski discovered the role of the pancreas in preventing diabetes. Dogs that had the pancreas removed developed the symptoms of diabetes and died shortly after the surgery. British neurosurgeon Victor Horsley, in 1891, demonstrated that patients with an underactive thyroid (hypothyroidism) could be treated with thyroid extracts.

British physiologists Edward Sharpey-Schafer and George Oliver demonstrated the existence and effects of adrenaline, as well as its secretion from the adrenal glands, in 1894, when they injected a dog with an extract from an adrenal gland and watched in surprise as its blood pressure shot up. Oliver and Sharpey-Schafer went on to show that extracts from the pituitary gland caused a rise in blood pressure, whereas extracts from the thyroid gland caused it to fall. In 1902, Ernest Starling and William Bayliss performed an experiment in which they identified a substance they called secretin, which triggered secretions from the pancreas when stomach acids entered the small intestine. »

The main endocrine glands





Edward Sharpey-Schafer

Regarded as a founder of endocrinology, Edward Albert Schafer was born in London in 1850 and studied medicine at University College London (UCL). There, he was taught by eminent physiologist William Sharpey, who so strongly influenced him that in later life he added Sharpey's name to his own.

Schafer was elected a Fellow of the Royal Society in 1878 and became professor at the Royal Institution in 1883 and chair of physiology at the University of Edinburgh in 1899. Always keen to try out new laboratory procedures, Schafer became more widely known after the publication in 1903 of his prone-pressure method of artificial respiration. He was president of the British Science Association in 1911–12. He retired in 1933 and died at home in North Berwick, Scotland, two years later.

Key works

1898 *Advanced Textbook of Physiology*
1910 *Experimental Physiology*

Starling and Bayliss were also able to show that secretin was a universal stimulant: secretin from one species triggered pancreatic secretions in any other species. Further research showed that this universality applied to all examples of what Starling went on to name hormones. In 1912, for example, German physiologist Friedrich Gudernatsch used extracts from a horse's thyroid tissue to trigger the development of tadpoles into frogs.

Understanding hormones

Sharpey-Schafer is credited with coining the name endocrine, from the Greek words *endon*, meaning within, and *krinein*, meaning to secrete. He set out the idea that hormones act on organs and cells within the body and are a system of communication and control distinct from that of the nervous system. In 1910, he proposed that diabetes results from a lack of a chemical produced in the islets of Langerhans in the pancreas. He called this chemical insulin from the Latin *insula*, meaning island.

In 1922, in another landmark demonstration of the universality of hormones, Canadian physician

> We have learned that there is an endocrinology of elation and despair.
> **Aldous Huxley**
> ***Literature and Science*, 1963**

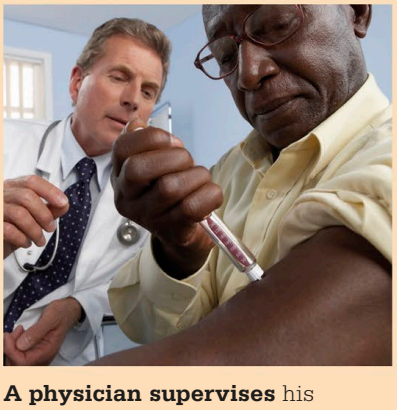
Frederick Banting used insulin extracted from the pancreas of a dog to treat 14-year-old diabetic Leonard Thompson.

In the early years of the 20th century, research was concentrated on identifying the source of hormones and uncovering their chemical nature. In 1926, British biochemist Charles Harington performed the first chemical synthesis of a hormone, thyroxine. Ten years later, American biochemist Edward Doisy defined four criteria by which hormones could be identified: a gland must be identified as producing an internal secretion; the substance produced must be detectable; it must be possible to purify the substance; and the pure substance needs to be isolated and studied chemically. Doisy's research into the role of ovarian hormones laid the groundwork for the development of hormonal contraceptives.

Hormones and regulation

The endocrine system is a complex interplay of actions and reactions between hormones, the glands that produce them, and the target organs they affect. Hormones carry instructions from more than a dozen endocrine glands and tissues to cells all over the body. About 50 different hormones have been identified in humans, controlling a variety of biological processes including muscle growth, heart rate, menstrual cycles, and hunger. A single hormone may affect more than one process, and one function may be controlled by several different hormones.

Hormones do more than communicate with target organs. For example, when the pancreas releases insulin, it stimulates muscle cells to take up glucose



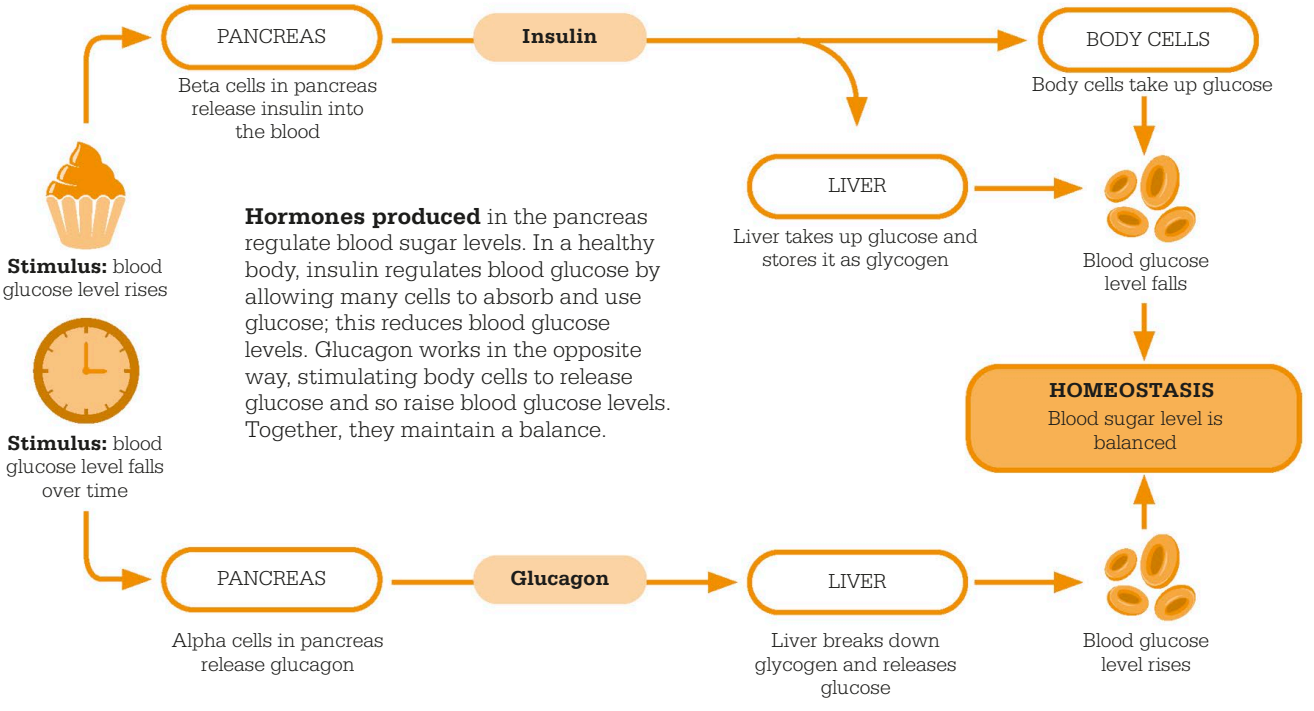
A physician supervises his diabetic patient, who is using an insulin "pen" to inject the hormone into his bloodstream.

Diabetes

One of the most familiar examples of where the body's homeostatic regulation has gone wrong, diabetes is a condition that causes a person's blood sugar level to become too high. If untreated, a diabetic coma and even death may result. There are two forms. Type 1 diabetes results from the body's inability to make insulin because the immune system mistakenly attacks the very cells in the pancreas that are involved in insulin production. Just why this happens is currently unknown.

As demonstrated by Frederick Banting, type 1 diabetes can be treated, although not cured, by administering doses of synthetic insulin.

People suffering with type 2 diabetes produce insulin, but they are unable to use it effectively—or they may not produce enough. This, by far the most common type of diabetes, is usually diagnosed in later life, and there are strong indications that lifestyle can play a role in its development.

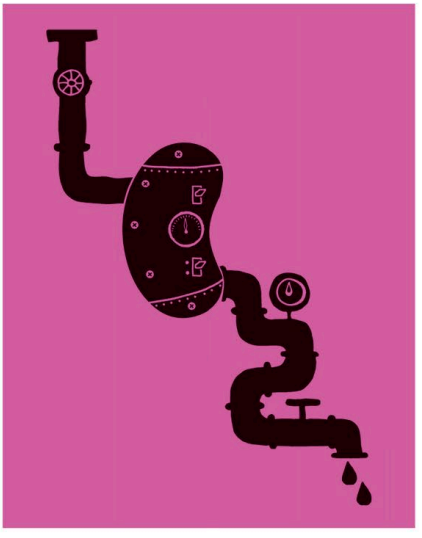


from the bloodstream, and it may also regulate the release of hormones from other endocrine glands. The so-called master gland of the endocrine system is the pituitary. This pea-sized gland, located just below the brain, controls the functions of many other endocrine glands. The pituitary gland secretes hormones that influence our responses to pain, signals the ovaries and testes to make sex hormones, and controls ovulation and the menstrual cycle.

Hormones circulate through the blood and come into contact indiscriminately with cells throughout the body. But they only trigger reactions with certain cells, called target cells. A target cell responds to a hormone because it has receptors for that hormone; cells lacking these receptors will not respond to the hormone. A hormone's effects depend on its concentration in the bloodstream. If it is too high or too low, then the result is almost always disease—for example, diabetes develops as a result of low levels of insulin, and hyperthyroidism occurs when the thyroid gland is overactive.

Feelings of hunger are triggered by the hormone ghrelin, which is released mainly by the stomach. Ghrelin may help prepare for food intake by increasing gastric acid secretion.

Sharpey-Schafer was not quite right in his belief that the endocrine system is separate from the nervous system. The two systems work to regulate and maintain a healthy balance within the other systems of the body. In particular, the endocrine system is intimately linked with the sympathetic and parasympathetic nervous systems. The sympathetic nervous system acts in response to stress, which can be anything that threatens well-being or disrupts homeostasis. It primes the body to react and activates glands in the endocrine system. On the other hand, the parasympathetic nervous system is responsible for calming things down, allowing the body to recover its equilibrium state once the stress has been dealt with. ■



THE MASTER CHEMISTS OF OUR INTERNAL ENVIRONMENT

KIDNEYS AND EXCRETION

IN CONTEXT

KEY FIGURE
Arthur Cushny (1866–1926)

BEFORE
4th century BCE Aristotle believes that the kidneys are not essential to waste production and are secondary to the bladder.

1628 English physician William Harvey establishes that blood circulates continually around the body.

1666 Marcello Malpighi reveals some of the fine structure of the kidney.

AFTER
1945 Willem Kolff shows that patients suffering from kidney failure can be kept alive by artificial dialysis.

1958 Danish scientist Hans Ussing undertakes detailed investigation of kidney function at the level of individual cells.

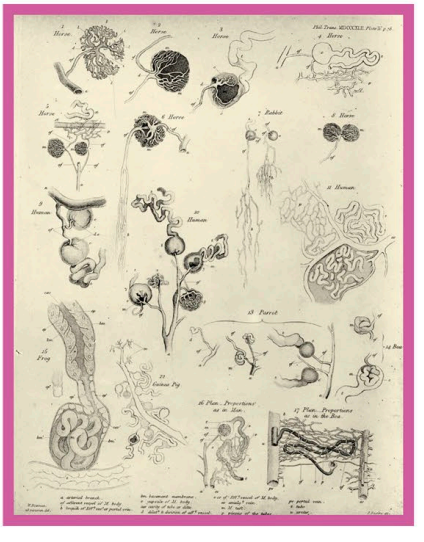
A major function of the kidneys is the removal of waste products and excess fluid from the blood by a process of excretion and reabsorption.

In 1666, Italian anatomist Marcello Malpighi provided the first microscopic description of the structure of a kidney. The early instruments available to him probably magnified no more than 20 or 30 times, but they revealed structures that Malpighi thought were glands and that he described as resembling "apples on a beautiful tree." He believed that the separation of urine from the blood began in these glands, a notion that proved to be accurate and far ahead of its time.

Conflicting ideas

In 1842, British anatomist William Bowman described the kidneys in detail. He had spent two years studying Malpighi's glands and noticed that the Malpighian bodies were formed from a mass of tiny capillaries (the glomerulus) held inside a capsule, later named Bowman's capsule in his honor. He discovered that the capsule formed a continuous part of the renal duct, which drains urine into the bladder. He believed that water was excreted from each glomerulus to flush the waste product urea along a tiny tube leading from the capsule.

At the time, Bowman's theory was disputed by German physician Carl Ludwig, who suggested that a filtering process took place in which the constituents of the blood plasma, apart from larger molecules such as fat and proteins, passed



William Bowman used a microscope ten times more powerful than the one used by Malpighi to study the kidneys. He produced very detailed diagrams such as the ones shown here.

See also: Anatomy 20–25 ▪ Metabolism 48–49 ▪ Digestion 58–59 ▪ Circulation of the blood 76–79 ▪ Capillaries 80 ▪ Hormones help regulate the body 92–97

> Extremely minute parts [are] so shaped and situated as to form a marvelous organ.
> **Marcello Malpighi**

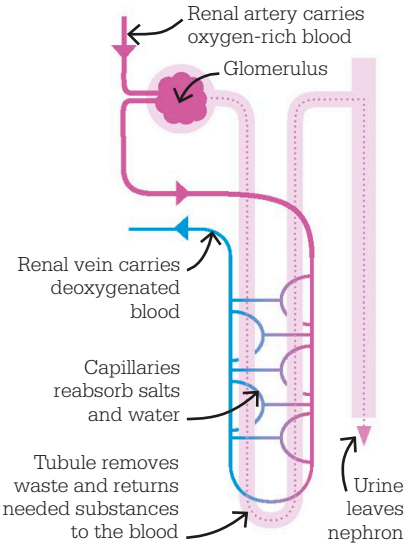
through the walls of the glomerulus capillaries. Ludwig reasoned that since the volume of filtrate was much larger than the volume of urine excreted, most of the former must be reabsorbed by the tubules.

German physiologist Rudolph Heidenhain disagreed with Ludwig. In 1883, Heidenhain published a calculation that seemed to show an average adult's kidneys would have to filter 148 US pints (70 liters) of fluid a day to account for the daily output of urea, requiring at least twice that volume of blood to flow through the kidneys. Heidenhain declared this so unlikely that urine had to be produced entirely by secretion from, he believed, the renal tubules rather than by filtration.

Modern theory

In 1917, Scottish physician Arthur Cushny published *The Secretion of Urine*, in which he came to the defense of Ludwig's filtration–reabsorption theory. Cushny experimentally disproved Heidenhain's assertion that the tubules would not be able to reabsorb water in the quantities required, and he dismissed the suggestion that urine was produced by secretion. He instead submitted what he called the "modern theory" of kidney function.

Cushny said that the amount of fluid reabsorbed meant that, along with a large volume of water, nearly all of the filtered glucose, amino acids, and salts must also be reabsorbed by the tubules. The varying concentrations of these substances meant they were reabsorbed to different degrees. For example, amino acids are completely or nearly completely reabsorbed, whereas waste products such as creatinine, produced by muscle metabolism, are hardly reabsorbed at all. ■



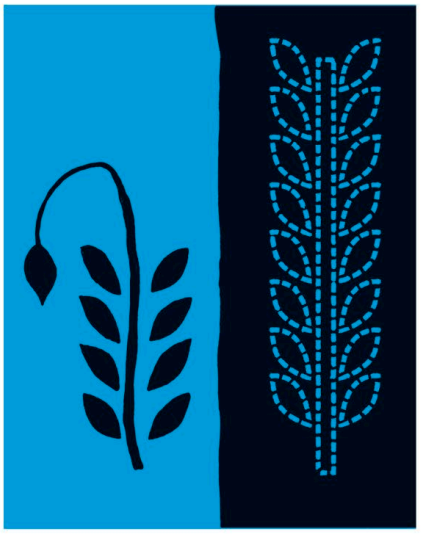
A human kidney contains hundreds of thousands of blood-filtering units called nephrons. Each of these has a glomerulus—a bundle of blood vessels surrounded by a capsule—which removes waste and excess water.

This later version of Kolff's original artificial kidney used 130 ft (40 m) of cellophane tubing wrapped around a wooden drum.

Dialysis

Before the mid-20th century, kidney failure was effectively a death sentence. Without the kidneys' ability to filter harmful waste products, the body cannot function. In the 1920s, German doctor Georg Haas had attempted the first dialysis treatment (the artificial removal of waste products) on human patients, using tubes of a cellulose-based membrane that has semipermeable properties. None of his patients survived, however, mainly because the procedure wasn't carried out for long enough. A breakthrough came in 1945, when Dutch physician Willem Kolff performed a week-long dialysis on a patient with acute kidney failure.

Kolff used an artificial kidney made of cellophane tubes wound around a wooden drum. The patient's blood passed through the tubes, and the drum rotated through a bath of an electrolyte solution called a dialysate. As the tubes turned through the solution, toxins were drawn into it from the blood by osmosis.



NO AUXIN—NO GROWTH

PLANT GROWTH REGULATORS

IN CONTEXT

KEY FIGURE
Frits W. Went (1903–90)

BEFORE
1881 Charles Darwin and his son Francis observe oat seedlings bend toward light.

1911 Danish scientist Peter Boysen-Jensen suggests that hormonelike signals travel through a plant.

1924 Frank Denny, a US Department of Agriculture (USDA) plant physiologist, explains that ethylene from farmers' kerosene lamps—not heat or smoke as is believed—induces ripening in fruit.

AFTER
1935 Japanese agrichemist Teijiro Yabuta isolates and names gibberellin.

1963 Botanists Frederick Addicott in the US and Philip Waring in the UK discover abscisic acid independently.

To survive, animals move toward food and water and away from danger. Plants must also respond to environmental stimuli, but are immobile, so they grow toward light, water, and oxygen, and defend themselves by growing defensive structures or emitting protective chemicals.

Physiological processes in plants are controlled by molecules that have similar roles to animal hormones secreted into animal circulatory systems. In plants, the molecules move through the tissues and have slower impacts than animal hormones, affecting more long-term patterns of growth; for this reason, they are called plant growth regulators (PGRs).

Ethylene gas is emitted by ripe fruits to coordinate ripening of surrounding fruits on the same plant. In a bowl of fruit, mature bananas can be used to ripen green fruits such as tomatoes.

PGRs are tiny proteins; like a key, each fits into another protein, or receptor, that acts as a lock. Once the protein "lock" opens, a cascade of events takes place, initiating survival mechanisms, such as the plant protecting itself from drought or growing toward a water source.

Discovery of auxin

The first PGR to be identified was auxin. In the 1880s, Charles and Francis Darwin found that if they covered an oat seedling's tip with dark paper or cut off the tip, the seedling did not bend toward light. They concluded that some "influence" at the shoot tip must control a plant's growth response to light (now called phototropism).

In 1927–28, Dutch plant physiologist Frits W. Went and Soviet microbiologist Nikolai Cholodny independently described the chemical, later named auxin. The Cholodny–Went model in 1937 combined their findings to describe auxin's role in phototropism and in

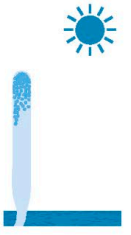
See also: Cell membranes 42–43 ▪ Photosynthesis 50–55 ▪ Plant transpiration 82–83 ▪ Homeostasis 86–89 ▪ Hormones help regulate the body 92–97 ▪ Plant translocation 102–03 ▪ Pollination 180–83 ▪ Trophic levels 300–01

Proving the action of auxin in phototropism

In nature, auxin stimulates cell growth on the shaded side of a shoot so that it bends toward the side with shorter cells—the side that has the most sunlight.

1. In full sunlight, auxin concentrates in the tip of any seedling or shoot.

2. If one side of the seedling is shaded from sunlight, the auxin diffuses to the shaded side.



3. Cells grow longer on the seedling's shaded side, so the shoot bends toward the light.

Went's experiment isolated the chemical auxin from the tip of an oat seedling, to manipulate the direction of the seedling's growth, revealing auxin's role in phototropism.

1. The tip of the seedling is cut off so it can be placed on an agar block. Auxin diffuses from the tip down into the agar block.

2. The agar block is placed on one side of the severed shoot. No light source is present, therefore light alone cannot cause any response.

3. Auxin diffuses from the agar into one side of the shoot. Cells diffused with auxin grow more than cells on the other side of the shoot.

geotropism (growth response to gravity) of roots. The model was a key step in understanding PGRs.

The main types of PGR

The role of ethylene gas was pieced together by various 19th- and early 20th-century scientists after it had been observed to promote ripening in fruits. In 1934, British phytologist Richard Gane proved that fruits could synthesize ethylene.

Ripe fruits are vital to a plant's life cycle, because they hold the future generation in their seeds, which must be dispersed at the appropriate time in a season. On an apple tree, for example, the first ripening apple emits ethylene gas so that other apples ripen together. Ethylene is now used commercially to time ripening of fruits that were picked while unripe, so that they ripen just as they are put on sale.

In the 1940s, Swedish-American plant physiologist Folke Skoog began studying the chemical that caused cells to divide and differentiate into plant organs—namely roots, leaves, flowers, or fruit. His student Carlos Miller isolated kinetin, now called cytokinin, in 1954. This PGR also affects aging; for example, a decrease in cytokinin degrades green chlorophyll in fall, revealing other pigments in leaves; in spring, cytokinin levels ramp up to support leaf-bud formation.

Other PGRs include gibberellin and abscisic acid. The former promotes cell elongation and division (in the presence of auxin) and breaks seed dormancy; it is used commercially to make seedless grapes swell. Abscisic acid controls responses to environmental stress, such as closing of stomata (pores) in drought, and dormancy.

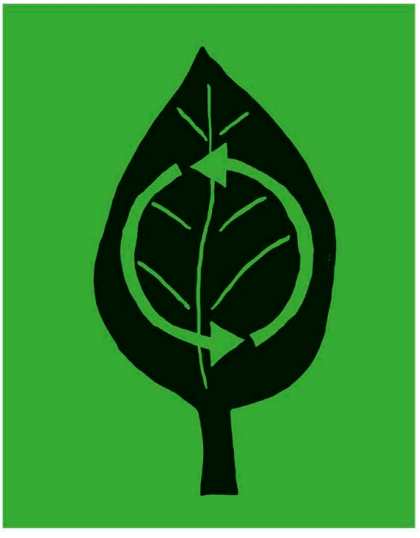
All the PGRs have multiple functions; auxin also regulates leaf and flower formation, fruit ripening, and production of new roots from a cutting. PGRs can also interact in complex ways in plant processes, sometimes together, sometimes against each other. ■

Phytochromes

American botanist Harry Borthwick and biochemist Sterling Hendricks of the US Department of Agriculture (USDA) first isolated phytochromes, light-sensitive plant proteins, in 1959. This protein is bound to a light receptor that, as in PGRs, works like a lock. In this case, the keys are wavelengths of red light in sunlight.

Different red wavelengths inform the plant of the time of day or whether it is in full sun or shade. Phytochromes also detect how long certain wavelengths are present and therefore what season it is.

With this information, a plant regulates its circadian (daily) rhythms, including photosynthesis, as well as timings of seed germination, flowering, and dormancy.



THE PLANT PUTS ITS FLUIDS IN MOTION

PLANT TRANSLOCATION

IN CONTEXT

KEY FIGURE
Ernst Münch (1876–1946)

BEFORE
1837 German botanist Theodor Hartig observes phloem cells, which he calls sieve tubes (*Siebröhren*).

1858 The term "phloem" is coined by Swiss botanist Carl von Nägeli, who proposes that long tubes of phloem may transport insoluble matter.

1928 Thomas Mason and Ernest Maskell's source/sink theory suggests that sugar travels up and down plant phloem by diffusion alone.

AFTER
1953 Entomologists John Kennedy from Britain and Thomas Mittler from Austria use aphids to prove that plant sap moves by flow pressure through phloem sieve tubes.

All biological organisms need energy from sugar to fuel cellular activity. In translocation in plants, sugar made in photosynthesis and other nutrients taken up by roots move around the plant in sap. In the 19th century, botanists observed phloem cells and found that sap flowed through vessels made from phloem. Debate focused on what force, from external pressure to diffusion or osmosis, drove sap along phloem vessels.

Source and sink

Irish botanist Thomas Mason and his English colleague Ernest Maskell showed that phloem transported sugars around the plant in 1928 and described their source/sink theory. Sugar originates at one location in a plant and is "shipped" to other locations in the plant as needed. The area where sugar originates is the "source" and an area where sugar is unloaded is a "sink".

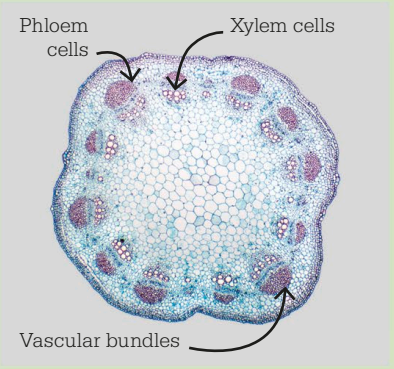
> Leaves make sugar. All the sugar that you have ever eaten was first made within a leaf.
>
> **Hope Jahren**
> **American geobiologist**

Source and sink can change in the plant, depending on season. For example, if unharvested carrots are left in the ground, the green tops die away over winter. In spring, the carrot root is the source because it has stored sugar. When sugar is sent to the carrot top to build new foliage, the young leaves and stems become the sink. Later in the growing season, the mature leaves begin photosynthesizing and are now the source, where sugar is made. The carrot roots, flowers, and young stems and leaves all need sugar and become sinks.

The process of translocation

Mason and Maskell had incorrectly suggested that sap flowed along phloem entirely by diffusion. Then, in 1930, German plant physiologist Ernst Münch published his theory, now known as the mass-flow (or pressure-flow) hypothesis, which is regarded as the best explanation of how sap flows from source to sink.

See also: The cellular nature of life 28–31 ▪ Cell membranes 42–43 ▪ Photosynthesis 50–55 ▪ Reactions of photosynthesis 70–71 ▪ Plant transpiration 82–83 ▪ Plant growth regulators 100–101 ▪ Pollination 180–83 ▪ Food chains 284–85



In a sunflower stem, vascular bundles of phloem cells and xylem cells are arranged in a ring around the central area of pithy tissue.

Phloem tissue

All the "shipping" and "receiving" of sugar during plant translocation requires specialized transport cells, called phloem. They are similar to xylem cells, which carry the plant's transpiration stream.

In 1969, German-American plant anatomist Katherine Esau described phloem structure and function in detail, with the aid of transmission electron microscopy (TEM). Phloem tissue consists of cylindrical cells with perforated ends, placed end-to-end to form vessels, known as sieve tubes.

In herbaceous plants, such as sunflowers, the water transport tissue (xylem) and sugar transport tissue (phloem) are bundled together. They run from the roots into the stems, leaves, flowers, and fruits. In woody plants, such as oak trees, the wood is made of xylem tissue, and bark contains the phloem.

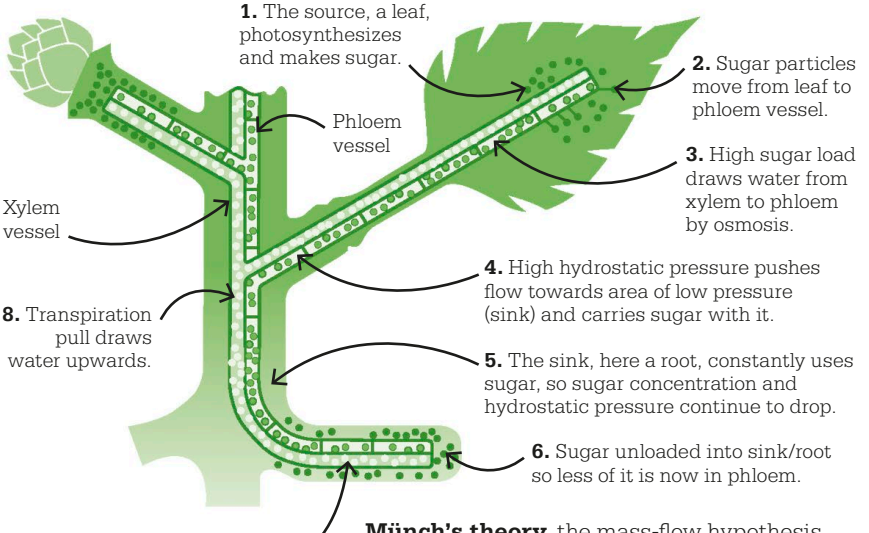
In winter, animals such as deer and elk eat bark off trees. "Ring barking", where bark is removed from the trunk's whole circumference, can kill the tree, as it cuts off the sugars supplied by the phloem in the bark.

In biological systems, in a process known as osmosis, water passively diffuses from areas of high water/low sugar concentration to areas of high sugar/low water concentration across cell membranes. Münch described how, when leaves unload photosynthesized sugar into nearby phloem cells, the high sugar load in the sap draws water into the phloem by osmosis from xylem, the water transport vessels. As when turning on a high-powered garden hose, the sudden rush of water into the confined space of the leaf phloem creates high pressure – a force known as hydrostatic pressure.

Münch also explained how sap moves down a pressure gradient, from areas of greater hydrostatic pressure at the source to areas of least hydrostatic pressure, at the sinks. Sinks, such as roots or buds, may be in different locations, so sap moves up or down the phloem.

Sinks constantly need sugar to fuel cell activity and actively extract sugar from the phloem. Once its sugar is lost, water in the phloem has less energy (called low water potential) than water in the xylem, which has higher water potential, so the water moves into the xylem, to be recycled and move up the plant in the transpiration stream.

Aphids (tiny insects) feed on plant sap by probing phloem vessels with needle-like mouthparts (stylets). Sucking sap would be like a human drinking from a high-pressure water hose, so aphids simply allow sap to stream through their bodies as they metabolize what sugars they need. The rate of sap flow was first measured in 1953 by severing the stylets of feeding aphids. ■



Münch's theory, the mass-flow hypothesis, explains how sugar translocates from source to sink in a plant by osmosis along a gradient of high to low hydrostatic pressure.

BRAIN AND BEHAVIO

R

Luigi Galvani shows how **electrical stimulation** makes a dead frog's **muscles twitch**.

1780s

Hermann von Helmholz develops his "**trichromacy**" theory of how humans perceive **color** using three types of **receptors**.

1850s

Emil du Bois-Reymond suggests that "animal electricity" is electrical **signals transmitted** by **nerves** through the nervous system.

c.1865

1815

By cutting into the brains of live pigeons and rabbits, Jean-Pierre Flourens establishes that different **brain areas control** different **functions**.

1861

From examination of brain-injured patients, Paul Broca identifies the **area of the brain** that controls **speech production**.

1873

Douglas Spalding contributes to the **nature versus nurture** debate by distinguishing between **innate** and **learned behavior** in young animals.

The fact that animals have the ability to move, and so to behave in certain ways, became a particular focus of research for scientists in the 19th century. Early investigations into the subject concentrated on the physical mechanisms that enable movement, but from these studies emerged the idea that the nervous system, and the brain in particular, control not only the organs of movement, but also the sensory organs, and are therefore at the center of animal behavior.

Electrical currents

One of the first scientists to give an insight into the workings of the nervous system was Luigi Galvani, who made a discovery while investigating the effects of the newly discovered electrical current on animal tissue. In a series of experiments in the 1780s, Galvani found that the legs of a dead frog would respond by twitching when subjected to electrical stimulation. From this, he inferred that muscle contraction, and, therefore, an animal's movement, is triggered by electrical impulse, a force he called "animal electricity." However, it was not until nearly a century later, in the 1860s, that Emil du Bois-Reymond suggested that Galvani's "animal electricity" is transmitted throughout the body through a system of nerves, and a better understanding of the nature of the nervous system came about.

The control center

By the beginning of the 19th century, it was accepted that the brain also had a central role in the control of animal movement and behavior, but little was known about its workings. In the spirit of Galen some 1600 years before, physiologist Jean-Pierre Flourens conducted a series of experiments on the brains of live pigeons and rabbits, cutting away parts of the brain tissue and observing the effects. What he discovered was that different functions of the body are controlled by specific parts of the brain. His findings were confirmed when Paul Broca, in a study of patients with brain injuries, found that those with speech problems had suffered from damage to a particular part of the brain, now known as Broca's area.

The idea that particular areas of the brain control different functions had become established, and now physiologists set about "mapping" the human brain according to

Examining specially stained nerve tissue under a microscope, Santiago Ramón y Cajal confirms that the **nervous system** is **composed of cells**.

1890s

Otto Loewi **discovers** the chemicals known as **neurotransmitters**, which carry nerve signals between cells.

1921

Eric Kandel confirms Ramón y Cajal's theory that **chemical changes** in the synapses are involved in **building memory**.

1960s

1909

Korbinian Brodmann creates the first detailed **functional map** of the cerebral **cortex**.

1954

The **chemical process** responsible for **muscle contraction** is **discovered** independently by Andrew Huxley and Rolf Niedergerke, and Hugh Huxley and Jean Hanson.

1960

Jane Goodall **observes chimpanzees** both **using** and **making tools**, prompting renewed interest in the subject of tool use by animals.

the specialized function of the various areas. They discovered, for example, that the part of the brain called the cerebral cortex is responsible for control of the most complex functions, such as memory, problem-solving, and communication, while other parts of the brain control the "lower" functions, such as movement.

By the early 20th century, using the latest techniques of microscopy, Korbinian Brodmann was able to create a detailed map of the brain, showing the specialized spatial organization of the cerebral cortex.

In the 1850s, research by Hermann von Helmholtz into the way animals perceive light (vision), had showed that the eyes also display specialization, specifically in the ability to distinguish color. His theory was that color vision is possible because of the presence in the eyes of receptors of different pigments, sensitive to specific wavelengths of light.

Processing signals

A breakthrough in understanding the way in which signals are transmitted from the sensory organs to the brain, and from the brain to the other organs, came at the end of the 19th century. Using a new staining technique, Santiago Ramón y Cajal was able to examine previously invisible aspects of nerve tissue, and discovered that nerves are composed of various different cells, called neurons, which carry the signals to and from the brain. It was later discovered, by Otto Loewi, that the neurons "communicate" with each other across the gaps between nerve fibers (synapses) by releasing chemicals that trigger electrical impulses in neighboring cells.

A detailed knowledge of the physiology of the brain and nervous system was gradually established, and this even went some way to explaining higher brain functions, such as memory and learning, which in the 1960s, Eric Kandel showed to be associated with a physical process in the brain.

But questions of animal behavior, and especially human behavior, remain unanswered. For example, how much of it is innate, resulting from the complex structure of the brain, and how much is shaped by learning from experience of the environment? And, given the process of evolution, how much of our behavior is inherited and can be passed down to subsequent generations? ■

THE MUSCLES CONTRACTED INTO TONIC CONVULSIONS

EXCITABLE TISSUES

IN CONTEXT

KEY FIGURE
Luigi Galvani (1737–98)

BEFORE
1st century CE Greek and Roman physicians use shocks from the Atlantic torpedo fish, a species of electric ray, to treat headaches and gout.

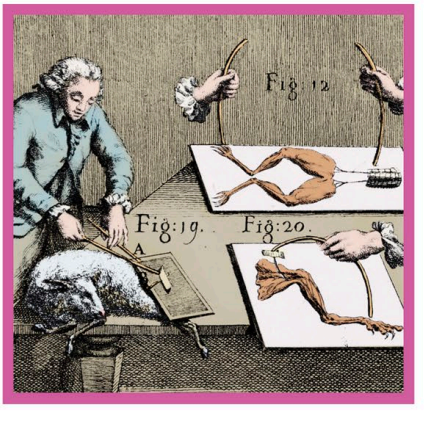
1664 Dutch microscopist Jan Swammerdam removes a frog's leg and makes it twitch when he pinches the nerves.

1769 American-born physician Edward Bancroft reports of other electric fish that have an ability to stun prey.

AFTER
1803 Italian physician Giovanni Aldini uses electricity to reanimate the corpse of a murderer recently executed in London.

1843 German physician Emil Du Bois-Reymond shows that electrical current applied to nerves makes muscles contract involuntarily.

In 1791, Italian anatomist Luigi Galvani publicized a discovery that revolutionized our understanding of not only animals but electricity. While dissecting a pair of freshly severed frog's legs held in place by a copper hook, Galvani found that touching the exposed nerve with his iron scalpel made them twitch. He recreated this set-up with a metallic arc with one tip made from iron and the other from copper. Using this device, Galvani could reanimate muscles of several animal species by touching them with both tips.



Luigi Galvani's experiments on frogs and other subjects led him to believe that animals were driven by an electrical force, which he called "animal electricity."

Dating back to Aristotle in the 3rd century BCE, scientists had subscribed to the theory of vitalism, which stated that all living organisms contained a non-physical "vital force" of life. At the time of Galvani's discovery, electricity was a poorly understood phenomenon, and Galvani proposed he had discovered that this vital force was electrical. Others disagreed, thinking the combination of two different metals and salty body fluids pointed to a chemical process, and in 1800, Italian physicist Alessandro Volta proved it by building the world's first battery with copper, zinc, and paper soaked in a salt solution. Nevertheless, in 1843 German physician Emil du Bois-Reymond proved the electrical nature of nerve signals when he detected an electrical current in frog muscles and nerves. ■

See also: Biochemicals can be made 27 ▪ Electrical nerve impulses 116–17 ▪ Nerve cells 124–25 ▪ Synapses 130–31

THE FACULTY OF SENSATION, PERCEPTION, AND VOLITION

THE BRAIN CONTROLS BEHAVIOR

IN CONTEXT

KEY FIGURE
Jean-Pierre Flourens (1794–1867)

BEFORE
6th–5th centuries BCE Greek natural philosopher Alcmaeon of Croton proposes that the brain is the center of thought.

1811 French physician Julien Jean César Legallois shows that a region of the medulla oblongata (lower half of the brainstem) controls respiration.

AFTER
1865 French anatomist Paul Broca establishes that a part of the human brain's frontal lobe is involved in language.

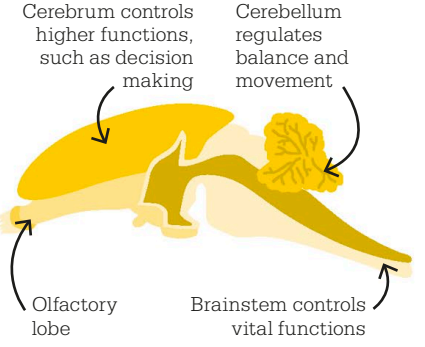
1873 Italian biologist Camillo Golgi develops a staining technique that makes neurons (brain cells) visible under the microsope.

1909 German neuroscientist Korbinian Brodmann defines 52 areas of the cerebral cortex in terms of function.

Early ideas about the functions of the brain varied, with ancient Greeks debating whether the mind and soul resided in the heart or the brain. Aristotle thought that the brain's function was to cool blood. However, some earlier Greeks—including Hippocrates—recognized the brain's role in sensation and thought, and in Rome in the 2nd century CE, Galen taught that the brain controls mental faculties.

Functions of the brain

During the first half of the 19th century, scientists observed that different parts of the brain might be responsible for different functions. Between 1822 and 1824, French physiologist Jean-Pierre Flourens carried out experiments on three main parts of animals' brains—the cerebellum (a structure at the back of the brain), the brainstem (the "root" of the brain, which connects to the spinal cord), and the cerebrum (large, paired lobes of tissue above the brainstem). He was able to establish that the cerebellum seemed to regulate voluntary movements; the brainstem controlled involuntary vital functions such as breathing and the circulation of blood; while the cerebrum was involved in higher functions such as perception, decision-making, and the initiation of voluntary movement. In other words, the cerebrum seemed to play a pivotal role in controling behavior. ■

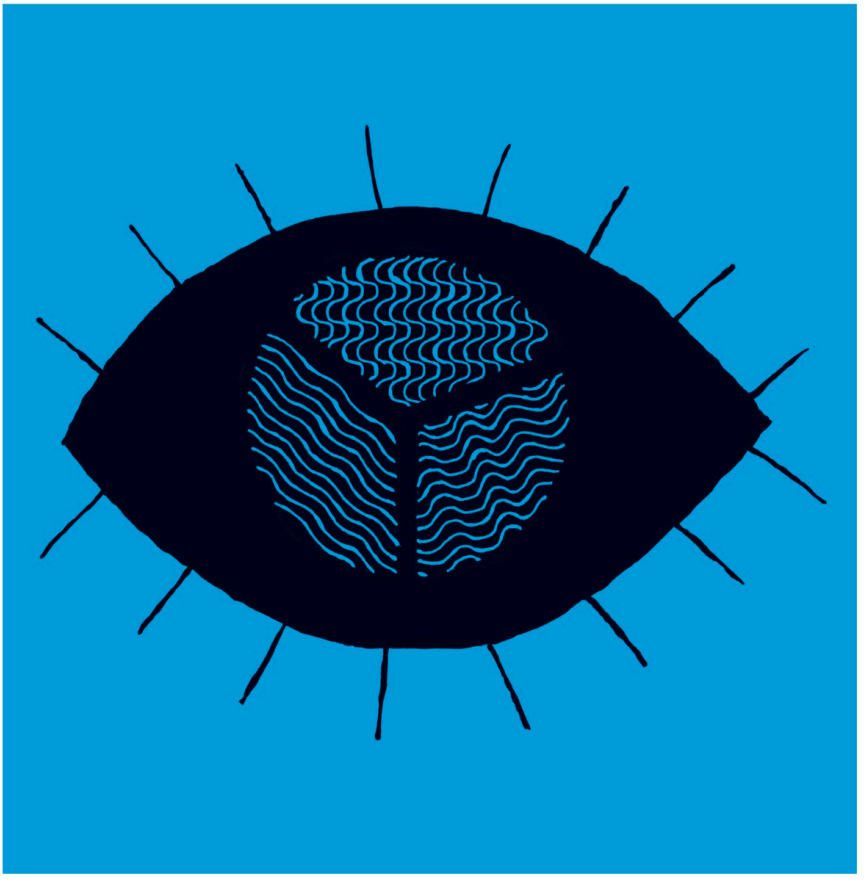


To see how the brain of a live rabbit worked, Flourens disabled different parts of the brain with incisions and observed the effects.

See also: Experimental physiology 18–19 ▪ Speech and the brain 114–15 ▪ Organization of the brain cortex 126–29

THREE PRINCIPAL COLORS, RED, YELLOW, AND BLUE

COLOR VISION



IN CONTEXT

KEY FIGURE
Thomas Young (1773–1829)

BEFORE
1704 Isaac Newton publishes *Opticks*, detailing experiments on the physical nature of light.

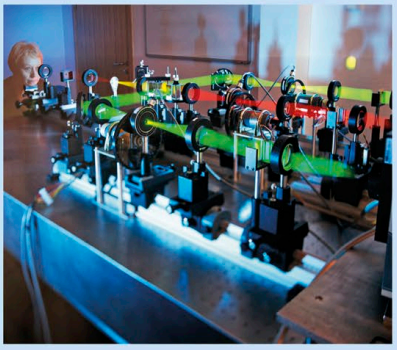
1794 British chemist John Dalton investigates color blindness, believing it to result from a discoloration of the aqueous humor in the eye.

AFTER
1876 German physiologist Franz Boll discovers rhodopsin, the light-sensitive protein found in the rods of the retina.

1967 American biochemist George Wald gets the Nobel Prize in Physiology or Medicine for his work on the photopsins, the photoreceptor proteins in the cone cells of the retina.

Color is one of the most important ways in which sighted people and animals experience the world. For centuries, light and color were believed to be two different phenomena: light was a carrier of color rather than the source of color itself; color was a property inherent in an object, carried from it to the observer by the light. English physicist Isaac Newton, in a series of ingenious experiments that he published in *Opticks*, showed that refracting a beam of white light through a prism split it into a spectrum of color, providing conclusive proof that color was indeed a property of light.

See also: Electrical nerve impulses 116–17 ▪ Nerve cells 124–25 ▪ Organization of the brain cortex 126–29 ▪ Chromosomes 216–19 ▪ Mutation 264–65



A test for tetrachromacy, or four-channel color vision, is carried out on a person (upper left), who is being subjected to beams of colored light.

Tetrachromacy

Each type of cone cell in the eye is thought to be able to distinguish among about 100 shades, so the three cone cells together allow us to distinguish around one million different colors.

Tetrachromacy in humans is thought to be due to variations in genes on the X chromosome that code for the red and green cone types. Although tetrachromacy is more likely in women, it also occurs in men. Six percent of men carry a gene that produces a different red or a different green cone and have color vision that is slightly different from normal. With their two X chromosomes, women can carry the normal red and green genes on one X chromosome and a variant gene on the other. This can result in them having four types of cones.

At the other end of the scale, most people who are color blind, in common with most other mammals, are dichromats, with just two functioning types of cone cells. They can distinguish only around 10,000 shades.

The question that remained to be answered was, "How do we see color?"

French scientist René Descartes, Newton, and others incorrectly suggested that the eye works by means of vibrations in the retina: light of different colors produces vibrations of different frequencies that are interpreted as color in the brain. British glass-maker George Palmer published a pamphlet in 1777 proposing that light consisted of just three rays—red, yellow, and blue—and that there were three types of detector in the retina, each one set in motion by one type of color ray. Mixed light triggered more than one kind of retinal detector, and if all were stimulated equally, the result was a perception of white light—but color blindness resulted when detectors were lacking. Palmer's idea first outlined the concept of trichromacy.

Trichromatic theory

British physicist Thomas Young was a man of such formidable intellect that his fellow students at Cambridge University dubbed him "Phenomenon Young." In 1801, in a series of lectures at the Royal Society in London, he put forward his theory of three-channel color vision to explain how the eye detected colors. Young's idea of color vision grew from his belief that light was a wave and that all that was required to perceive a full color spectrum was three types of receptor corresponding to the three primary colors. It was, he said, "almost impossible to conceive each sensitive point of the retina to contain an infinite number of particles, each capable of vibrating in perfect unison with every possible undulation, [so] it becomes necessary to suppose the number limited … to the three principal colors, red, yellow, and blue."

Young had no anatomical evidence to back up his idea, and his wave theory was in contradiction to the generally accepted notion put forward by Newton, that light was a stream of minute particles. As a result, Young's trichromatic theory found little support.

Over the next few decades—thanks to the work of French physicist Augustin-Jean Fresnel, Young, and others—the wave nature of light became indisputable. German scientist Hermann von Helmholtz, at the University of Königsberg, investigated color mixing in a series of experiments with prisms in the mid-19th century. At first, he could only obtain white light by mixing blue and yellow. Since this contradicted the well-known fact that mixing yellow and blue »

> The nature of light is … of no material importance to the concerns of life.
>
> **Thomas Young**
>
> **"On the Theory of Light and Colors," 1801**

pigments produced green, Helmholtz investigated the distinction between the mixing of light of different wavelengths (additive mixing) and the mixing of pigments of different colors (subtractive mixing). When pigments are mixed, only the wavelengths that both reflect are left. In 1853, German mathematician Hermann Grassmann was able to show mathematically that each point on the color circle ought to have a complementary color. Inspired by this, Helmholtz returned to his experiments—with new equipment—and did indeed find more complementary pairs.

Around the same time, Scottish physicist James Clerk Maxwell was similarly conducting color measurements. Maxwell's interest in color vision started when he was introduced to the topic by one of his professors at the University of Edinburgh. Maxwell carried out research into color vision—and specifically into how people see mixtures of colors. He used two- or three-colored disks mounted on spinning tops, arranged so that different percentages of each color could be seen. When the tops were spun rapidly, the colors blurred together. Maxwell carefully recorded the different colors and proportions needed to get the inner and outer colors of his rings to match. His demonstrations of trichromatic color mixing provided the best physical evidence yet that Young's trichromatic theory was right. What was needed next was to fill in the biological details.

Sensory receptors

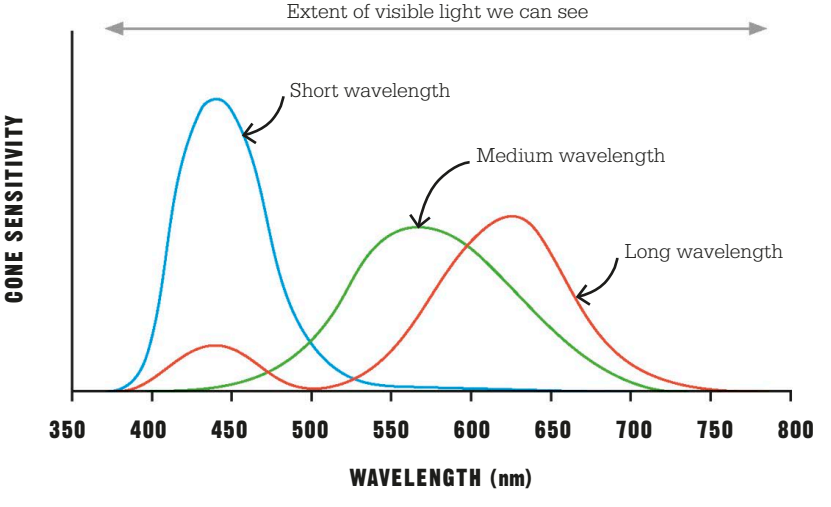
Animals' sensory receptors are the dendrites of sensory neurons, which are specialized for receiving specific stimuli. Neurons pass information to the brain, which then quickly organizes, prioritizes, analyzes, and responds to it. Photoreceptors in the eyes detect light, thermoreceptors and mechanoreceptors in the skin sense temperature and pressure changes, nociceptors throughout the body detect pain, and chemoreceptors in the nose and tongue sense dissolved chemicals. Sensors can also be classified as exteroceptors, which receive external stimuli; interoceptors, which detect stimuli from the visceral organs and blood vessels; and proprioceptors, which receive stimuli from skeletal muscles that inform body position.

The retina

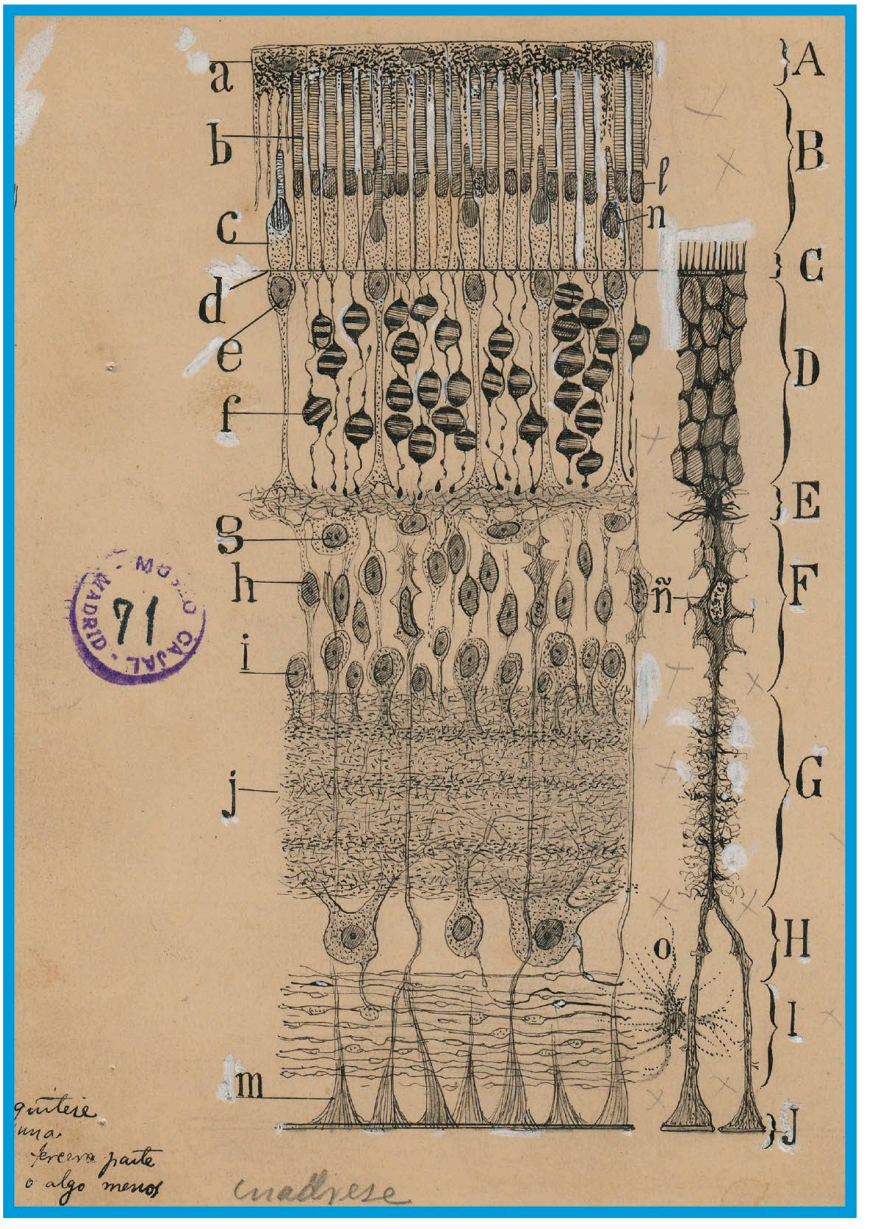
Spanish neuroanatomist Santiago Ramón y Cajal is often considered to be the father of modern neuroscience. He used his artistic talents and anatomical skills to produce detailed drawings of nerve cells, describing in the 1890s the complex, layered structure of the retina.

> Apprehension by the senses supplies, directly or indirectly, the material of all human knowledge.
>
> **Hermann von Helmholtz**
>
> ***The Recent Progress of the Theory of Vision*, 1868**

The retina is in fact part of the central nervous system. Roughly 0.5 mm thick, it lines the back of the eye, covering about 65 percent of its interior surface. The layer of the retina closest to the lens at the front of the eye consists of the ganglion cells, the nerve cells that



In 1850, Helmholtz developed Young's ideas to explain that three types of cones are each sensitive to different wavelengths of light—short (blue), medium (green), and long (red). In view of Helmholtz's contribution, the trichromatic theory was named the Young–Helmholtz theory.



This drawing by Ramón y Cajal shows the complexity of the structure of the retina. Ramón y Cajal defines the retina's various layers, including the rod and cone cells at the top of the picture.

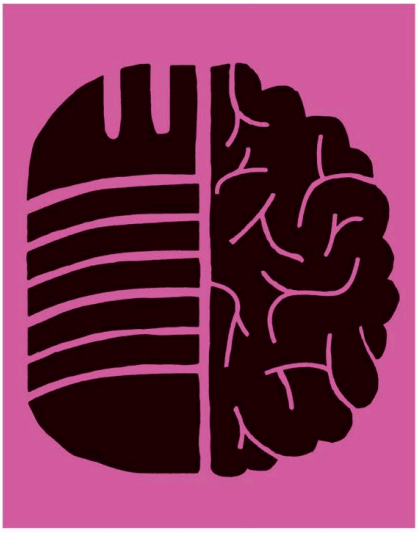
carry information from the eye to the brain via the optic nerve. The photosensors (the rods and cones) lie in the innermost layer of the retina against the pigment epithelium (cell layer) and choroid (tissue made up of blood vessels). This means that light entering the eye must first travel through almost the full thickness of the retina before striking and activating the rods and cones.

The most numerous of the photoreceptors are the rods: there are approximately 120 million on average in a human retina. The rods are around a thousand times more sensitive to light intensity than the cones, but not to color. They allow us to see in low light conditions and are also sensitive detectors of motion, especially in the peripheral vision, where the rods predominate over the cones.

Cones and color

As Thomas Young suspected and the research undertaken by Maxwell and von Helmholtz helped confirm, the colors we see are determined by the wavelengths of light that enters our eyes. Most humans are trichromats, which means that we have three types of color-sensitive cone cells in our eyes. There are about 6 or 7 million of these cone cells, which are mostly concentrated on the 0.3-mm fovea centralis, a small depression on the retina. Almost two-thirds of the cone cells in the retina respond most strongly to red light, about a third are most sensitive to green light, and just 2 percent respond best to blue light. When you look at an apple, various cones are stimulated to different degrees, sending a cascade of signals along the optic nerve to the visual cortex of the brain. Here, the information is processed, and your brain then decides whether the apple is red or green.

It is now known that not all vertebrate animals have the same number of types of retinal cones. While humans and other primates are trichromats, whales, dolphins, and seals are monochromats, with just one type of visual cone, and most other mammals are dichromats (with two types of cones). Some bird species—as well as a few exceptional humans—are tetrachromats, with four types of cones. ■



WE SPEAK WITH THE LEFT HEMISPHERE

SPEECH AND THE BRAIN

IN CONTEXT

KEY FIGURE
Paul Broca (1824–80)

BEFORE
1664 English doctor Thomas Willis publishes *Cerebri Anatome* (*Anatomy of the Brain*), assigning various human faculties to different parts of the brain.

1796 German anatomist Franz Joseph Gall describes his theory of phrenology—that personality traits are readable from the bulges of the skull.

AFTER
1874 Carl Wernicke relates certain neurological disorders to specific areas of the brain.

1909 German neurologist Korbinian Brodmann maps 52 regions of the cerebral cortex.

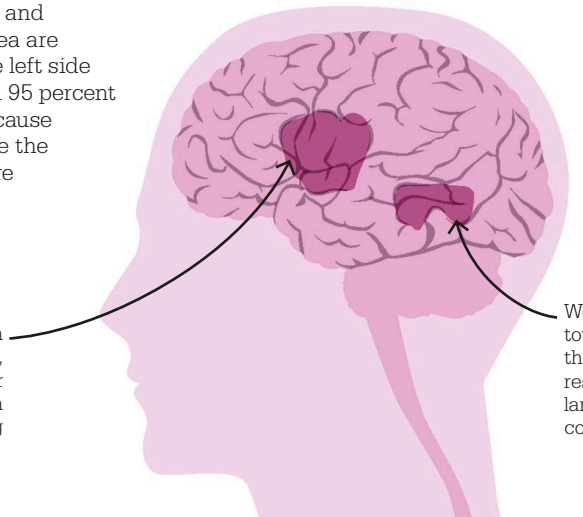
1981 American psychobiologist Roger Sperry wins the Nobel Prize in Physiology or Medicine for his work on hemispheric functional specialization.

For centuries, the study of the brain was ruled by the intuition that different parts of the organ were responsible for different faculties, such as emotion, intelligence, and speech. Although this assumption was later found to be broadly correct, for a long time it was based on guesswork. By the early 19th century, the dominant theory was phrenology, which mapped brain functions onto the skull and held that an individual's intellect, talents, and even vices could be determined by carefully measuring its shape. This idea gradually fell out of favor due to a lack of any clinical evidence. Then in 1861, French physician Paul Broca provided the first anatomical proof that brain function is indeed localized, when he discovered that a specific ability—the power of speech—is controlled by a specific part of the brain.

Broca's area

The region that Broca identified is located in the frontal lobe. Broca discovered it by studying two patients in his Paris hospital, both of whom had aphasia—problems with formulating language—as a result of serious neurological conditions. The first was Louis Victor Leborgne, a 51-year-old man

Broca's area and Wernicke's area are located on the left side of the brain in 95 percent of humans because in most people the left hemisphere is dominant.



See also: The brain controls behavior 109 ▪ Innate and learned behavior 118–23 ▪ Organization of the brain cortex 126–29 ▪ Memory storage 134–35

> The special nature of the symptom of aphemia [aphasia] did not depend on the nature of the illness, but only on its location.
> **Paul Broca, 1861**

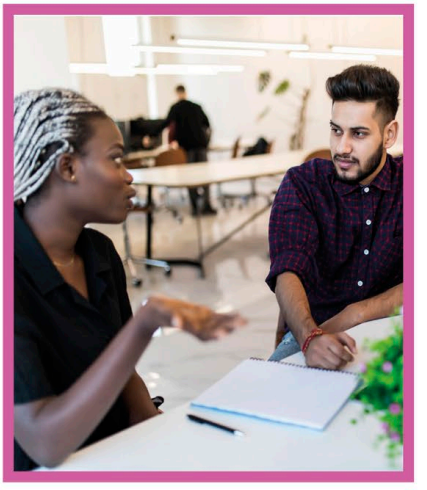
who had lost the ability to speak at the age of 30. All he could say was "tan," and he became known by that name. Tan was able to hear perfectly well and could make himself understood by varying his intonation and using hand signals, from which it seemed clear that his cognition was unaffected.

Tan had been physically deteriorating for several years, and he died just days after Broca met him. Broca performed an autopsy and found a lesion in Tan's brain in the region that is now called Broca's area.

Soon afterward, Broca met Lazare Lelong, an 84-year-old who had suffered a stroke. He could say only five words: "oui," "non," "trois," "toujours," and "lelo" (part of his name). After he died, Broca found that Lelong had damage in the same area of his brain as Tan. Today, both patients would be diagnosed with Broca's aphasia (or expressive aphasia), which is the inability to speak fluently. Sufferers can usually comprehend speech but can make only short, telegraphic utterances.

Wernicke's area

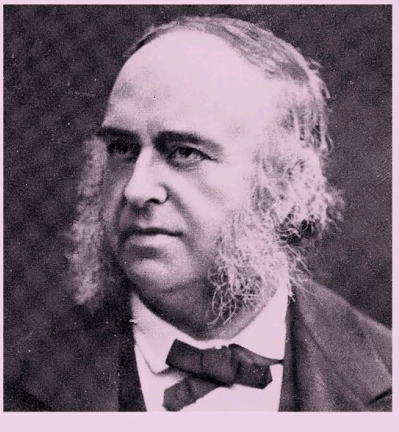
In 1874, German physician Carl Wernicke identified another speech center in the brain. Damage to this area causes Wernicke's aphasia (or receptive aphasia), characterized by "word salad": sufferers speak fluently but not in meaningful sentences. They are often unaware that they are not making sense and also have difficulty comprehending what is said to them.



Women tend to have smaller brains than men, due to their smaller body sizes, but they have bigger Broca's areas—in contrast to the sexist beliefs Paul Broca held at the time.

In the 1960s, it was discovered that each hemisphere of the brain experiences the world differently. While the left half is abstract and analytical, the right half is visual–spatial. In most people, language function is on the left, but in some it is on the right or is bilateral. ■

Paul Broca

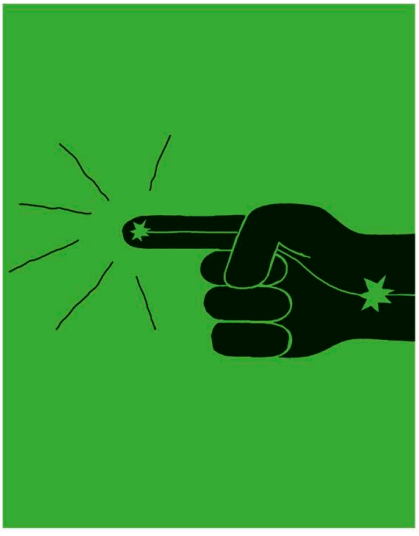


Born in 1824 in Sainte-Foy-le-Grande, near Bordeaux, Paul Broca was something of a prodigy in his youth, earning his bachelor's degree at the age of just 16 and qualifying as a doctor at 20. He had a distinguished medical career and was an influential figure in many medical societies. In addition to his work in neuroscience, he had a keen interest in anthropology and, in 1859, founded the Société d'Anthropologie de Paris.

Broca believed that different races were different species with different origins, and his interest in brains arose from his search for a link between intelligence, place of origin, and skull size. Without his anthropology work, he would not have met the patients who led to his most famous discovery, but it is important to recognize the contemporary sexist and racist assumptions involved. Broca later served in the French senate, and he died in 1880.

Key work

1861 "Remarks on the Seat of the Faculty of Articulated Language, Following an Observation of Aphemia (Loss of Speech)"



THE SPARK EXCITES THE ACTION OF THE NERVO-MUSCULAR FORCE

ELECTRIC NERVE IMPULSES

IN CONTEXT

KEY FIGURE
Emil du Bois-Reymond (1818–96)

BEFORE
1791 Italian physician and physicist Luigi Galvani finds that an electric current stimulates muscle contractions.

1830 Carlo Matteucci shows that cell membranes have a potential difference between the inside and outside.

1837 Czech researcher Jan Evangelista Purkinje identifies the first nerve cells.

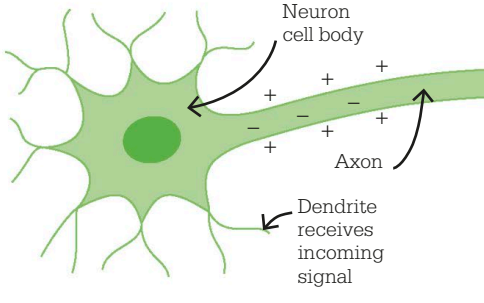
AFTER
1862 French neurologist Duchenne de Boulogne is able to control facial expressions of test subjects by applying electrodes to nerves.

1952 Andrew Huxley, Alan Hodgkin, and British physician Bernard Katz publish findings on the chemical process that creates the action potential.

The nervous system is a network of billions of long nerve cells, or neurons, that permeates every part of the body. Signals are constantly sent and received along and between these neurons. The signals that pass along a single neuron do so as pulses of electric charge—the "action potential." Once triggered, the all-or-nothing response—it occurs fully or not at all—surges along the neuron from its dendrites and along its axon. This phenomenon was discovered by German physiologist Emil du Bois-Reymond in the late 1840s.

> The zoologist is delighted by the differences between animals, whereas the physiologist would like all animals to work in fundamentally the same way.
>
> **Alan Hodgkin**
> ***Chance and Design*, 1992**

Du Bois-Reymond was a founding figure in electrophysiology, which is a broader field concerned with the electric properties of biological tissues and the measurement of such electric flow. The field has its origins in electromagnetism—a branch of physics that emerged in 1820, when it was observed that electricity and magnetism were aspects of the same physical force. One result of that realization was the invention of the galvanometer, a device that uses magnets to measure the presence and strength of an electric current.



The action potential is a pulse of positive charge flowing along a nerve cell. It stimulates voltage-gated channels to open, allowing sodium ions (Na^+) into the next section of the nerve. After a millisecond, these gates close and others open, pushing out potassium ions (K^+).

See also: Excitable tissues 108 ▪ Nerve cells 124–25 ▪ Synapses 130–31 ▪ Muscle contraction 132–33

Early research in electrophysiology was carried out by Italian physicist Carlo Matteucci, who used a galvanometer to show that living tissue is electrically active. He then created a voltage detector—which measures the electric potential difference across two points—a frog's leg muscle and its sciatic nerve. The muscle twitched when exposed to an electric charge.

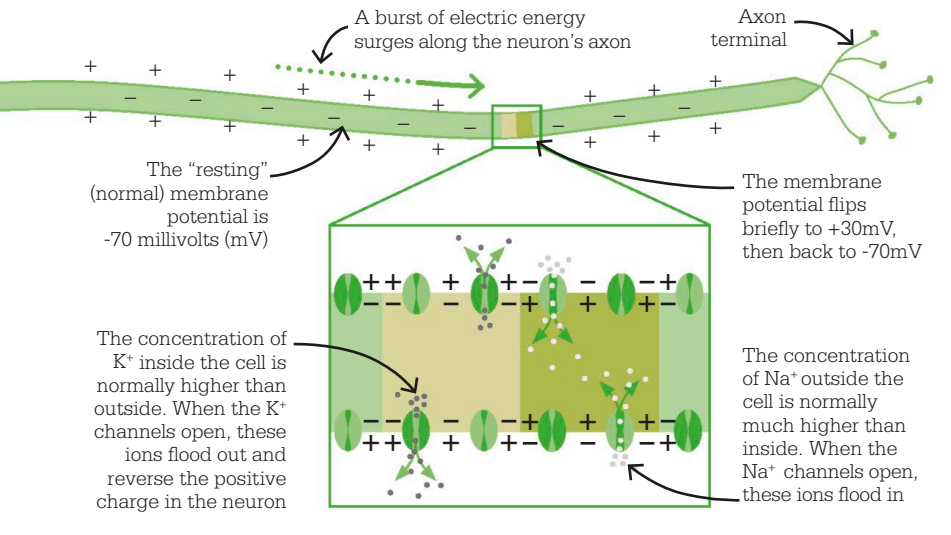
Membrane potential

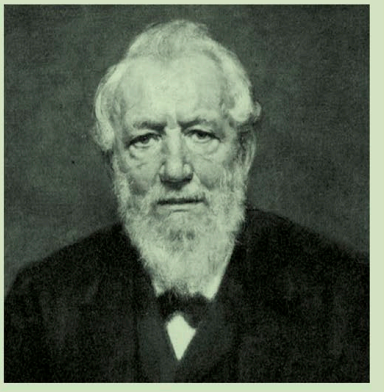
Du Bois-Reymond replicated Matteucci's "frog electroscope" and found that while the charge in the nerve went up when electrified, it dropped when the charge in the muscle increased. He interpreted this as evidence of a pulse of charge moving along the nerve, and suggested that living tissue might be made up of "electric molecules."

A former student of du Bois-Reymond, Julius Bernstein hypothesized in 1902 that the mechanism of this electric pulse was a change in the concentration of positively charged sodium and potassium ions (Na^+ and K^+) across the membranes of nerve cells. However, it was not possible at the time to measure such tiny and fleeting electric effects.

In the 1940s, with the benefit of microelectrode recording methods, British physiologists Alan Hodgkin and Andrew Huxley confirmed Bernstein's hypothesis. Using the giant neurons of squid—thick enough to measure voltage across the membrane—they found that the cell in its resting state maintains a delicate balance of charged particles, resulting in a negative charge inside relative to outside the cell. This difference in charge—polarization—is the membrane potential.

When electrically stimulated, the cell membrane opens pores (voltage-gated channels) that allow sodium ions to flood inside, causing the cell to depolarize. The interior charge flips briefly to positive, which stimulates adjacent Na^+ channels to open, too—creating a surge of current along the nerve. The Na^+ pores then close and K^+ pores open, releasing potassium ions and restoring the membrane potential. ■





Emil du Bois-Reymond

Born in Berlin in 1818, Emil du Bois-Reymond was educated at the French college in the city and then studied medicine at the University of Berlin. His talents were recognized by anatomy and physiology professor Johannes Peter Müller, who made the young undergraduate his assistant.

Müller introduced his protégé to the publications of Carlo Matteucci on electric phenomena in animals. Du Bois-Reymond was inspired and chose "Electric Fishes" for his graduation thesis—the start of a long career in bioelectricity.

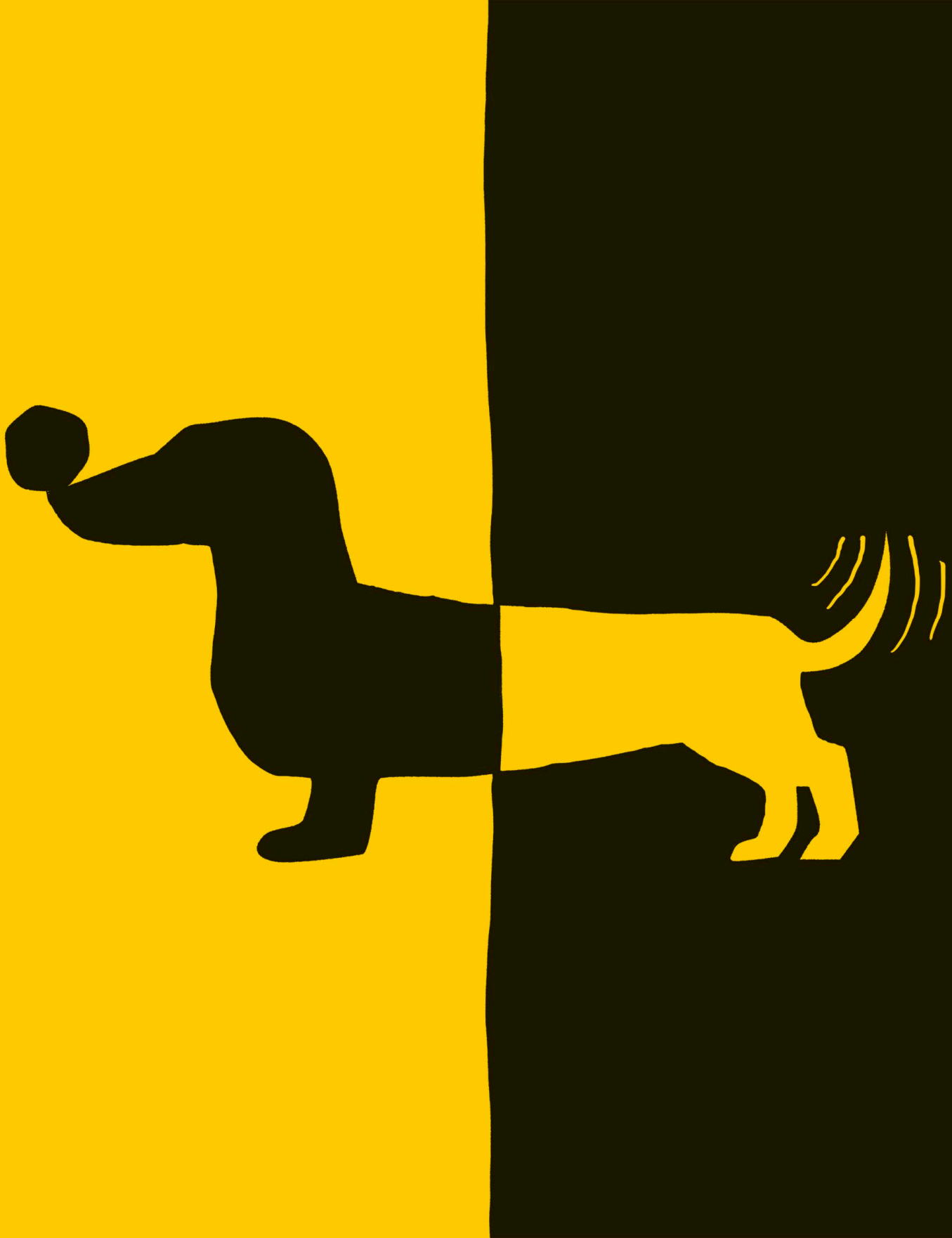
In 1858, du Bois-Reymond became professor of physiology at Berlin, and in 1867 he was appointed secretary of the Academy of Sciences of Berlin. Ever philosophical, in a speech to the academy in 1880, he set out seven "world riddles," conundrums to be tackled by science, some of which—such as the question of free will—remain unanswered today. Du Bois-Reymond died in 1896 in the city of his birth.

Key work

1848/84 *Investigations into Animal Electricity*

INSTINCT AND LEARNING GO HAND IN HAND

INNATE AND LEARNED BEHAVIOR



IN CONTEXT

KEY FIGURE
Douglas Spalding (1841–77)

BEFORE
4th century BCE Aristotle describes detailed observations of the behavior of animals.

13th century CE Albertus Magnus carries out studies of animals based on their abilities and behavior.

AFTER
1927 Ivan Pavlov publishes his discovery of the conditioned reflex in dogs.

1975 E.O. Wilson's book *Sociobiology* prompts an interest in the study of social, rather than individual, aspects of behavior.

2004 American ornithologist Peter Marler researches birdsong and discovers that some features of it are innate, while others are learned.

Weaverbirds build complex nests. Researchers have discovered that older birds refine their technique, showing that this is a combination of learned and innate behavior.

Knowing how an animal was likely to react would have been invaluable to prehistoric humans who were hunting or trying to avoid becoming prey themselves. Later, in the 4th century BCE, Aristotle was one of the first people to set down his observations on all aspects of animal life, including their habits, but for millennia there was little effort to approach animal behavior in a scientific fashion.

One person who attempted to do so was 13th-century German philosopher Albertus Magnus, who studied both the physiology and psychology of animals. He recorded his findings in the 26-volume *De Animalibus* (*On Animals*). He argued that whereas some animals, such as dogs, had outstanding memories and could learn and engage in simple forms of reasoning, others, such as flies, had no memory and never learned.

Recording behavior

John Ray, an English naturalist, was one of the first to discuss the idea of animal behavior as something that was innate. In 1691, he wrote about the instinctive behavior of birds, describing their ability to build a nest in such a way that "one can know with certainty to which type of bird it belongs." A bird could construct a nest, Ray said, even if it had never seen one being built as a chick.

French naturalist Georges Leroy wrote one of the first books that was specifically about animal behavior. In his *Lettres sur les Animaux* (1768), he discussed the development of wolves, foxes, and deer in their natural surroundings. He saw sensory experience and intelligence as the driving forces behind the behavior that aimed to satisfy instinctive needs such as hunger and thirst.

Best known for his theory of evolution by natural selection, Charles Darwin was one of the 19th

Charles Darwin identified instinctive and learned behaviors in his first child William, whom he monitored closely from a newborn to the age of five.

See also: The brain controls behavior 109 ▪ Memory storage 134–35 ▪ Animals and tools 136–37 ▪ Pollination 180–83 ▪ The laws of inheritance 208–15 ▪ Life evolves 256–57 ▪ Natural selection 258–63

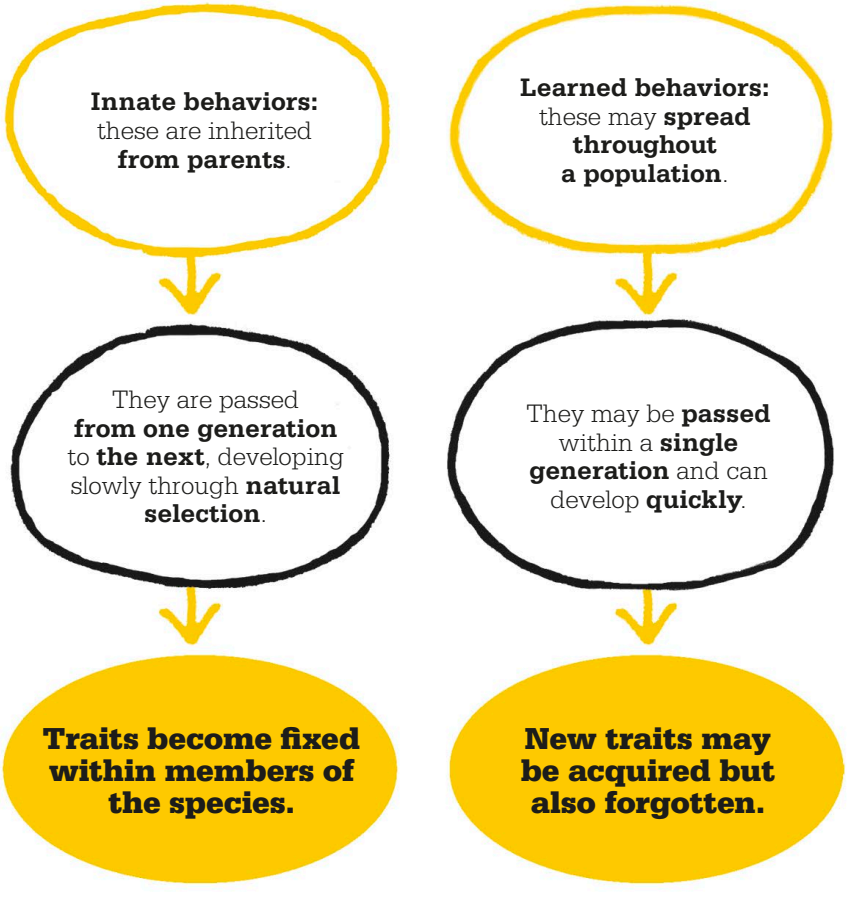
century's most prominent animal behaviorists. In addition to devoting a chapter of *On the Origin of Species* (1859) to instinct, he also published *The Expression of the Emotions in Man and Animals* in 1872. He was particularly interested in the behavior of domestic animals and how it relates to their wild forebears. Darwin also made a close study of the behavioral development of his own infant son, publishing the findings in the paper "Biographical Sketch of an Infant" in 1877.

A natural history approach

One of Darwin's contemporaries was the largely self-educated British biologist Douglas Spalding. Both Spalding and Darwin studied behavioral responses in a natural environment rather than in a laboratory setting. Spalding studied what came to be known as imprinting but what he called "stamping in." This is a behavioral characteristic by which a very young animal instinctively latches onto the first moving object it encounters, generally its mother.

Imprinting must occur within a certain critical period: if the mother is absent for any reason, imprinting will not take place. Spalding reared chicks in darkness for the first three days of their lives, noting that when they were exposed to light, they followed his hand—the first moving thing they saw. He believed that this behavior had to be innate as it clearly could not have been acquired through previous experience.

While Spalding was convinced that instinct was innate and inherited, he also believed it to be linked to learning, with one being guided by the other. He published his observations of imprinting »



Douglas Spalding

Born in London in 1841, Douglas Spalding relocated with his family to Scotland when he was young. He worked for a while as a roof slater, but academic Alexander Bain persuaded Aberdeen University to allow him to attend courses there without having to pay. Spalding moved back to London to train as a lawyer but contracted tuberculosis and traveled in southern Europe in the hope of finding a cure. Fascinated by animal behavior, he was one of the first people to show how learning and instinct worked together to determine behavior, and the first to describe the phenomenon of imprinting. Recognition of his work led to his appointment as a reviewer on the journal *Nature*, a position he held until his early death from tuberculosis in 1877.

Key work

1873 "Instinct: With Original Observations on Young Animals"

and instinctive feeding behavior in ducklings and chickens in 1873. Darwin read it and recommended it as "an admirable article."

The idea of imprinting was advanced about 40 years later by German biologist Oskar Heinroth who, while unaware of Spalding's earlier experiments, observed the same phenomenon in waterfowl. He called it *Prägung*, meaning "stamping," practically mirroring Spalding's term. Heinroth also demonstrated, at least for the species he studied, that imprinting was to the species and not to the individual, so a gosling imprinted to a human would treat all humans as if they were members of its species. Heinroth was also the first biologist to use the term ethology for the study of animal behavior.

Self-conditioning

One of Heinroth's pupils was Konrad Lorenz, an Austrian who became a seminal figure in the study of animal behavior. As a young man, Lorenz kept jackdaws and other birds, and he corresponded with Heinroth about his observations of the birds' behavior. In 1932, he published a paper setting out his view that the jackdaws solved problems by "self-conditioning," which is a kind of trial-and-error process.

Taking the investigation of imprinting further, Lorenz said it was the process that allowed a duck or goose, for example, to recognize its own species and develop appropriate mating behavior. One of his more extraordinary findings was that some geese that had imprinted on babies' strollers as goslings later attempted to mate with them in a Vienna park.

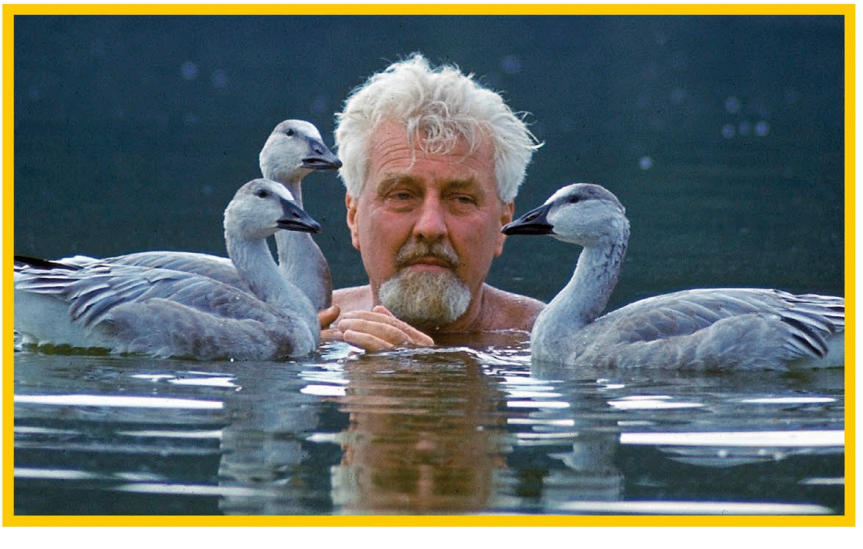
Lorenz held that all behavior could be divided into that learned through experience and that which was innate or instinctive. Instincts, according to Lorenz, are expressed in what he called "fixed action patterns," which are triggered by specific stimuli. Examples include a female stickleback fish's courtship behavior, prompted by the sight of a breeding male's red belly, and a goose that will roll an egg back into her nest if she sees it outside. These patterns of behavior are innate, and they will even be performed by animals encountering the triggering stimuli for the first time. Instincts arise through a process of natural selection acting on behavior and are inherited from the animals' parents. For example, wolves that hunt in packs are more likely to make kills and live longer. So, pack-hunting wolves are more likely than lone hunters to pass their genes to their offspring, and over many generations, pack-hunting behavior has become an inherited characteristic of wolves.

> "[The] connection between the external agent and the response [is] an unconditioned reflex …"
> **Ivan Pavlov**

Stimuli and behavior

Lorenz developed many of his ideas while working with Dutch biologist Nikolaas Tinbergen, another key name in 20th-century ethology. The pair carried out experiments with "supernormal stimuli," exaggerating certain stimuli to produce more intense responses than natural ones. Tinbergen discovered, for example, that birds would brood dummy eggs on which markings of spots and color had been emphasized in preference to natural eggs.

Along with Austrian ethologist Karl von Frisch, Tinbergen and Lorenz were jointly awarded the 1973 Nobel Prize in Physiology or



Konrad Lorenz conducted imprinting experiments with geese. If he was the first moving object a newly hatched gosling saw, the gosling would continue to follow him as if he were its mother.

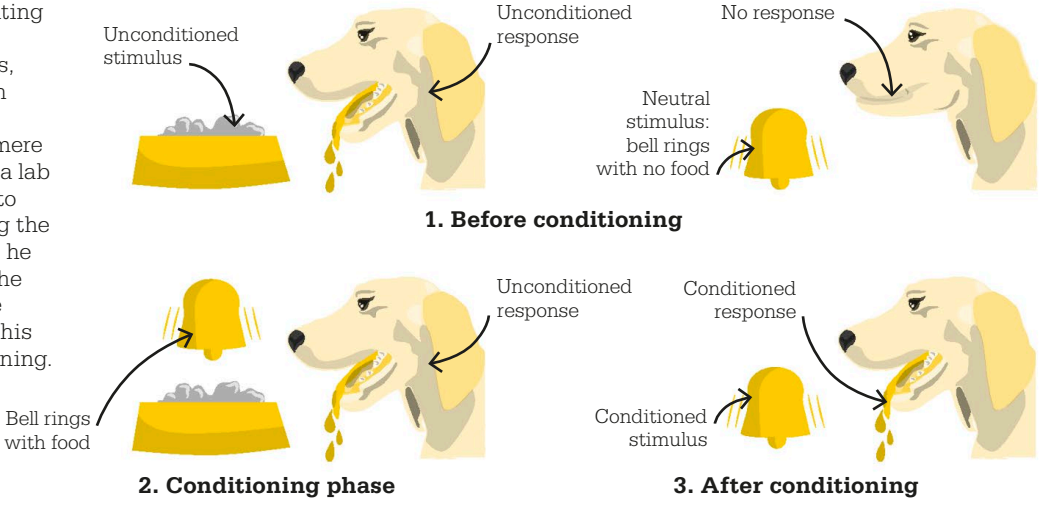
> Even insects express anger, terror, jealousy, and love.
> **Charles Darwin**

Medicine for their studies. Von Frisch is perhaps best known for his work with bees. In 1919, he had demonstrated that bees can be trained to distinguish between various tastes and odors. Even more remarkably, he found that they communicate the distance and direction of a food supply to other members of the colony by dancing. A bee that has found a source of nectar performs a "round dance," which stimulates other bees to circle around the hive searching for the nectar source. If the source is more than about 165 ft (50 m) from the hive, the returning bee performs a "waggle dance" instead, repeatedly running forward a short distance and wagging her abdomen. The direction of her waggle run informs the hive bees about the direction of the nectar source relative to the position of the Sun.

In his 1963 paper, "On Aims and Methods of Ethology," Tinbergen set out four questions: What stimuli produce the behavior? How does the behavior contribute to the animal's success? How does the behavior develop over the course of the animal's life? How did the behavior first arise in the species? Tinbergen believed that answering these questions was necessary to understanding any behavior fully. In recent decades, much more has been learned about innate and learned behaviors, and it is now recognized that many behaviors are actually a combination of both. ■

Bees' waggle dance informs other members of the hive where to find pollen and nectar. Bees adopt this behavior without being taught.

While studying how eating stimulated salivary and gastric secretions in dogs, Russian physiologist Ivan Pavlov noticed that they began to salivate at the mere appearance of anyone in a lab coat who they expected to feed them. By associating the sound of a bell with food, he showed that eventually the dog would salivate to the sound of the bell alone. This is an example of conditioning.



CELLS WITH DELICATE AND ELEGANT SHAPES

NERVE CELLS

IN CONTEXT

KEY FIGURE
Santiago Ramón y Cajal (1852–1934)

BEFORE
Early 10th century Persian physician al-Razi describes seven cranial nerves and 31 spinal nerves in his medical encyclopedia *Kitab al-Hawi*.

1664 Dutch microscopist Jan Swammerdam causes frog muscle contraction by the mechanical stimulation of a nerve.

1792 Italian naturalist Giovanni Fabbroni suggests that nerve action involves both chemical and physical factors.

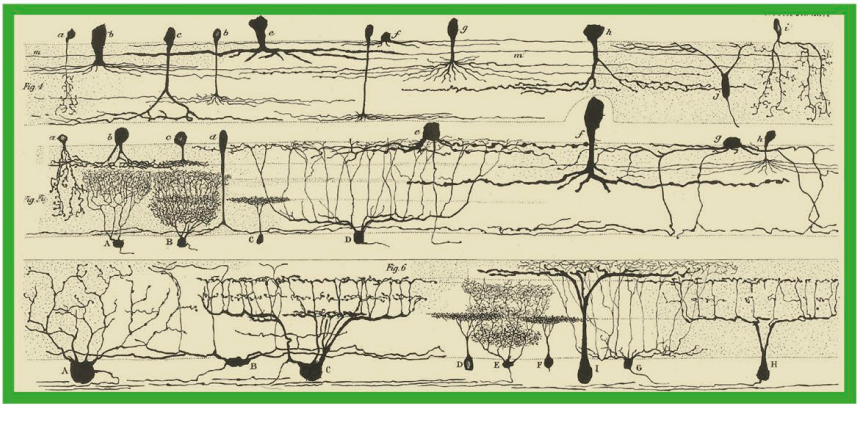
1839 Theodor Schwann proposes the cell theory.

AFTER
1929 American physiologists Joseph Erlanger and Herbert Spencer Gasser show that nerves work with a single electrical signal.

The nervous system is a network of fiberlike cells spreading from the brain and spine to every corner of the body. But they are so hard to see that when German physiologist Theodor Schwann proposed the cell theory in 1839—the idea that the entire body is made of tiny cells—nerves were thought to be exceptions. It took a breakthrough in microscope technique by Italian biologist Camillo Golgi and then studies by Spanish neuroscientist Santiago Ramón y Cajal to show that nerves are indeed a special kind of cell—the neuron.

To 19th-century microbiologists, nerves looked like spiders with countless spindly legs they called processes. Nerves seemed more like electric wires linking cells than cells themselves. However, in 1873, Golgi found he could use potassium dichromate and silver nitrate to stain nerves an inky black, which made them show up clearly under a microscope. Golgi saw that the processes consisted of a single long tail and spindly branches that spread from the main cell body.

Fourteen years later, Ramón y Cajal began using an improved version of Golgi's stain to make



Meticulous drawings—made by Santiago Ramón y Cajal as part of his groundbreaking microscopic studies—show that he saw neurons from animal retinas as individual cells.

See also: Excitable tissues 108 ▪ Electrical nerve impulses 116–17 ▪ Synapses 130–31 ▪ Muscle contraction 132–33

Dendrites for sensory neurons are on the side of the **nerve cell body** nearest the **sense receptors**.

Axons for sensory neurons are on the side of the **nerve cell** leading to the **central nervous system**.

In **motor neurons**, the axons and dendrites are **reversed**.

Nerve signals must flow one way only, from dendrite to axon.

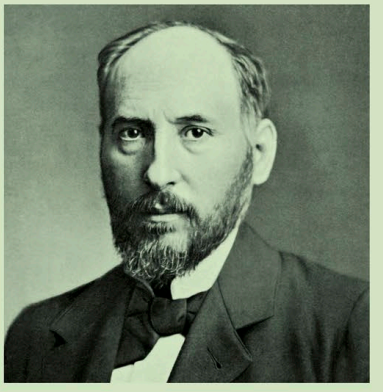
detailed sketches of nerve cells, and he realized there were gaps between the processes of each nerve, convincing him that the nervous system is made up of discrete individual cells, or neurons. The long tail of a neuron became known as an axon, and the branching threads were named dendrites.

Relay race between cells

Ramón y Cajal believed nerve signals were passed from neuron to neuron as in a relay race. He identified cone structures on the end of each axon that he thought transmitted signals across a small gap, later called a synapse. Ramón y Cajal also noticed that neurons linking to sensory receptors such as those on the skin are wired the opposite way to those linking to muscles. Sensory neurons had axons pointing inward and dendrites extending outward, while axons on neurons that make muscles move (motor neurons) point the other way.

In conclusion, Ramón y Cajal proposed that neurons must carry signals in one direction only, taking messages in through the dendrites and transmitting them through the axon. He realized that signals travel along particular pathways and that it might be possible to trace their paths through the nervous system.

From the 1930s onward, it was discovered how sensory inputs from the body are wired into particular parts of the brain. Scientists also discovered the combination of chemistry and electricity that sends signals through the cells and an array of chemicals that transmit signals across synapses, called neurotransmitters. We now have a detailed picture of the physical structure of nerves, even if we do not fully understand how they make the brain work. ■



Santiago Ramón y Cajal

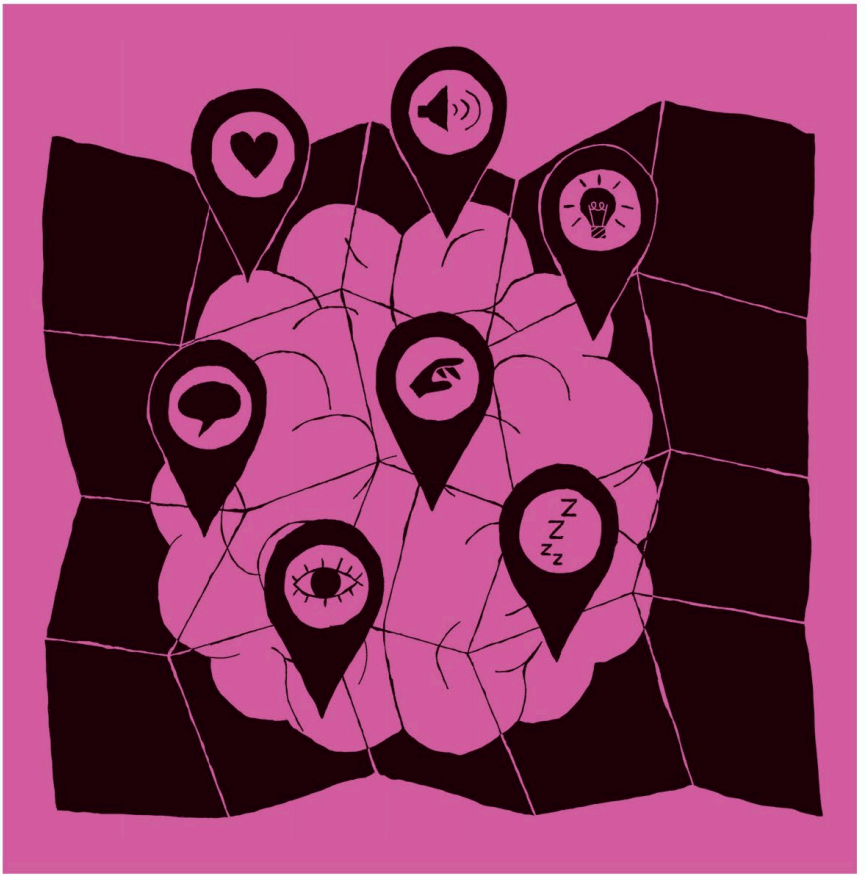
Born in 1852 at Petilla de Aragón in Spain, Santiago Ramón y Cajal was persuaded by his father to study medicine and served as an army doctor in Cuba. Returning to Spain, he received his doctorate in medicine in 1877 and worked as a director of Zaragoza Museum and at the University of Zaragoza before being appointed professor of anatomy at the University of Valencia. Ramón y Cajal moved to Barcelona in 1887, where he made key discoveries about the nervous system. In 1899, he was made head of the National Institute of Hygiene. He shared the 1906 Nobel Prize in Physiology or Medicine with Camillo Golgi for their work on the nervous system. He continued his research into the nervous system until his death in 1934.

Key works

1889 *Manual of Normal Histology and Micrographic Technique*
1894 *New Ideas on the Fine Anatomy of the Nerve Centres*
1897–99 *Textbook on the Nervous System of Man and the Vertebrates*

BRAIN MAPS OF MAN

ORGANIZATION OF THE BRAIN CORTEX



IN CONTEXT

KEY FIGURE
Korbinian Brodmann
(1868–1918)

BEFORE
1837 Czech physiologist Jan Purkinje is the first to describe a type of neuron; Purkinje cells are located in the hindbrain.

1861 Paul Broca identifies a part of the brain corresponding to a specific function—the production of speech.

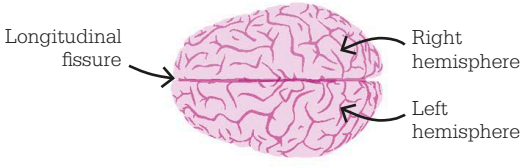
AFTER
1929 American psychologists Karl Lashley and Shepherd Franz show the brain's equipotentiality, when healthy parts of the brain take on the roles of damaged areas.

1996 Functional magnetic resonance imaging (fMRI) allows researchers to watch the brain in action, helping link cognitive activity to specific areas of the brain.

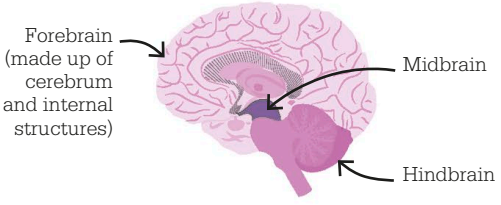
The vertebrate brain—the organ seen in everything from fish to humans—is composed of three sections: the forebrain, midbrain, and hindbrain. The hindbrain and midbrain are the most primitive structures; we know this because they are the dominant parts of brains that evolved long ago, and they are devoted to fundamental functions such as breathing. The forebrain is associated with more advanced and cognitive roles, such as intelligence. The human forebrain makes up 90 percent of the whole organ, and animals understood to have advanced abilities, such as other primates and dolphins,

See also: The brain controls behaviour 109 ▪ Speech and the brain 114–15 ▪ Memory storage 134–35

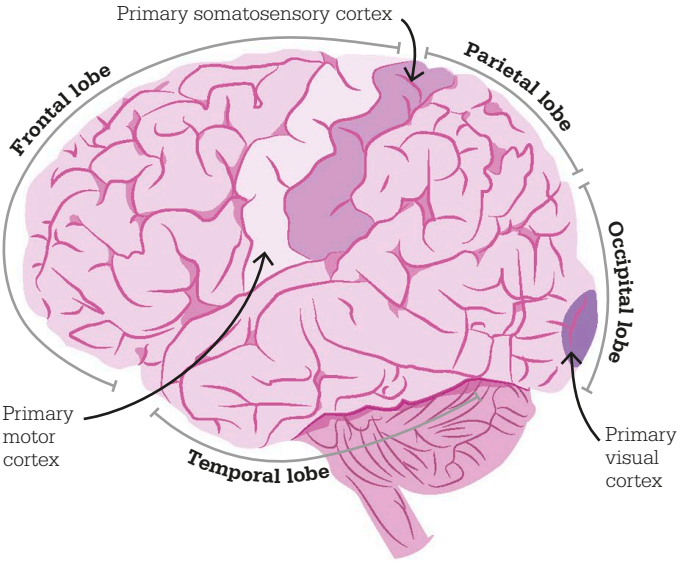
The largest part of the brain is the cerebrum, which is divided into two hemispheres. Its outer layer is the cerebral cortex, which has four lobes, each with different functions.



The cerebrum



The forebrain, midbrain, and hindbrain



The four lobes of the cerebral cortex

also have large forebrains. In the early 20th century, German neurologist Korbinian Brodmann created the first detailed functional map of the most highly developed part of the forebrain, which is the cerebral cortex.

White and gray matter

By volume, the forebrain is mostly white matter—bundles of neural pathways that appear white because the nerves are sheathed in a layer of fat called myelin. Myelin works much like the insulating plastic around an electric wire and allows nerve signals to travel faster over longer distances. The white matter connects to the midbrain and beyond, as well as carrying signals between regions of the forebrain. The forebrain contains the entire cerebrum—the largest part of the brain—as well as deeper structures, such as the thalamus, hypothalamus, pineal gland, and limbic system.

The outer layer of the cerebrum is the cerebral cortex. This is gray matter; the nerve cells (neurons) here are more densely packed and do not have myelin sheaths, hence appear gray. The cerebral cortex is where advanced cognitive functions such as thought, memory, speech, and imagination are processed, and all this takes place in a mass of gray matter about 0.1 in (2.5 mm) deep. The cortical neurons extend down from the surface to different depths depending on which part of the brain they connect to. The deeper layers connect to the hindbrain »

The **human brain** has a **large forebrain** and an extensive folded surface layer called the **cerebral cortex**.

The **cortex** comprises many **distinct networks of nerve fibers**, connected to each other.

These distinct cortical areas are closely associated with specific functions, such as speech and voluntary motor control.

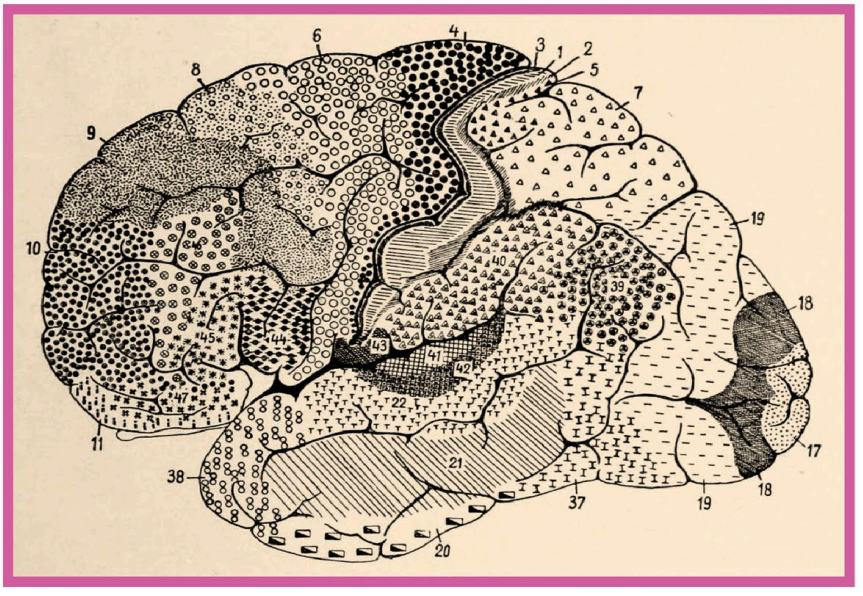
Motor, sensory, and visual cortices

By the 1870s, it was understood that muscle movements could be stimulated by applying electric currents to different parts of the cerebral cortex. In the 1880s, Scottish neurologist David Ferrier found by means of animal vivisections that voluntary movements were mediated through a band of the frontal lobe at the boundary with the parietal lobe, later identified as Brodmann area 4. Further research showed that body parts are mapped to areas of this primary motor cortex—the control of the toes, for example, located deep in the longitudinal fissure between the hemispheres.

The primary somatosensory cortex, in the parietal lobe (Brodmann areas 1, 2, and 3) processes sensory information such as touch and pain, while the primary visual cortex (Brodmann area 17) interprets information from the retinas. In each case, the left cortex relates to the right side of the body, and the right cortex to the left.

and the thalamus (the forebrain's junction box, linked to the central nervous system). The neurons that connect with intervening layers send and receive signals from elsewhere in the cortex.

This vertical layering means that the processing power of the cerebral cortex is limited by surface area, so to increase that area, the cortex of humans and most mammals is highly folded. The surface features of the cortex are marked out by deep grooves, called sulci, and ridges, which are the gyri. The deepest sulci mark the boundaries between the four cortical lobes, which are named after the cranial bones that they sit beneath: frontal, temporal, parietal, and occipital. Additionally, the cerebrum is divided into left and right hemispheres, which broadly mirror each other. The two hemispheres communicate via a thick bundle of white matter called the corpus callosum.



This diagram by Brodmann of the lateral (side) view of the human brain shows many of his numbered areas. The areas were defined by their cellular structure and arrangement in layers.

Today, it is widely understood that the frontal lobe of the cortex is associated with memory, the occipital lobe controls vision, and the temporal lobe is the center of language. This idea of functional zoning is broadly true, but the various zones also work closely with each other.

Mapping the functional zones was largely a matter of guesswork until the 1860s, when French surgeon Paul Broca found a region in the frontal lobe that controlled the physical articulation of speech. During autopsies, he identified what is now called Broca's area in the damaged brains of patients who could not speak. Observations of brain damage have also helped pinpoint other functional areas.

Joined or separate?

In the late 19th century, a debate between two giants of neuroscience about how the neurons of the brain were connected was resolved. Italian pathologist Camillo Golgi had argued that the brain was made of a continuous "nerve net," with every part connected by some route to every other part, while Spanish physician Santiago Ramón y Cajal declared that there was no physical connection between the cells.

These opposing views mirrored the men's political positions. Golgi, who was a young man during the unification of Italy, was tied to the idea of the brain being organized in a federation of units, just as the Kingdom of Italy grew from smaller fiefdoms. Ramón y Cajal's politics were focused on the power of the individual. He referred to a neuron

> The specific … differentiation of the cortical areas proves irrefutably their specific functional differentiation.
> **Korbinian Brodmann**

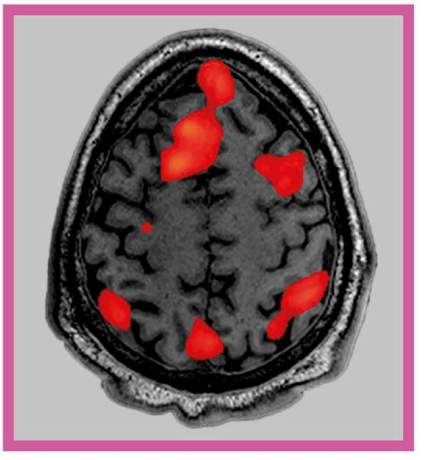
as an "autonomous canton," a self-governing unit that chose when and how to work with its neighbors.

In the 1870s, Golgi discovered "the black reaction"—a means of dyeing neurons so that their ultrafine filaments stood out against the surrounding mass of cells. Fourteen years later, Ramón y Cajal, using the black reaction with a more powerful microscope and better microtome (a device that cuts matter into slices a few cells thick), could see that the neurons were separated by a minute gap, or synapse. This suggested that the brain is constructed of discrete circuits of nerve isolated from those around them. Several researchers, among them Korbinian Brodmann, began to map out the discrete areas of the cerebral cortex.

Organizational map

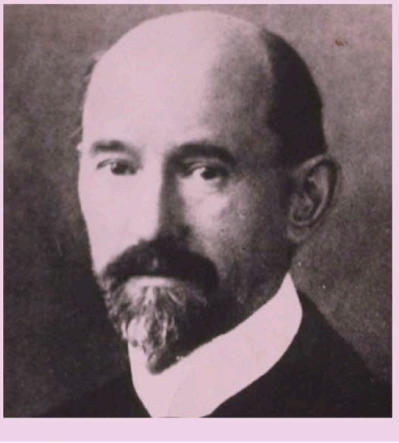
Brodmann used dyes that showed sites of protein manufacture in cells, which was ideal to highlight the tangle of slender nerve fibers against the background. He was able to identify 52 areas of the cortex where the cells formed distinct physical networks. Using tissue from the brains of macaque monkeys as well as from human brains, he found few differences in their organization. Some of the areas, called Brodmann areas, were already familiar—areas 44 and 45 matched Broca's area, for example. Brodmann's organizational map—and others like it—meant that neuroscientists could begin linking functions with cortical locations. It continues to guide the study of neuroscience even today.

Since the 1970s, safe medical imaging techniques have enabled neuroscientists to get an ever-closer view of the living brain in action. The main tool now available is the fMRI (functional magnetic resonance imaging) machine. This excites hydrogen atoms with a powerful magnet and then pinpoints their location with radio waves, scanning it in fine cross-sectional slices to build up a detailed image of the brain. In addition to its use in assessing brain damage, fMRI is valuable in psychological research, such as in the analysis of learning processes: by having test subjects perform mental tasks, neurologists can monitor the associated activity that occurs in the brain. ■



The red areas in this fMRI scan, seen from above, show parts of the brain at work while the subject is undertaking tasks using memory.

Korbinian Brodmann

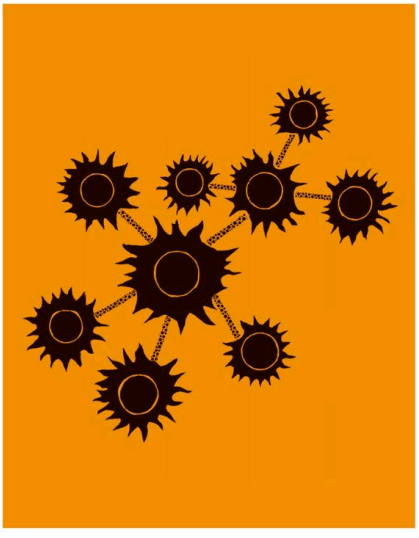


Born in 1868 in southern Germany, Brodmann studied medicine in several institutions across the country and qualified as a doctor at the age of 27. Following a short period in general practice, in his early 30s, he began to specialize in psychiatry and neurology, which brought him into contact with Alois Alzheimer (who identified the dementia that took his name). Alzheimer encouraged him to pursue research into the brain, and in 1909 Brodmann produced his map of the cerebral cortex while working at a private research institute in Berlin. The institute was run by neurologists Oskar and Cécile Vogt, who created a similar map.

Brodmann became a professor at the University of Tübingen in 1910 and maintained a role at the university psychiatric clinic. He later returned to full clinical practice, in Halle, then Munich. In 1918, soon after his move to Munich, he died from pneumonia.

Key work

1909 *Localization in the Cerebral Cortex*



THE IMPULSE WITHIN THE NERVE LIBERATES CHEMICAL SUBSTANCES

SYNAPSES

IN CONTEXT

KEY FIGURE
Otto Loewi (1873–1961)

BEFORE
1839 Czech anatomist Jan Evangelista Purkinje discovers nerve cells in the cerebellum, later named Purkinje cells.

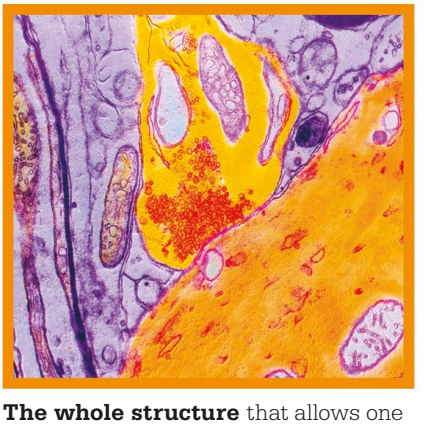
1880 Santiago Ramón y Cajal shows that electric signals always flow through nerves in one direction and later suggests there are gaps between cells.

1897 Charles Sherrington coins the term "synapse" for the then mysterious "surface of separation" between communicating neurons.

AFTER
1952 Australian physiologist John Eccles finds the excitatory postsynaptic potential that starts an action potential moving through a nerve.

Present More than 200 neurotransmitters have been identified in humans, but the total number is still unknown.

While nerve signals travel along cells as electric pulses, they travel between cells as chemical messages. This fact was proven in 1921 by German-American pharmacologist Otto Loewi, who was responsible for the discovery of these chemicals, now known as neurotransmitters. The search for the precise form of communication between neurons had begun more than 30 years earlier, when Spanish physician Santiago Ramón y Cajal proposed that there is no physical connection between one neuron and the next.



The whole structure that allows one (presynaptic) neuron to pass a chemical signal to another (postsynaptic) neuron is the synapse. The gap between the two is called a synaptic cleft.

Instead, there is a gap between neighboring cells, across which the cells must communicate. In 1897, British neurophysiologist Charles Sherrington named this gap, or "surface of separation," the synapse, meaning "clasp together." He and British electrophysiologist Edgar Adrian shared the 1932 Nobel Prize in Physiology or Medicine for their 1920s work on the nervous system.

Thanks to the advent of the electron microscope, the synapse's minuscule 40-nanometer width was finally imaged in 1953, long after Loewi and others had figured out how the synapse worked.

Connection rules

Ramón y Cajal showed that electric signals always move in the same direction through cells. The signal travels away from the central cell body along the cell's single axon, generally the longest and thickest filament. The tip of the axon may branch into several terminals, each one associated with a different neighboring cell. Across the synapse from an axon terminal is a dendrite (a threadlike extension of a nerve cell) of the next neuron. Most neurons have several dendrites that in turn carry several nerve

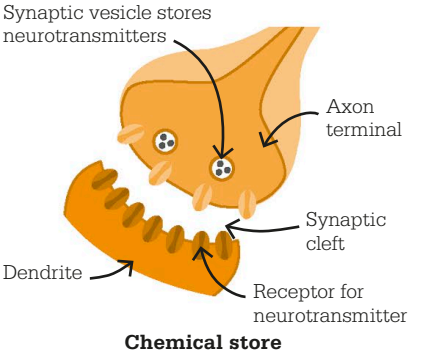
See also: Electric nerve impulses 116–17 ▪ Nerve cells 124–25 ▪ Organization of the brain cortex 126–29

signals into the cell body, where they either stimulate or inhibit an electric signal that is transmitted down the axon to the next set of synapses, and so on. This was well understood by neuroscientists by the 1920s, but the mechanism of nerve-signal communication across the synapse remained a mystery. It was unclear whether it was chemical or electrical. Loewi claimed that the idea of an experiment to uncover the answer came to him in two dreams.

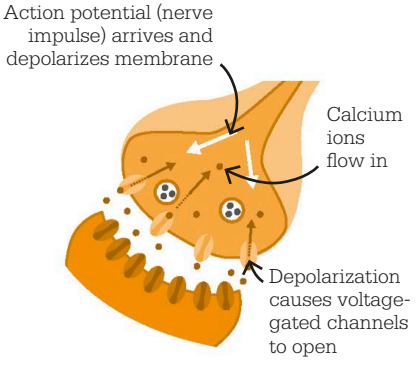
Chemical communications

Loewi's technique was to dissect the hearts of two living frogs. Both hearts were bathed in saline to keep them beating outside of the body. One had its vagus nerve, which links the heart to the brain, removed, while the other was left intact. Loewi stimulated the latter with a small current to slow that heart. He then collected some of the liquid bathing the slowed heart and transferred it to the bath with the nerveless heart. The second heart's beat immediately slowed in the same way. Loewi deduced that the vagus nerve produced a chemical to communicate with the heart, and that this chemical sent the same message to the nerveless heart. Loewi eventually identified the chemical as acetylcholine.

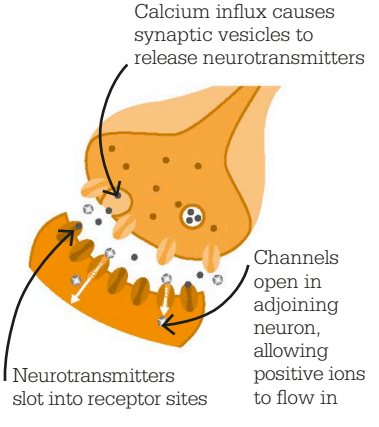
In 1914, Henry Dale had isolated acetylcholine from ergot, a toxic fungus, and found that it inhibited heartbeat in the opposite way to adrenalin, which stimulated it. These two chemicals were the first neurotransmitters to be identified. More than 200 chemicals, most simple proteins, are now known to be involved in transmitting signals across the synapse, but the process remains opaque. ■



Chemical store



Nerve impulse received



Chemical message passed on

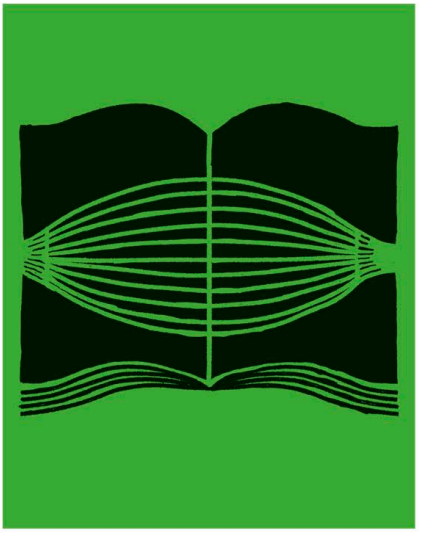
Neurotransmitters are made in the cell body of the neuron and travel along the axon to vesicles (membrane sacs). The membrane is depolarized when an action potential moves down the axon. This allows calcium ions into the cells, and neurotransmitters are released to cross the synapse to the next neuron.

Otto Loewi

Born in Frankfurt, Germany, in 1873, Otto Loewi qualified as a doctor in Strasbourg, France. After seeing the terrible suffering caused by tuberculosis and other untreatable diseases, he chose to switch from a clinical career treating patients to one of researching cures. In 1902, he relocated to London and became a colleague of Henry Dale. The following year, Loewi took up a position in Graz, Austria, where he did the work for which he would be remembered: he and Dale later shared the 1936 Nobel Prize in Physiology or Medicine for their discovery of neurotransmitters. He remained in Austria until the Anschluss of 1938—as a Jew, Loewi had to flee from the country's new Nazi government, and he eventually moved to the US, where he joined the faculty of the New York University College of Medicine. He became a US citizen in 1945 and died there in 1961.

Key work

1921 "On the Transferability of the Humoral Heart Nerve Effect"



A COMPLETE THEORY OF HOW A MUSCLE CONTRACTS

MUSCLE CONTRACTION

IN CONTEXT

KEY FIGURES
Jean Hanson (1919–73)
Hugh Huxley (1924–2013)

BEFORE
1682 Antonie van Leeuwenhoek describes seeing striations in muscles.

1780s Luigi Galvani finds that electrical sparks make muscles contract.

1862 French neurologist Duchenne de Boulogne can contort the facial expressions of test subjects by applying electrodes to nerves.

AFTER
1969 Hugh Huxley proposes the swinging cross-bridge hypothesis, where the head of the myosin molecule bonds to actin and then rotates to drag the actin forward.

1990 Artificial muscles made from electroactive polymers are developed for potential use in robotics.

The study of nerves has always gone hand in hand with the study of muscle, because a contracting muscle is an indication that the nervous system is at work.

In 1954, just two years after the mechanism behind the action potential—the electrical pulse that carries nerve signals—had been unpicked, the chemical process behind muscle contractions was similarly laid bare. The discovery was made simultaneously by two pairs of researchers; one was British physiologist Andrew Huxley, who had been a major figure in the action potential research, and German physiologist Rolf Niedergerke; the second pair was British biologists Jean Hanson and Hugh Huxley (no relation to Andrew Huxley).

Types of muscle

There are three kinds of muscle in the human body. Skeletal muscles, which move the limbs and body in a voluntary fashion, are made of striated tissue, so called because it has a striped appearance under the microscope. The involuntary muscles, such as those at work in the digestive system, are smooth muscle tissue, so named because they lack the striations. The third type is cardiac muscle, found only in the heart. This has an appearance somewhere between the two others.

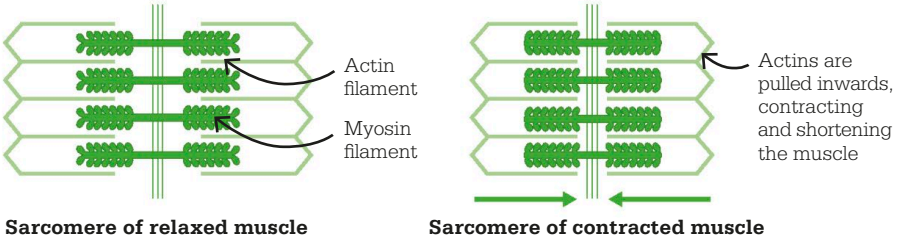
All muscle works by contracting in length, or at least by increasing in tension. The contraction creates a pulling force that acts on a body part, making it move. A muscle never pushes on anything. In general, skeletal muscles work in agonistic pairs, which pull in opposite directions: as one muscle contracts, the other stays relaxed.

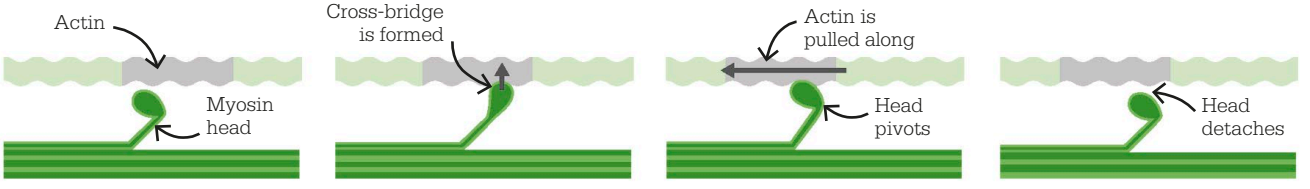
How muscles work

Muscle is composed mostly of protein. Two types of protein—myosin and actin—form long filaments that bundle together to make muscle fibers called myofibrils. Inside each myofibril, the thinner actin filaments are interleaved with the thicker myosin ones. Together, these proteins create contractile structures called sarcomeres. One muscle fiber has thousands of these sarcomeres strung together; a biceps fiber typically contains 100,000 of them. The stripes in striated muscle—and, to a lesser extent, cardiac muscle—are due to the sarcomeres in one fiber broadly lining up with those

See also: Excitable tissues 108 ▪ Electrical nerve impulses 116–17 ▪ Synapses 130–31

Filaments of actin and myosin form sarcomeres. When a muscle contracts, the myosin filaments pull the actin filaments along, until they get closer together, shortening the muscle. This happens repeatedly during a single contraction.





The myosin head is energized by an energy-carrying adenosine triphosphate (ATP) molecule.

The head sticks to the actin filament, forming a cross-bridge.

The head releases energy and pivots, sliding the actin filament along.

The cross-bridge falls apart, the muscle relaxes, and the head is re-energized by an ATP molecule.

on the fibers above and below. In smooth muscle, sarcomeres are more jumbled but work in the same way.

Several myofibrils are bound by a single cell membrane, forming a single muscle cell—which has many nuclei. When a nerve signal arrives, it sends neurotransmitters across a synapse to stimulate a spike in voltage in the myofibril's membrane. As is the case with a nerve, this results in a wave of electric charge—an action potential—surging along the muscle fibers. The temporary change in voltage results in calcium ions passing into the myofibrils. The rise in calcium coupled with a supply of energy from the muscle fibers makes the actin and myosin proteins slide over one another, shortening each sarcomere by about 10 percent, and every one of those tiny contractions accumulate to create the muscle's pulling force. This state is maintained as long as there are enough calcium ions in the muscle fiber and enough energy being supplied to the sarcomeres. Once they run low, the muscle relaxes.

Each pair of researchers, Hanson and Huxley, and Niedergerke and Huxley, gave slightly different versions of this sliding-filament theory, still the accepted mechanism for muscle contraction. ■

Jean Hanson

Born in 1919 inDerbyshire, UK, Jean Hanson received her Ph.D. at King's College London, and spent most of her working life there in biophysics research.

She met Hugh Huxley, a fellow Briton, in 1953, after taking up an offer of a Rockefeller Fellowship at the Massachusetts Institute of Technology (MIT), and the pair formulated their sliding-filament theory of muscle contraction. Their discovery was met with scepticism, even after they used an electron microscope in 1956 to visualize the contraction of muscle fibers. Hanson then turned her attention to studying invertebrate muscles.

In 1966, Hanson became a professor and was made head of the biophysics unit at King's. However, at the height of her career, in 1973, she died following a rare brain infection.

Key work

1954 "Changes in the Cross-Striations of Muscle During Contraction and Stretch and Their Structural Interpretation"

MEMORY MAKES US WHO WE ARE

MEMORY STORAGE

IN CONTEXT

KEY FIGURE
Eric Kandel (1929–)

BEFORE
4th century BCE Plato likens the human brain to a wax block that may vary in "size, cleanliness, and consistency."

1949 Canadian psychologist Donald Hebb introduces the idea of synaptic plasticity.

1959 American neuroscientist Brenda Milner identifies the hippocampus as where short-term memories are changed to long-term memories.

AFTER
1971 At University College London, John O'Keefe and his student Jonathan Dostrovsky discover "place cells" in a rat hippocampus that establish its memory of locations.

2008 Israeli-Canadian microbiologist Nahum Sonenberg discovers the importance of protein synthesis in laying down memories.

Recording **a memory** must make **changes** in the **brain**, however small.

These **changes** must be **physical** and, therefore, must be **observable**.

In **Kandel's** experiments with sea slugs, he observes **chemical changes** to their synapses as they learn to react to stimuli.

The building of memory must be linked to physical changes in the synapses.

Soon after Spanish physician and neuroscientist Santiago Ramón y Cajal discovered synapses, the gaps between nerve cells across which nerve signals are transmitted, in the 1890s he suggested that these gaps might be important to the laying down of memories. But it was not until 1970 that Austrian-American neurobiologist Eric Kandel showed, using his experiments with sea slugs, that synapses are indeed at the center of memory and that Ramón y Cajal was right.

In his work, Kandel showed that memories are captured by the nerves through changes at synapses, and that learning activates cascades of neurotransmitter chemicals to reinforce connections between neurons along particular pathways.

Kandel's research focused on simple learned responses, namely conditioning the sea slugs to behave in a certain way when they received a particular stimulus. Conditioning animals was not new. In 1902, Russian scientist Ivan Pavlov had famously shown that dogs can be trained to respond to a stimulus such as a bell associated with food. The dogs' reactions involved their whole bodies—from jumping and

See also: The brain controls behavior 109 ▪ Electrical nerve impulses 116–17 ▪ Innate and learned behavior 118–123 ▪ Nerve cells 124–25 ▪ Synapses 130–31

barking, to salivating at the signal—so how did the nervous system learn to coordinate the entire body in this complex way?

Types of memory

In 1949, Canadian psychologist Donald Hebb introduced the idea that forming a new memory involves rerouting nerve fibers and altering synapses—a process he called synaptic plasticity. Neuroscientists distinguish between short-term memory, memories that last for a few hours at most, and long-term memories, which last for weeks or even a lifetime. Creating a new long-term memory, Hebb argued, involves repetitions that reinforce certain synaptic connections—famously saying, "Neurons that fire together wire together." Neuroscientists also distinguish between "declarative" and "procedural" memory. Declarative memories are facts or events recalled consciously, such as a favorite story. Procedural or non-declarative memories are skills and habits learned so deeply that they are performed subconsciously—for example, hitting a ball.

The hippocampus

In 1953, an operation to control the epilepsy of "patient H.M." involved removing a part of the brain called the hippocampus—and left him unable to create new memories. Her study of H.M. allowed American neuroscientist Brenda Milner to demonstrate that the hippocampus is where short-term memories are converted to long-term memories.

It was evident that creating memories depends on changing nerve connections within the hippocampus. But when Kandel began his work in the 1960s, he realized it would be impossible to study synapses in detail in the extraordinarily complex human hippocampus. So, he decided, controversially, to target his research on the brain of the sea slug *Aplysia*, which has just a few thousand nerve cells. *Aplysia* has a reflex to close its gills in response to danger. Kandel taught the slug to perform the gill reflex in response to an electric prod. Weak stimuli caused particular chemical changes in the slug's synapses, linked to short-term memory, while stronger stimuli caused different synaptic changes, which created long-term memories.

Kandel and other neuroscientists went on to work out that encoding a new long-term memory involves persistent changes in the synapses. A typical neuron links to 1,200 others, but one that has been exposed to repeated stimuli can make connections to twice this number or more. The brain has a high degree of synaptic plasticity—that is, it is particularly open to making such connections—especially early in life. This is why skills that are learned when young, such as language, stick with us. But the brain continues to learn, adapt, and remember as it gets older, albeit more slowly with age. ■

> … life is all memory, except for the one present moment …
>
> **Eric Kandel**
>
> **Quoting American playwright Tennessee Williams**

Aplysia californica is a species of sea slug, an aquatic gastropod. Its natural response when it recognizes a threat is to release toxic purple ink.

THE OBJECT IS HELD WITH TWO PAWS

ANIMALS AND TOOLS

IN CONTEXT

KEY FIGURE
Jane Goodall (1934–)

BEFORE
1887 British marine surveyor Alfred Carpenter observes long-tailed macaques using stones to break open oysters.

1939 American naturalist Edna Fisher describes a sea otter using a stone like an anvil to smash open shellfish.

AFTER
1982 Elizabeth McMahan, an American biologist, reveals that assassin bugs "fish" for termites using the dead skins of termites as bait.

1989 A research team from Cambridge University finds that Egyptian vultures' use of stones to break open eggs is innate behavior, not learned.

2020 In Australia, researcher Sonja Wild observes bottlenose dolphins trapping fish inside conch shells, then shaking the fish into their mouths.

People have long been aware of tool use by some animals. In 1871, Charles Darwin referred to primates using tools in *The Descent of Man*. But the scientific world did not take much notice of this behavior until November 1960, when young British field researcher Jane Goodall watched a chimpanzee she named David Greybeard using a dried grass stem to "fish" for termites. When she contacted her supervisor, the paleoanthropologist Louis Leakey, from her base at Gombe, Tanzania, telling of her discovery, his response was, "Now we must redefine tool, redefine Man, or accept chimpanzees as humans."

The observation caught the world's attention because it offered scientists a window into the mind of early humans. The chimpanzee is humankind's closest living relative, and it is tempting to see in its behavior how our ancient

Some chimpanzee communities "fish" for termites exclusively above ground, while others only prey on those living underground. This is an example of chimps' cultural diversity.

See also: Innate and learned behavior 118–23 ▪ Memory storage 134–35 ▪ Food chains 284–85 ▪ Predator–prey relationships 292–93 ▪ Niches 302–03

> Neither the naked hand nor the understanding … can effect much. It is by instruments and aids that work is done.
>
> **Francis Bacon**
>
> **English philosopher (1561–1626)**

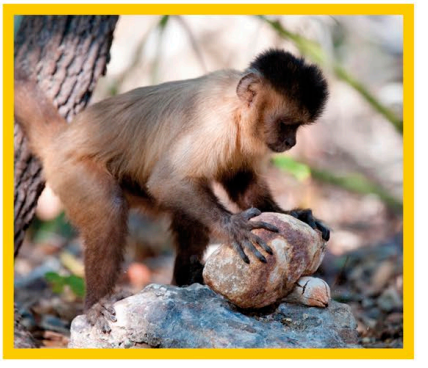
ancestors might have gone about their daily life millions of years ago. Goodall also found that her chimps were stripping leaves off stems so that they could be pushed more easily into termite nests, meaning they were not only using tools but making them as well.

Building toolkits

Goodall identified nine different ways the chimpanzees use stems, twigs, branches, leaves, and rocks to accomplish tasks related to feeding, drinking, and cleaning—and as weapons. Later researchers added much more data. In the Congo Basin, observers found that chimps chew slender sticks to flatten the ends, creating spatulas to dip for honey in wild bees' nests. In Senegal, they gnaw the ends of branches into sharp points, with which they skewer galagos (bush babies) hiding in tree hollows. And in Côte d'Ivoire, chimps use large rocks to crack panda nuts, with members of the troop lining up to use an especially attractive stone.

Small brains, big intellects

Another surprise came in 2004, when it was revealed that cracking nuts is not the sole preserve of chimpanzees. In Brazil, bearded capuchin monkeys use anvils and stone-pounding tools to crack open cashew nuts, and they do it very skillfully. A nut is placed on the anvil for maximum effect, and the force the monkey uses to hammer it varies according to the size, shape, and toughness of the cashew.



Bearded capuchins are well known for using large stones, which require fewer strikes, to crack open the hard outer shells of nuts.

In all these primate examples, tool manufacture and use is learned from others in the troop—behavior known as social learning. Some members of the social group will be experts who have acquired their skills after years of practice. Their "apprentices" will watch them avidly in order to learn. Because each population has its own way of doing things, primatologists believe this amounts to these primates having distinct cultures. ■

New Caledonian crows have the skill and dexterity to be able to construct a hook tool by bending the end of a twig.

Bird brains

In 1905, American ornithologist Edward Gifford saw Galápagos woodpecker finches using cactus spines to winkle out grubs. In 2018, New Caledonian crows were discovered to have taken tool-making to another level. They shape twigs into two kinds of hook to extract insects from holes in tree bark. Like chimps, these birds manufacture very precise tools, the likes of which first appeared in human cultures after the Lower Paleolithic, about 200,000 years ago.

Surely, though, the use of fire sets humans aside from other animals? Maybe not. In 2017, Australian ornithologist Bob Gosford described black kites, brown falcons, and whistling kites picking up firebrands (burning twigs or branches) and carrying them to unburned areas of grass to start new fires, so they could grab the fleeing insects and reptiles. It turns out that the indigenous people of Australia's Northern Territory knew about this behavior long ago and have even incorporated it into their sacred ceremonies.

HEALTH
DISEASE

AND

In his medical school, Hippocrates teaches that **disease** is **caused by an imbalance** of the four "humors" in the body.

400 BCE

Robert Koch **identifies bacteria** in sufferers of infectious disease, confirming the **germ theory** of disease.

1860s

Campbell de Morgan establishes that the **spread of cancer** from its original site (metastasis) is due to **tumor cells** breaking away and circulating in the body.

1874

1500s

The foundations of **modern pharmacology** are laid by Paracelsus when he advocates doses of appropriate **medicines** to cure disease.

1860s

Extrapolating from the germ theory of disease, Robert Lister uses **chemical antiseptics** to kill infectious microbes.

Ever since prehistoric times, people have sought ways to deal with illness. Belief in the supernatural meant disease could be treated only by magic or a religious remedy. However, some healers developed treatments that would form the basis of medical sciences, and in ancient Egypt and Greece, interest in understanding the causes of disease grew, in order to find better ways to combat it.

Ancient medicine

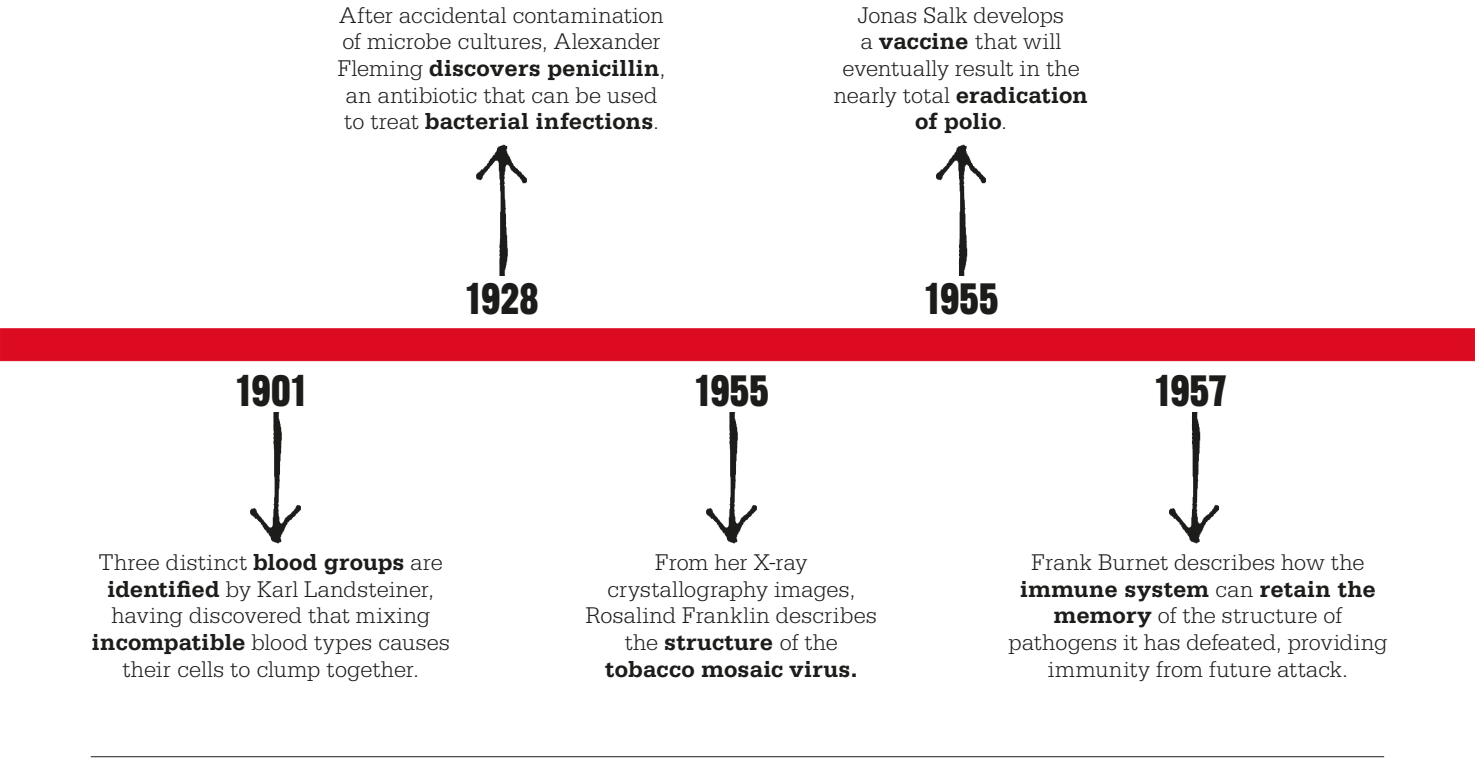
The Greeks in particular placed great emphasis on providing rational explanations for natural phenomena, including diagnosing and treating illness. They believed that everything in the Universe is composed of four basic elements—earth, fire, air, and water—and from this evolved the idea that the body consists of four "humors": blood, yellow bile, black bile, and phlegm. In a healthy body, these humors are in a state of balance, but any excess or deficiency of one of these fluids is the cause of disease.

A medical theory developed by Hippocrates derived from this idea, and was the basis for the practice of medicine in the West for almost 2,000 years. However, the advent of the Renaissance ushered in a new era of scientific discovery, including advances in the field of medicine. A pioneer in this was the physician and alchemist Paracelsus, who advocated an approach of methodical observation to study disease. This led him to the conclusion that disease is not caused by an imbalance of the humors, but by an invasion of the body by "poisons." These poisons, Paracelsus believed, could be counteracted by administering antidotes in the form of measured doses of medicinal compounds.

Germ theory

It was not until the 19th century, however, that a more accurate explanation of disease was found. Numerous theories of how infectious diseases are spread had been posited, but it was the experiments by Louis Pasteur and Robert Koch that pointed to microbes being responsible for causing infectious illnesses. This so-called germ theory of disease was an idea later confirmed by Koch's discovery of bacteria in the bodies of infected patients.

Poor hygiene was identified as a major factor in the spread of disease and that microbes were also



likely to be the cause of infection in wounds. From this, Joseph Lister developed the idea that the use of antiseptics (chemicals that kill infectious microbes) could be used to significantly reduce the risks of infection when treating wounds and during surgical operations.

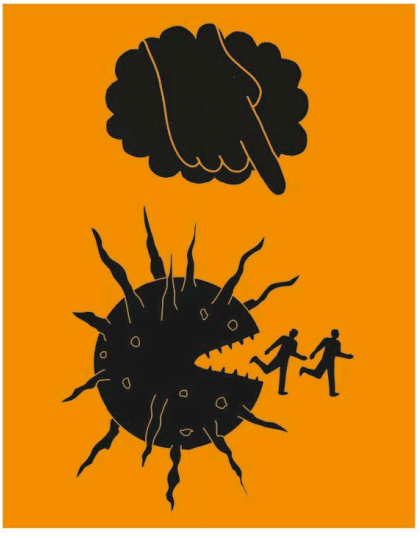
Another important weapon in the battle against disease was discovered by chance in 1928, when Alexander Fleming noticed the action of a contaminated microbe culture in his laboratory. The accidental introduction of what is now known as penicillin demonstrated that there are certain microbes and fungi that produce chemicals that suppress the growth of other microbes. This discovery meant that the antibiotic property of these chemicals can be targeted to fight bacterial infections.

Creating immunity

The idea of inoculation—infecting a patient with a mild dose of a disease to prevent contraction of a more serious disease—probably originated in medieval Islamic medicine. It did not become widespread practice in the West until Edward Jenner observed that sufferers of the mild disease cowpox appeared to be immune to the more serious smallpox that was prevalent in Europe at the end of the 18th century. By inoculating a young boy with pus from a blister of cowpox, Jenner effectively triggered an immune response that protected him from smallpox.

Creating immunity through vaccination became an important tool in the eradication of disease. Examples include Louis Pasteur's vaccine against rabies, and later the virtual elimination of polio thanks to Jonas Salk's vaccine in the 1950s. The importance of vaccination was highlighted by the fact that many infectious diseases are caused not by bacteria, but viruses, which are not susceptible to treatment by antibiotics.

Rosalind Franklin's work on determining the non-cellular structure of viruses led to an understanding that they reproduce by invading and altering genetic systems in their hosts. Further research into the way that vaccines work, by stimulating the production of antibodies, resulted in Frank Burnet's theory that the immune response to the presence of substances called antigens triggers the reproduction of clones of specific antibodies, which can then counter future attacks. ■



SICKNESS IS NOT SENT BY THE GODS

THE NATURAL BASIS OF DISEASE

IN CONTEXT

KEY FIGURE
Hippocrates (*c.* 460–375 BCE)

BEFORE
***c.*2650 BCE** Ancient Egyptian Imhotep is revered as a god of medicine, having diagnosed and treated over 200 diseases.

500 BCE In India, followers of the Jainism religion think that tiny creatures, called *nigoda*, bring diseases to the body.

AFTER
***c.*4th century BCE** An ethical code for physicians, called the Hippocratic Oath, is written.

***c.*180 CE** In Rome, the physician Galen establishes in medical orthodoxy the idea that imbalances in body fluids, or humors, cause disease.

1762 Austrian physician Marcus Plenciz suggests that microbes may cause diseases.

1870s Louis Pasteur and Robert Koch formulate the germ theory of disease.

For many, medicine begins with Hippocrates, a famous physician who lived on the Greek island of Cos 2,500 years ago. At the time, most people believed disease to be bad magic or sent by the gods, but some began to search for natural remedies, such as garlic and honey. Others, including Plato and Aristotle, argued for logic, and rational explanations of the world.

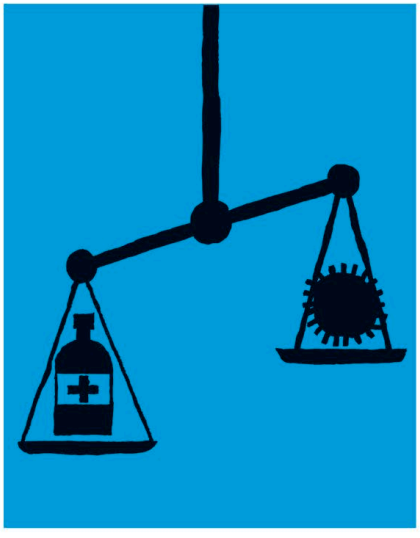
Greek thinkers developed the belief that all natural matter is made from four elements —earth, air, fire, and water—into an idea that the body was made of four fluids, or humors. For good health, the fluids—blood, yellow and black bile, and phlegm—must balance.

Hippocrates codified the four humors into a medical theory. It ultimately proved mistaken, but established a purely rational basis for understanding and treating illness. Medicine was a science, not witchcraft. "Sickness is not sent by the gods or taken away by them. It has a natural basis," Hippocrates insisted. "If we can find the cause," he said, "we can find the cure."

Hippocrates urged all doctors to examine patients carefully, take a thorough history, and observe their symptoms—now standard medical practice. The practice of medicine had traditionally passed from father to son, but Hippocrates set up training courses to allow anyone to become a doctor. Trainees had to take an oath to put the patient's needs above all. That oath, known as the Hippocratic Oath although he may not have written it, put ethics at the heart of medical practice and is still used in some countries. ■

> I will abstain from all intentional wrongdoing and harm.
> **Hippocratic Oath**

See also: Experimental physiology 18–19 ▪ Drugs and disease 143 ▪ Germ theory 144–51 ▪ Antisepsis 152–53 ▪ Antibiotics 158–59



THE DOSE MAKES THE POISON

DRUGS AND DISEASE

IN CONTEXT

KEY FIGURE
Paracelsus (1493–1541)

BEFORE
***c.*60 CE** Dioscorides, a Greek military surgeon, compiles *De Materia Medica*—the definitive summary of herbal remedies for 1,500 years.

***c.*780** Jabir ibn Hayyan pioneers ways of making chemical drugs.

1498 Florentine authorities publish the first official pharmacopeia, later known as the *Ricettario Fiorentino*.

AFTER
1804 Armand Séguin and Bernard Courtois, French chemists, isolate morphine as the active principle in opium.

1828 Friedrich Wöhler is the first person to synthesize an organic chemical, urea, thereby realizing Paracelsus's view of the body as chemistry.

Treating ailments with certain plants or minerals goes back to prehistoric times. Folk healers passed down their ancient knowledge of herbal remedies, which were compiled by Greek physician Dioscorides in *De Materia Medica*. Islamic polymath Jabir ibn Hayyan later pioneered the idea of chemical drugs. However, in medieval Europe, physicians still treated illness as an imbalance of the four humous.

The first printing of *De Materia Medica* in 1478 sparked new interest in drugs and the publication of pharmacopeias—lists of medicinal drugs with directions for use. Then in the 1500s, Swiss physician and alchemist Paracelsus began to argue that disease is not a result of imbalanced humors, but an invasion of the body, or a "poison," to be treated with an antidote.

Paracelsus suggested that an antidote might even be a poison itself: "All things are poison and nothing is without poison," he insisted, "Only the dose makes sure a thing is not a poison."

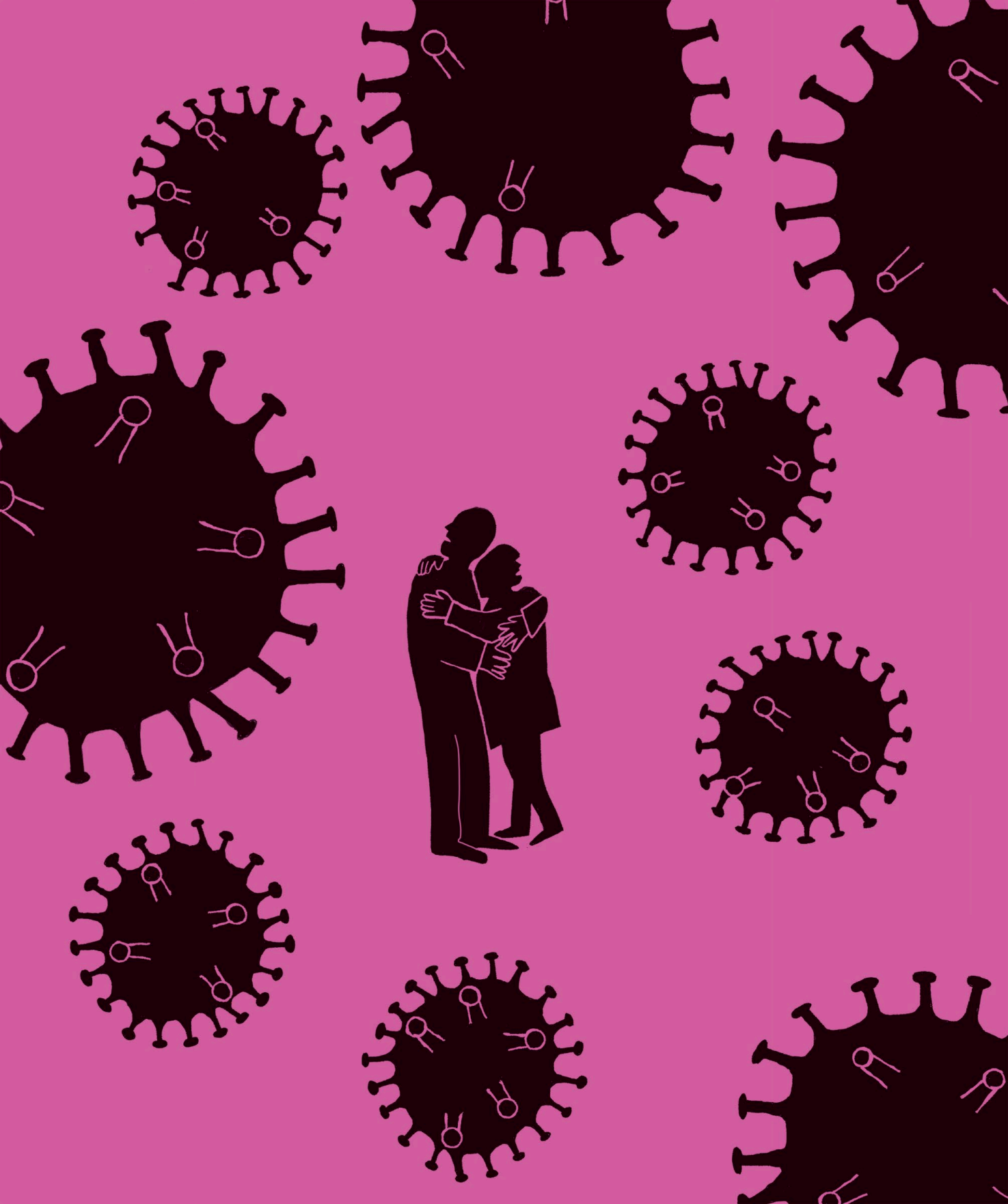
Paracelsus was born Aureolus von Hohenheim. His chosen name means "greater than Celsus"—Roman Aulus Cornelius Celsus wrote a famous 1st-century medical encyclopedia.

A physician, Paracelsus said, must extract chemicals like a miner and harvest them like a farmer. He experimented in his laboratory to find medicinal compounds. Among his discoveries were laudanum, made from powdered opium and alcohol and used as the prime pain relief for centuries, as well as small doses of mercury to treat syphilis. ■

See also: Experimental physiology 18–19 ▪ Biochemicals can be made 27 ▪ The natural basis of disease 142 ▪ Germ theory 144–51 ▪ Antibiotics 158–59

THE MICROBES WILL HAVE THE LAST WORD

GERM THEORY



IN CONTEXT

KEY FIGURES
Louis Pasteur (1822–95),
Robert Koch (1843–1910)

BEFORE
***c.*180 CE** In ancient Rome, physician Galen believes that the plague is spread by "seeds of plague," carried on the air.

1762 Austrian physician Marcus Plenciz suggests that microbes cause some diseases, but his ideas are not accepted at the time.

1854 John Snow links the spread of cholera to contact with contaminated water.

AFTER
1933 A virus is identified as the source of human influenza, following the "Spanish flu" pandemic of 1918–19.

1980 Smallpox is eradicated.

2019 The SARS-CoV-2 virus that is the cause of COVID-19 is first isolated.

> Certain minute creatures … float in the air and enter the body through the mouth and nose and there cause serious diseases.
>
> **Marcus Terentius Varro**
> ***De Re Rustica* (*On Agriculture*), 35 BCE**

Disease-bearing miasma was believed for centuries to roll off the polluted Thames River into London, as depicted in the mid-19th century by the figure of Death in a rowing boat.

Germ theory is the idea that many diseases are caused by germs, or microbes, such as bacteria. When a germ enters, or infects, the body, it multiplies and causes a particular disease, giving rise to certain symptoms in the host.

Germ theory was established by the late-19th-century experiments of French chemist Louis Pasteur and German physician Robert Koch. At the time, many doctors believed in the miasma, or "bad air," theory—the idea that disease is spread by the air alone and, in particular, damp, misty, smelly air near stagnant water.

In the 1st century BCE, Roman architect and writer Vitruvius advised against building anywhere near swamps since miasma would drift in on morning breezes, bearing the poisonous breath of marsh creatures that made people sick.

Some sceptics of miasma theory contended that diseases spread by contagion—that is, through direct contact with others or with contaminated material—without any idea that it involved germs. Yet the idea that diseases might be spread by microbes is an old one. Jainists in India believed about 2,500 years ago that miniscule beings they called nigoda brought diseases. The Roman scholar Marcus Terentius Varro wrote that precautions must be taken in swamps so tiny, disease-bearing creatures would not enter the body.

Similar ideas were considered by some Islamic physicians who witnessed the way plague ravaged 14th-century Andalucia. Ibn Khatima believed "minute bodies" were to blame for the contagion, while Ibn al-Khatib described how these bodies were transferred by contact between people.

First microbe sightings

The problem was that microbes are just too small to see with the naked eye. But all that changed in the late 16th century with the invention of the microscope. In 1656, German priest and scholar Athanasius Kircher saw "little worms" as he studied the blood of plague victims in Rome through a microscope. He believed they were to blame for the

See also: How cells are produced 32–33 ▪ Fermentation 62–63 ▪ Antisepsis 152–53 ▪ Antibiotics 158–59 ▪ Viruses 160–63 ▪ Vaccination for preventing disease 164–67 ▪ Immune response 168–71

disease. It is not likely that he actually saw the *Yersinia pestis* bacterium, which causes plague, but he was right in asserting that microbes are the cause. Kircher published his theory in 1658 and even recommended ways to stop its spread: isolation and quarantine of victims, and burning their clothes.

In the late 1660s, Dutch scientist Antonie van Leeuwenhoek made a simple microscope that magnified things by 200 times. Over the following years, he saw that apparently clear water was full of minute creatures (what we now know to be bacteria, protozoa, and nematodes). In fact, he realized that there are tiny creatures almost everywhere.

In 1683, van Leeuwenhoek published the first drawing of so-called "animalcules"—bacteria that he had observed in plaque taken from teeth. He drew them carefully; in all, he recorded four different shapes of bacteria, from spirals to rods, but did not link the microbes specifically to diseases. Today, microbiologists have identified more than 30,000 kinds of bacteria, in three basic shapes (see below).

The silkworm disease called muscardine is common in the species *Bombyx mori*. The fungus that causes the disease was named *Beauveria bassiana*, after Agostino Bassi.

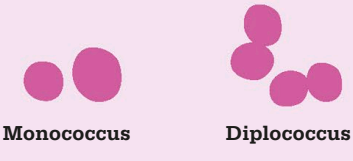
Mounting evidence

Despite discoveries such as van Leeuwenhoek's, miasma theory continued to hold sway. Then in 1807, Italian entomologist Agostino Bassi began to study the disease called muscardine, which was decimating the Italian and French silkworm industries. He discovered that a microscopic parasitic fungus was causing the disease and that it was also contagious, spreading among silkworms by means of infected food and contact. He published his findings in a paper in 1835 and suggested that microbes caused diseases in humans, as well as in animals and plants.

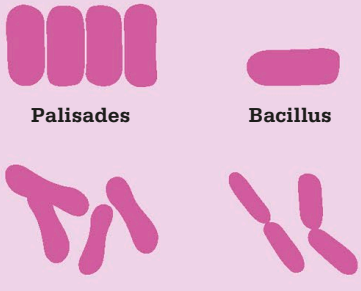
Ideas like this began to gather some support. In 1847, Hungarian Ignaz Semmelweis, a physician in Vienna, revolutionized childbirth in the labor wards, where previously puerpural (childbed) fever had run amok among new mothers. »

Major types of bacteria

Coccus bacteria are round bacteria, occurring as single- to multicelled forms, which cause diseases such as meningitis, pneumonia, scarlet fever, and strep throat.



Bacillus bacteria are long, thin rods, some in chains or clumps (palisades), that can cause diseases such as diphtheria, tetanus (lockjaw), tuberculosis, and pertussis.



Curved bacteria include spiraled spirilla types; corkscrew-shaped spirochetes; and vibrios, curved like commas, which cause diseases such as cholera.

Semmelweis argued that puerpural fever was spread by "cadaverous particles" carried by students from dissection rooms to the labor wards. His hygiene regime, which included handwashing, resulted in a dramatic reduction in cases of the fever, yet many doctors were unconvinced of the effectiveness of hygiene in fighting disease.

Cholera

Another twist to the story of germ theory occurred when a cholera epidemic hit London's Soho district in 1854. British physician John Snow doubted that miasma theory tied in with the pattern of the outbreak. Some victims were contained in a very small area, but others lived in clusters far away.

With meticulous research and mapping of the area, Snow showed that all the victims had drunk water from a single water pump. The water had been contaminated by human excrement deposited near the pump. Snow had proved his theory about cholera transmission; miasma was clearly not the culprit. The local authorities were sceptical, but even so began to improve the city's water supply.

> "It is a terrifying thought that life is at the mercy of the multiplication of these minute bodies …"
> **Louis Pasteur**

Cholera struck Florence, Italy, that same year. Local anatomist Filippo Pacini studied mucus taken from the gut linings of victims and in every case he saw comma-shaped bacteria, which he named *Vibrio cholerae*. For the first time, a major human disease had been clearly linked to an individual pathogen. Yet the medical establishment continued to favor miasma theory and ignored Pacini's work.

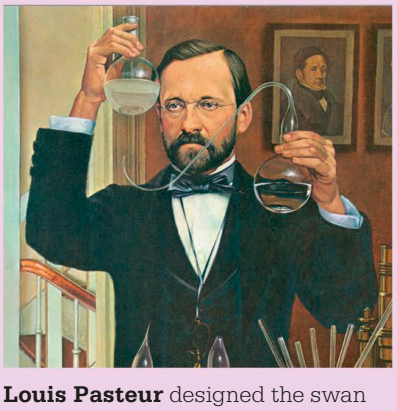
Wine and yeast

In France in the late 1850s, Louis Pasteur embarked upon a series of experiments that would demolish miasma theory and lead to his pioneering work on germ theory. While head of science at the University of Lille, he was asked by a local wine producer to research the process of fermentation.

Beer and winemakers had assumed that fermentation was a purely chemical reaction. However, Pasteur saw that mature wine contains tiny, round microbes, called yeast; he rightly concluded that the yeast microbes fermented the wine. Pasteur then discovered that only one type of yeast makes wine mature properly; another type of yeast makes lactic acid, which ruins the wine.

Pasteur found that he could kill off the harmful yeast in wine, while leaving the good yeast unharmed, by heating the wine gently to about 140°F (60°C). He later patented this technique in 1865. It came to be called pasteurization and is widely used today in the wine and beer industries, and to kill potential pathogens in fresh produce, such as milk and fruit juice.

Pasteur started to explore how microbes such as yeast appeared in the first place. At the time, people still believed that life could appear



Louis Pasteur designed the swan neck of the flask so that any airborne particles would settle in the bend of the neck and not reach the broth.

Pasteur disproves spontaneous generation

In 1745, British naturalist John Needham boiled meat broth to kill any microbes, but when the broth then became cloudy, with microbes in it, he assumed that they had generated spontaneously from the matter of the broth.

In 1859, Pasteur modified this simple experiment by using his specially designed swan-neck flask. He boiled meat broth inside the flask to prevent airborne microbes from contaminating the broth. Pasteur then sealed the neck to stop air from getting in; the broth stayed clear indefinitely. But as soon as he broke the tip of the neck and let air in, the broth quickly turned cloudy, indicating that microbes were multiplying in it.

Pasteur proved beyond doubt that the microbes that made the broth go off—and similarly the yeast microbes that caused fermentation—came from the air. By debunking spontaneous generation, his experiment had discredited the principal opposition to germ theory.

Anthrax is a serious infectious disease that affects animals including humans. It is caused by the spores of the soil bacteria *Bacillus anthracis*.

out of nothing and that mold simply appeared on bad food spontaneously. This belief was known as spontaneous generation. Then, in 1859, Pasteur discredited the idea of spontaneous generation with a famous experiment (see box, opposite). It now seemed to him very likely that airborne microbes spread diseases, not the air itself as miasma theory asserted.

The turning point came a few years later. In 1865, Pasteur began trying to find a solution to pébrine, a disease that killed the silkworms on which the silk industry of southern France depended. He read about Bassi's work from 30 years earlier on muscardine disease in silkworms. Pasteur soon found that a microbe, a tiny parasite now classed as a microsporidia, was the cause of pébrine. He published his findings in 1870 and stated that the only way to stop the disease was to burn all the infested worms and mulberry trees. The silk makers followed Pasteur's advice and the disease was eradicated.

> … a long time has also been necessary before old prejudices were overcome and the new facts were acknowledged to be correct by the physicians.
>
> **Robert Koch**
> **Nobel lecture (1905)**

Researching germ theory

It was now clear to Pasteur that germs were to blame for many infections, so he began to explore further how diseases are spread among humans and animals. Reading about Pasteur's work, British surgeon Joseph Lister realized that killing the microbes was the best way to stop disease spreading. So in the late 1860s, Lister insisted wounds were cleaned and dressings sterilized to kill any microbes. Deaths from operations dramatically declined as other surgeons adopted the same antiseptic procedures.

In Germany in 1872, inspired by Pasteur's findings, physician Robert Koch began his own research into germ theory in his private laboratory. In 1876, Koch succeeded in identifying the anthrax germ as a bacillus bacteria, called *Bacillus anthracis*. In fact, he went further and conducted an ingenious experiment that proved for the first time that bacteria can cause a disease.

First, Koch extracted the anthrax bacillus from the blood of a sheep that had died from anthrax. Then he left the bacteria to multiply in his laboratory, in a culture dish of nutrients that had had no contact with diseased animals—initially the liquid from an ox's eye, but later a broth of agar and gelatine. Then Koch took the cultured bacteria and injected them into mice. The mice soon died of anthrax. There could be no doubt that it was the bacteria that caused the disease of anthrax.

Pasteur responded to this stunning experiment by confirming Koch's result and went on to prove that the anthrax bacteria could survive for a long time in the soil. Just by grazing in a field previously occupied by a sick sheep, a healthy sheep could pick up the disease.

Previously, in the 1790s, British surgeon Edward Jenner had found that he could give people immunity to the disease of smallpox—by vaccinating them with cowpox, a similar disease affecting cows that had only a mild impact on humans.

Pasteur developed a vaccine for anthrax by heating the anthrax bacteria just enough to weaken them. This was tested successfully in sheep, goats, and cattle. Just like the mild cowpox, the weakened anthrax bacteria activated a defense response in the body that was strong enough to give immunity, without causing the disease. »

Experiments prove **fermentation and molding** do not happen spontaneously, but because of **microbes in the air**.

Particular microbes are also present in the bodies of diseased animals, but **do the germs simply feed** on the **disease?**

Transferring the suspect **microbes** to **healthy animals** makes those animals **sick**.

Therefore the microbes, or germs, cause the disease.

Since Pasteur's breakthrough on anthrax, vaccines made with weakened or "attenuated" germs have become major weapons in the fight against diseases such as diphtheria and tuberculosis.

Linking germs and disease

Pasteur had proved that microbes are in the air, and now he and Koch had shown that some microbes cause diseases. Crucially, each disease was caused by a particular microbe or germ. The germs may be microscopically small, but we now know that they do their damage by getting inside the body, through the respiratory, urogenital, or gastrointestinal tracts, as well as through breaks in the skin. The germs then multiply rapidly and interfere with the body's functions or release a toxin.

During his research in the 1880s, Koch devised a series of four tests to confirm the link between a germ and a disease and set out criteria for identifying a pathogen (a disease-causing germ). These four tests came to be known as Koch's postulates (see below) and modified versions of them are still in use today.

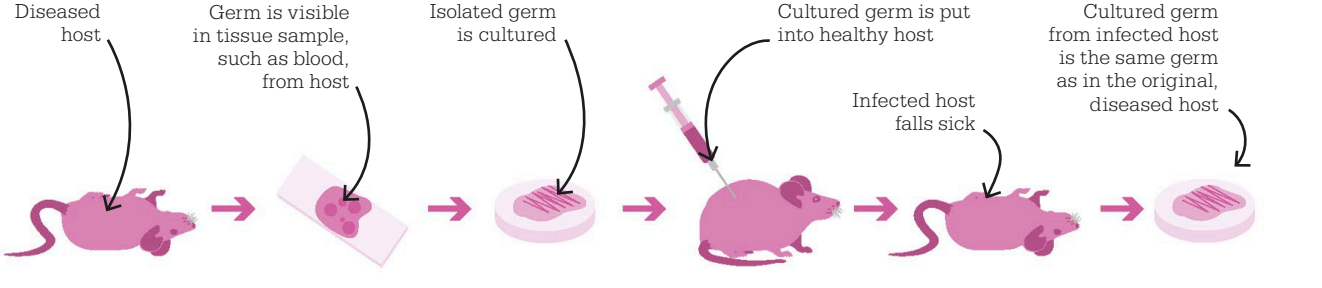
Koch quickly went on in 1882 to identify the germ responsible for tuberculosis—*Mycobacterium tuberculosis*. He wanted to find the germ that caused cholera as well, so he traveled to India and Egypt to get samples. By 1884, he had pinned it down as the comma-shaped bacterium, *Vibrio cholerae*, the same bacterium that Pacini had spotted in Florence 30 years earlier.

Koch realized that the cholera bacterium thrived in contaminated water, and suggested measures to stop its spread. Pasteur also continued to find more proof of germ theory, and in 1885, he developed a vaccine for rabies.

The hunt for germs

Despite the brilliant work of Pasteur and Koch, there was still plenty of opposition to germ theory. In 1878, German pathologist Rudolf Virchow for instance dismissed Koch's work on anthrax as "improbable" and

Koch's postulates

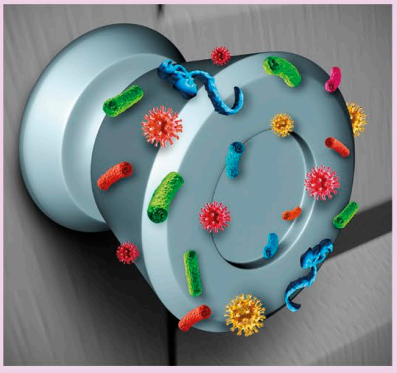


1. Association
The same germ must be present in every case of the disease.

2. Isolation
The germ must be taken from the diseased host and grown in a pure culture.

3. Inoculation
The cultured germ from the diseased host must cause the disease in a healthy host.

4. Re-isolation
The germ taken from the inoculated host must be identical to the germ in the original host.



Viruses can survive for up to 24 hours on a hard surface such as a doorknob; bacteria can survive from a few hours to days or even months.

How germs spread

Most germs, including viruses and bacteria, cannot move by themselves and each has its own route of transmission. When a new disease emerges, it is crucial to establish quickly exactly what modes of transmission are used by that germ, so that preventative measures can be taken.

There seem to be four main ways in which a germ can spread from host to host. Contact is an obvious method: directly with infected skin, mucous membranes, or body fluids, or indirectly, for example when an infected person touches a surface such as a doorknob. Airborne germs, especially viruses, can linger in droplets in air—from sneezing, coughing, or even breathing—to be breathed in by the next host. The virus SARS-CoV-2 spreads mainly through contact and the air, so distancing, hand hygiene, and masks are vital to its control.

Germs are also transmitted in vehicles: substances such as food, water, or blood. Mosquitos, mites, and ticks are examples of vectors—organisms that carry diseases that infect others.

took 10 years to come on board. However, by the 1890s, it was clear that miasma theory could no longer be sustained, and scientists began the hunt to identify the pathogens responsible for each and every infectious disease. Since then, scientists have identified about 1,500 microbes that can cause disease; some have complex life cycles involving different carriers, or vectors. However, 99 percent of microbes are completely harmless.

Initially, bacteria, microsporidia, and protozoa were thought to be the principal types of germs. Then in 1892, Dmitri Ivanovsky, a Russian microbiologist, discovered that an even tinier germ—although it was invisible even under the most powerful microscopes of the time—could also cause disease. It was named a virus in 1898.

We now know that viruses are not even properly alive—they are just incredibly small particles of reproductive material that have to invade living organisms in order to replicate and spread. They exist nearly everywhere in the air, oceans, and soil. Although only a tiny number of these—just over 200—cause diseases in humans, illnesses range from minor colds to more dangerous diseases such as pandemic flu and COVID-19.

Battling disease

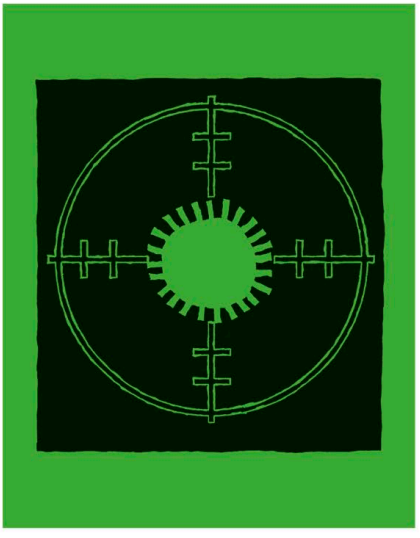
Germ theory transformed the battle against disease. Now there were clear, proven measures that could stop the spread of germs, such as hygiene, sanitation, quarantine, distancing, and masks. Scientists quickly gained an understanding of how vaccines confer immunity and how to develop vaccines against a disease by isolating the pathogen.

Following Pasteur and Koch's proofs of germ theory, scientists realized that when invading germs of infectious diseases mount an attack on cells in the body, the body has its own, sophisticated defenses for fighting them off, called the immune system. Many symptoms of disease such as fever and inflammation are actually signs of the immune response to germs.

> The pure culture is the foundation for all research on infectious disease.
> **Robert Koch**

Microbiology became the key focus for exploring disease in the 20th century. Research focused on lab cultures led to Alexander Fleming's discovery of antibiotics, the first effective medicines against bacteria. Drugs such as antivirals were developed to eliminate the microbes and halt a disease, rather than just alleviating symptoms.

A century or so ago, infectious diseases such as cholera, enteritis, pneumonia, smallpox, tuberculosis, and typhus brought widespread misery and death. Today, advances in germ theory mean that those diseases kill far fewer people, although infectious diseases still kill about 17 million each year prior to the spread of COVID-19 in 2020 (which has killed 2 million in 2020). The genome of the SARS-CoV-2 virus was known within a few months, enabling vaccines to be developed in record time. ■



THE FIRST OBJECT MUST BE THE DESTRUCTION OF ANY SEPTIC GERMS

ANTISEPSIS

IN CONTEXT

KEY FIGURE
Joseph Lister (1827–1912)

BEFORE
4th century BCE Hippocrates recognizes that pus in a wound can prove fatal.

1847 Ignaz Semmelweis proposes the use of hand-washing on obstetric wards to reduce the risk of infections after childbirth.

1858 Florence Nightingale's report on British Army deaths in the Crimean War shows that most could have been prevented with better hygiene.

AFTER
1884 Robert Koch formulates "Koch's postulates," describing the causative link between specific microorganisms and particular diseases.

1890 American surgeon William Halsted initiates the use of thin rubber gloves by surgeons—the beginning of aseptic techniques.

The idea that keeping clean is important in the defense against infection seems self-evident today. But scientific understanding of the mechanisms of infection and the benefits of hygiene did not emerge until the late 19th century. In the 1860s, French chemist Louis Pasteur discovered that fermentation and also the spoiling of milk, beer, and wine were caused by microorganisms in the air. This was the first major step toward proof of germ theory—the idea that organisms invisible to the human eye exist in the environment and can cause disease. The link to disease was made in the 1880s by German physician Robert Koch. But the connection between poor hygiene and risk of infection had already been noticed by others, such as Hungarian doctor Ignaz Semmelweis in the 1840s and British nurse and statistician Florence Nightingale in the 1850s.

In 1867, British surgeon Joseph Lister was inspired by Pasteur's work to try a new approach to reducing infections acquired during surgery. At the time, about half the patients who underwent surgery

Infection is found to be caused by **microorganisms (germs)**.

↓

Germs in the air and on surfaces **enter wounds during surgery**.

↓

Applying antiseptic chemicals to wounds during surgery kills germs and prevents infection.

See also: Fermentation 62–63 ▪ Germ theory 144–51 ▪ Antibiotics 158–59 ▪ Immune response 168–71

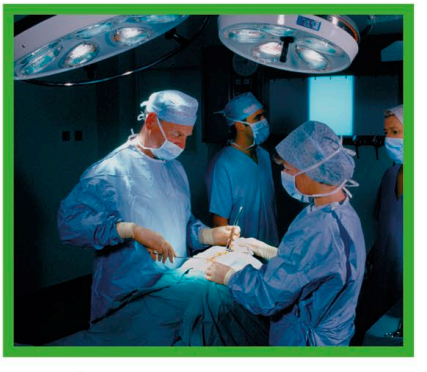
> Decomposition in the injured part might be avoided … by applying as a dressing some material capable of destroying the life of the floating particles.
> **Joseph Lister**

died, often due to infections as a result of unclean equipment. Before Pasteur's discovery, the prevailing theory was that such infections were caused by internal body parts being exposed to miasma, or "bad air"—a poisonous vapor that came from rotting material. Convinced that the cause was in fact germs, Lister searched for a chemical that could be applied to patients' wounds to kill germs before they took hold. He chose a solution of carbolic acid (now better known as phenol), which was derived from creosote, having heard that creosote had been used to eliminate the odor from sewage spread on fields.

Antiseptic efficacy

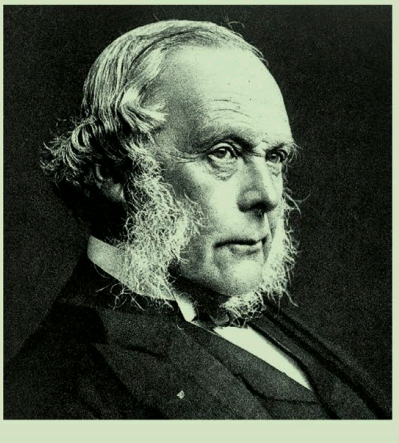
Lister first tested his antiseptic (*sepsis* means "to make rotten" in Greek) in 1865 at the Glasgow Royal Infirmary on an 11-year-old boy named James Greenlees, who had suffered a compound leg fracture. Lister used phenol to wash out the wound and also applied it to the dressing, which was renewed as healing progressed. James suffered no infection and made a remarkable recovery. Encouraged by this, Lister instructed the surgeons in the wards under his care to use phenol to clean their surgical instruments and their hands, which resulted in a dramatic fall in infection levels. He also experimented with spraying a mist of phenol over patients during surgery, though with limited effect.

Lister's ideas met with initial opposition from the medical establishment, not least because germ theory was not yet widely accepted. However, his results soon began to persuade clinicians worldwide. Within a few decades, surgical techniques had developed to include the aseptic (sterilized) procedures used today to minimize the risk of microbial contamination, such as clinical staff wearing sterile masks, gowns, and gloves. Operating rooms are kept isolated from crowded areas of the hospital and are ventilated with filtered air. ■



In modern surgery, the most common antiseptics used for preparation of the skin area are iodine, chlorhexidine gluconate, and alcohol. Phenol is no longer used because it irritates the skin.

Joseph Lister



Born in 1827 into a wealthy Quaker family near London, Joseph Lister studied classics and botany at University College London (UCL), then medicine at the university's medical school. He took a post in Edinburgh as a surgical assistant and progressed to become regius professor of surgery at Glasgow University. In 1861, Lister was appointed surgeon at Glasgow Royal Infirmary. His work there on antiseptic techniques earned him the position of professor of surgery at Edinburgh University and then at King's College Hospital in London. He later became the senior surgeon to Queen Victoria, who gave him a peerage in 1883. Lister pioneered the use of catgut for stitching and made innovations in kneecap repair and mastectomy. The bacterial food poisoning *Listeria* is named after him. He died in 1912.

Key works

1867 *On the Antiseptic Principle in the Practice of Surgery*
1870 *On the Effects of the Antiseptic System of Treatment upon the Salubrity of a Surgical Hospital*

REMOVE IT, BUT IT WILL SPRING UP AGAIN

CANCER METASTASIS

IN CONTEXT

KEY FIGURE
Campbell de Morgan
(1811–76)

BEFORE
***c.*1600 BCE** The Edwin Smith papyrus of ancient Egypt, describes breast cancer.

***c.*400 BCE** Hippocrates uses the term carcinoma (meaning "crablike") to describe tumors, leading to the word "cancer.

1855 Rudolf Virchow links the origin of cancers to normal cells but wrongly believes that the cause is irritation of the tissues.

AFTER
1962, 1964 The UK Royal College of Physicians and US Surgeon General report a link between smoking and cancer.

1972 The CT scanner enables tumors to be targeted for surgery or radiation therapy.

Cancer is one of the biggest causes of death worldwide, second only to diseases of the heart and circulation. A cancer starts when an ordinary cell begins to grow abnormally. Normally, cells divide to create new ones to replace those that are old or damaged. With cancer, this process breaks down, and new cells form when they are not needed. Cells may divide uncontrollably, forming tumors.

An important breakthrough in the understanding of cancer was made in the 1870s, when British surgeon Campbell de Morgan argued that it arose in one location in the body but could then spread to other parts—a process now called metastasis. This realization was crucial to the understanding that surgery must be followed up with checkups to ensure the cancer has not reappeared.

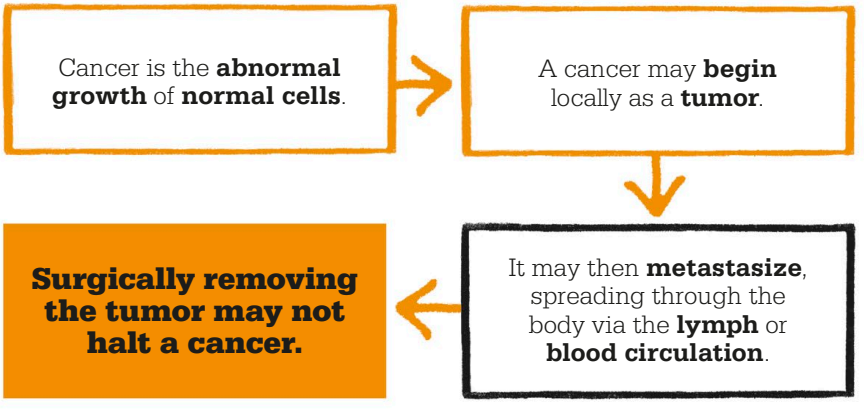
> "Today all [cancer] may be in range of our operation; tomorrow [it] may be distributed far beyond."
> **Campbell de Morgan**

Early theories

Cancer has been observed since ancient times. The Greek physician Hippocrates believed that it arose from an excess of black bile—one of the four humors—and his theory endured for nearly 2,000 years. By the 18th century, physicians realized that cancers are abnormal growths, and once anesthetics became available in the 1840s, the surgical removal of tumors became common. In 1839, German biologist Theodor Schwann proposed that the body is composed of cells; and in 1855, German physician Rudolf Virchow was the first to realize that cancer originates in normal cells.

By this time, it was widely recognized that environmental factors were associated with some cancers—in the 18th century, a high incidence of cancer of the scrotum was noted in men who had been chimney sweeps as boys—and also that heredity played a part. But physicians wrangled over

See also: How cells are produced 32–33 ▪ Immune response 168–71 ▪ Mitosis 188–89 ▪ Chromosomes 216–19 ▪ The Human Genome Project 242–43



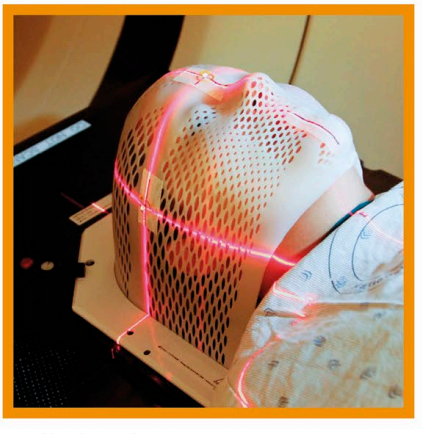
the nature of cancer—in particular, whether it was a disease of the constitution or localized in the body.

Cancer cells

Over several decades, de Morgan conducted a systematic clinical study of cancer, and in 1874 he presented his findings. He argued that cancer starts locally, then spreads from its point of origin. Cancer cells, he said, can travel independently: through the tissues surrounding a tumor, via the lymph system, or via the bloodstream. Such "cancer-germs" may lie dormant for years—sometimes even indefinitely. He acknowledged that the reasons for this were still unclear but pointed to other changes in the body that manifest at certain times of life, such as the enlargement of the prostate gland in older age or the growth of female facial hair from follicles that had been inactive for years.

De Morgan's logical, evidence-based reasoning convinced his peers and focused the direction of future research. In 1914, German zoologist Theodor Boveri suggested that cancer originates in cells with chromosomal irregularities; in other words, it is genetic. Six decades later, American geneticist Alfred Knudson proposed a model of gene mutation that led to the concept of tumor suppressor genes, which are mutated in cancerous cells. Such mutations could be inherited or caused by external damage.

Cancer remains one of the most serious health conditions today, but early intervention to prevent its spread can save lives. Early diagnosis is also critical, which is why screening programs for some cancers are a key health strategy. ■



Radiation therapy uses high-energy rays such as X-rays to kill cancer cells. For cancers of the head or neck, a mask with laser lines holds the patient in position and marks the target precisely.

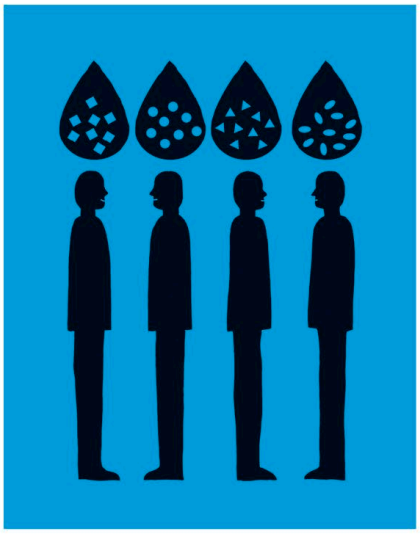
Campbell de Morgan

Born in 1811 in Clovelly, Devon, UK, Campbell de Morgan studied medicine at University College in London and then became a surgeon at Middlesex Hospital, where he worked for the rest of his life. He was closely involved in founding the hospital's medical school, where he held the role of lecturer, then professor. In 1861, de Morgan was made a Fellow of the Royal Society. His research on cancer in the 1870s led him to discover that it arose locally and then spread to other sites. He was also the first to describe the non-cancerous crimson skin lesions associated with age that bear his name: Campbell de Morgan spots.

De Morgan was renowned for his humility and kindness. He died in 1876 of pneumonia, just a few days after selflessly tending to a dying friend who was suffering from the same illness.

Key works

1872 *The Origin of Cancer*
1874 "Observations on Cancer"



THERE ARE FOUR DIFFERENT TYPES OF HUMAN BLOOD

BLOOD GROUPS

IN CONTEXT

KEY FIGURE
Karl Landsteiner (1868–1943)

BEFORE
1665 The first recorded successful blood transfusions are completed between dogs, by English physician Richard Lower.

1667 French physician Jean-Baptiste Denis carries out the first direct transfusion to a human, using the blood of a sheep.

1818–30 British obstetrician James Blundell completes several successful person-to-person blood transfusions.

AFTER
1903 Hungarian physician and microbiologist László Detre coins the term "antigen."

1907 American hematologist Reuben Ottenberg carries out the first blood transfusion based on Karl Landsteiner's research at Mount Sinai Hospital, New York.

During the 19th century, several successful human blood transfusions were carried out in Britain. But some other attempts had ended with the patient's death, and doctors could not understand why. By about 1870, the medical profession had largely abandoned transfusions because they seemed too risky.

In 1875, German physiologist Leonard Landois shed some light on the mystery. He showed that if the red blood cells (RBCs) of an animal belonging to one species are mixed with the fluid part of blood taken from a different species, the RBCs usually clump, clogging blood vessels and restricting circulation. Sometimes, the RBCs burst, causing a life-threatening condition known as a hemolytic crisis. This suggested that in unsuccessful transfusions, some undesirable reaction occurs between the fluid part of blood and the RBCs that are recognized as "not-self." However, it did not explain why some transfusions were successful and others not.

The **blood of individuals** varies in whether its **red blood cells** clump when it is mixed with the **blood serum of other people**.

People can be divided into **blood groups**, the eight most common being **A+**, **A-**, **B+**, **B-**, **O+**, **O-**, **AB+**, and **AB-**.

Blood groups are used to determine which blood can be safely given to a patient who needs a transfusion.

See also: Circulation of the blood 76–79 ▪ Hemoglobin 90–91 ▪ Immune response 168–71 ▪ The laws of inheritance 208–15 ▪ Mutation 264–65

Then, in 1901, Austrian biologist and physician Karl Landsteiner took blood samples from scientists working at his own laboratory, separated each sample into RBCs and serum (the fluid part of blood, with cells and clotting factors removed), and then mixed serum samples of each scientist with RBC samples from other scientists.

Blood group system

Landsteiner realized the scientists' blood could be divided into three groups: A, B, and C. The serum from each group would not clump the RBCs from their own group, but serum from group A would always clump group B RBCs, and vice versa. Serum from group C would clump RBC samples from both of the other groups, but the reverse was not the case: RBC samples from group C seemed never to clump.

This led Landsteiner to propose that the red cells of people in both group A and group B carry different substances called agglutinogens (now called antigens) and that the fluid part of their blood contains agglutinins (now called antibodies) that trigger clumping if they encounter a "not-self" antigen. For example, group A serum contains antibodies that cause clumping of red cells carrying B antigens, and vice versa. As for people with group C blood: their red cells carry neither of the antigens, but their serum contains antibodies that react with both A and B antigens. This finding meant blood transfusions could be performed much more safely. Any patient requiring transfusion, and all blood donated for transfusion, could now be tested to establish its blood group (by mixing samples with serum from known blood groups). Procedures could then be followed to make sure no transfusion patient received blood of an incompatible blood group.

Blood compatibility charts help ensure safe blood transfusions. In an emergency, when a compatible blood type is unavailable, type O- (O rhesus negative) can be given because it is most likely to be accepted by all blood types. However, there is still some risk involved.

Key

- Compatible
- Incompatible

Donor blood type \ Recipient blood type	O-	O+	A-	A+	B-	B+	AB-	AB+
O-	✓	✓	✓	✓	✓	✓	✓	✓
O+	✗	✓	✗	✓	✗	✓	✗	✓
A-	✗	✗	✓	✓	✗	✗	✓	✓
A+	✗	✗	✗	✓	✗	✗	✗	✓
B-	✗	✗	✗	✗	✓	✓	✓	✓
B+	✗	✗	✗	✗	✗	✓	✗	✓
AB-	✗	✗	✗	✗	✗	✗	✓	✓
AB+	✗	✗	✗	✗	✗	✗	✗	✓

Further developments

In 1902, two of Landsteiner's colleagues found a fourth blood group, AB, which contains both the A and B antigens but no antibodies to either. In 1907, the C blood group was renamed O. In 1937, Landsteiner and American serologist Alexander S. Wiener discovered a second blood group system, the rhesus (Rh) system. Many further blood group systems have since been discovered, but the ABO and rhesus (+ or -) systems remain the most important in terms of blood matching for safe transfusions. It is now known that a person's blood group is a genetic trait that is inherited in the same way as eye or hair color. ■

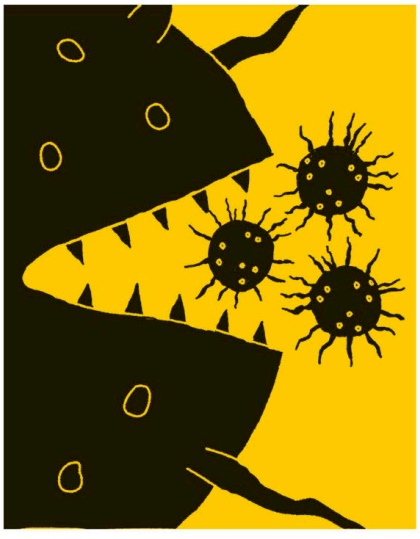
Components of blood

Blood is a body fluid in humans and other vertebrate animals composed of blood cells suspended in a yellowish fluid called plasma. The blood cells are of three different types.

The function of red cells, which contain hemoglobin, is to carry oxygen and deliver it to the body's tissues. The function of white cells is to play an important role in fighting infection. Finally, platelets play a critical part in the process of blood clotting.

Plasma makes up 55 percent of blood and is mostly water but also contains important dissolved proteins (including antibodies and clotting factors), glucose, and various other substances. Blood serum is plasma that has had the clotting factors removed.

Today, it is unusual for whole blood, containing all its components, to be transfused. The most common transfusions are of red cells only, in a minimal amount of fluid (called packed red blood cells), or of plasma.



A MICROBE TO DESTROY OTHER MICROBES

ANTIBIOTICS

IN CONTEXT

KEY FIGURE
Alexander Fleming
(1881–1955)

BEFORE
1877 Louis Pasteur shows that the soil bacteria anthrax can be made harmless by exposure to airborne bacteria.

1907 German medical scientist Paul Ehrlich discovers synthetic antibiotics derived from arsenic, leading to the development of antibacterial treatments.

AFTER
1942 The first penicillin-resistant bacteria are discovered, just one year after the introduction of penicillin.

2015 The World Health Organization warns that unless the misuse of antibiotics stops, 10 million people each year will die from drug-resistant bacterial infections by 2050.

Antibiotics are medicine's wonder drugs, and their use has a surprisingly long history. Ancient civilizations used a variety of molds to combat infection. The application of moldy bread to wounds was widely practiced everywhere from Ancient Egypt to China, Greece, and Rome.

In 1877, Louis Pasteur and Robert Koch had both observed that some types of bacteria inhibited the growth of other bacteria. Other biologists, too, investigated what came to be called antibiosis, the chemical warfare waged by one microorganism on another.

Thanks to improvements in public health, most infectious diseases were in decline by 1900 but still accounted for a large proportion of deaths—34 percent in the US, for example. Scottish bacteriologist Alexander Fleming's accidental discovery of penicillin in 1928 pointed the way to a major new weapon to fight infectious diseases. By the middle of the century, it seemed possible that many might be eradicated.

Ancient Egyptians discovered that infections healed faster when treated with moldy bread, although they did not know the reason for this.

A serendipitous finding

In 1928, Fleming began a series of experiments with the bacterium *Staphylococcus aureus*. Returning from vacation, Fleming noticed a mold that had appeared on one of his samples was killing the bacteria that were in contact with it. He identified the mold as *Penicillium notatum* and found that it was also effective against the bacteria responsible for scarlet fever, pneumonia, and diphtheria. He realized that it was not the mold itself but the "juice" it produced that killed the bacteria. However, Fleming struggled to isolate more than the tiniest amounts of the substance, which he named "penicillin." When he published the

See also: Drugs and disease 143 ▪ Germ theory 144–51 ▪ Vaccination for preventing disease 164–67 ▪ Immune response 168–71

> … I certainly didn't plan to revolutionize all medicine …
> **Alexander Fleming**

findings of his experiments in 1929, he made only a passing reference to penicillin's potential therapeutic powers—and the scientific community took little notice of his paper.

The wonder drug

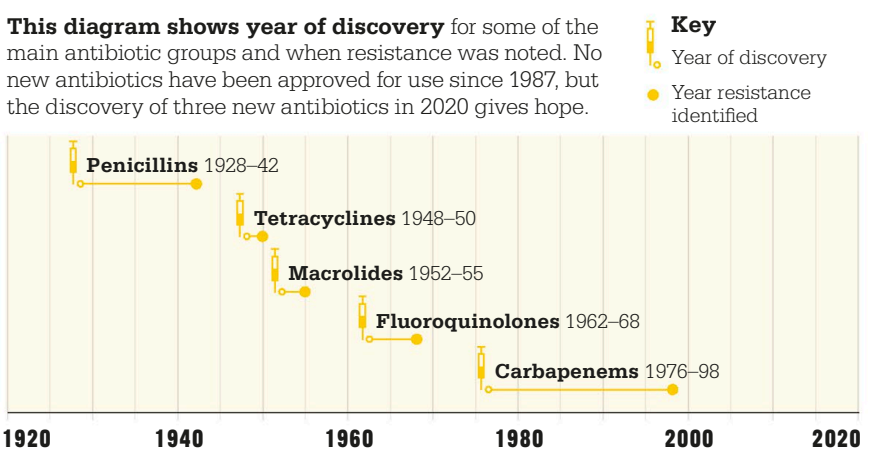
In 1938, a group of researchers at Oxford University turned their attention to purifying penicillin. Pathologist Howard Florey and biochemist Ernst Chain transformed their laboratory into a penicillin factory. They grew the *Penicillium* mold in huge quantities and stored it in any available container, including milk churns and baths.

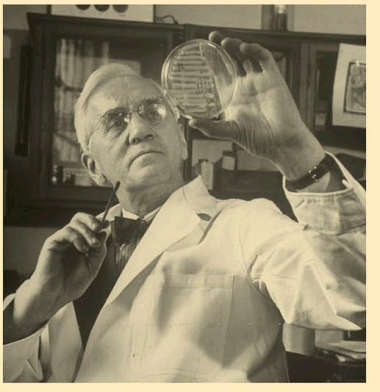
In 1941, 43-year-old policeman Albert Alexander became the first human recipient of the Oxford penicillin and began to make a remarkable recovery from what was a life-threatening infection. But Chain and Florey did not have enough pure penicillin to eradicate the infection entirely, and Alexander died a few days later.

A fortunate discovery led the team to the mold *Penicillium chrysogeum*, which produced far greater yields of penicillin. Production was stepped up enormously during World War II, and by September 1943 there was enough for the needs of the Allied armed forces. By the end of the war, huge numbers of lives had been saved, and penicillin had earned the name "the wonder drug."

Fleming, Florey, and Chain shared the 1945 Nobel Prize in Physiology or Medicine for their work. In his Nobel lecture, Fleming warned that the misuse of penicillin might lead to bacterial resistance. Indeed, the widespread use of antibiotics has led to the emergence of new strains of germs that are resistant to one or more of them. ■

This diagram shows year of discovery for some of the main antibiotic groups and when resistance was noted. No new antibiotics have been approved for use since 1987, but the discovery of three new antibiotics in 2020 gives hope.





Alexander Fleming

Born in Ayrshire, Scotland, in 1881, Alexander Fleming was the seventh of eight children in a farming family. In 1901, he won a scholarship to St. Mary's Hospital Medical School in London.

As a medical bacteriologist at St. Mary's, Fleming joined the staff of the Inoculation Department in 1906, where the focus of research was on strengthening the body's immune system through vaccine therapy. In 1921, he discovered a substance in his own nasal mucus that caused some bacteria to disintegrate. The substance, which Fleming named lysozyme, is an important component of many animals' innate immune systems—a natural antibiotic. In 1927, he began investigating the properties of bacteria in the genus *Staphylococcus*, work that would lead to his discovery of penicillin the following year. Fleming died in 1955 and was buried in St. Paul's Cathedral, London.

Key work

1929 *On the Antibacterial Action of Cultures of a Penicillium*

A PIECE OF BAD NEWS WRAPPED IN PROTEIN

VIRUSES

IN CONTEXT

KEY FIGURE
Rosalind Franklin (1920–58)

BEFORE
1st century BCE Roman scholar Marcus Varro suggests that some infectious diseases might be caused by invisible living agents.

1880s Louis Pasteur develops a vaccine against rabies.

1915 British bacteriologist Frederick Twort discovers "filterable agents" that can infect bacteria.

AFTER
1962 American physician John Trentin reports that human adenovirus can cause tumors in infected animals.

1970 Reverse transcriptase—an enzyme that certain viruses use to make DNA copies of their RNA—is first described.

In the mid-19th century, Dutch farmers noticed dark green tobacco leaves turning a mottled brown and yellow before dying. In 1879, German plant pathologist Adolf Mayer named the affliction tobacco mosaic disease. He showed that the sap from a sick tobacco leaf could pass the disease on to a healthy leaf. But he could not grow the disease-causing agent in a culture (as could usually be done with a bacterium); nor could he detect it with a microscope.

In 1887, Russian botanist Dmitri Ivanovsky strained the sap from sick tobacco leaves through a porcelain filter with pores too small for bacteria to slip through. When

See also: The cellular nature of life 28–31 ▪ Cell membranes 42–43 ▪ Germ theory 144–51 ▪ Vaccination for preventing disease 164–67 ▪ Immune response 168–71 ▪ The double helix 228–31 ▪ Genetic engineering 234–39 ▪ Gene editing 244–45

This tobacco leaf has brown and yellow mottling due to tobacco mosaic disease. The only way to eliminate the virus is to destroy infected plants.

he put the filtered sap on a healthy tobacco leaf, it became diseased. He concluded that either tobacco mosaic disease was caused by a poison secreted by bacteria, or that some bacteria had squeezed through a crack in the porcelain.

Smaller than bacteria

Dutch microbiologist Martinus Beijerinck conducted similar experiments with filters but came to a different conclusion. He proposed that the causative agent of tobacco mosaic disease was not a bacterium but something smaller and non-cellular. When he published his findings in 1898, he introduced the word "virus" to refer to this new kind of pathogen. Like Mayer and Ivanovsky before him, Beijerinck was unable to grow it in a culture but, from his experiments, became convinced that it could invade and proliferate within the cells of a living plant.

Scientists began to look into other diseases of unknown cause. In 1901, for example, American researchers concluded that yellow fever was also caused by a "filterable agent"—that is, something small enough to pass through a porcelain filter. Scientists suspected that foot-and-mouth disease in livestock was caused by a similar agent. However, the researchers were still not convinced that these diseases were caused by a non-cellular pathogen, as Beijerinck had proposed.

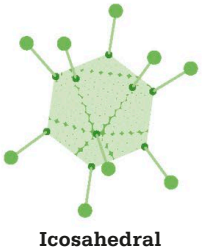
Viruses are particles

In 1929, American biologist Francis O. Holmes reported that dilute sap from infected tobacco plants could produce small, discrete areas of necrosis (death) when spread onto non-infected, live tobacco leaves. The more dilute the sap, the more widely spaced the "death spots" became. This discovery suggested that the causative "virus" was in the form of discrete particles, or large molecules, rather than dissolved substances with small molecules.

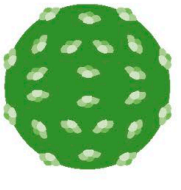
In the early 1930s, the first electron microscopes were developed. They had a much higher resolution than light microscopes, and by the end of the decade, the first clear images of viruses started to appear. These proved that viruses were particles. In most cases, they looked quite unlike bacteria, and they differed in shape and size from one disease to another, typically measuring 20–1,000 nanometers (nm) across. Bacteria are generally much larger: they average 2,500 nm across, and the largest known has a diameter of 0.03 in (0.75 mm).

In the mid-1930s, scientists made progress in determining the composition of viruses. American biochemist Wendell Stanley created a crystalized sample of the tobacco mosaic virus (TMV), and by treating samples with various chemicals and examining the breakdown products, he discovered that viral particles are an aggregate of protein and nucleic acid molecules. »

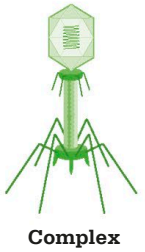
Examples of virus particle shapes



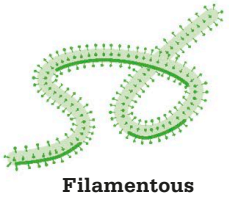
Icosahedral
Adenovirus



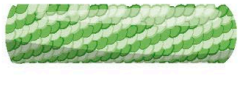
Spherical
Influenza virus



Complex
Bacteriophage



Filamentous
Ebola virus



Helical rod
Tobacco mosaic virus

Bullet-shaped
Rabies virus

From the 1940s, researchers used the relatively new technique of X-ray crystallography to study the structure of viruses. Many of the final details of the structure of TMV were established by British X-ray crystallography expert Rosalind Franklin, who had previously contributed to the discovery of DNA's structure. In 1955, she made the clearest X-ray diffraction images of TMV to date. Later that year, she published a research paper stating that all TMV particles are of the same length. Franklin was soon postulating that each TMV particle has two parts, the outer part being a long, thin hollow rod or tube consisting of protein molecules, arranged in helices (spirals), and the inner part being a spiral strand of RNA wound along the inner surface of this tube. These ideas were later proven correct. With fellow researchers, Franklin also investigated the structures of other plant viruses, as well as the virus that causes polio.

By the late 1950s, thanks to the work of Franklin and others, it was established that viruses are made of nucleic acid (either RNA or DNA) wrapped in a solid, rigid outer protein covering called a capsid—a structure very different from that of bacteria. In the 1960s, scientists discovered that some animal viruses have an additional lipid (fatty) outer layer, called an envelope, often with embedded protein molecules.

Virologists now know that the protective capsule or envelope has two functions: to protect its core RNA or DNA from enzymes in the host organism's immune sysem; and to attach to a specific receptor on a prospective host cell.

Each **tobacco mosaic virus (TMV) particle** is known to contain some **RNA (ribonucleic acid)** and some **protein**.

X-ray diffraction studies suggest that the **protein** component is a **hollow tube**, consisting of many subunits arranged in **helices (spirals)**.

The protein provides a protective capsule for the virus particle's genetic material, or RNA, which lies inside the hollow tube subunits.

Life cycle and replication

By the late 1950s, biologists were broadly in agreement that viruses multiply within the cells of the animals or plants that they infect,

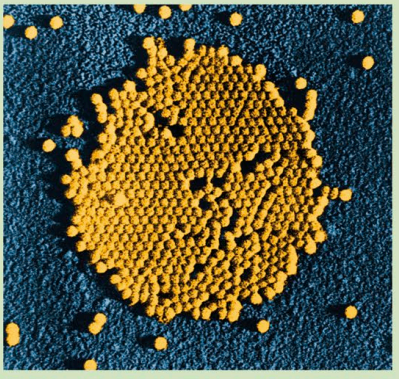
Rosalind Franklin

Born in London, UK, in 1920, Franklin was identified at school as someone with outstanding scientific talents. She studied natural sciences at the University of Cambridge, graduated in 1941, and earned a doctorate in 1945. Two years later, she moved to Paris, where she became an expert in X-ray diffraction. Returning to London, in 1951, Franklin joined a team at King's College that was using this technique to establish the 3D structure of DNA. One of her students took Photograph 51, the critical evidence in this quest.

In 1953, Franklin started to investigate the structures of RNA and the tobacco mosaic virus, laying the foundations of structural virology. Although she was diagnosed with ovarian cancer in 1956, she continued working until her untimely death in 1958, aged 37.

Key works

1953 "Evidence for 2-Chain Helix in Crystalline Structure of Sodium Deoxyribonucleate"
1955 "Structure of Tobacco Mosaic Virus"



The polio virus was first imaged in 1952. This picture was made by an electron microscope in 2008 and colourized for clarity.

The electron microscope and virus detection

An electron microscope (EM) directs a beam of fast-moving electrons at the object to be imaged. The first electron microscope was developed in 1931 by German scientists Ernst Ruska and Max Knoll and could magnify 400 times. The most powerful modern electron microscope can create images to a resolution of half the width of a hydrogen atom.

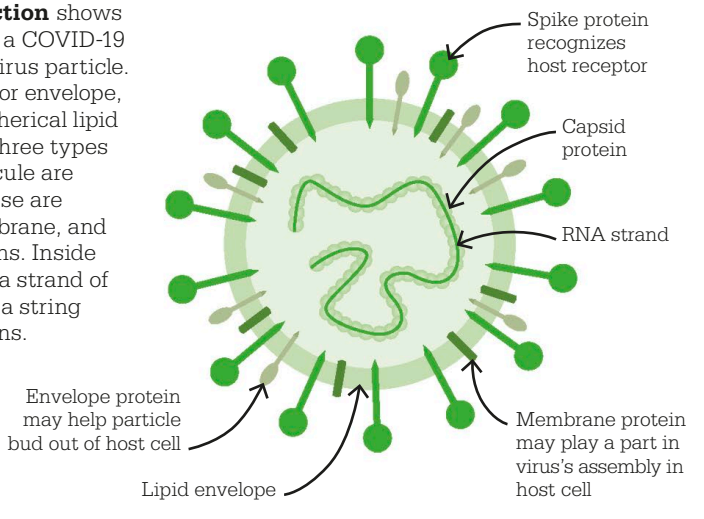
Electron microscopes have been invaluable tools in both identifying viruses and detecting new ones. In 1939, Ruska and two colleagues were the first to image a virus (TMV). Then, in 1948, differences were shown between the viruses responsible for smallpox and chickenpox. Virologists also use electron microscopy to investigate the cause of new outbreaks of disease. In 1976, they used it to detect the pathogen responsible for Ebola virus disease in Africa. It is also invaluable for studying the interactions between viruses and their host's cells and tissues.

though exactly how they did so was something of a mystery. During the 1960s, by putting together evidence gathered over the previous 25 years, biologists were finally able to work out how viruses replicate.

A virus needs a host cell in order to replicate. It will remain inert if it does not infect an organism. Once a virus has encountered a suitable host cell, it usually attaches itself and injects its nucleic acid through the cell's outer covering. Alternatively, the whole virus particle may be swallowed into the cell, where it releases its nucleic acid. The viral nucleic acid then hijacks the cell's protein manufacturing systems and DNA replicating mechanism to make many copies of itself, and part of the nucleic acid directs the manufacture of protein components for new viral particles. The new nucleic acid and protein components then self-assemble into new virus particles, which finally burst out of the cell, destroying it and then spreading the infection by rapidly invading and destroying other cells in similar fashion. The fine details of life cycle and replication vary somewhat from one virus to another—with specific differences, for example, between viruses that carry DNA and those that carry RNA as their nucleic acid. An enormous amount of research has been devoted to understanding different groups of viruses and their life cycles—and devising methods for combatting them. Examples of common viral infections include various strains of influenza, chickenpox, and mumps. Ebola virus disease was discovered in 1976, and COVID-19 in 2019. In 2020, scientists developed vaccines to prevent COVID-19.

Research has shown how viruses are everywhere in the environment. For example, there are approximately 10 million viral particles in a single teaspoon of seawater. Most of these are viruses that infect bacteria and cyanobacteria. The overwhelming majority of them are harmless to humans and other animals and are essential to the regulation of marine ecosystems. ■

This cross-section shows the structure of a COVID-19 (SARS-CoV-2) virus particle. The outer part, or envelope, consists of a spherical lipid layer in which three types of protein molecule are embedded. These are the spike, membrane, and envelope proteins. Inside the envelope is a strand of RNA packed in a string of capsid proteins.



THERE WILL BE NO MORE SMALLPOX

VACCINATION FOR PREVENTING DISEASE

IN CONTEXT

KEY FIGURE
Jonas Salk (1914–95)

BEFORE
1796 Edward Jenner uses cowpox to inoculate against the highly contagious and often deadly smallpox disease.

1854 In his work with cholera, Italian physician Filippo Pacini is the first to link a disease to a specific bacterium.

1885 Louis Pasteur creates a vaccine for rabies.

AFTER
1962 The world's first anti-polio vaccine to be administered orally is licensed.

1968 A measles vaccine developed by Maurice Hilleman is distributed.

1980 The World Health Organization (WHO) announces that smallpox has been eradicated globally.

A vaccine gives a person, or animal, active immunity to a disease. American virologist Jonas Salk's great contribution to science was to introduce the first effective vaccine for poliomyelitis (or polio), a disease that causes spinal and respiratory paralysis and is often ultimately fatal. This infectious and incurable illness has existed for thousands of years, but major outbreaks started to occur in Europe and the US in the late 19th century. In 1952, there was an outbreak in the US of 58,000 cases, leaving more than 3,000 people dead and 21,000 with some form of paralysis. Salk believed he could create immunity by killing

See also: Biochemicals can be made 27 ▪ Drugs and disease 143 ▪ Germ theory 144–51 ▪ Viruses 160–63 ▪ Immune response 168–71 ▪ Mutation 264–65

the polio virus and injecting it into the bloodstream of healthy people. He argued the harmless dead virus would stimulate the body's immune system to produce antibodies, which would defend against future poliovirus attacks. Salk was right, and in 1954 a polio immunization trial was rolled out to children in Canada, the US, and Finland. His vaccine, called an inactivated vaccine because it used dead viral material, was adopted in the US the next year. In 1961, only 161 polio cases were recorded in the US.

Also during the 1950s, Polish-American virologist Albert Sabin became convinced the polio virus lived primarily in the intestines before attacking the central nervous system. He isolated a mutant form of the virus that was not capable of producing the disease and administered this to friends, family, work colleagues, and himself. His vaccine used a weakened, non-lethal form of the virus and displaced the lethal form, providing protection; this is known as an attenuated vaccine. It could be given orally, making it quicker and cheaper to inoculate large numbers of people. Licensed for use in the US in 1962, this vaccine was given to millions of people around the world. In 2020, the World Health Organization (WHO) announced that poliovirus was transmitted in just two countries: Pakistan and Afghanistan.

> There is no patent. Could you patent the Sun?
>
> **Jonas Salk**
>
> **When asked who owned the patent for his polio vaccine**

Long history of treatments

An infectious disease that is thought to have emerged in around 10,000 BCE, smallpox is estimated to have killed up to 300 million people worldwide in the 20th century alone. Efforts to fight it began with 15th-century physicians in China, who blew powdered smallpox scabs up the nostrils of healthy people to prevent the disease. Another approach, which grew to be more widespread, involved taking pus from a smallpox sufferer and introducing it to a non-immune person via a scratch. Called variolation, these treatments often worked, but not always—and the recipient of the inoculation sometimes died.

In the 1760s, British physician Edward Jenner took an interest in smallpox. At the time, it was common knowledge that smallpox survivors became immune, and he himself had been variolated as a child. Jenner heard that dairy workers rarely caught smallpox because they often contracted cowpox from the cattle that they milked; cowpox produces only mild symptoms in humans. In 1796, he took some pus from the hand of Sarah Nelms, a milkmaid who »

Widespread vaccination against polio began in the 1950s. Children were encouraged to think of vaccination as "fun" and rewarded with a lollipop.

Variolation

While in Constantinople (now Istanbul) in 1716, English aristocrat Mary Montagu learned that the practice of variolation to protect against smallpox was widespread in the Ottoman Empire. She and her brother had previously contracted the disease, and her brother died. At her insistence, the British Embassy's surgeon inoculated her young son. Montagu became a passionate advocate of inoculation when she returned to England.

In 1768, Catherine the Great, Empress of Russia, invited Scottish physician Thomas Dinsdale to variolate her and her son to demonstrate to her people that it was safe and effective. She developed a mild case of the disease after the procedure, but it cleared up 16 days later. Her action persuaded 20,000 of her subjects to follow her example over the next three years. Despite this, smallpox variolation was not risk-free. Recipients could pass a mild form of the disease on to others and sometimes died themselves.

Dairy workers in the 1700s rarely caught **smallpox**.

It was usual for dairy workers to **contract mild cowpox**—though **once recovered**, they did not catch it again.

It seemed that **contracting cowpox** offered protection **against smallpox**.

Doctors were persuaded they should infect people with cowpox to inoculate them against smallpox.

had contracted cowpox, and scratched it into the arm of eight-year-old James Phipps. Phipps developed a mild fever, but within 10 days he was better. Six weeks later, Jenner inoculated him with smallpox. The boy did not develop the disease.

Despite scepticism, Jenner was successful in persuading many doctors to employ cowpox as a vaccine for smallpox in the early 19th century. While he was not the first to advocate its use, it was Jenner's relentless campaigning that meant it was adopted widely. Later versions of his vaccine would save millions of lives. What made this even more remarkable was that scientists at the time did not understand that disease was caused by germs. That discovery would be made later, by French microbiologist Louis Pasteur.

Further vaccinations

Pasteur made great breakthroughs in the development of vaccines in the 1880s. He noticed old cultures of the bacterium (*Pasteurella multocida*) that causes chicken cholera had, over many generations, become less virulent (attenuated). When he then inoculated chickens with attenuated bacteria, they became resistant to the original virulent strain.

Next, Pasteur turned his attention to anthrax, a disease caused by the bacterium *Bacillus anthracis*. Anthrax, which is fatal for humans, was killing thousands of sheep at that time. Pasteur began experimenting with two groups of sheep and demonstrated that those vaccinated with an attenuated culture of the bacterium survived when later given a strongly virulent dose. In contrast, the unvaccinated animals died.

Pasteur's final vaccination challenge concerned rabies, which was caused by a virus too small for him to see through his optical microscope. Nevertheless, he was able to grow the virus in rabbits and then attenuated it by drying the rabbits' virus-affected nerve tissue. In 1885, he treated a boy who had been bitten by a rabid dog: over 11 days, he administered 13 inoculations, each increasingly virulent. Three months later, the child was back to good health,

Jenner's smallpox vaccination faced opposition for some time, despite its obvious success. James Gillray's 1802 cartoon satirized it by depicting cows sprouting from bystanders as a woman is inoculated.

with no symptoms of rabies, and Pasteur's vaccine was hailed as a great success.

Acquired immunity

Scientists now understand that the body's immune system is a network of cells, tissues, and organs that work together to fight the bacteria and viruses that cause illness. When such pathogens invade the body, a healthy immune system responds by creating large proteins, called antibodies. Each type of antibody is specific to a particular pathogen and destroys those that remain in the body after the infection has gone. If it returns, the immune system has a "memory" of the pathogen and can quickly respond.

Vaccines operate on the same principle but provide immunity before the body has been invaded. A vaccine contains a weakened, inactive, or artificial form of the pathogen being inoculated against. When injected, it triggers an immune response and only mild (if any) symptoms of the disease. In the 1940s, an inactivated vaccine was developed to protect against influenza. However, the viruses responsible for this common illness change so quickly that the vaccine's effectiveness was reduced over time. Today, anti-flu vaccines are updated every year: inactivated versions are given to pregnant women and people with certain chronic medical conditions, while an attenuated version is given to people without underlying health conditions.

> Smallpox is dead!
> **World Health Organization, 1980**

In 1968, Maurice Hilleman, an American microbiologist, developed an attenuated vaccine for measles, the most infectious disease known. Before the early 1960s and the widespread introduction of vaccination, measles caused an estimated 2.6 million deaths each year. The vaccine is now given to millions of children around the world. In the 1990s, both attenuated and inactivated vaccines were created to prevent hepatitis A, a liver infection caused by another virus.

Targeting toxins

Tetanus and diphtheria are two examples of diseases that occur when pathogenic bacteria secrete toxins. They are treated with toxoid vaccines, which stimulate an immune response that targets the toxin rather than the whole pathogen. Subunit vaccines target specific parts of a pathogen—its protein, sugar, or outer casing.

One example is the vaccine for human papillomavirus (HPV), a sexually transmitted infection that can cause cancers. The vaccine is made from tiny proteins that resemble the outside of the real HPV. The body's immune system is fooled into thinking this is HPV and produces antibodies. When someone is exposed to the real virus, these antibodies prevent it from entering cells. Since the vaccine doesn't contain the actual virus, it can't cause cancer, but it does provide immunity. ■

An Ebola outbreak in West Africa between 2014 and 2016 killed 11,000 people. Ring vaccination was used to help prevent many more deaths.

Ring vaccination

By the mid-1960s, vaccination programs had eliminated smallpox in Europe and North America. However, in 1967, 132,000 cases were still being reported elsewhere in the world, and this figure was almost certainly an underestimate.

The World Health Organization (WHO) decided to move away from using mass vaccination, which was expensive and not targeted, and successfully deployed ring vaccination instead. This approach involves identifying all the individuals who might have been in contact with someone with the disease (the so-called inner ring) and quarantining and vaccinating those people. An outer ring—anyone who had been in contact with these individuals—is then also vaccinated.

India, one of the last bastions of smallpox, had 86 percent of the world's smallpox cases in 1974, but within two years of starting ring vaccination, there were no cases there at all. In 1980, the WHO announced the global eradication of smallpox.

ANTIBODIES ARE THE TOUCHSTONE OF IMMUNOLOGICAL THEORY

IMMUNE RESPONSE

IN CONTEXT

KEY FIGURE
Frank Macfarlane Burnet (1899–1985)

BEFORE
1897 Paul Ehrlich proposes the side chain theory to help explain how the immune system works.

1955 Niels Jerne describes what Frank Burnet would call clonal selection.

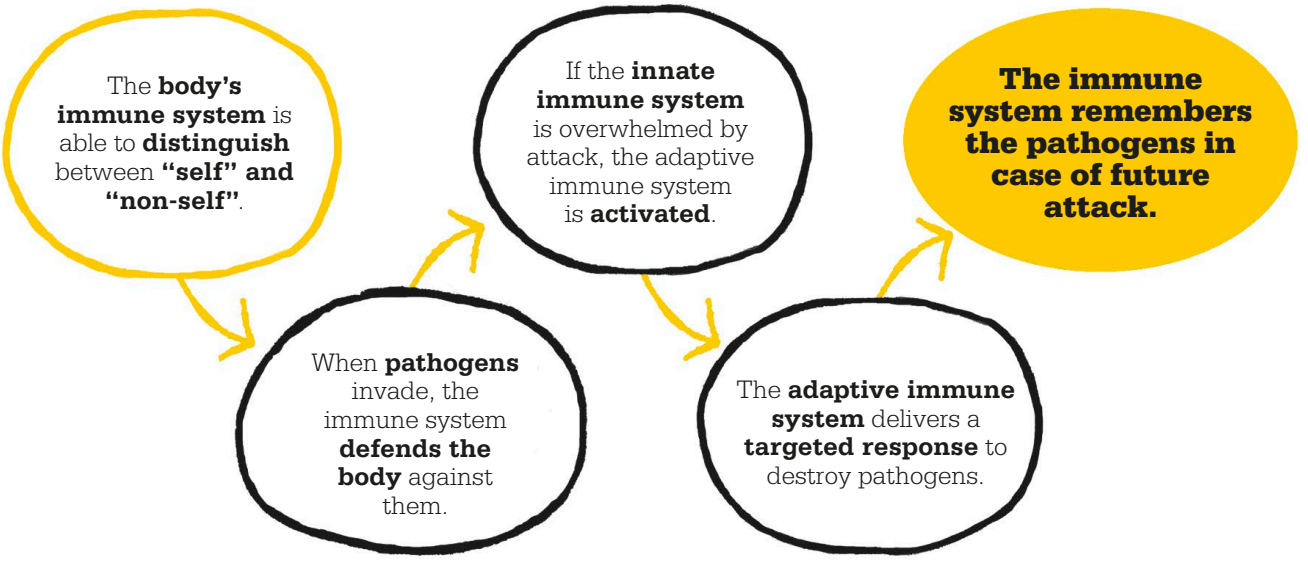
AFTER
1958 Australian immunologist Gustav Nossal and American geneticist Joshua Lederberg show that one B-cell always produces only one antibody—evidence for clonal selection.

1975 Hungarian-Swedish immunologist Eva Klein discovers natural killer cells.

1990 Gene therapy for severe combined immunodeficiency (SCID) is developed in the US.

The body is protected from hostile pathogens (fungi, bacteria, and viruses), parasites, and cancers by its immune system, which is formed of several lines of defense and can broadly be divided into innate and adaptive. The innate immune system is a combination of general defenses, including the skin and a variety of cells that attack invading pathogens. These cells include phagocytes, which ingest pathogens, and natural killer cells, which destroy infected cells that host viruses. If the innate immune system cannot cope with a pathogenic attack, the adaptive immune system is activated to join

See also: Germ theory 144–51 ▪ Cancer metastasis 154–55 ▪ Blood groups 156–57 ▪ Viruses 160–63 ▪ Vaccination for preventing disease 164–67 ▪ What are genes? 222–25 ▪ The genetic code 232–33



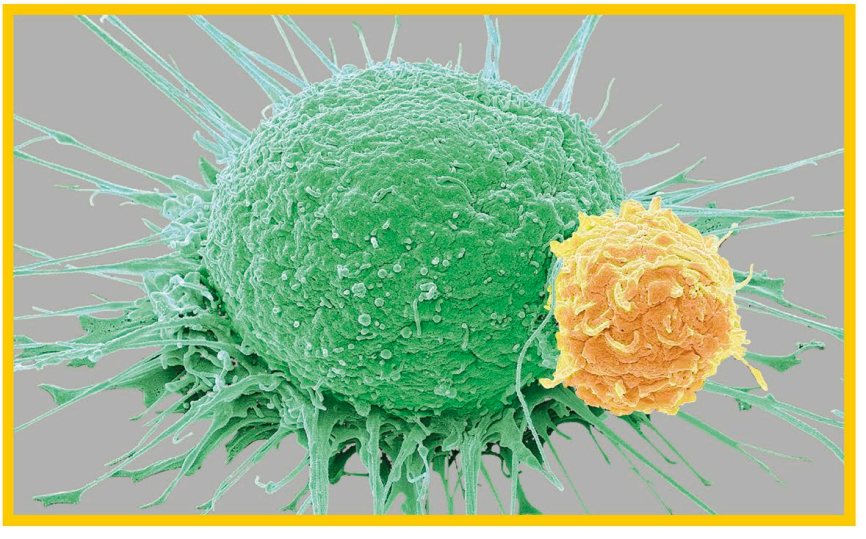
the fight. The adaptive immune system uses a type of white blood cell called lymphocytes to deliver a more targeted response. The most important of these are called B-cells and T-cells.

Clonal selection

In 1955, Danish immunologist Niels Jerne proposed that there is a vast array of lymphocytes in the body prior to any infection—and that when a pathogen enters the body, one type of lymphocyte is selected to match it and produce an antibody to destroy it. Australian immunologist Frank Macfarlane Burnet supported Jerne's idea when, in 1957, he said that the selected lymphocyte is reproduced (cloned) on a grand scale to ensure enough antibodies to defeat the infection.

Burnet named this process clonal selection and went on to explain the ability of the immune system to remember the unique molecular structure (antigen) found on the surface of pathogens. He suggested that, while some lymphocytes act immediately to attack the pathogen, others retain the memory of the antigen in case of future attack. These remain in the immune system for a long time, providing the body with immunity.

Jerne and Burnet owed much to the research conducted by German bacteriologist Paul Ehrlich. In 1897, he proposed the side chain theory of antibody production, in which each cell in the immune system expresses (generates) many »



A T-cell lymphocyte is pictured (in yellow) attached to a prostate cancer cell in this electron micrograph. Some T-cells recognize tumor antigens on the surface of a cancer cell and bind to it.

different "side chains" (receptors)—proteins that can bind to molecules outside the cell. He believed that these cells act as antibodies, protecting the body against subsequent exposure to infection.

Ehrlich was not entirely correct. He thought that every immune cell expressed all the many types of receptors that can give rise to antibodies. However, he could not explain how a single cell could express the required receptors for the many different kinds of antigen. Another problem was later flagged by Austrian immunologist Karl Landsteiner, who showed that antibodies can be generated to target chemically synthesized antigens. This raised the question as to why cells would have preformed receptors for non-organic substances. But Burnet realized that each cell has only one receptor.

The main agents of the body's adaptive immune system, B-cells and T-cells, each have receptors (BCRs and TCRs) that can bind to other cells, but they also undergo a remarkable process when they divide. A deliberate reshuffle of their genetic material gives each new cell a unique receptor—a staggering diversity, enabling the body to recognize and respond to any potential antigen.

The function of all B-cells and T-cells is to identify and destroy pathogens and cancers, but they operate very differently. B-cells produce antibodies and act against pathogens outside the body's cells, such as bacteria. T-cells act against pathogens that invade cells, such as viruses, and against cancers, which cause changes within cells.

When a pathogen enters the body, specialized phagocyte cells investigate and destroy it. They then present (display) the pathogen's specific antigen on their membranes. This enables a B-cell or T-cell with a receptor that recognizes the antigen to bind to it. It then rapidly clones itself, creating an army to target the invader.

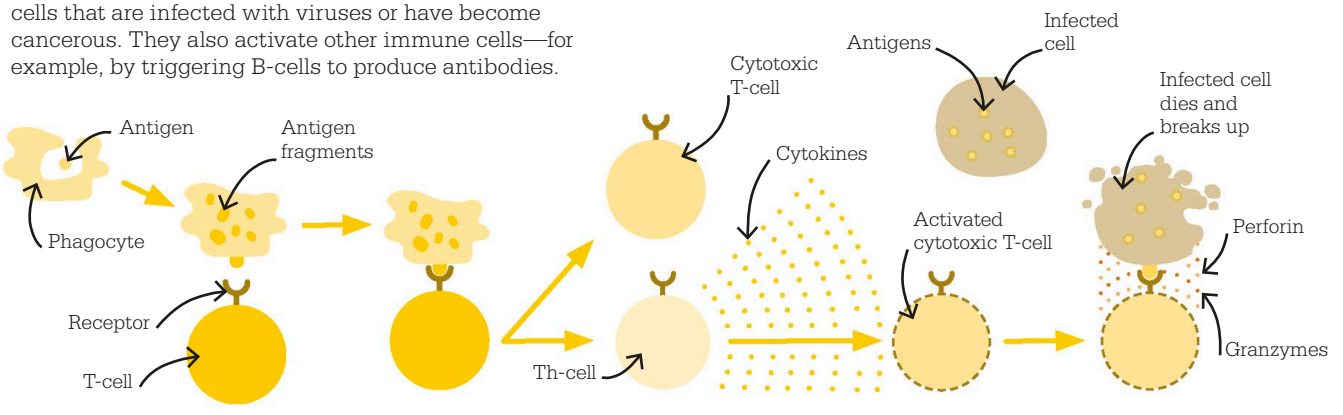
Both B-cells and T-cells are produced in bone marrow, but T-cells develop further in the thymus. They then circulate around the body

> The immune system embodies a degree of complexity which suggests … striking analogies with human language.
> **Niels Jerne**

until they meet an antigen they recognize, which triggers them to multiply and mature into different types. A type called a T-helper cell (Th-cell) activates other immune cells and helps B-cells produce antibodies, while cytotoxic ("killer") T-cells destroy affected cells directly. Th-cells release signaling proteins called cytokines, which activate the cytotoxic cells.

Following infection, antigen-specific, long-lived-memory T-cells and B-cells are formed. These are

T-cells play a vital role in the adaptive immune response. They specialize in cell-mediated immunity, destroying cells that are infected with viruses or have become cancerous. They also activate other immune cells—for example, by triggering B-cells to produce antibodies.



A T-cell meets a phagocyte that has ingested an antigen that it recognizes. The phagocyte presents fragments of the antigen on its surface.

The T-cell receptor binds to the antigen, and the cell starts to clone itself, producing about 1,000 new cells.

New cells mature into two different types: cytotoxic cells that kill infected cells, and T-helper cells (Th-cells), which secrete cytokines.

Cytokines activate the cytotoxic cells to attack the infected cells.

A cytotoxic cell locks onto an infected cell and kills it by releasing the toxins perforin and granzymes.

able to multiply very quickly in response to the reappearance of their target antigen.

Employing vaccination

Vaccines provide the body with acquired immunity by exposing it to something that it recognizes as a pathogen—often killed or inactivated microbes—which stimulates the immune system to attack without causing disease. The effectiveness of vaccines relies on the ability of the adaptive immune system to memorize antigens of pathogens. The result is that if the live pathogen later infects the body, the immune system recognizes its antigens and responds quickly to prevent infection spreading.

Vaccines act in many different ways according to the number and characteristics of their ingredients. Broadly, there are two types, producing either active or passive immunization. Active immunization stimulates the body to generate its own anti-infection response through its B-cells and T-cells. This takes time to develop, but the effect is long-lasting, as with the varicella (chickenpox) vaccine. Passive immunization involves providing the immune system with ready-made antibodies; this gives protection that is immediate but short-lived—examples include temporary immunization for diphtheria, tetanus, and rabies.

> The AIDS crisis has brought us a consciousness of the immune system as the most important health-maintenance element …
>
> **Gloria Steinem**
>
> **American feminist political activist**

Organ transplant rejection

A fundamental feature of an immune system is that it can distinguish between pathogens and the body's own healthy tissue. However, this is a problem when it comes to transplantation. Since the first successful kidney transplant, carried out by American surgeon Joseph Murray in 1954, thousands of people with damaged or diseased organs or tissues have benefited from receiving healthy donated replacements, but there is always the danger that the donated organ or tissue will be rejected by the recipient's immune system.

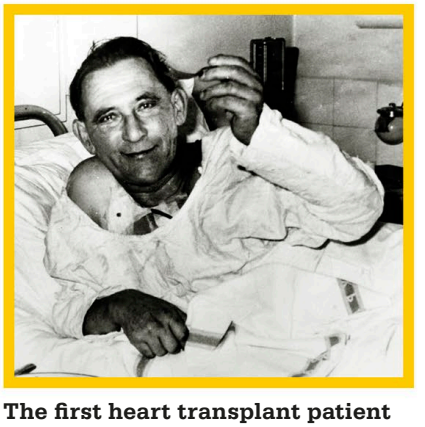
The human leukocyte antigen (HLA) complex is a group of genes that encodes the proteins on the surface of all cells. Everyone has their own near-unique set of HLA proteins, and these act as "self badges." The immune system will ignore such badges, but a transplant recipient's immune system may attack any donor cells that it sees as foreign, causing the organ to be rejected. The donor and recipient in the 1954 kidney transplant were identical twins, so there was only a limited risk of rejection, but this option is rare.

Clinicians mitigate the risk of organ rejection by ensuring that the blood groups and tissues of donor and recipient are compatible. They can also treat recipients with immunosuppressant drugs, which reduce the strength of their body's immune response. ■

The search for vaccines

In 1981, a new virus affecting humans was observed in the US, and in 1984 it was identified as the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS). The virus invades T-helper cells, reducing their numbers critically and leaving the body increasingly vulnerable to infections and cancer. By the mid-1980s, AIDS was a global epidemic, with sub-Saharan Africa the hardest hit. By 2019, an estimated 32 million people had died from the disease. While treatments exist to control the virus, a successful vaccine to prevent infection has not yet been found.

The coronavirus COVID-19, identified in China in November 2019, caused a pandemic that led to global economic and social disruption. By the end of 2020, over 83 million people had been infected and 1.8 million had died. In the race to find a vaccine, many options were developed, and by the start of 2021, several had passed clinical trials and were being administered.



The first heart transplant patient was Louis Washkansky, aged 53, shown here recovering in a hospital bed in South Africa in 1967. However, he died 18 days later from pneumonia.

GROWTH
REPROD

AND
UCTION

With his observation of sex cells, Antonie van Leeuwenhoek confirms William Harvey's theory that **all animals develop from eggs**.

1678

Christian Sprengel explains the **fertilization of plants** by both insect and wind pollination.

1793

Oscar Hertwig is the **first** to **observe fertilization**, the fusion of sperm and egg cells.

1878

1740s

Independently, Abraham Trembley and Charles Bonnet both describe **asexual reproduction**.

1828

Using observation of **embryos** from ovum to birth, Karl von Baer shows that they are **not preformed**.

A defining feature of living organisms is an ability to grow and reproduce, so the mechanisms of reproduction and growth are an important area of study in biology. However, as with many other fields of biological research, comparatively little was known about these areas until the development of microscopes allowed scientists to examine the processes at a cellular level.

Ideas of how sexual intercourse led to pregnancy and birth before then were largely assumptions—and, as such, these explanations lacked detail and were often erroneous. One of the first truly scientific propositions to emerge in the 17th century was William Harvey's suggestion that all animals—including mammals—begin life and develop from eggs. At much the same time, Antonie van Leeuwenhoek was examining semen under a microscope, and observed tiny organisms with an apparent head and wriggling tail.

Homunculus theories

Two competing theories emerged. One held that the ovum, or egg, contains a minuscule version of the adult—a homunculus—which then simply grows; the other that such a homunculus is in the head of the sperm cell, which is deposited in the female, who provides the right conditions for its development. The debate raged for almost a century, until Lazzaro Spallanzani suggested the possibility that both sperm and egg are necessary to form a new individual. This idea was only definitively confirmed in the 1870s, when Oscar Hertwig was able to observe fertilization—the fusion of sperm and egg cells—in sea urchins.

One misconception, however—that of a preformed homunculus existing in either the sperm or the ovum—was scotched by Karl von Baer in the 1820s. From his observation of embryos at every stage from ovum to birth, he showed that they begin as simple, undifferentiated eggs, and gradually develop increasingly complex body parts.

Asexual reproduction

The debate had focused around sexual reproduction of animals such as mammals and birds, but it had been known since the mid 18th century that some other animals and less complex organisms reproduce asexually. In the 1740s,

August Weismann identifies the role of **meiosis** in reducing the **number of chromosomes** by cell division in sexual reproduction.

1890

Lewis Wolpert develops his "French flag" theory of the development of an embryo from an **asymmetrical fertilized egg**.

1969

A team led by Keith Campbell creates Dolly the sheep, the **first mammal** to be successfully **cloned**.

1996

1878

The **stages of mitosis**—the growth and then division of cells—are **described** by Walther Flemming.

1892

In his research on sea urchins, Hans Driesch **discovers stem cells** in early-stage embryos have the potential to develop into any part of the adult.

1978

The first human baby created by **in vitro fertilization**, using techniques developed by Robert Edwards and Patrick Steptoe, is born.

Abraham Trembley described the asexual reproduction of hydra by budding, and his colleague Charles Bonnet described a form of "virgin birth" in aphids. Also in the 18th century, Christian Sprengel noticed that cross-fertilization is necessary for plants to produce a fertile seed, a process achieved by pollination, either by insects or the wind.

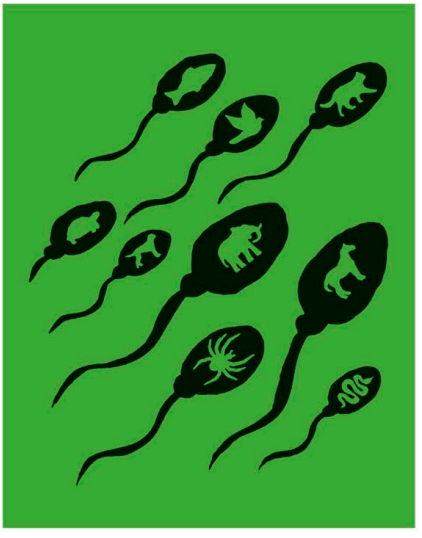
New discoveries

The discovery that cells are the basic building blocks of all living organisms was a game-changer in the study of reproduction and growth, and Rudolf Virchow's assertion that cells are only formed by cells challenged some long-standing assumptions. In light of this idea, the growth of organisms was examined at a cellular level, and in 1878, Walther Flemming observed a cycle of changes in the cells of a developing organism involving growth and then division: the process of mitosis. He also noted that after division, each new cell retains the same number of chromosomes, preserving a complete duplicate of the genetic information of the original cell. A few years later, August Weismann also focused on the chromosomes, describing a particular kind of cell division—meiosis—in sexual reproduction that prevents doubling of the number of chromosomes when a sperm fuses with an egg.

Stem cells

Other research into the cells of early embryos confirmed that embryos developed from simple cells to more complex organisms. Furthermore, Hans Driesch observed that the very early cells, known as stem cells, each contain a full set of an organism's genetic information, and have the potential to become a fully formed adult. Some 70 years later, Lewis Wolpert, explained how, when all the cells of an embryo are genetically identical, the different organs of the adult can develop. His theory was that the fertilized egg itself is asymmetrical, which is responsible for an uneven distribution of certain chemicals triggering genetic responses.

Recent advances in theoretical embryology and biotechnology have found several important applications—cloning of animals to provide genetic material for stem cell research and therapy, for example, and successful human in vitro fertilization for couples having problems with conception. ■



THE LITTLE ANIMALS OF THE SPERM

THE DISCOVERY OF GAMETES

IN CONTEXT

KEY FIGURE
Antonie van Leeuwenhoek (1632–1723)

BEFORE
***c.*65 BCE** Roman philosoper and poet Lucretius writes that men and women produce fluids containing seeds for procreation.

***c.*1200s** Islamic physicians suggest seeds for reproduction are made in several organs and congregate in the sex organs.

1651 William Harvey's *On the Generation of Animals* states, "Everything from an egg."

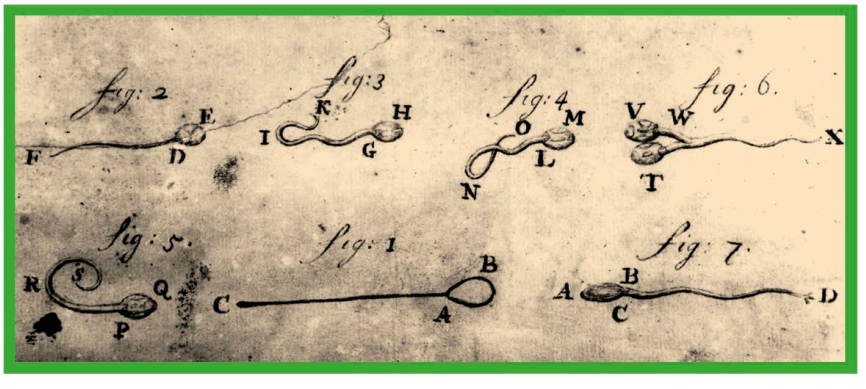
AFTER
1916 American gynecologist William Cary introduces the first "sperm count" tests for men unable to father children.

1978 Louise Brown is the first human baby born after in vitro fertilization (IVF).

From ancient times, people knew that female–male sexual intercourse preceded pregnancy and birth, and that male semen (seminal fluid) was vital. Suggestions about how conception happened included the mixing of female and male fluids, the passing of seeds between partners, and a mystical "generative spirit" in the body that migrated to the genitals.

Early beliefs

Following the invention of the microscope around 1590, early users trained their instruments on all kinds of objects and materials. A favorite was the semen of male animals, including humans. In 1677, Dutch cloth merchant and microscope innovator Antonie van Leeuwenhoek reported that semen contained minute wriggling organisms. He was not the first to see them—later, he would credit Johan Ham, a medical student in Leiden. Van Leeuwenhoek drew and described, in his native Dutch, "very small living animals," showing that each had a head and a thrashing tail. In noting such details, van Leeuwenhoek was ahead of his time. His self-made microscopes magnified much more, and much more clearly, than those of his contemporaries.



Human sperm as observed and drawn by Antonie van Leeuwenhoek, and included in his letter to the Royal Society of London, 1677; the heads and tails he described are clearly visible.

See also: Asexual reproduction 178–79 ▪ Fertilization 186–87 ▪ In vitro fertilization (IVF) 198–201 ▪ The chemicals of inheritance 221

As other investigators began to observe what we now call sperm cells, an early suggestion of van Leeuwenhoek's gained popularity: they were parasites that lived in the male body, especially in the sex organs, the testes. Another view gaining credence was that a sperm was the sole precursor of a baby. The female body supplied conditions for its growth, but not much else. This was the "spermist" belief. By 1685, van Leeuwenhoek suggested that inside a sperm's head was a tiny human body, or homunculus, ready to enlarge and be born.

> The male seed of whatever members of the animal kingdom contains … all the limbs and organs which an animal has when it is born.
> **Antonie van Leeuwenhoek**

Spermists and ovists

In the late 1670s, Dutch naturalist Nicolaas Hartsoeker also witnessed squirming sperm cells. He too adopted the spermist view, and his 1694 *Essai de Dioptrique* (*Essay on Dioptrics*) included a sketch of a minute human curled up inside a sperm cell head, but he admitted he never actually saw this.

The "ovists" also had a preformist view: there was a ready-made, tiny human being, but inside the egg, not the sperm. Inside that being was another egg, enclosing another even smaller body, and so on. However, at that time, the actual egg cell itself, or ovum, had not been identified. In the female sex organ, the ovary, what most biologists believed to be an egg was in fact a ripe ovarian follicle, a fluid-filled container about 10–20 mm in diameter. The actual ovum inside the follicle, discovered by Estonian biologist Karl Ernst von Baer in 1827, is 100 times smaller: 0.1–0.2 mm across. Ovists argued that there was vastly more room in their "egg" (the follicle) for an endless succession of preformed beings. In comparison, the male sperm cell was tiny, with a head that was just 0.005 mm long. Later, in 1878, these reproductive cells, egg and sperm, would be named gametes by Polish botanist Eduard Strasburger.

In the 1780s, Italian priest and biologist Lazzaro Spallanzani, while he was experimenting with mating amphibians, covered the male's genital opening with well-wrapped taffeta material. This prevented his seminal fluid from reaching the female's eggs, and as a result they were not fertilized. Spallanzani tried filtering the seminal fluid into thinner liquid (non-sperm) and thicker (sperm) portions, and even used the thicker fluid to bring about fertilized eggs, but his conclusions were colored by his ovist views.

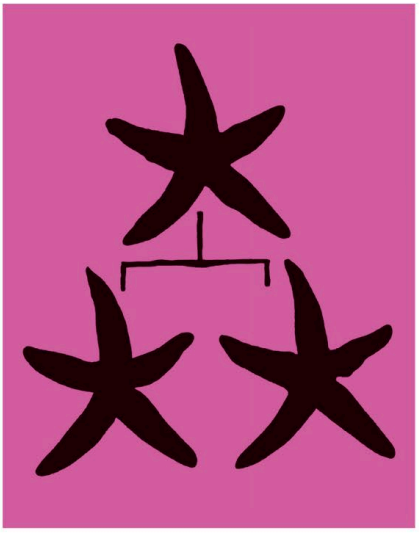
After conducting experiments with animals in 1824, French chemist Jean-Baptiste Dumas and Swiss physician Jean-Louis Prévost were convinced that sperm are not parasites but are involved in fertilization. It was not until the 1870s, however, that biologists understood that both sperm and egg are required to produce offspring. ■

Early microscopes

In many respects, Antonie van Leeuwenhoek's microscopes would not be bettered for almost two centuries. Popular during his time was a design using two convex lenses, magnifying 30–40 times, but the combination introduced blurring and hazy coloring. Van Leeuwenhoek employed just one lens, in some versions almost spherical and barely the size of a pea, like a high-powered magnifying glass. He made these lenses himself using his own closely guarded techniques. Samples were placed on a metal point almost adjacent to the lens and viewed closely from the other side. His magnifications improved to 200–250 times, and even more in later models.

Enormously productive, van Leeuwenhoek made some 500 lenses and at least 25 microscope frames, and wrote almost 200 illustrated reports to the Royal Society in London. However, few others could corroborate his findings at the time, and it was 200 years before some of his achievements were accepted.

This is a replica of the first microscope by van Leeuwenhoek, who achieved up to 300 times magnification using a single lens.



SOME ORGANISMS HAVE DISPENSED WITH SEXUAL REPRODUCTION

ASEXUAL REPRODUCTION

IN CONTEXT

KEY FIGURES
Abraham Trembley (1710–84),
Charles Bonnet (1720–93)

BEFORE
***c.*2000 BCE** Roman winemakers take cuttings from their best vines to grow new plants—a form of asexual propagation.

1702 In his drawings of microscopic life, Antonie van Leeuwenhoek shows a hydra in the process of budding.

AFTER
1758 Swedish taxonomist Carl Linnaeus names the genus of hydra pond animals *Hydra*.

1871 German zoologist Karl von Siebold coins the term "parthenogenesis."

1974 American zoologist Samuel McDowell reports that offspring of the brahminy blind snake are all female and that this species' reproduction is always by parthenogenesis.

Humans and most other animals produce offspring in a similar way—that is, a female and a male undertake sexual reproduction. The female's egg cell joins with the male's sperm cell to form a fertilized egg, which grows and develops into a new individual. Many plants also have female and male parts—in some cases on different individuals; in others, on the same one. Again, their female and male cells come together to produce seeds or spores. This female–male method of breeding is widespread and is known as sexual reproduction. But there is another system, employed by various animals, fungi, and many plants, that does not involve sex. This "single parent" method is termed asexual reproduction, or asexual propagation.

> After having cut the polyp … each of the two [parts] appeared perceptibly to be a complete polyp, and they performed all the functions that were known to me.
> **Abraham Trembley**

Many plants carry out what is called vegetative propagation—stems, including runners on the surface and rhizomes just below, corms, tubers, and bulbs can all make buds or other parts that grow into new, separate individuals, with no sexual reproduction involved. Until the 18th century, few biologists considered that animals might breed in a similar way.

Pond organisms and aphids

In 1740, Abraham Trembley, a Genevan naturalist, studied a small organism he noticed in pond water. It looked something like a tiny tree with multiple branches—similar to a sea anemone. Trembley carried out many experiments, including cutting and slicing the organism, which was only a few millimeters long; often, each part grew into a whole new individual. He also saw "babies" forming on one parent, like buds on a plant stem. But

See also How cells are produced 32–33 ▪ The discovery of gametes 176–77 ▪ Pollination 180–83 ▪ Fertilization 186–87 ▪ Cloning 202–03 ▪ Naming and classifying life 250–53

A budding hydra was used by Trembley in his experiments. When food is plentiful, this aquatic animal reproduces asexually by producing buds that grow into miniature adults.

in addition to these plantlike abilities, the tiny life form could also move, wave its tentacles, shuffle on its "stalk," wriggle, and loop—it was more like an animal. Trembley named it the hydra, after the mythological, many-headed Greek water monster that grew two more heads if one was severed.

In the 1740s, Trembley wrote letters to French academician René de Réaumur, a well-regarded naturalist and general scientist. Trembley's 1744 *Mémoires pour Servir à l'Histoire d'un Genre de Polypes d'Eau Douce* (*Memoirs on the Natural History of Freshwater Polyps*) described and illustrated his observations and was one of the first descriptions of animal asexual reproduction by budding. Trembley was not aware that some 40 years earlier, in 1702, Dutch microscopist Antonie van Leeuwenhoek had also seen and drawn these polyps, which he described as a type of "animalcule" (very small animal).

Meanwhile, Trembley's nephew Charles Bonnet, also Genevan and a friend of de Réaumur, was investigating aphids—sap-sucking greenflies and blackflies. Around 1740, he designed experiments to show that female aphids could bear young without mating or having any contact with males. Bonnet's 1745 publication *Traité d'Insectologie* (*Treatise on Insects*) explained this form of asexual reproduction in animals, which was later named parthenogenesis, meaning "virgin birth."

Since then, the list of female animals known to breed using only their own egg cells, without the need for male sperm, has increased to include many kinds of worms, insects, and other invertebrates, and some species of sharks, amphibians, reptiles, and even domesticated quails and turkeys.

Other asexual reproduction methods include fragmentation and regeneration, in which separate parts of one individual grow into new whole individuals. This is commonly seen in hydra, as Trembley described, and also in some worms, as investigated by Bonnet in the 1740s, as well as in starfish. In plants, apomixis is reproduction by a seed produced by an unfertilized egg cell and so is a clone of the female parent. ■

Cows have been cloned (each grown from a single donor cell) since the late 1990s. Reasons include better milk and meat yields, as well as studying resistance to disease.

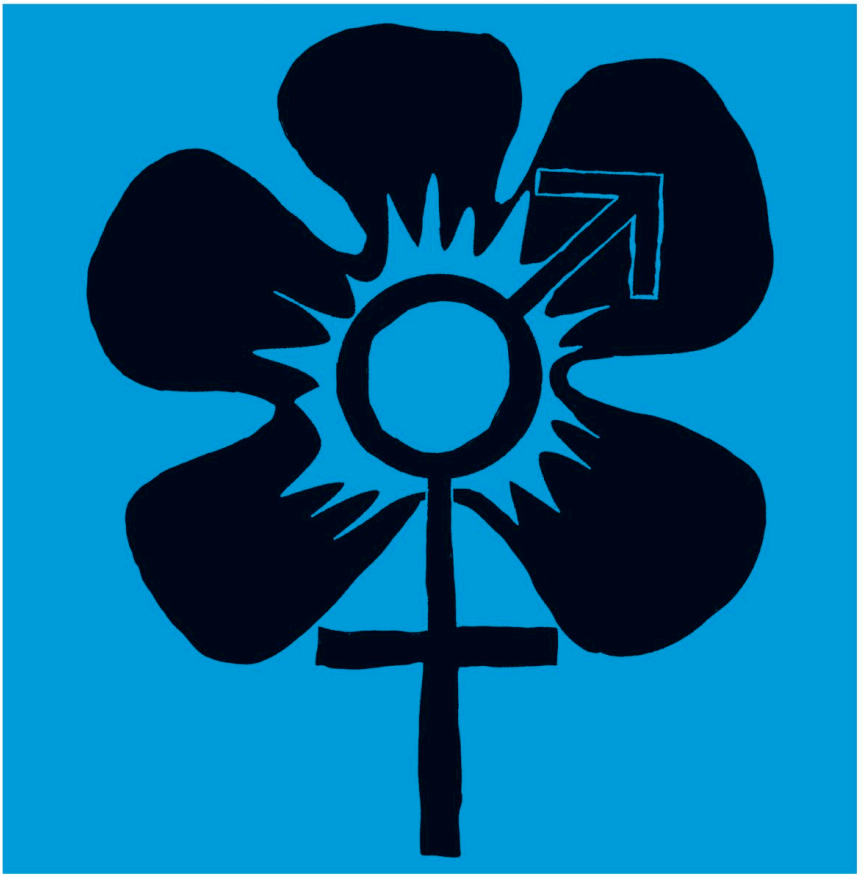
Sex versus no sex

In sexual reproduction, an offspring inherits a set of genes. When egg and sperm cells are first made, these genes, like a deck of cards, are shuffled into new combinations. So, the offspring has a unique mix of genes that could provide features and traits that improve its chances of survival—for example, it might be resistant to a new disease. This genetic variation among offspring provides evolution with raw material from which to select the best survivors.

In asexual reproduction, a single parent can yield many more offspring more rapidly than by sexual reproduction. All of these offspring inherit exactly the same genes as the parent. Organisms that are genetically identical (or virtually so) are known as clones. However, the lack of genetic variety can be a drawback. All the individuals have very similar features and traits; therefore, should a new disease strike, there is a lack of variation on which natural selection can act, and survival is less likely.

A PLANT, LIKE AN ANIMAL HATH ORGANICAL PARTS

POLLINATION



IN CONTEXT

KEY FIGURE
Christian Konrad Sprengel (1750–1816)

BEFORE
1694 Rudolf Jakob Camerarius discovers sexual organs in the flower and isolates flowers that have only male or female organs to show they cannot produce seeds by themselves.

1793 Carl Linnaeus uses the stamens and stigmas of flowers to classify plants.

AFTER
1860s Charles Darwin studies orchids and their relationships with insect pollinators.

1867 Federico Delpino coins "pollination syndrome," to describe the coevolution of flowers and their pollinators.

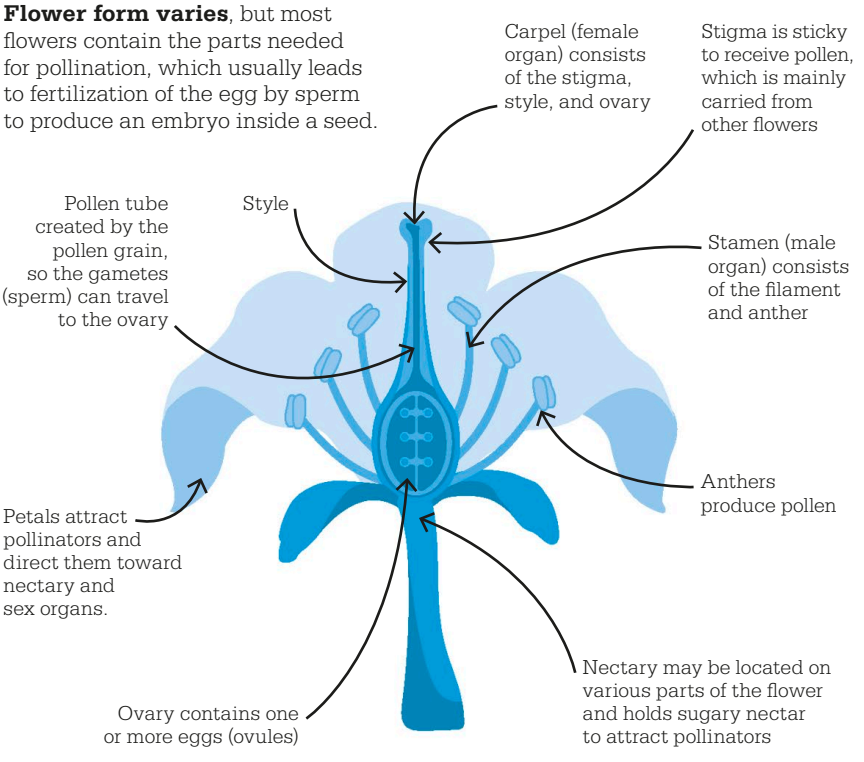
In flowering plants, pollination is the transfer of pollen from the anther to the stigma of a flower in order to fertilize it and produce seeds. Self-pollination, or inbreeding, is when a flower's pollen lands on its own stigma; cross-pollination, or outcrossing, occurs when pollen travels to the stigma of a different flower.

Fertilization occurs when one sperm from the pollen grain migrates from the stigma to the ovary, where it fertilizes the egg in order to create an embryo. Another sperm merges with other female tissues in the ovary to form the endosperm, the substance within the seed that feeds the growing embryo.

Understanding how any flower is pollinated depends on identifying its sex organs. Yet, until the 17th

See also: The discovery of gametes 176–77 ▪ Fertilization 186–87 ▪ The laws of inheritance 208–15 ▪ Life evolves 256–57 ▪ Natural selection 258–63

Flower form varies, but most flowers contain the parts needed for pollination, which usually leads to fertilization of the egg by sperm to produce an embryo inside a seed.



century, blooms were regarded simply as nonsexual ornaments. In 1694, German botanist Rudolf Jakob Camerarius described reproductive parts—the anther and carpel, or pistil—in the flower. He also found that, if he isolated plants that had only male or female flowers, no seeds formed.

German botanist Joseph Gottlieb Kölreuter cross-pollinated flowers in 1761 to create hybrids, proving that pollen grains are needed to fertilize flowers. He described flowers that could not fertilize themselves as self-incompatible. We now know the sperm and egg in such flowers have differing protein signatures, like a mismatched lock and key, so they cannot fuse and achieve fertilization. This ensures that the flowers are cross-pollinated by other flowers.

In the mid-18th century, Austrian monk Gregor Mendel amassed data from cross-pollinating pea flowers that revealed how distinct traits are passed down from parent plants to their offspring. He showed that cross-pollination promotes genetic variation in plants, and laid the way for future study of heredity and genetics. The more variation a plant species shows by recombining its genes, the more likely it will survive adverse conditions such as drought, grazing, or disease.

Sprengel's theories

It was German botanist Christian Konrad Sprengel who realized that specific flower structures enabled pollination. From 1787, he studied hundreds of plants, at all times of day and in all weathers. Sprengel »

Christian Konrad Sprengel

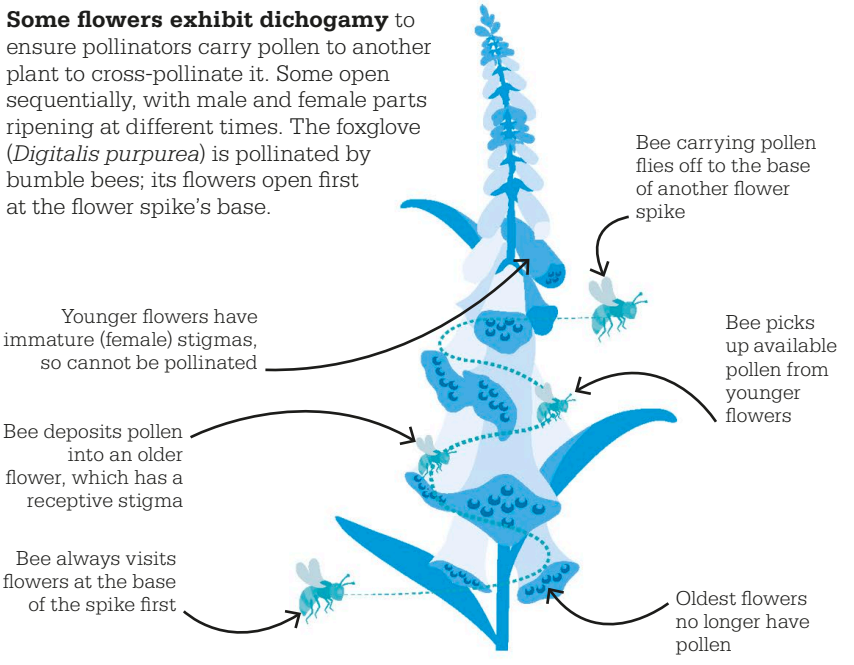
A theologian turned botanist, Sprengel was born in 1750 in Brandenburg, Germany. In 1780, he became a school headmaster and parish rector in Spandau and took up botany in his spare time. He studied reproduction of plants and developed his general theory of pollination, which still holds true today. Sprengel's major and only work on the subject was not widely recognized at the time it was published, although he had hoped it would found a new field of study in biology.

Sprengel had neglected his teaching and religious duties to pursue his botanical interests. When he was finally dismissed in 1794, he retired to Berlin. After Sprengel's death in 1816, the true significance of his work was recognized by Charles Darwin in 1841, and became the foundation for Darwin's own work on pollination and on the evolution of flowers.

Key work

1793 *Discovery of the Secret Nature in the Structure and Fertilization of Flowers*

Some flowers exhibit dichogamy to ensure pollinators carry pollen to another plant to cross-pollinate it. Some open sequentially, with male and female parts ripening at different times. The foxglove (*Digitalis purpurea*) is pollinated by bumble bees; its flowers open first at the flower spike's base.



noted the importance of insects in cross-pollination. Bees are the most numerous pollinators with around 20,000 or so species, but butterflies, moths, and some flies, wasps, and beetles are also important.

Sprengel realized that sugary nectar did not exist to moisten the carpel or feed the seed, as others believed, but to lure insects to feed on a flower so they would transfer its pollen to another flower and fertilize it. Other traits, such as flower color, shape, and scent, were entirely used to attract insect pollinators. Sprengel described how the bright colors of the corolla (petals), calyx (sepals), bracts, or even nectary, attracted insects. For example, night-opening flowers are mostly white so that they are easier for moths to locate in the dark. He also found varied, colored markings on some petals, called them nectar guides, and suggested that they point the insect to the nectary.

In a series of experiments from 1912, Australian zoologist Karl von Frisch established that bees can see most colors of the visible spectrum except red and, unlike humans, can also see ultraviolet light. Some flower pigments reflect and combine ultraviolet and yellow light, which bees perceive as "bee's purple," and these pigments are common in nectar guides.

Flower shape can also help its pollinators: as Sprengel observed, a large, flat flower head, or extra-large lower petal (lip) provides a landing pad. Some flowers might suit only one type of insect: narrow, tubular flowers can be probed only by the long proboscis of a moth or butterfly.

Another feature Sprengel noted is scent: for example, some moth-pollinated flowers, such as evening primrose (*Oenothera biennis*), close up by day and open at twilight to release strong scents; other flowers smell of carrion, to attract flies.

Cross-pollination strategies

Most plants are hermaphrodite, with male and female sexual organs in each flower. However, some plants with many flowers displayed a strategy that Sprengel named dichogamy: female and male parts mature at different times, forcing pollinators to move from flower to flower in search of ripe pollen.

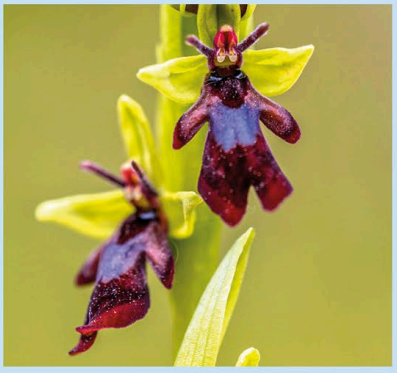
Sprengel confirmed Kölreuter's theory that self-incompatibility in flowers was also a cross-pollination strategy. He further suggested that single-sexed plants (now called dioecious plants) had developed flowers with only a male or female sex organ to ensure pollination by

Most plants **reproduce sexually** by **male pollen** fertilizing the female sex organ.

About **90 percent** of plants have sexual parts designed to **prevent self-pollination** or **self-fertilization**.

Pollen is **carried** between flowers by **animals** and **wind**.

Cross-pollination results in **genetic diversity**, increasing the ability of plants to survive adverse conditions.



The fly orchid (*Ophrys insectifera*) has a large, divided lower petal and a scent that mimics that of female *Argogorytes* digger wasps.

Sexually deceptive flowers

Most flowers use odor, nectar, shape, or color to attract their pollinators. A few plants, though, use sexual mimicry to lure male insects to a flower. Some orchid flowers, for example, look like female wasps. The flowers even release pheromones that smell like the female insects. The flower sometimes provides its lure before the female insects are active, to increase its chances of success.

A male wasp will land on the flower's "female" and try to mate with her. The movement of the copulating male wasp triggers a hinge mechanism in the orchid flower, depositing pollen sacs on the wasp's head. The pollen sacs perfectly align to the stigma of the next flower that the male wasp tries to copulate with.

Other orchids entice male insects into their funnel-shaped flowers with scents that smell like pheromones. Unlike bees or butterflies that collect pollen and nectar, the male wasp gains absolutely no reward for pollinating the orchid flowers.

other plants. He also described some flowers as "false nectar flowers"; they have no nectar, but use a nectar guide or scent to lure insects into transferring the pollen.

Sprengel realized that some plants were wind pollinated, since they lacked nectar, corollas, scent, or colored calyces, but did have light, abundant pollen. The earliest flowering plants on Earth were wind-pollinated and many, such as grasses, birches, and oaks, still are. They do not need to attract pollinators, so have inconspicuous, odourless, pale green flowers, often clustered on tassels that shed their pollen while waving in the wind. Leaves block the wind, so wind-pollinated trees and shrubs flower in spring before the leaves emerge.

Grasses are monoecious, with stamens and carpels on separate flowers on the same plant, so pollen is more likely to travel on the wind to female flowers of another plant.

Evolution

Sprengel concluded that very few flowers fertilize themselves, but did not examine the purpose of cross-pollination. Charles Darwin later developed Sprengel's ideas within the context of natural selection, explaining how flowers and their animal pollinators evolved together, usually in mutually beneficial relationships. In 1862, for example, Darwin predicted that a white orchid (*Angraecum sesquipdale*), from Madagascar, with a modified petal extending 12in (30cm) above its nectary, must be pollinated by a moth with a proboscis of similar length. The moth was later found to be *Xanthopan morganii praedicta*.

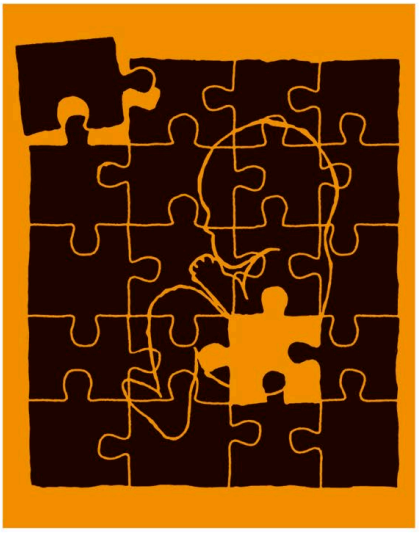
The plant–pollinator relationship has played an important role in the evolutionary success of flowering plants for more than 100 million years. Italian botanist Federico Delpino's "pollination syndrome" of 1867 explains how unrelated plants evolve similar floral traits if they share the same pollinator, whether it is an insect, bird, bat, or the wind.

African sunbirds and North and South American hummingbirds have long, thin bills and feed on trumpet-shaped flowers that have copious nectar. A plant expends a huge amount of energy producing nectar to attract the birds, but it is wasted if insects fill up on the nectar by visiting only one flower. So the plants evolved deep red, orange, and rust-colored blooms, which reflect color wavelengths invisible to most insects but highly visible to, and preferred by, birds.

The few self-pollinating plants tend to grow where pollinators are sparse and the plants do not need to evolve to survive environmental disruption. They may self-pollinate before the flower even opens.

Bees pollinate more than 90 percent of the world's crops. They are in serious decline, due to human activity, habitat and plant loss, and climate change. ■

> … a flower and a bee might slowly become, either simultaneously or one after the other, modified and adapted in the most perfect manner to each other …
>
> **Charles Darwin**
>
> ***On the Origin of Species* (1859)**



FROM THE MOST GENERAL FORMS THE LESS GENERAL ARE DEVELOPED

EPIGENESIS

IN CONTEXT

KEY FIGURE
Karl Ernst von Baer
(1792–1876)

BEFORE
320 BCE Aristotle originates the theory that an embryo begins as an undifferentiated mass and forms gradually.

1651 William Harvey records the stages of chicken embryos developing in eggs and proposes that "every living thing comes from an egg."

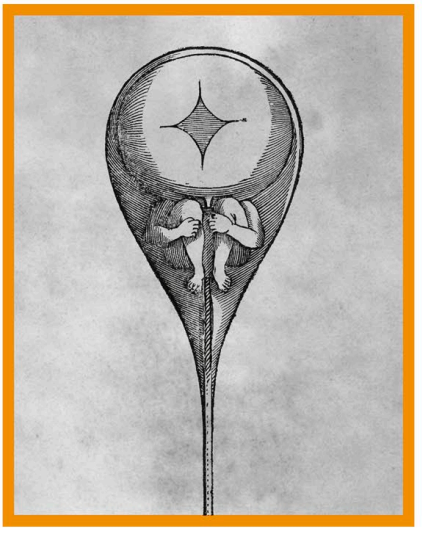
1677 Antonie van Leeuwenhoek makes the first microscopic observations of sperm and is struck by the tiny wriggling "organisms" inside.

1817 Christian Pander describes the three germ layers in chicks.

AFTER
1842 Robert Remak provides microscopic evidence of the three distinct germ layers and names each of them.

From the time of Aristotle until the late 19th century, scientists were unable to agree on the principles of how animals reproduce. Two possible alternatives put forward by Aristotle, preformation and epigenesis, were fiercely debated.

Some proponents of preformation believed that a miniature version of the future adult was already present in each egg, others believed it was inside each sperm, and that the process of producing an organism was a simple enlargement of something that already existed.



Hartsoeker's sketch of the homunculus, a tiny human that he believed lived inside a sperm cell head, was published in his 1694 *Essai de Dioptrique* (*Essay on Dioptrics*).

Supporters of epigenesis thought that both males and females contributed material to produce an organism, and that each individual developed gradually from a formless undifferentiated mass.

Microscopic observations

In 1677, Antonie van Leeuwenhoek examined semen from various animals, including humans, and observed many wriggling sperm under the microscope. While studying human sperm in the late 1670s, Dutch physicist Nicolaas Hartsoeker also observed wriggling cells and postulated that tiny men might exist inside the sperm heads, thus supporting preformation.

A proponent of epigenesis, German physiologist Caspar Friedrich Wolff microscopically studied chick embryos and found no evidence to support preformation. In 1759, he published his doctoral dissertation refuting the theory and arguing that the organs of animals are formed gradually. He also stated

See also: Making life 34–37 ▪ The discovery of gametes 176–77 ▪ Fertilization 186–87 ▪ Embryological development 196–97 ▪ The chemicals of inheritance 221

in 1789 that he believed each individual's development was triggered by an "essential force," but he eventually abandoned this research after deciding that the individual forces did not exist.

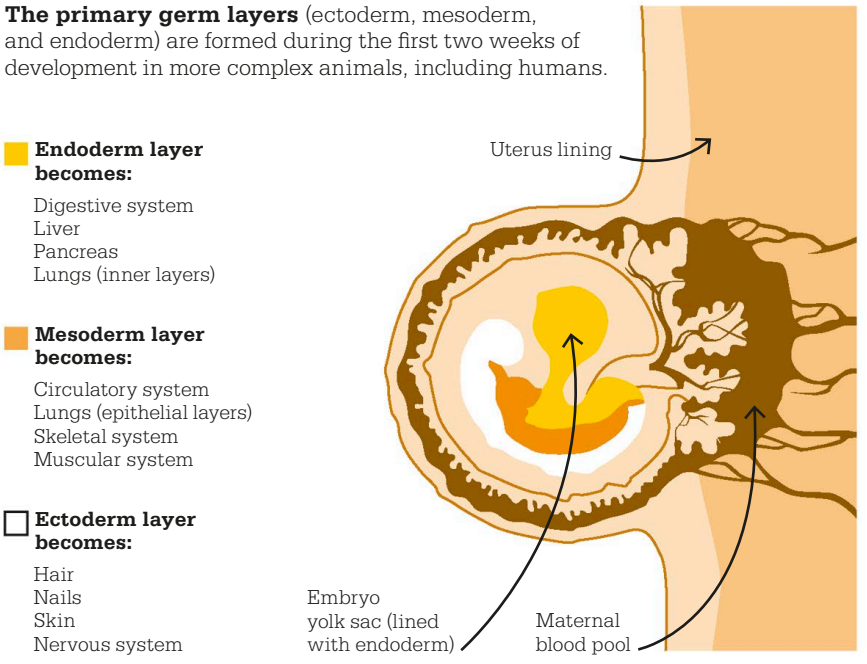
Germ layer theory

In 1817, Russian biologist Christian Pander described the early development of the chick and identified three distinct regions of the chick embryo, now known as the primary germ layers. German embryologist Karl Ernst von Baer went on to expand Pander's findings. In 1827, he discovered the human ovum (egg) and published a theory of embryo development based on observation and experiment. Baer described how embryos start with distinct layers that gradually differentiate into more complex body parts. In his words, "the embryo separates into strata."

In 1842, German embryologist Robert Remak provided microscopic evidence for the three germ layers. In an embryo, each germ layer is a group of cells which develops into the organs and tissues. Sponges have a single germ layer; jellyfish and sea anemones have an inner layer called the endoderm, and an outer layer called the ectoderm. Complex animals with bilateral symmetry (in which the body's right and left sides are similar) develop a third germ layer called the mesoderm.

In 1891, German biologist Hans Driesch separated sea urchin eggs at the two-cell stage and found that each developed into a complete sea urchin, thus refuting preformation. But it was in 1944 that the idea of an "essential force" guiding embryo development was corroborated when DNA was found to be the carrier of genetic information. ■

The primary germ layers (ectoderm, mesoderm, and endoderm) are formed during the first two weeks of development in more complex animals, including humans.

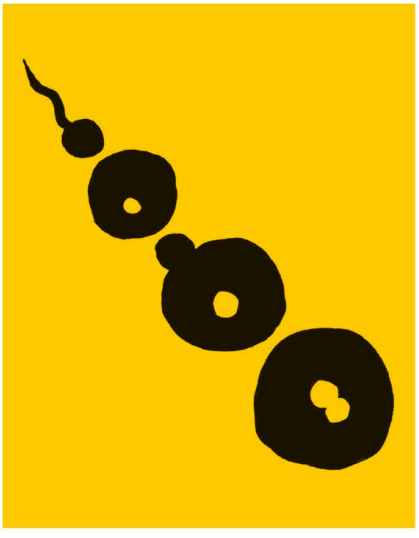


Karl Ernst von Baer

Born into Prussian/German nobility in Piep, Estonia, in 1792, Baer enrolled at the University of Dorpat to study medicine and graduated in 1814. The following year, he moved to Würzburg, Germany, to further his medical studies and there he met physiologist and anatomist Ignaz Döllinger, who encouraged him to research chick development. Most of Baer's contributions to embryology followed between 1819 and 1834, when he made several important discoveries, including the blastula (an embryo at the early hollow ball stage) and the notochord (a rodlike structure that becomes part of the spinal column). In 1834, Baer moved to Saint Petersburg, Russia, and entered the Academy of Sciences. He retired from active membership in 1862 and became an explorer, mostly traveling in the Russian North. Baer died in Dorpat in 1876.

Key works

1827 *On the Genesis of the Ovum of Mammals and of Man*
1828 *On the Developmental History of Animals*



THE UNION OF EGG-CELL AND SPERMATIC CELL

FERTILIZATION

IN CONTEXT

KEY FIGURE
Oscar Hertwig (1849–1922)

BEFORE
2nd century BCE "Dual seed theory" is the predominant theory of conception. It states that both males and females produce seeds that combine to create a new human.

1761–66 German botanist Joseph Gottlieb Kölreuter shows that hybrid offspring receive traits from male and female reproductive structures in plants.

1781 Lazzaro Spallanzani demonstrates that toad semen filtered to remove sperm cannot fertilize eggs.

AFTER
1902 German biologist Theodor Boveri conducts research on the behavior of egg and sperm chromosomes following fertilization.

The subject of animal reproduction was theorized extensively during the 17th and 18th centuries, although the human ovum (egg) was not discovered until 1827. In 1677, Antonie van Leeuwenhoek studied semen from animal species and observed sperm cells moving under the microscope. Scientists had previously proposed that a vapor or odor from semen fertilized the egg and Leeuwenhoek's discovery stimulated a lot of debate as to the function of sperm. Some speculated that sperm were associated with impregnation; Leeuwenhoek suggested that they were parasites and later that inside sperm heads were miniature preformed adults.

The life cycle of the sea urchin begins with the release of eggs and sperm into water. Fertilized eggs hatch into larvae and drop to the ocean floor where they attach to rocks.

The union of egg and sperm

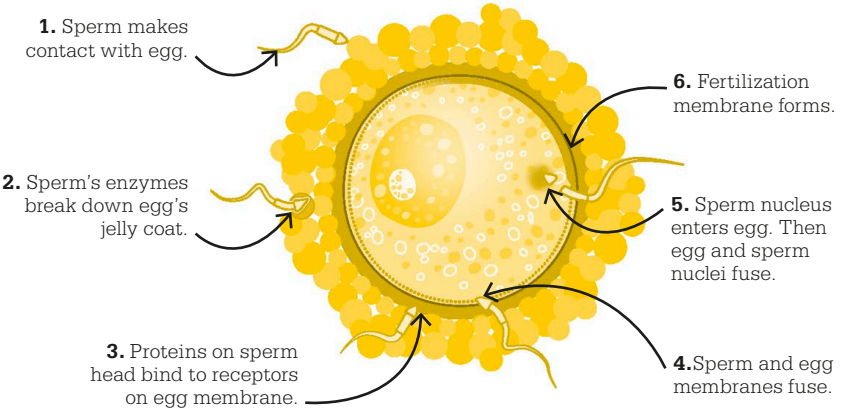
In 1768, Italian biologist Lazzaro Spallanzani's experiments with amphibians demonstrated that contact between egg and sperm was needed to fertilize eggs. At this time, scientists studied fertilization in animals that use external fertilization, where sperm and eggs are released into an external environment and the sperm fertilizes the egg outside the body. With internal fertilization, the male inseminates the female and sperm unites with an egg inside the body.

By the 19th century, many scientists studying external fertilization used the sea urchin. Sea urchin eggs and embryos are relatively transparent and adult urchins are easily encouraged to release male and female gametes (sperm and eggs), so fertilization can be observed on a microscope slide.

Although the penetration of the sperm into the egg had long been suspected, it was German zoologist Oscar Hertwig who, in 1875 while

See also: Making life 34–37 ▪ Epigenesis 184–85 ▪ Embryological development 196–97 ▪ The laws of inheritance 208–15 ▪ Chromosomes 216–19

Fertilization is the fusion of gametes (sperm and eggs). Hertwig found that only one sperm is required to fertilize an egg, and that once the sperm enters the egg, the egg forms a "fertilization membrane," blocking entry to others.



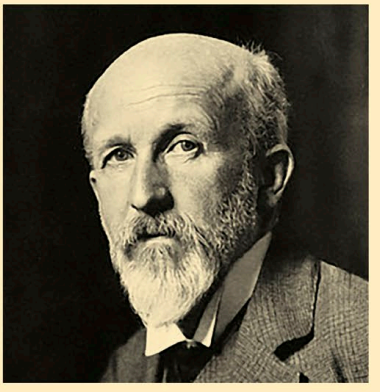
studying the sea urchin, first observed the moment of fertilization under a microscope. He saw a single sperm enter the urchin's egg, the two nuclei fuse into one, and the formation of a newly fertilized egg called a zygote.

The role of the nucleus

Hertwig witnessed the appearance of a single nucleus where there had been two, and wrote that "it arises to completion like a sun within the egg," an image that conveys the beauty of the moment of fertilization. He recognized that the embryo develops from the division of the newly formed nucleus and was the first to suggest that the nucleus is responsible for the transmission of inherited traits to the offspring. In 1885, he wrote that he believed there is a substance contained in the nucleus that "not only fertilizes but transmits hereditary characteristics."

Almost simultaneously, yet independently of Hertwig's work, Swiss zoologist Hermann Fol confirmed the process of fertilization. In 1877, using starfish, Fol observed a single sperm penetrating an egg membrane and the sperm nucleus progress toward the egg's nucleus for fusion. By using large, transparent eggs, Hertwig and Fol were able to make pioneering discoveries that provided the first evidence of the role of the cell's nucleus in biological inheritance, passing on characteristics from one generation to another. ■

> The cell is itself an organism, constituted of many small units of life.
> **Oscar Hertwig**

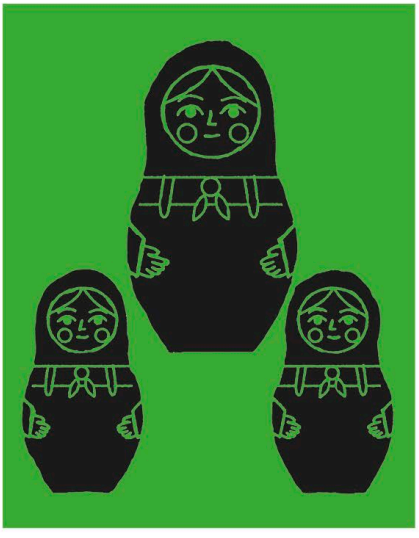


Oscar Hertwig

Born in 1849 in Hessen, Germany, Oscar Hertwig attended the University of Jena and studied with his brother Richard under Ernst Haeckel, a prominent comparative anatomist. Hertwig initially studied embryo development, but switched to researching the nature of the fertilization process. In 1875, during a research trip with Haeckel in the Mediterranean, Hertwig discovered the fertilization of sea urchins and began documenting his observations. In 1890, while studying starfish, he was the first to observe parthenogenesis in animals (the development of an embryo from an unfertilized egg cell). Hertwig was the first chair of both cytology and embryology in Berlin from 1888 to 1921 and director of the new Anatomical-Biological Institute there. He died in 1922 in Berlin.

Key works

1888 *Text-book of the Embryology of Man and Mammals*
1916 *The Origin of Organisms—a Refutation of Darwin's Theory of Chance*



THE MOTHER CELL DIVIDES EQUALLY BETWEEN THE DAUGHTER NUCLEI

MITOSIS

IN CONTEXT

KEY FIGURE
Walther Flemming
(1843–1905)

BEFORE
1665 In *Micrographia*, Robert Hooke reveals the existence of cells, the smallest units of life.

1858 Rudolf Virchow proposes his famous dictum *omnis cellula e cellula*—"all cells come from cells."

AFTER
1951 American biologist George Gey and his team succeed in growing and maintaining cells in the laboratory, using cancer cells taken from African American cancer patient Henrietta Lacks without her permission. These cells are still used for medical research.

1970 British biologist John Gurdon succeeds in cloning a *Xenopus* frog, although it does not develop beyond the tadpole stage.

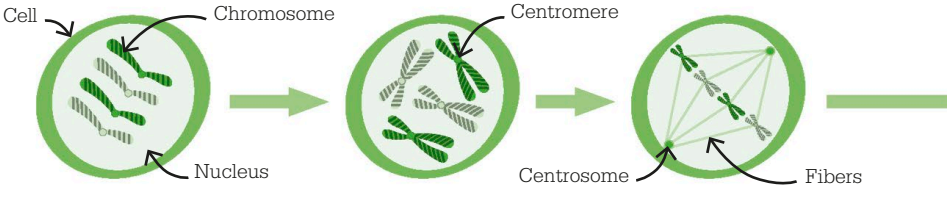
All life is made of cells. The growth and repair of an organism requires the reproduction and replacement of the cells of which it is made. This is accomplished by the growth and division of the existing cells in a sequence called the cell cycle. The process of cell division that produces two daughter cells with the same genetic makeup as the parent cell is called mitosis.

In 1831, British botanist Robert Brown discovered a structure within every plant cell he studied. He called it the nucleus. What role the nucleus played in the cell was a mystery. In 1838, German botanist Matthias Schleiden suggested that all plants were made of cells and originated from a single cell. The following year, physiologist Theodor Schwann concluded that the same applied to animals. Schleiden and Schwann mistakenly believed that new cells grew in a similar way to the formation of crystals. Pathologist Rudolf Virchow expanded on Schleiden and Schwann's cell theory in 1858, when he proposed that all cells must arise from preexisting living cells, famously declaring that "all cells come from cells."

Division of the nucleus

Attempts to study cells in any detail had been thwarted by the transparent nature of the cell, making it hard to differentiate any internal structure. Matters were

The process of mitosis



The cell duplicates its DNA, then carries out any necessary repairs before the mitosis stage begins.

In prophase, two exact copies of each chromosome (chromatids) are seen, joined by a centromere.

Metaphase sees the chromatid pairs align along the center of the cell, with fibers now attached.

See also: The cellular nature of life 28–31 ▪ How cells are produced 32–33 ▪ Meiosis 190–93 ▪ Chromosomes 216–19 ▪ The chemicals of inheritance 221 ▪ What are genes? 222–25

improved by the discovery that synthetic dyes would combine with some cell structures but not others, enabling scientists to begin figuring out the inner workings of the cell. In 1875, botanist Eduard Strasburger reported seeing material inside the nucleus of a dividing plant cell. By 1882, he had concluded that new cell nuclei arose from the division of an existing nucleus.

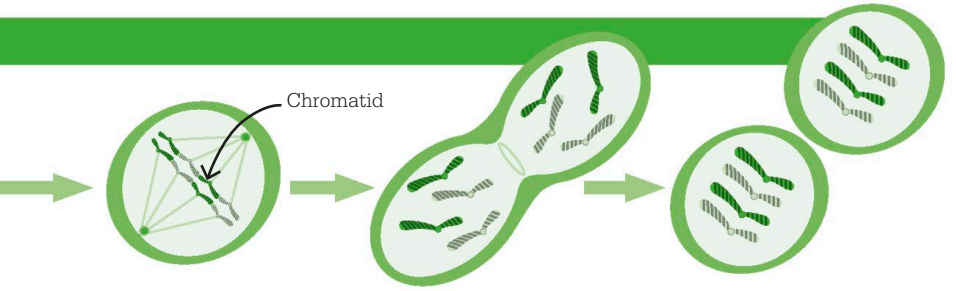
In that same year, 1882, German biologist Walther Flemming wrote his *Cell Substance, Nucleus, and Cell Division*. In it, he detailed his observations of salamander embryo cells, using aniline dyes, a byproduct of coal tar, to stain them. He described the process of cell division when the material inside the nucleus, which Flemming called chromatin, gathered into threadlike filaments (later called chromosomes). He termed the process of nuclear division "mitosis," from the Greek word for thread.

A number of phases

Flemming described how mitosis unfolded in two phases, in which the chromosomes first formed and then separated. Modern science describes four distinct phases. The phase when the nuclear material condenses into a compact form and chromosomes first become visible is termed prophase. Each chromosome consists of a pair of sister chromatids, connected at a point called a centromere. It was later established that chromatids contain the same genetic sequence. Between cell divisions, most animal cells have a structure called a centrosome, near the nucleus. As division begins, the centrosome divides, and each new one positions itself at opposite ends of the nucleus. A complex system of fibers extends from each centrosome toward the centromeres; the fibers connect the twin chromatids of each chromosome. During the next stage, metaphase, the duplicated chromatids are positioned so that they are ready to be pulled apart.

The centrosomes move outward, pulling each chromatid away from its sister and toward opposite ends of the cell. This separation of the chromatid pairs is called anaphase.

As telophase begins, a new nuclear membrane starts to form around each set of separated chromatids. Once formed, each new membrane encloses a full set of chromosomes, and two identical daughter cells are made. ■



In anaphase (separation), fibers pull the chromatids apart, dragging one half of each pair to opposite ends of the cell.

During telophase (splitting), a nuclear membrane starts forming around each group of chromosomes.

Two daughter cells form, with each containing an exact copy of the DNA from the parent cell.

Walther Flemming

Born in Sachsenberg, Germany, in 1843, Walther Flemming graduated in medicine from the University of Prague, Czech Republic, in 1868. He then served as a military doctor in the Franco-Prussian War of 1870–71, after which he held posts at the University of Prague and the University of Kiel, Germany. Flemming was a pioneer in the use of dyes to reveal structures inside cells.

Known for his generosity, Flemming gave food to the homeless, donated a sizable amount of money to homeless shelters, and taught science and mathematics to children who were too poor to attend school. In his late 40s, he developed a neurological disease from which he never recovered, and he died in 1905 at the age of 62.

Key work

1882 *Cell Substance, Nucleus, and Cell Division*

ON THIS, THE RESEMBLANCE OF A CHILD TO ITS PARENT DEPENDS

MEIOSIS

IN CONTEXT

KEY FIGURE
August Weismann
(1834–1914)

BEFORE
1840 Swiss scientist Rudolf Albert von Kölliker establishes the cellular nature of sperm and eggs.

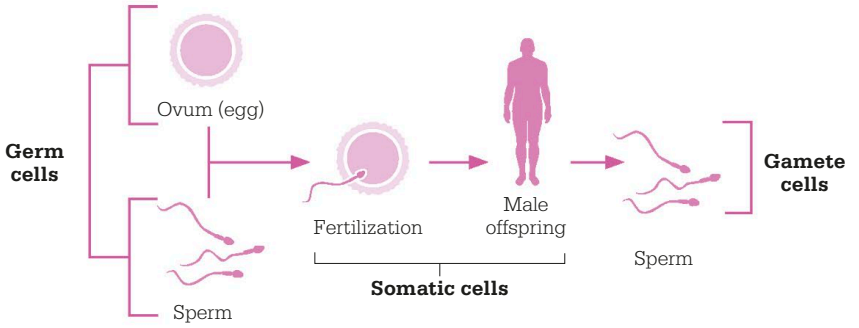
1879 Walther Flemming conducts systematic studies of the behavior of chromosomes during mitotic cell division.

AFTER
1909 Through his study of fruit flies, Thomas Hunt Morgan confirms genes are located on the chromosomes.

1953 James Watson and Francis Crick discover the structure of deoxyribonucleic acid (DNA), the molecule that encodes genetic information.

Walther Flemming's observations of chromosomes in the nucleus of dividing cells in 1882 led to speculation that chromosomes might be the carriers of heredity. German embryologist Wilhelm Roux was one of the first to suggest, in 1883, that a fertilized egg receives substances that represent different characteristics of the organism, and that these then become aligned on the chromosomes as cell division occurs. In 1885, Carl Rabl, an Austrian anatomist, was studying salamander cells and discovered that their chromosomes were constant in number and occurred

See also: The cellular nature of life 28–31 ▪ Making life 34–37 ▪ The discovery of gametes 176–77 ▪ Fertilization 186–87 ▪ Mitosis 188–89 ▪ The laws of inheritance 208–15 ▪ Chromosomes 216–19 ▪ Natural selection 258–63 ▪ Mutation 264–65



A germ line is the lineage of an organism's germ cells (eggs and sperm) that pass on their genetic information to the next generation. The individual resulting from the joining of the parents' male and female sex cells can produce either eggs or sperm, not both.

in similar arrangements shortly before and after cells divided. Based on his findings, he suggested that chromosomes were in fact permanent features of the cell that retained their individuality even though they only became visible during cell division.

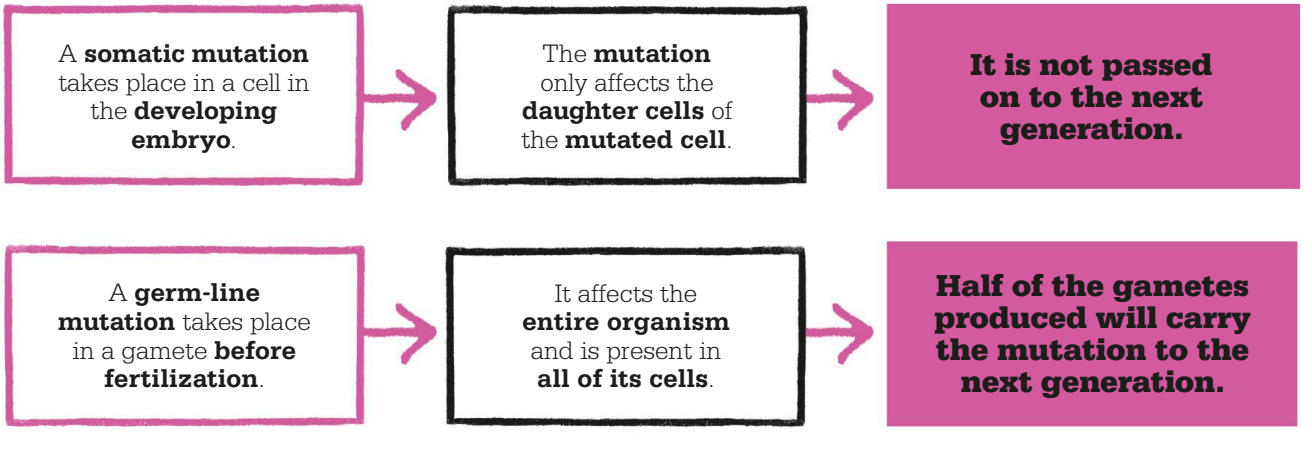
In 1890, Roux described a series of experiments in which he killed one of the cells resulting from the first division of a fertilized frog's egg. Roux observed that the remaining cell grew into half an embryo and concluded that each of the two cells must hold only half of the full set of chromosomes. He theorized that the development of an embryo results from portions of the chromosomes being parceled out according to the particular cell type for which they hold the hereditary information—such as nerve or muscle tissue.

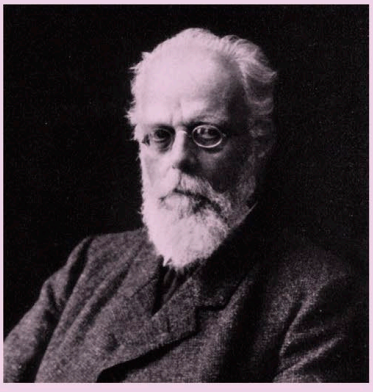
Roux's theory posed a crucial question: if only a portion of the complete chromosome set is passed to new cells during development, how then does the complete set get passed from one generation to the next? This was a problem that German evolutionary biologist August Weismann began working to address.

Germplasm theory

In 1885, Weismann proposed germplasm theory as the physical basis of heredity, and seven years later he developed this idea in *Das Keimplasma* (*The Germplasm*). He argued that there are two categories of cells: germ (or reproductive) cells, which produce eggs and sperm (collectively, gametes); and somatic (or body) cells, which form ordinary tissues. Although he accepted Roux's suggestion that somatic cells only contain partial sets of chromosomes, Weismann argued that germ cells contain a complete chromosome set and that they are thus the carriers of hereditary information. Roux was later shown to be wrong about somatic cells—every cell contains a full set of chromosomes, but cells become specialized since they use only part of the chromosome set.

According to the germplasm theory, in a multicellular organism, inheritance only takes place by »





August Weismann

Born in Frankfurt, Germany, in 1834, the son of a teacher, Weismann would become one of the most important evolutionary theorists of the 19th century. He graduated as a doctor from the University of Göttingen in 1856, and worked for a while as a physician. After reading Charles Darwin's *On the Origin of Species*, he became a firm supporter of evolutionary theory. In 1861, he began studying the development of insects at the University of Giessen.

In 1863, Weismann joined the medical facility of Freiburg University, teaching zoology and comparative anatomy. At his urging, a zoological institute and museum was built in 1865, and he was appointed its head. He remained at Freiburg until he retired in 1912. After his eyesight deteriorated, Weismann's wife Marie helped his observational studies, while he turned to more theoretical work. He died in Freiberg in 1914.

Key works

1887 *Essays on Heredity and Kindred Biological Problems*
1892 *The Germplasm*

means of the germ cells. The somatic cells do not function as agents of heredity. The effect is one way: germ cells produce somatic cells and are not affected by anything that the somatic cells experience or learn during the life of the organism. This means that genetic information cannot pass from somatic cells to germ cells and so on to the next generation. This is referred to as the Weismann barrier.

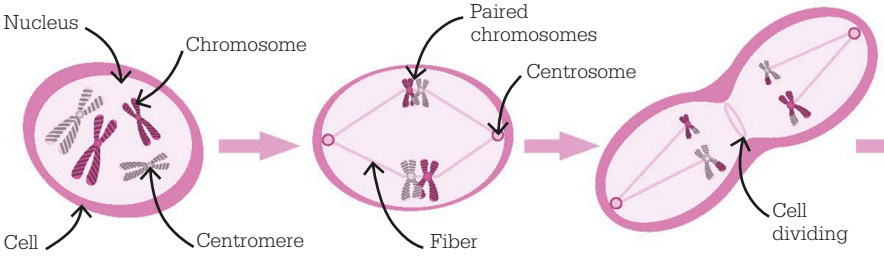
In *The Germplasm*, Weismann coined four terms: biophors, determinants, ids, and idants. Biophors were the smallest units of heredity. Determinants were combined biophors, initially found in the germ cells but able to transmit to somatic cells and determine their structure and function. Ids were groups of determinants, derived from germ cells and scattered during development into the cells of different tissues. At the highest level were idants, which carried ids and would later become known as chromosomes.

Weismann predicted that in sexual reproduction, the number of idants normally present in cells must reduce to half, so that the offspring got half of its idants from the mother's germ cell and half from the father's germ cell. This explained why the offspring had some traits that resembled those of the mother and some that were like those of the father. The key to this was meiosis.

> No matter how we twist and turn, we shall always come back to the cell.
> **Rudolf Virchow**

Weismann's view was a major contributory factor to biologists' understanding of how evolution occurs. It directly contradicted French naturalist Jean-Baptiste Lamarck's theory of acquired characteristics, which was then a highly favored explanation. Lamarck had argued in 1809 that characteristics acquired during the lifetime of an organism could be transmitted to its offspring. In 1888, Weismann disproved this theory by

The process of meiosis



Meiosis begins with a diploid parent cell in which the chromosome pairs make identical copies of themselves (replication).

Before division, chromosomes of similar length and centromere location pair up. Sections of DNA are swapped.

The nucleus and cell start to divide. Fibers attached to centrosomes pull the chromosomes to opposite ends of the cell.

cutting off the tails of 900 mice over five generations, demonstrating that their descendants continued to grow tails. He theorized that variations between individuals in a species result from different combinations of determinants in the germ cells. The stronger determinants outcompete the weaker ones, which are gradually eliminated. Weismann argued that this selection process is adaptive rather than simply random.

Although Weismann was an enthusiastic supporter of Darwin's theory of natural selection, his own germ cell theory dealt a blow to pangenesis, another of Darwin's ideas. The latter had proposed that each organ in the body produces small particles he called gemmules, which contain information about the organ. The gemmules travel through the body, he theorized, and accumulate in the sperm and eggs in the reproductive organs. In this way, Darwin argued incorrectly, information about the organs is passed on to the next generation.

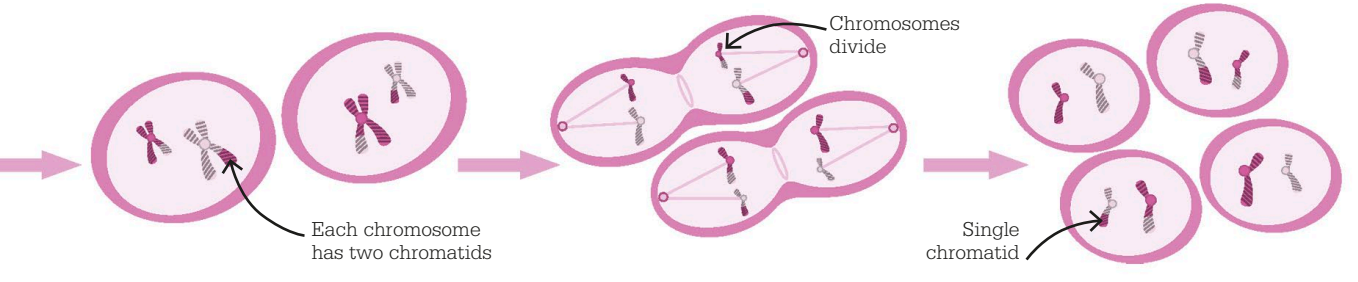
Defining meiosis

The key issue remained of how cell division occurs in the germ line. In 1876, German biologist Oskar Hertwig had observed the fusion of a sea urchin egg and sperm cell during fertilization. He concluded that the nuclei of the two cells each contribute to the traits inherited by the offspring. When Belgian zoologist Edouard van Beneden studied the *Ascaris* roundworm, an organism that has only two chromosomes, he discovered that each parent contributes one chromosome to the fertilized egg. In 1890, Weismann observed that sperm and egg cells contain exactly half the number of chromosomes found in the somatic cells. It was essential, he noted, to reduce the germ cell chromosome number by half, otherwise the chromosome number at fertilization would continue to double through successive generations. This reduction is achieved through the process of meiosis.

Meiosis has both similarities to and differences from mitosis, in which a parent cell divides to produce two identical daughter cells. Meiosis produces four gamete cells, in each of which the number of chromosomes is reduced by half. During reproduction, when the sperm and egg unite to form a single cell, the number of chromosomes is restored (doubled) in the offspring. Meiosis begins with a parent cell that is diploid, meaning that it has two copies of each chromosome. The parent cell undergoes one round of DNA replication followed by two separate cycles of nuclear division. The process results in four daughter cells that are haploid, which means that they contain half the number of chromosomes of the diploid parent cell.

> The cell is itself an organism, constituted of many small units of life.
> **Oskar Hertwig**

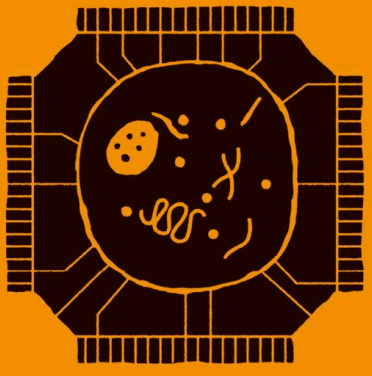
Although there was much Weismann could not have known at the time, his germplasm theory was key to explaining the physical process of inheritance through meiotic cell division. ■



Pairs of chromosomes will divide into haploid daughter cells. Haploid cells have only half the chromosomes of the parent diploid cell. The new cells differ from each other and the parent cell.

The chromosomes separate at the centromeres, and a nuclear envelope forms around each set of chromosomes.

Cytokinesis (the physical process of cell division) is complete. Meiosis cell division produces four genetically different haploid cells (gametes).



FIRST PROOF OF THE AUTONOMY OF LIFE

STEM CELLS

IN CONTEXT

KEY FIGURE
Hans Driesch (1867–1941)

BEFORE
1855 German pathologist Rudolf Virchow states that all cells arise from cells.

1888 Wilhelm Roux observes that cell damage in early embryos has an effect on their development.

AFTER
1909 Russian histologist Alexander Maximow proposes that all blood cells originate in the same multipotent stem cells.

1952 American biologists Robert Briggs and Thomas King clone leopard frogs by transplanting a nucleus from the cell of an older animal to an unfertilized egg.

2010 American scientists use the iPS technique to treat rats suffering from Parkinson's disease; they use nerve cells made from human skin cells.

Stem cells have the unique ability to develop, or differentiate, into other cell types. They are critical in the embryonic development of multicellular organisms, and also in an organism's internal repair system, replacing other cells.

Early-stage embryonic stem cells can differentiate into all other cell types in the body and are called "totipotent." However, as the embryo grows, the stem cells' ability to differentiate narrows to more specific cell types. Adult stem cells normally only generate the cell types of the organ from which they originate. The term "stem cell" was first used by German biologist Ernst Haeckel in 1868 to describe the single fertilized egg cell that would eventually give rise to a mature multicelled organism.

In 1888, German embryologist Wilhelm Roux published the results of experiments in which he took two- and four-cell frog embryos and destroyed half the cells of each embryo. He found that the remaining cells grew into half-embryos and concluded that the roles of the cells in development had been determined even at this very early stage.

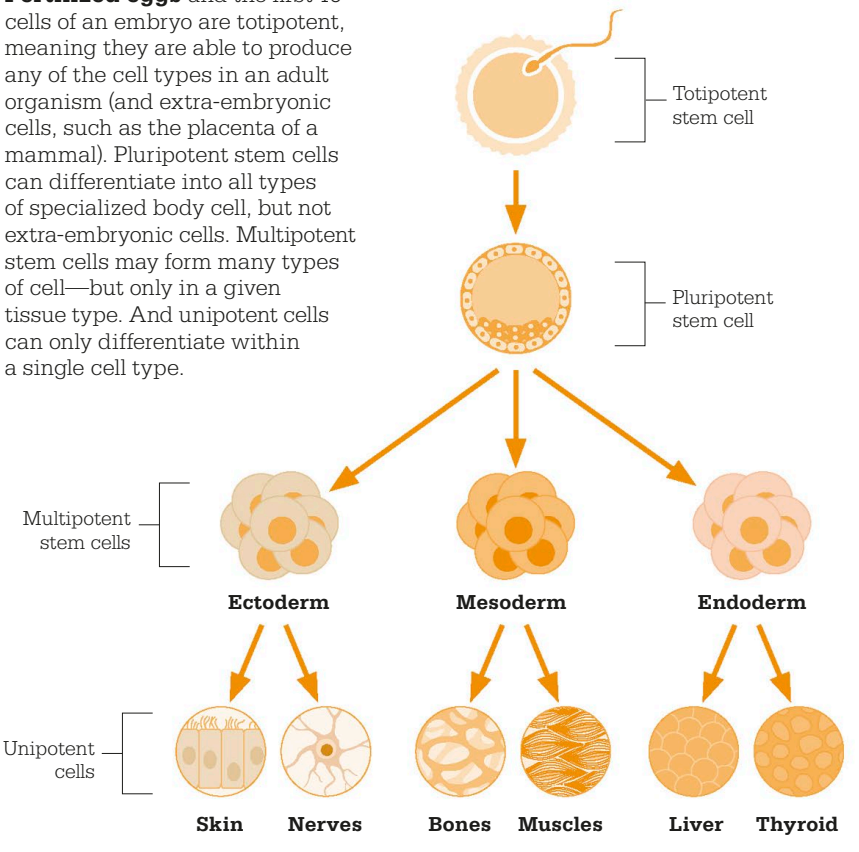
Totipotent embryonic cells

In 1891, German biologist Hans Driesch performed an experiment similar to Roux's, with two-cell sea urchin embryos. Rather than destroy one of the cells, though, he separated them and found that while one cell would often die, the

Hans Driesch shook two-celled sea urchin embryos to separate the cells, placed the single cells in seawater, then observed them as they developed into healthy, multicelled larvae.

See also: How cells are produced 32–33 ▪ Cancer metastasis 154–55 ▪ Epigenesis 184–85 ▪ Embryological development 196–97 ▪ In vitro fertilization (IVF) 198–201 ▪ Cloning 202–03 ▪ Gene editing 244–45

Fertilized eggs and the first 16 cells of an embryo are totipotent, meaning they are able to produce any of the cell types in an adult organism (and extra-embryonic cells, such as the placenta of a mammal). Pluripotent stem cells can differentiate into all types of specialized body cell, but not extra-embryonic cells. Multipotent stem cells may form many types of cell—but only in a given tissue type. And unipotent cells can only differentiate within a single cell type.



surviving cell developed into a complete but smaller-than-normal sea urchin larva. This suggested that Roux had been wrong and the developmental fate of the embryonic cells was not fixed. Driesch's experiments led him to conclude that embryonic cells in the early stages of development are totipotent. His research confirmed that each cell in the early embryo has its own complete set of genetic instructions and has the capacity to develop into a full organism.

American researcher Leroy Stevens was experimenting with cancer tissues in mice in 1953 when he found that some tumors contained mixtures of undifferentiated and differentiated cells, including hair, bone, and intestinal cells. He concluded that the cancer cells were "pluripotent," capable of differentiating into any cell type but without the ability to develop into a complete organism.

In 1981, British researchers Martin Evans and Matt Kaufman identified, isolated, and successfully cultured embryonic stem cells from mice. This allowed scientists to manipulate mouse genes and study their function in disease. Researchers can now modify the genome of a mouse in its embryonic stem cells and inject the modified cells into a mouse embryo. When the mouse embryo then matures, every one of its cells will have been modified.

> Any effort to control scientific advances is doomed to fail … But we must not forget the basic respect for life …
>
> **Joseph E. Murray**
>
> **Pioneering human transplant surgeon (1919–2012)**

A major breakthrough

In 1998, American embryologist James Thomson successfully removed cells from human embryos, grew them in the laboratory, and established the world's first human embryonic stem cell line, which still exists today. Although he only used embryos from donors who no longer wanted to use them to develop into children, the research was controversial.

Then, in 2006, Japanese scientists found a way to turn adult skin cells from mice into stem cells, named induced pluripotent stem cells (iPS cells). Medical researchers have since used reprogrammed iPS cells in clinical trials to treat neurological conditions, heart disease, and retinal disease. They have also been used to grow new tissue and even new organs for transplants. The medical potential for this treatment is enormous. ■

MASTER CONTROL GENES

EMBRYOLOGICAL DEVELOPMENT

IN CONTEXT

KEY FIGURE
Lewis Wolpert (1929–2021)

BEFORE
4th century BCE Aristotle's theory of epigenesis states that an embryo begins as an undifferentiated mass, with new parts added during its development.

1600 Italian physician Hieronymus Fabricius publishes *On the Formed Fetus*.

AFTER
1980 German geneticist Christiane Nüsslein-Volhard and American geneticist Eric Wieschaus classify 15 genes that determine cell differentiation in fruit fly embryo development.

2012 Japanese stem cell researcher Shinya Yamanaka discovers that mature mouse cells can be reprogrammed to become immature, pluripotent stem cells.

In 1891, German biologist Hans Driesch demonstrated that it was possible to split fertilized sea urchin eggs at the two-cell stage and still obtain normal, though smaller, sea urchin larvae. Driesch believed that the embryo had a system of coordinates, like the x and y axes on a graph, that specified the position of cells within the embryo and that this position determined the way each cell would develop. He also concluded that an embryonic cell's development was guided by a force he called entelechy.

Attempting to explain Driesch's ideas, other early embryologists theorized that part of the embryo acted as an "organizer," guiding the development of the cells. German embryologist Hans Spemann studied gastrulation, the rapid process of rearrangement in an embryo into distinct germ layers of cell types that will eventually form all the tissues and organs of the developing organism. In 1918, Spemann discovered that cells transplanted from one part of the embryo to another before gastrulation could become any of the main cell types. After gastrulation, the embryonic cells could no longer change their identity.

> It is not birth, marriage, or death, but gastrulation which is truly the most important time in your life.
> **Lewis Wolpert**

In 1924, Spemann and doctoral student Hilde Mangold described how they had identified a group of cells, subsequently called the Spemann–Mangold organizer, that was responsible for the development of neural tissue in amphibian embryos.

Morphogenesis

The changing shape of an early embryo—a process known as morphogenesis—mainly occurs during gastrulation, when rearranging cell layers and the directed movement of cells from one location to another results in a two-dimensional sheet of cells

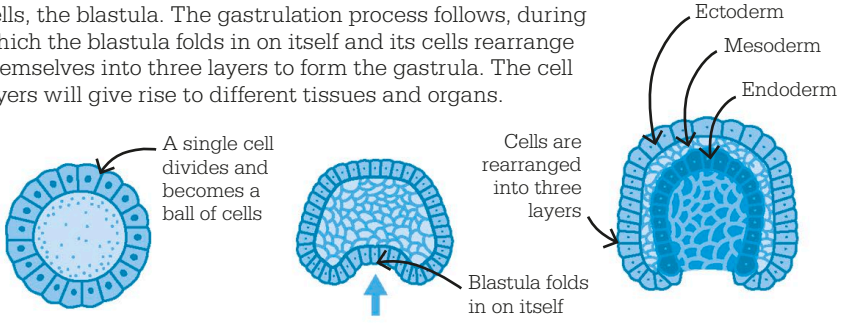
See also: The cellular nature of life 28–31 ▪ How cells are produced 32–33 ▪ Making life 34–37 ▪ Epigenesis 184–85 ▪ Fertilization 186–87 ▪ Meiosis 190–93 ▪ Stem cells 194–95 ▪ What are genes? 222–25

being transformed into the complex three-dimensional body of a multicellular organism. Researchers recognized that the development of cells in embryos was somehow, as Driesch had suggested, coordinated into spatial patterns. The belief grew that this might be achieved by variations in the concentrations of substances or properties that could be chemically transmitted from one part of an embryo to another. However, the nature of the signals that triggered development remained unknown.

Cell organization

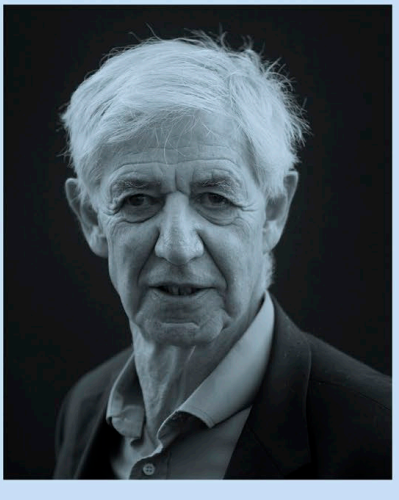
In 1952, British mathematician Alan Turing developed a model of a growing embryo in which he explored how uniformly distributed signals in cells can spread, self-organize, and form patterns, turning a group of identical cells into an organized collection of various types. Turing called the signals "morphogens." His ideas were met with scepticism and were more or less ignored for nearly two decades.

A zygote undergoes rapid cell division to form a ball of cells, the blastula. The gastrulation process follows, during which the blastula folds in on itself and its cells rearrange themselves into three layers to form the gastrula. The cell layers will give rise to different tissues and organs.



In 1969, British developmental biologist Lewis Wolpert described what he called the "French flag" model—no matter what size a flag might be, it always follows the same pattern, just as Driesch's halved embryos developed into normal sea urchins. Wolpert hypothesized that the physical location of cells in the embryo confers how they behave—for example, which of their genes are switched on or off—and how they respond to external signals, giving rise to the correct formation and positioning of anatomy. Wolpert believed the fate of each cell was determined by variations in concentration of a signaling chemical across the cells. He stipulated that the effects of these signals occurs over small distances of 100 cells or fewer, which he called positional fields.

Wolpert's notion that embryo cells' positional information could be determined by the concentration of diffusing chemicals was groundbreaking. The science underpinning his model has since been challenged, but it remains important for understanding how morphogenesis operates. ■



Lewis Wolpert

Born in South Africa in 1929, Lewis Wolpert studied civil engineering at the University of Witwatersrand before working as a soil mechanic for a building research institute. Leaving South Africa, he moved to the UK and enrolled at Imperial College London to study soil mechanics before transferring to King's College to complete his doctorate on the mechanics of cell division.

In 1966, he became professor of biology at Middlesex Hospital Medical School and, later, went on to become professor of cell and developmental biology at University College London. As an author and broadcaster, Wolpert was an advocate for the public understanding of science and helped raise awareness of the problems of aging and mental illness. He died in 2021.

Key work

1969 "Positional Information and the Spatial Pattern of Cellular Differentiation"

THE CREATION OF THE GREATEST HAPPINESS

IN VITRO FERTILIZATION

IN CONTEXT

KEY FIGURES
Robert Edwards (1925–2013), **Patrick Steptoe** (1913–88)

BEFORE
1678 Dutch scientists Antonie van Leeuwenhoek and Nicolas Hartsoeker make the first microscopic observation of sperm cells.

1838 French physician Louis Girault publishes the first account of successful human artificial insemination.

AFTER
1986 Robert Edwards and Patrick Steptoe celebrate 1,000 children born through IVF at their clinic, Bourn Hall.

1992 The first baby is born using ICSI (intracytoplasmic sperm injection), where a single sperm is injected directly into the egg.

For most of human history, a woman's ability to bear children has been used to determine her worth, and such attitudes persisted well into the 20th century. In vitro fertilization (IVF) is a method of assisted reproduction that offers the possibility for anyone to have a child when they cannot conceive in a natural way.

British physiologist Robert Edwards was dubbed the "Creator of the Greatest Happiness" for his role in solving the riddle of IVF in 1978, in collaboration with obstetrician and gynecologist Patrick Steptoe and nurse and embryologist Jean Purdy.

See also: Making life 34–37 ▪ Epigenesis 184–85 ▪ Fertilization 186–87 ▪ Embryological development 196–97

The birth mother is given medication to **suppress** her **natural menstrual cycle** and spontaneous **ovulation**.

The mother takes **fertility drugs** to **increase** the **production of eggs**.

Physicians regularly **monitor** the size and quantity of the mother's follicles (fluid-filled sacs containing an immature egg) by ultrasound.

Mature eggs are **retrieved** from the mother's ovaries, and a **semen sample** is taken from her partner or sperm donor.

The egg and sperm cells are **mixed in a laboratory** and left in an incubator for several hours to allow **fertilization** to take place.

After several days, the best one to three **fertilized eggs** (embryos) will be **transferred into the mother's uterus**. If the embryo implants successfully, it is likely to develop into a baby.

In vitro (Latin for "in glass") fertilization was first studied in animals with external fertilization, such as frogs. But for animals with internal fertilization, including humans, it was necessary to first solve many practical problems before a similar technique was feasible. The first attempt at IVF in mammals was performed by Viennese embryologist Samuel Leopold Schenk in 1878, using rabbit and guinea pig sperm and eggs under the microscope, but his experiments were poorly controlled and did not succeed. Schenk and his contemporaries were unaware of the roles of temperature, pH, and reproductive hormones, and understanding these "building blocks" of fertilization would be key to gaining the ability to manipulate human reproduction outside the body. In 1934, American biologist »

Robert Edwards

Born in 1925 in Yorkshire, UK, Robert Edwards went on to study agriculture at the University College of North Wales in Bangor, but his studies were interrupted by World War II, when he served in the army. After the war, he returned to Bangor, transferred to zoology, and was later awarded a doctorate in reproduction genetics.

In the 1960s, Edwards worked with the leaders of animal reproductive physiology, Alan Parkes and Colin "Bunny" Austin. At that time, he became aware of the work of Patrick Steptoe, and their collaboration began in 1968, culminating in the birth of the first IVF baby in 1978. Edwards continued his research as director of the world's first IVF clinic; he was awarded the 2010 Nobel Prize in Physiology or Medicine, and was knighted a year later.

Key works

1970 *Fertilization and cleavage in vitro of human oocytes matured in vivo*
2005 "Ethics and moral philosophy in the initiation of IVF, preimplantation diagnosis and stem cells"

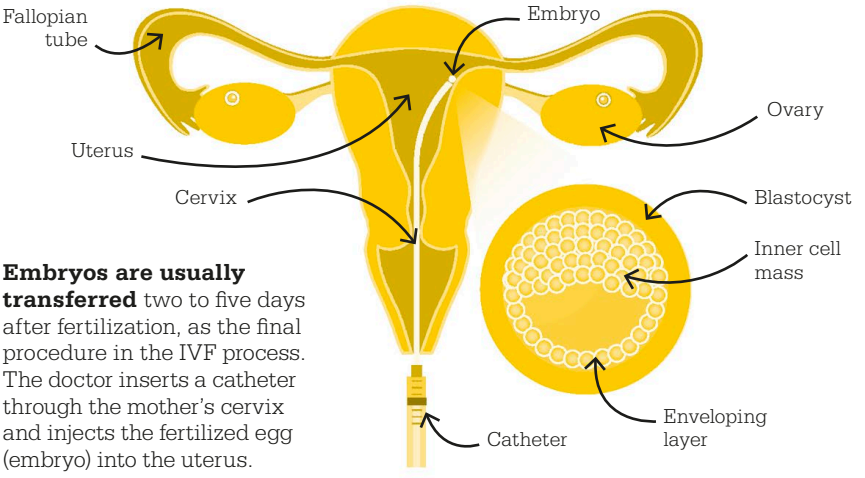
Gregory Pincus, also working with rabbits, introduced sperm to the eggs outside the body and later implanted the eggs back into the uterus. The rabbit became pregnant, but the eggs had been implanted before fertilization actually occurred—the fertilization occurred inside the rabbit's body and was therefore "in vivo" ("in a living thing"), rather than "in vitro".

The function of hormones

By the late 19th century, biologists observed that the pituitary gland in the brain was enlarged during pregnancy, and in 1926, German-born Israeli gynecologist Bernhard Zondek and American endocrinologist Philip Edward Smith independently, but almost simultaneously, discovered that hormones secreted by the pituitary gland control the function of reproductive organs.

A decade later, Pincus described the physiological changes that human eggs must undergo in order to be ready for fertilization (known as maturation). It wasn't until 1951 that Chinese-American scientist Min Chueh Chang and British professor Colin "Bunny" Austin discovered that sperm must also mature in the female reproductive tract before they acquire the ability to penetrate and fertilize eggs (known as sperm capacitation). Once the processes required for preparing sperm and eggs for fertilization had been recognized, IVF became much more feasible.

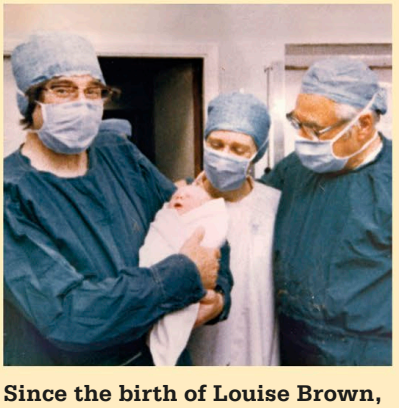
Chang went on to demonstrate that eggs from a female black rabbit could be fertilized in vitro by sperm from a black male. He then transferred the eggs to a white female, resulting in the birth of a litter of black rabbits. Chang's clever use of different colored rabbits avoided the problems that Pincus and Enzmann had faced in 1934 when they could not confirm whether fertilization had occurred in vitro or in vivo.



Embryos are usually transferred two to five days after fertilization, as the final procedure in the IVF process. The doctor inserts a catheter through the mother's cervix and injects the fertilized egg (embryo) into the uterus.

Egg retrieval

In the 1950s, Edwards entered the exciting field of reproductive biology as a doctoral student in Edinburgh, Scotland, where he studied the development of mouse embryos. During his six years in Edinburgh, he published 38 papers,



Since the birth of Louise Brown, the IVF techniques pioneered by Edwards and Steptoe have been adopted around the world.

Birth of Louise Brown

In 1978, at Oldham General Hospital, near Manchester, UK, the birth of the first IVF baby, Louise Brown, was a milestone in reproductive biology and a worldwide media sensation. Before her birth, Robert Edwards and Patrick Steptoe faced a lot of criticism from both their peers and wider society for focusing on what some saw as unethical and dangerous research. Church leaders accused the pair of "playing God" and critics called the technique "dehumanizing."

Concerns were raised about emerging techniques such as cloning, genetic engineering, and "designer babies," and whether the disposal of extra embryos was morally problematic. Both men felt it was their duty to speak with the press rather than let wild speculations propagate and this raised the public profile of their work. However, once healthy little Louise arrived after a full-term pregnancy, many of the critics were silenced and a new generation of children was born.

and his prodigious output made him one of the rising stars in the field. Edwards' true passion lay in understanding human reproduction, but he was frustrated by his limited access to human eggs until he read a paper by Steptoe, who had pioneered the use of the laparoscope in gynecological surgery. Steptoe's technique enabled the retrieval of human eggs with minimal incisions when compared with open surgery. Edwards began collaborating with Steptoe in 1968, and in the same year recruited Jean Purdy as his laboratory assistant.

Now that Edwards and his research team had secured a reliable source of human eggs, they were able to experiment with the ideal conditions to achieve fertilization. Graduate student Barry Bavister showed that by increasing the alkaline levels of the culture media in the IVF Petri dish—a solution used to support cell growth—they could obtain higher rates of fertilization. Edwards, Bavister, and Steptoe then published a paper in 1969 in which they described fertilizing human eggs in vitro. Their next challenge was to determine how to reintroduce the fertilized egg back into a woman, so that the resulting embryo could develop into a healthy pregnancy.

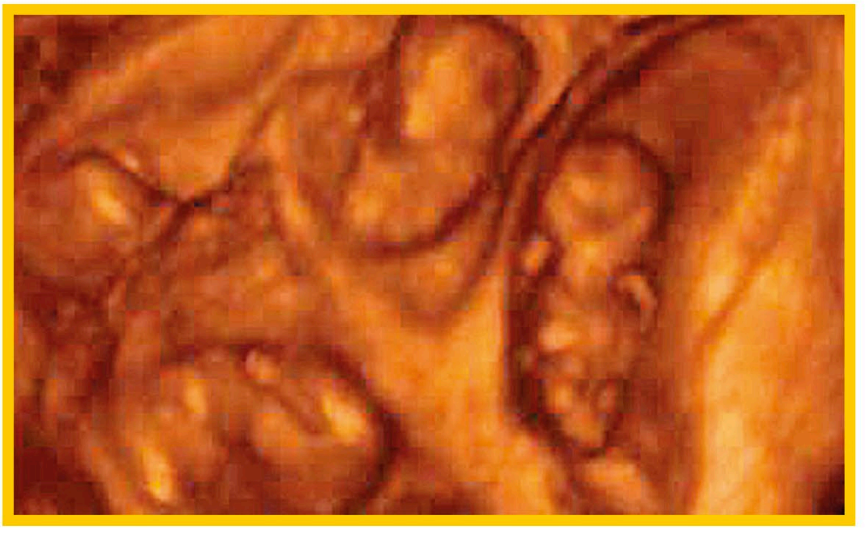
The first procedures

The trio of Edwards, Purdy, and Steptoe began transferring embryos back into women in 1972, but Edwards had not realized that the rate of successful implantation would be so low. The team was elated in 1976, when one of their patients became pregnant after an embryo transfer, but their joy was short lived because the embryo implanted in the fallopian tube—known as an ectopic pregnancy—and had to be terminated.

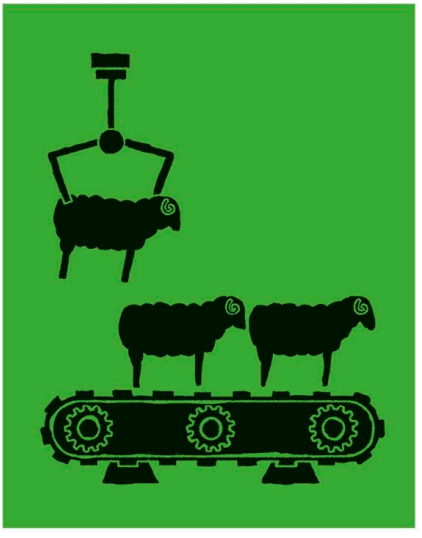
In 1976, Lesley Brown was referred to Steptoe for infertility treatment after unsuccessfully trying to conceive for nine years and being diagnosed with blocked fallopian tubes. By analyzing Lesley's hormone levels, Edwards and Steptoe determined her natural ovulation cycle. In November 1977, Steptoe removed one of Lesley's eggs, Edwards fertilized it with her husband's sperm in a Petri dish, and then Purdy waited for the fertilized egg to divide. Once it had developed into an embryo with eight cells, it was implanted. When Edwards and Steptoe announced they had achieved a successful pregnancy, it created a sensation in the media, and after the press found out that Steptoe had scheduled a cesarian delivery, he moved the procedure a day earlier to keep the birth a secret. Lesley gave birth to a healthy daughter named Louise on July 25, 1978, and newspapers around the world hailed her arrival as a triumph of the value of perseverance.

> "I am not a wizard or a Frankenstein. All I want to do is to help women whose child-producing mechanisms are slightly faulty."
> **Patrick Steptoe**

Today, IVF remains the most popular assisted reproductive technology designed to help those who are infertile achieve a successful pregnancy. By the 40th anniversary of Louise Brown's birth in 2018, more than 8 million children worldwide had been born using IVF and similar assisted-conception methods. ■



Quadruplets may develop when up to four separate eggs are fertilized. They occur naturally in about 1 in 700,000 pregnancies. In IVF, several embryos are placed into the womb, and nearly 30 percent of pregnancies are multiple.



DOLLY, THE FIRST CLONE OF AN ADULT ANIMAL

CLONING

IN CONTEXT

KEY FIGURE
Keith Campbell (1954–2012)

BEFORE
1903 American plant physiologist Herbert Webber coins the word "clone" to describe organisms produced by asexual reproduction.

1952 American biologists Robert Briggs and Thomas King clone leopard frogs by transferring a nucleus from the cell of a developing embryo to an unfertilized egg.

AFTER
2003 In San Diego Zoo in the US, two rare banteng cattle calves are born to a domestic cow after being cloned from frozen cells. This raises hopes that cloning can assist endangered species.

2003 A Pyrenean ibex is cloned by using cells from preserved skin cells. This animal had previously been declared extinct.

A clone is an organism that has an exact copy of the genome—the complete set of genetic instructions—of another, older organism. Clones are found in nature, mostly among plants and invertebrate animals and less commonly in some fish, reptile, and amphibian species. Natural clones are created when a female reproduces asexually, without any input from a male. In sexual reproduction, the sex cells (the egg and sperm) each contain half the genetic material required to make a new individual. These sets are combined when the egg is fertilized, transforming it into a zygote—the first cell of a new organism. Generally, during asexual reproduction, the female produces an egg that already has a full set of genes, a like-for-like copy of her own DNA, and thus the cell can act as a zygote.

Dolly the sheep

The term clone is more often used to describe organisms that have been created in an artificial process. Cloning technology involves taking genetic information from one organism and creating identical copies of it that can be implanted in the egg of another. The process transforms an egg into a zygote, which then develops in the normal way. Cloning was first achieved with frogs in 1952, but the big breakthrough came in 1996, when a sheep named Dolly became the first mammal clone.

Dolly was created using a technique called somatic cell nuclear transfer. During this process, she had three mothers

Dolly's birth offered the prospect of new ways to fight disease, but it also raised ethical issues. In particular, critics feared that it would lead to human cloning, but a global ban has been put in place to prevent that.

See also: How cells are produced 32–33 ▪ Making life 34–37 ▪ Asexual reproduction 178–79 ▪ Fertilization 186–87 ▪ Meiosis 190–93 ▪ Stem cells 194–95 ▪ Embryological development 196–97 ▪ In vitro fertilization (IVF) 198–201

A **naturally fertilized egg's** unique set of genes is **supplied by two parents**.

→

The **egg can also** be fertilized by transferring a **full set of genes** from a cell taken **from one of the parents**.

→

The egg develops into a clone of that adult, with an exact copy of its genes.

and no father. First, an egg was collected from one sheep. Its nucleus, which contained a half-set of DNA, was removed, but the egg's cytoplasm was left intact. This included the mitochondria, which provide energy for the cell and carry their own small amount of DNA. So, Dolly's mitochondrial DNA was provided by this first sheep.

Next, a cell was taken from the udder of a second sheep. This cell's nucleus, which contained a full set of DNA, was placed into the empty egg, creating Dolly's zygote. The zygote was given an electric shock to stimulate it to divide and steadily grow into a ball of cells. This was then implanted into the uterus of a third sheep, which acted as Dolly's surrogate mother.

Dolly was created at the Roslin Institute in Edinburgh, Scotland, where a research team made 277 attempts at cloning. Of these, 29 early embryos developed, and three lambs were born, though Dolly was the only one to survive. She lived for six years and gave birth to six lambs. Four ewes cloned from the same udder cell line in 2007 lived longer than Dolly. The technique pioneered for Dolly has since been used to clone other mammals, including monkeys in 2017, but there is a global ban on human cloning.

Cloned stem cells

The most important application of cloning technology has been in stem cell research. Cloned stem cells are capable of developing into any body cell or tissue. They can be used to regenerate and repair damaged or diseased tissues and perhaps whole organs. As such, they have opened up an exciting new area of medicine. ■

> The road to immortality is not through cloning.
>
> **Arthur L. Caplan**
> **Bioethics professor**

Keith Campbell

Born in Birmingham, England, in 1954, Campbell studied at King's College London and had a successful career in microbiology before starting research work at Edinburgh's Roslin Institute in 1991. Four years later, he and Bill Ritchie produced Megan and Morag, sheep that had been grown from cells taken from one embryo and then allowed to develop separately. This pair of sheep were genetic clones, made by a process more akin to creating identical twins artificially, rather than cloning an adult sheep. Campbell, Ian Wilmut, and Shinya Yamanaka were the research team that created Dolly in 1996. Wilmut later said that Campbell deserved "66 percent" of the credit for the project's success.

In 1998, Campbell moved to the University of Nottingham to take up a professorship. He also worked for private companies and, with one of these, produced the first cloned pigs in 2000. He died in 2012.

Key work

2006 "Reprogramming Somatic Cells into Stem Cells"

INHERIT

ANCE

Gregor Mendel's experiments show how **inherited characteristics** can **skip a generation**, suggesting the action of "particles," later known as **genes**.

1866

Nettie Stevens discovers the **two kinds of chromosome** that determine the sex of fertilized eggs.

1905

George Beadle and Edward Tatum demonstrate that the **production of enzymes** is determined by genes, and a **gene encodes** for a particular **protein**.

1941

1904

The **particles of inheritance** Mendel described are shown by Thomas Hunt Morgan to be **carried by chromosomes**.

1928

Experiments on **bacteria** by Frederick Griffith show that **inherited characteristics** are caused by **chemicals**.

1950

Barbara McClintock describes the **action of genes** that "jump" from one chromosome to another, and the ability of chromosomes to switch **genes on or off**.

While it was recognized from very early times that children tend to resemble their parents physically and in their personalities, the reasons for inheritance were poorly understood. Erroneous theories of the process of reproduction, such as the idea of preformation either in the ovum or the sperm, were in conflict with the obvious contribution of both parents to the characteristics of their offspring.

It was the much older theory of pangenesis, dating back to the ancient Greeks, that was closer to the truth: that "seed material" from both parents mixed to produce offspring. Biologists in the 18th century revisited this idea with experiments involving the breeding of hybrid plants and crossing animals from different species.

Genetics

Gregor Mendel provided the key that unlocked the problem of inheritance, and opened up what was to become the field of genetics. In a study of the characteristics of pea plants, such as height, he showed that they are not inherited by a simple blending of material from the parents, because certain forms (traits), such as tall or short, would sometimes skip a generation. Instead, he suggested that these inherited characteristics are determined by pairs of particles, which are now known as genes. Mendel published his theory in 1866, but its importance was not recognized until the beginning of the next century.

In their studies of chromosomes under a microscope, Walter Sutton and Theodor Boveri both identified chromosomes as the carriers of the pairs of particles Mendel had described, a point confirmed by Thomas Hunt Morgan's study of inheritance in fruit flies. In 1905, Nettie Stevens found two kinds of chromosomes in the sperm of beetles, the sex chromosomes (later called X and Y chromosomes), which determine the sex of fertilized eggs.

Understanding DNA

In 1928, Frederick Griffith showed that the inherited characteristics of bacteria could be altered by chemicals, implying that inherited characteristics themselves are caused by chemicals. Later, George Beadle and Edward Tatum found that molds with defective genes were incapable of producing a particular enzyme, and from this

1953
A model of the **double-helix structure** of **DNA** is created by James Watson and Francis Crick.

1964
Marshall Nirenberg and Philip Leder establish that **DNA embodies** the **genetic code** in all living organisms.

1973
The first **genetically modified (GM) cells** are produced by Herbert Boyer and Stanley Cohen.

1979
Frederick Sanger applies his **technique for deciphering** the sequence of long-chain biological molecules to **sequence DNA**.

2000
The Human Genome Project, led by Francis Collins, presents the **first draft** of a map of the **human genome**.

2011
Jennifer Doudna pioneers a technique of **gene therapy** using edited bacteria genes to **target defective** human genes.

they deduced that a gene is a section of DNA that encodes for a particular kind of enzyme, or more generally that a gene encodes for a particular protein.

The link between chromosomes and genes was firmly established by the 1930s, when Barbara McClintock began her study of chromosome behavior. Having shown that during meiosis (cell division in sexual reproduction), genes carried on a chromosome may move position, she went on to describe transposable elements —genes that "jump" to positions on entirely different chromosomes. She also discovered that genes are not continuously active, but can be turned on and off.

What remained to be explained, however, was how DNA is capable of self-replication. James Watson and Francis Crick believed this was due to an inherent quality of the structure of the DNA molecule and, working from Rosalind Franklin's X-ray diffraction photo, managed to create a 3D model of the DNA molecule in 1953. This showed the now familiar double-helix structure of DNA, explaining its ability to replicate by unwinding.

Genetic sequencing

Given the basic definition of a gene as encoding for a particular protein, the next goal was to establish the relationship of a sequence of units (bases) in DNA with the sequence in the relevant protein, that is, how the bases encode to determine an amino acid. Marshall Nirenberg and Philip Leder discovered that in all living things, the genetic code consists of three bases encoding for a specific amino acid. Another advance in the understanding of the involvement of genes in all living organisms came with the development of sequencing: analyzing the sequence of units of long-chain molecules, such as proteins and DNA. A pioneer of the technique, Frederick Sanger, successfully managed to sequence the DNA of a virus in 1979. This paved the way for research such as the Human Genome Project, which aimed to sequence the entire human genome.

With a greater knowledge of the structure and behavior of genes, practical applications have been found, opening up the possibilities of using techniques such as genetic engineering to modify the genetic composition of cells, and gene editing to combat diseases. ■

IDEAS OF SPECIES, INHERITANCE, VARIATION

THE LAWS OF INHERITANCE

IN CONTEXT

KEY FIGURE
Gregor Mendel (1822–84)

BEFORE
4th century BCE Hippocrates suggests that "seed material" is passed from parents, a material basis for inheritance.

1760s German botanist Joseph Kölreuter demonstrates that the characteristics of offspring in plants result from equal contributions from both parents.

AFTER
1900 The results of Gregor Mendel's experiments with pea plants are independently replicated by others, including Dutch botanist Hugo de Vries.

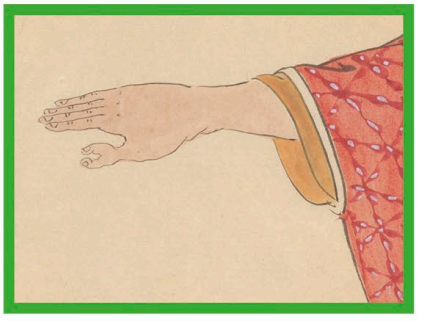
1902–03 German biologist Theodor Boveri and American biologist Walter Sutton independently demonstrate that particles of inheritance—later called genes—are carried on chromosomes.

For much of the history of biology, the greatest mystery was inheritance. What makes offspring resemble their parents? Until as recently as the 18th century, many people doubted that in sexual reproduction both parents contribute equally to making young—despite the obvious similarities that they share with both mother and father. A popular idea was that each offspring was preformed—either in the eggs or sperm—and some biologists were convinced they had seen evidence of this through their microscopes. Others favored an idea that had its roots in Greek philosophers such as Hippocrates: "seed" material coming from all body parts was sent to the sex organs before being mixed to produce offspring. This theory, called pangenesis, was closer to the truth but still a long way from the modern notion of genes.

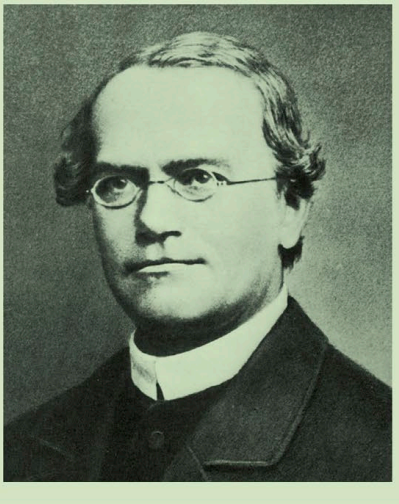
Husbandry and hybrids

Practical approaches in the mid- to late 18th century facilitated an understanding of inheritance, either by looking back through family trees or looking forward in the results of breeding experiments. For example, German botanist Joseph Kölreuter cross-bred plants to produce intermediate hybrids with an equal contribution from each parent, which disproved the idea of preformation. Hybrids between different species were usually sterile—and sterile hybrids supported Kölreuter's idea that species were fixed: they had an ideal type, and any natural variation was accidental and not important.

This so-called essentialist view was shared by many notables, including Carl Linnaeus, the Swedish originator of the system



Polydactyly is a condition of having an extra finger or toe. In 1751, French scholars Pierre Maupertuis and René de Réaumur traced the inheritance of the condition and found it to be dominant.



Gregor Mendel

Born in Austrian Silesia in 1822, the son of poor peasants, Mendel was accepted into the monastery at Brno (now part of the Czech Republic). The friars changed his given name from Johann to Gregor, and he was ordained in 1847, before receiving training in natural sciences at the University of Vienna so he would be qualified to teach. Influenced by his professor's interest in the origin of species, Mendel was intrigued by nature; this and his passion for gardening influenced his direction as he began to cultivate plants—notably garden peas—in order to test ideas about the nature of inheritance. Despite the publication of his discoveries in 1866, Mendel's findings were little recognized during his lifetime, although he would later be dubbed the "father of genetics." He died in 1884.

Key work

1866 "Experiments in Plant Hybridization"

See also: Pollination 180–83 ▪ Fertilization 186–87 ▪ Chromosomes 216–19 ▪ The chemicals of inheritance 221 ▪ What are genes? 222–25 ▪ The double helix 228–31 ▪ The genetic code 232–33 ▪ Natural selection 258–63 ▪ Mutation 264–65

of biological classification still used today. Linnaeus thought that a plant variety could be explained by where it grew—its soil or climate—and would revert to "type" when these factors were corrected. This view hindered any progress in understanding how inheritance worked: if varieties were purely the consequence of local surroundings, then it would be pointless to seek their explanation in family trees.

In the 19th century, naturalists such as Charles Darwin changed this view—variation in species was not only widespread, it was highly significant as the raw material of evolution. His idea that new species could emerge inspired plant breeders to study inheritance as a way to find out exactly how that occurred.

The right approach

In 1866, Austrian Augustinian friar Gregor Mendel published a paper about his investigations into the "species problem." It is likely he had been encouraged to carry out this research while studying at the University of Vienna. His professor there, Franz Unger, had suggested that new species arose from variation in an existing species. Mendel's understated work, which he began in 1856, would go on to revolutionize biology in a different way, but it would take nearly half a century to do so. Indeed, during his own lifetime, Mendel's meticulously documented pea-breeding experiments were overlooked.

Mendel's success came down to his approach. He saw inheritance as mainly a problem of numbers—something that undoubtedly came from his mathematics and physics studies at the university. He knew that copious data improved statistical reliability, so he carefully replicated plant crosses over many generations and counted inherited variations to reveal patterns of inheritance. He ended up working with 10,000 garden pea plants, cultivated in a 4-acre (1.6-ha) plot at the abbey of St. Thomas in Brno (now in the Czech Republic). Mendel had the full support of his abbot, who even had a greenhouse built to help with the research. Most critically, Mendel studied the inheritance of one characteristic of his pea plants at a time, which revealed the crucial patterns.

Mendel's choice of the garden pea (*Pisum sativum*) for his experiments was a careful one: the plants have several observable characteristics and are easily cross-bred.

> Genetics, an important branch of biological science, has grown out of the humble peas planted by Mendel in a monastery garden.
>
> **Theodosius Dobzhansky**
> **Ukrainian-American geneticist**

Crossing pea plants

Mendel chose to study seven pea plant characteristics in turn, each of which has two forms (traits). For example, plant height is either tall or short, and pea color yellow or green. He then crossed alternative pure-breeding varieties, such as tall plants with short ones, and grew the next generation »

from the pea seeds they produced. For each cross, he counted the number of offspring that showed each trait and then repeated the process many times.

Although earlier plant breeders such as Kölreuter had shown that hybrids could be true intermediates of parents, this was only the view when looking at the plants in their entirety with all their combined characteristics. By studying each of the individual characteristics separately, Mendel saw that one trait dominated the other, so that when they were crossed together, only the dominant one appeared in the offspring. For height, tall plants dominated short ones: all offspring from a tall–short cross produced tall plants. In a similar way, yellow peas dominated green ones. In each case, Mendel called the hidden trait "recessive."

Reappearing traits

Next, Mendel crossed his hybrid offspring to produce yet another generation. Now, the recessive trait of one of the original parents reappeared, having skipped a generation. This was nothing new: earlier plant breeders knew that some offspring from hybrids could revert to the parental type, but Mendel was different because he counted the numbers. A pattern started to emerge: the recessive trait came through in one-quarter of the offspring, leaving three-quarters with the dominant trait.

Mendel had proposed that characteristics were somehow determined by physical particles, which he called "elements." Each kind of element was responsible for a particular trait, such as tall or short plants. He thought that elements in a plant came in pairs that formed at fertilization: one inherited through the pollen and one through the egg. This meant that pure-breeding plants had two doses (the number of copies of a gene) of either the tall element or the short element. In the next generation, all plants inherited one of each element, although only the tall element affected the offspring's height. But in the generation after that, some plants ended up with two doses of the short element, making short plants appear again. According to Mendel's paired-particle hypothesis, if the parents of these tall plants had carried half tall and half short elements, the chance of two short elements coming together was ½ x ½ = ¼. This was supported by his counts: one-quarter were short pea plants.

> "Traits disappear entirely in the hybrids but reappear unchanged in their progeny."
> **Gregor Mendel**

	Seed shape	Seed color	Seed coat color	Pod shape	Pod color	Flower position	Plant height
Dominant trait	 Round	 Yellow	 Colored	 Full	 Green	 Side	 Tall
Recessive trait	 Wrinkled	 Green	 White	 Pinched	 Yellow	 End	 Short

Mendel selected seven garden pea traits for his studies. He found that some traits were dominant and others recessive—for example, round and yellow seeds were dominant, while wrinkled and green seeds were recessive.

Laws of inheritance

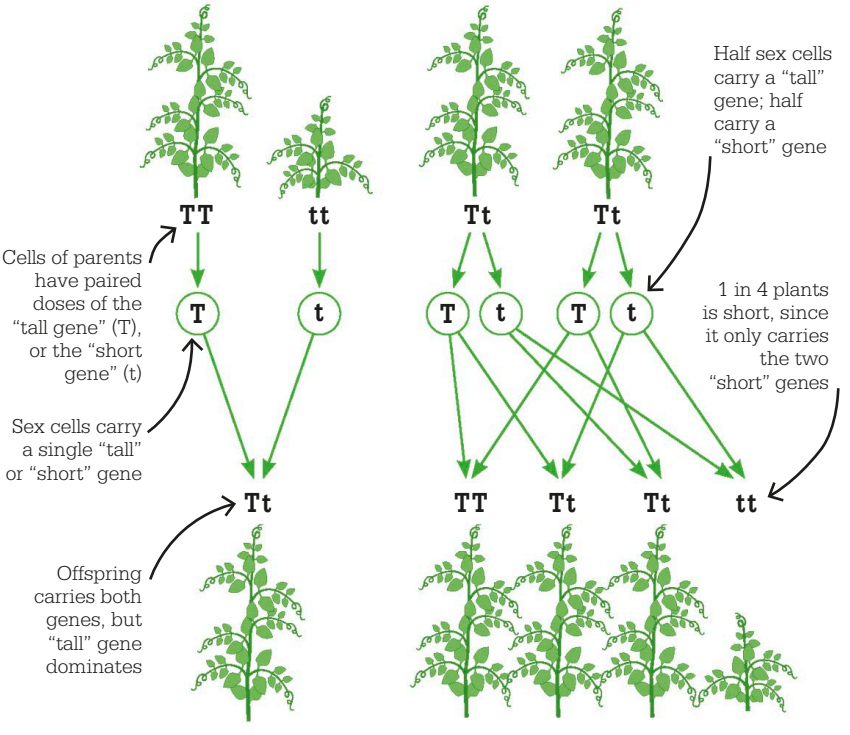
Once Mendel had identified the dominant and recessive traits that accounted for the different characteristics of his pea plants, he studied how multiple characteristics are inherited together—for example, if height affects pea color, or vice versa. To find out, he crossed plants having two dominant traits (tall, yellow peas) with ones having two recessive ones (short, green peas). Then, as before, he continued to cross for subsequent generations.

Mendel discovered that each trait was inherited independently of the other—as he would expect if they were controlled by independent pairs of elements. All plants of the first generation were double-dominant (tall, yellow peas), and

First law of segregation

In a first-generation cross, a pure-breeding tall plant is crossed with a pure-breeding short plant.

A second-generation cross sees offspring from the previous generation crossed together.



every combination emerged in the generation after that. However, when considering each character alone, a quarter of them were still short, and a quarter had green peas.

Mendel's discoveries about inheritance can be distilled into two main laws. First, inherited characteristics are determined by pairs of particles (now called genes), which separate into sperm (or pollen) and egg cells before pairing up again at fertilization. Second, each characteristic is determined by a gene pair that is inherited independently of any others.

Disregard and rediscovery

Before Mendel's time, improved microscopes had begun to reveal more about the nature of life—particularly that bodies were made up of cells, and these contained nuclei. Further advances meant that by the time Mendel died in 1884, biologists thought that a substance in nuclei was passed down through cell divisions, and fertilization involved fusing this material from each parent. Mendel's idea about particles being inherited in pairs could have refined this view had his work been recognized in his lifetime.

In 1900, Dutch botanist Hugo de Vries, German botanist Carl Correns, and Austrian botanist Erich von Tschermak independently achieved the same results as Mendel. Each of them, after reading back through the literature, acknowledged that Mendel had made the discovery first. In the »

Pollination control

Cross-breeding experiments that have been designed to investigate inheritance rely critically on knowing which offspring are produced by which parents. That is not always clear in plants, where male pollen from a single flower can scatter to pollinate many others of the same kind indiscriminately. Some plants—including pea plants—can also self-fertilize.

To control pollination, plant breeders remove the male stamens from a flower, while the female stigmas or entire flowers are covered by tiny "pollination bags" to prevent accidental contamination. A small paintbrush is then used to transfer pollen from the stamens of one known parent to the stigmas of another. In this way, the researcher knows that any seeds that grow are products of this particular cross. Mendel used this technique. Today, pollination bags are used by plant breeders who need to control pollination when growing new varieties for commercial use.

Many plant breeders control pollination by transferring pollen from one flower to another with a small brush.

years that followed, this spawned a rapid advance in the understanding of inheritance. Within 20 years, the reality of Mendel's paired particles (genes) was established beyond reasonable doubt, as interlinked components carried on threads called chromosomes.

Each body cell of a human contains more than 20,000 different genes—paired to make more than 40,000 in total. Pea plants contain even more: Mendel's seven were just a tiny fraction of the estimated 45,000 genes in that species (90,000 pairs). As Mendel suggested, each pair is constituted at fertilization, when a gene in an egg combines with its equivalent in sperm or pollen. This happens for each of the thousands of genes involved in making the body of a human or a pea plant—although Mendel had no idea about the true scale of the number of "elements" involved.

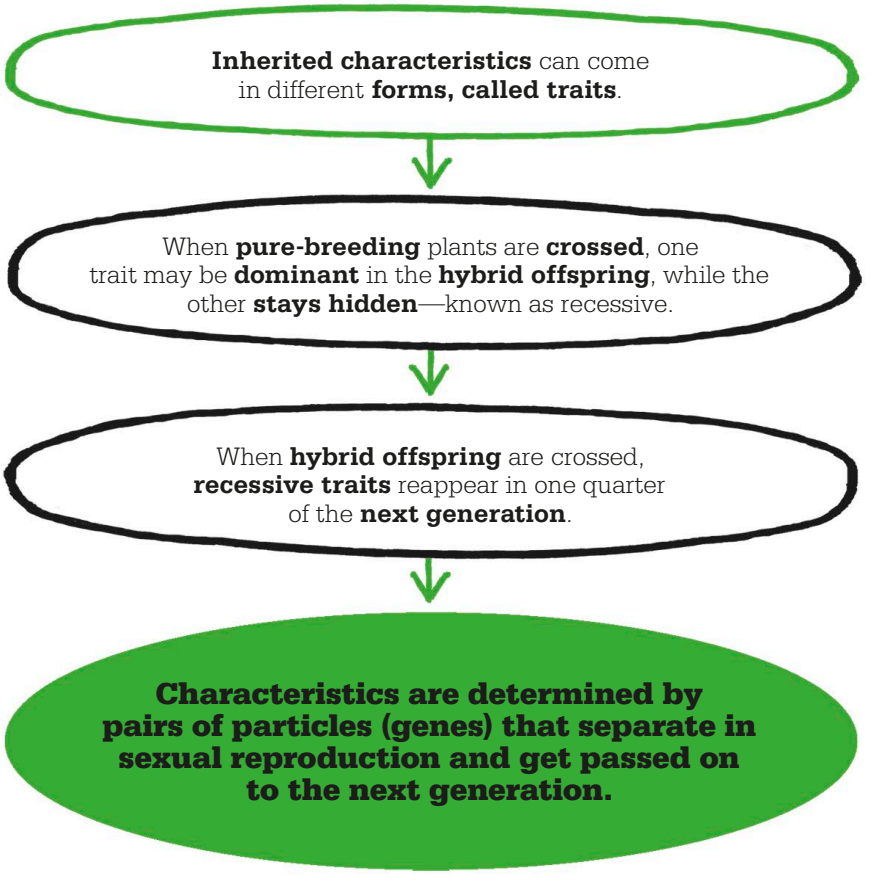
Revising Mendel

Mendel's idea about the particulate nature of inheritance especially satisfied biologists, who thought that sudden stark changes, or mutations, were the main drivers of evolution. Initially, not everyone was convinced, though. Supporters of Darwin's idea—that evolution happens through gradual selection of slight, continuous variations—could not reconcile this with Mendel's particle-like elements. Darwin himself had thought that inherited matter was partly blended between parents, which would help explain intermediates and continuous variation. But blending inheritance also meant a gradual dilution of variation through generations—and that would make evolution, as Darwin understood it, impossible. Even after Mendel, no one could explain continuous variation with particles. A big part of the problem was that genetic makeup and inherited characteristics were more or less regarded as equivalent.

> In the 50 years since Mendel's laws were so dramatically rediscovered, genetics has been transformed … to a rigorous and many-sided discipline.
> **Julian Huxley, 1951**

Clarity came in 1909, with the work of Danish botanist Wilhelm Johannsen. By breeding self-fertilizing garden beans, which are genetically uniform, he still managed to produce variation by altering soil fertility, light, and other factors—but this environmentally induced variation was not passed on to offspring.

In addition to coining the term gene, Johannsen introduced the word phenotype for observed characteristics, as distinguished from genotype for an organism's genetic makeup. Phenotypes had characteristics that could vary continuously—such as height in humans—or come in discrete, discontinuous categories, like



Worldwide, most people have brown eyes. Around 10 percent have blue eyes, and a further 12 percent have hazel, green, or amber.

Inheritance in humans

Any characteristic inherited in the way discovered by Mendel—with alternative dominant and recessive traits determined by versions of a single gene—is said to be a Mendelian trait. Some diseases in humans are inherited like this—for example, cystic fibrosis is recessive, and Huntington's disease is dominant. However, many other human characteristics traditionally thought to show simple Mendelian inheritance are actually passed down in more complex ways.

Blue eye color, for instance, is widely regarded as a recessive trait and brown eyes dominant, but this is an oversimplification. Biologists have identified at least eight genes involved in controlling pigment production in the eye's iris, and the final eye color that develops comes from interactions between all of them. This explains why other colors, such as hazel or green, are possible—and why it is possible for blue-eyed parents to have a brown-eyed child.

the purple and white flowers of pea plants. Some of the variation in a phenotype (whether continuous or not) is due directly to environmental influence, such as bigger bean plants in richer soil or darker tanned skin in brighter sunlight. The rest comes from the influence of the genotype.

In contrast, genotypes—with their gene particles—were always discrete and never blended. One big question remained: how can particulate genotypes determine some of the smoothly continuous variation that is obviously inherited? For example, how can they account for short-necked ancestors of the giraffe gradually evolving into its long-necked descendants, according to Darwinian selection?

Pairing elements

Mendel himself had previously proposed an explanation for continuous variation. He suggested that it could be caused by more than a single pair of elements (genes) affecting a characteristic. In 1908, Swedish scientist Herman Nilsson-Ehle bred wheat plants with red seeds of varying shades of color—something that was caused by three gene pairs interacting together. Each gene pair was inherited in conventional Mendelian fashion, but it was their combined effects that made the redness of the seed appear continuously blended.

By 1909, when Johannsen and Nilsson-Ehle had helped validate Mendelism to the satisfaction of Darwin's supporters, additional support for the paired-particle idea of inheritance had come from biologists studying the behavior of cells and the structures they contain. They found a physical basis for Mendel's particles in threads called chromosomes, which carried the genes like beads on a necklace. A new branch of biology—genetics—was now firmly established, paving the way for others to work out the chemical basis for inheritance and the crucial role of the double helix. Genes were no longer theoretical constructs: they were real particles made from self-replicating DNA. ■

Many characteristics—such as human body build—depend on both genetic and environmental factors, with genes, diet, and physical training all playing a part.

THE PHYSICAL BASIS OF HEREDITY

CHROMOSOMES

IN CONTEXT

KEY FIGURES
Theodor Boveri (1862–1915), **Walter Sutton** (1877–1916), **Thomas Hunt Morgan** (1866–1945)

BEFORE
1866 Austrian friar Gregor Mendel establishes that pairs of "units" control inherited characteristics.

1879 German biologist Walther Flemming calls material inside cells chromatin; when cells divide, it forms filaments, later called chromosomes.

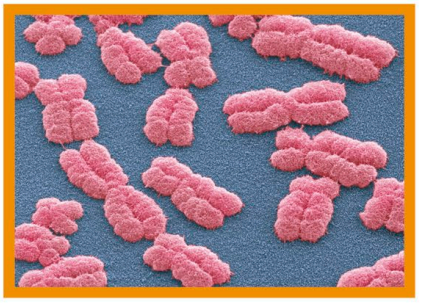
1900 Botanists Hugo de Vries, Carl Correns, and William Bateson independently "rediscover" Mendel's laws of inheritance.

AFTER
1913 Alfred Sturtevant, an American geneticist, produces the first sequence of genes along a chromosome.

By the late 19th century, microscopes were powerful enough to reveal that living things are made of structures called cells and that these contain even tinier structures, which scientists came to believe may contain the key to inheritance. Biologists discovered that dividing cells contain filaments made of a substance that could be stained with dyes. This prompted Walther Flemming to call the substance chromatin, meaning "colored material."

This was also a time when biologists began to understand that inherited characteristics were dependent upon physical particles that were apparently passed down

See also: Mitosis 188–89 ▪ Meiosis 190–93 ▪ The laws of inheritance 208–15 ▪ What are genes? 222–25 ▪ The genetic code 232–33



Pairs of human chromosomes are shown here in a scanning electron micrograph. One chromosome of each pair has replicated during cell division to form an identical copy, or chromatid.

through the generations in cells—including sperm and eggs. Gregor Mendel's experimental confirmation of this was largely overlooked at the time, but other scientists later had similar ideas. Notable among them was German biologist August Weismann, who suggested that inherited particles were carried together in units that he called idants. These later became known as chromosomes—a term coined in 1889 by another German, Wilhelm von Waldemeyer, for Flemming's threads of colored chromatin.

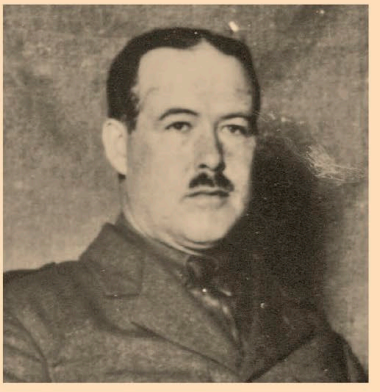
Chromosome continuity

There was a potential problem with chromosomes as carriers of inherited particles: they only appear when cells divide. In non-dividing cells, they seem to dissolve, so biologists began to wonder how any particles they carry could be transmitted intact between generations. Then, in 1885, using a staining technique and a powerful microscope, Austrian anatomist Carl Rabl noticed something important: the chromosome threads inside a cell are not random and disordered; rather, each kind of organism carries a particular chromosome set. The number of chromosomes in each cell stays fixed, and individual chromosomes—have unique identities—and particular lengths—that are preserved from one cell division to the next. We now know that when cells have finished dividing, their chromosomes unravel—only to rewind and thicken at the next division. For biologists in the late 19th century, this continuity of chromosomes meant they could realistically be the vehicles for passing on particles of inheritance—genes—intact.

The Boveri–Sutton theory

In the 1860s, Mendel's experiments breeding varieties of pea plants indicated, specifically, that particles of inheritance came in pairs, with one inherited from each parent. When his theory was rediscovered in 1900, biologists studying cells recognized a physical basis for his idea in chromosomes. In the first decade of the 20th century, corroboration came independently from either side of the Atlantic. In Italy, »

> Where a sperm contains chromosomes that have a characteristic size and shape, corresponding chromosomes … will be present in the egg.
>
> **Theodor Boveri**



Walter Sutton

Born in 1877 and raised on his parents' farm in the American Midwest, Walter Sutton had an aptitude for fixing farm machinery that led him to study engineering at the University of Kansas, but he later switched to biology. For his thesis, he studied sperm production in a grasshopper species native to his parents' farm, before continuing his studies at Columbia University in New York. He made a discovery that helped establish the role of chromosomes as carriers of genes.

After briefly reviving his interest in engineering to develop a device for deep-well oil extraction, he returned to his studies at Columbia, obtaining a doctorate in 1907. During World War I, he became surgeon-in-chief at the American Ambulance Hospital, near Paris. He died in 1916 of complications arising from appendicitis.

Key works

1900 "The Spermatogonial Divisions of Brachystola Magna"
1903 "The Chromosomes in Heredity"

German zoologist Theodor Boveri made an important discovery while researching sea urchins—animals whose fertilization and embryo development can be observed easily on a microscope slide. Boveri discovered that a complete set of 36 sea urchin chromosomes is needed for a healthy embryo to develop.

Meanwhile, while studying grasshoppers in the US, biology student Walter Sutton deduced that their chromosomes came in pairs that separated during the formation of sperm. He recognized that this paralleled the behavior of Mendel's genes and was more evidence that genes are carried on chromosomes. Sutton's detailed observations showed that each chromosome has a unique identity—just as Rabl had proposed two decades previously—suggesting that its genes are unique, too.

Cell division works in such a way that every new cell ends up with a complete set of chromosomes and genes. In fact, body (somatic) cells have two doses, or pairs, of both. A special kind of cell division (meiosis) makes sperm and egg cells. Meiosis separates the pairs, so halving the chromosome number. Fertilization restores the pairs when a sperm or pollen grain combines with an egg. This is what August Weismann had suggested in 1887—and Mendel had proposed even earlier. In contrast, when body cells divide by mitosis, the entire chromosome set is duplicated each time, so every daughter cell always receives a complete set: the number of chromosomes is maintained.

Linked genes

The first decade of the 20th century led some investigators to see a striking link between certain chromosomes and characteristics: males, at least in the animals that they studied, had a different chromosome set from females. This discovery of sex chromosomes was the first obvious connection between chromosomes and inherited characteristics, and the amount of experimental evidence showing exactly how chromosomes carried genes would soon snowball from one specific source.

In 1909, American biologist Thomas Hunt Morgan began to study inheritance through breeding experiments with fruit flies. He had been inspired by the research of Dutch botanist Hugo de Vries, who had studied inherited variations in plants; de Vries called these variations "mutations."

> We are interested in heredity not primarily as a mathematical formulation but rather as a problem concerning the cell, the egg, and the sperm.
> **Thomas Hunt Morgan**

Fruit flies proved perfect for studying inheritance. Breeding them produces varieties that differ in ways that can be seen with the naked eye—such as body color and wing shape. In his "fly room" at Columbia University, Morgan and his team crossed fruit fly varieties in abundance and—like Mendel—counted variations in the offspring to work out patterns of inheritance.

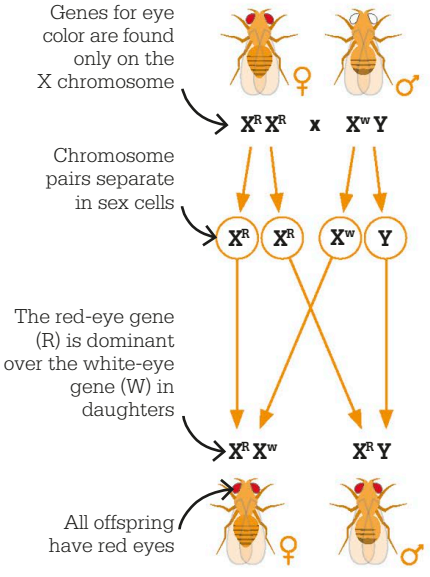
For Morgan, the arrangement of genes on chromosomes was a central consideration. The first variation—white eyes instead of the usual red—appeared more frequently in males than females. This led Morgan to deduce that genes for eye color and gender were linked—literally so—on the same sex chromosome.

Gradually, Morgan and his team identified other characteristics that were similarly linked. Altogether, they established that genes came in four groups, corresponding to the four pairs of chromosomes in

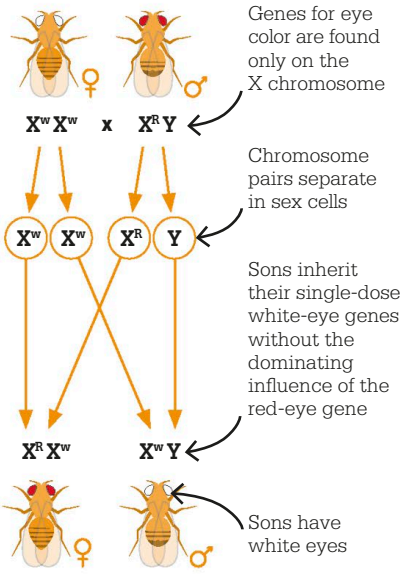
The tiny fruit fly *Drosophila melanogaster* is perfect for studying inheritance, since it can be bred quickly, has many visible traits, and has only four chromosomes.

Inheritance of genes on the X chromosome

In this first example, a normal (red-eyed) female fruit fly is crossed with a mutant (white-eyed) male.



For the second crossing, a mutant (white-eyed) female is crossed with a normal (red-eyed) male.



fruit fly cells. They then worked out the exact order of genes along the chromosomes.

In fact, chromosomes are not so faithfully preserved and indivisible as Rabl and Weismann had earlier suggested. During meiosis—the kind of cell division that produces sex cells—the pairs of chromosomes carrying similar sets of genes, called homologues, temporarily join together to exchange pieces. The result is that genes that were once linked together can become unlinked. Genes that are farther apart are more likely to get exchanged in this way, whereas those carried side by side may scarcely unlink at all. The closer together they are, the less likely it is that a breakage will occur between them, so the more likely they—and the characteristics they control—will be inherited together.

By keeping track of the number of times this happens for any two characteristics, the biologists in the fly room deduced the relative positions of the genes on the chromosomes. One of the Columbia team, Alfred Sturtevant, performed the first such analysis and, in 1913, produced the first-ever chromosome map—that of the fruit fly's sex (X) chromosome.

The human genome

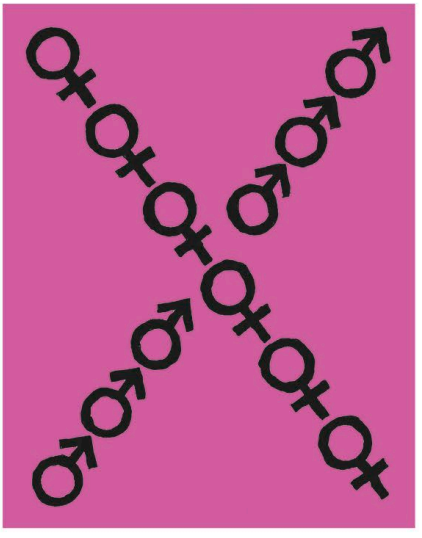
Genetics was starting to become an increasingly tangible part of biology—as the physical arrangements of genes within cells were being uncovered. This progress foreshadowed later developments on a scale that was unimaginable at the time: the Human Genome Project, completed less than a century later. ■

Queen Victoria is known to have passed hemophilia to three of her nine children. Her youngest son bled to death after a minor fall, aged 30.

Sex linkage

Hemophilia is a sex-linked disorder that has been called the "royal disease" because of the way Britain's Queen Victoria (1819–1901) passed it on to her children and grandchildren. The disorder is caused by a mutation in the gene that produces blood factor IX, which is a blood-clotting protein. The mutation prevents normal clotting and makes sufferers susceptible to blood loss. The gene responsible is carried on the X chromosome, which means boys are especially vulnerable. This is because, unlike in XX girls, the gene is paired to a Y chromosome, which cannot carry a dominant gene to override its defect.

Because none of Victoria's ancestors appear to have had hemophilia, it is likely to have originated in her by mutation. Her youngest son Leopold died from the disease, and two of her daughters (Alice and Beatrice) were carriers. The daughters passed it on to at least six of their own children.



THE X ELEMENT

SEX DETERMINATION

IN CONTEXT

KEY FIGURE
Nettie Stevens (1861–1912)

BEFORE
1891 Hermann Henking finds a dark structure in sperm heads, which he labels X.

1901 Clarence McClung identifies Henking's X structure as a chromosome that determines sex.

1902–04 Walter Sutton and Theodor Boveri demonstrate that chromosomes carry genes determining inherited characteristics.

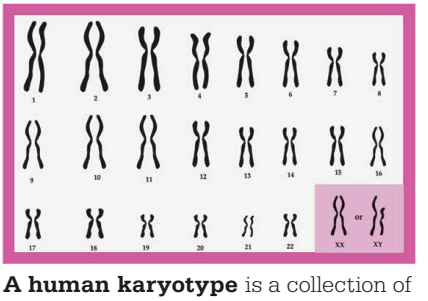
AFTER
1909 In the US, zoologist Edmund Wilson calls the sex chromosomes X and Y.

1966 French zoologist Madeleine Charnier describes temperature-dependent sex determination in reptiles, showing that in African agama lizards, eggs that are kept warmer hatch into males.

In 1891, German biologist Hermann Henking noticed a cellular difference between the sexes, in the form of a dark structure that only appeared in the heads of sperm. Not knowing what it was, he dubbed it simply "X". In 1901, American zoologist Clarence McClung decided that X was a sex-determining chromosome. It was carried by half the sperm cells, and McClung thought it controlled the male sex—but this was incorrect.

Clarity came from American biologist Nettie Stevens in her 1905 study of mealworm beetles. Chromosomes come in structurally similar pairs, but she found one pair was unequal in males, with a short, stout chromosome alongside a longer one. These pairs separate into sex cells during meiosis (a type of cell division), so half of the sperm cells contain the short chromosome, and half the longer one. The longer chromosome was Henking's X, and the shorter one became known as Y. Stevens established that it was the presence of the Y chromosome that determined maleness, not the X as McClung had supposed. Females carry two X chromosomes, so all eggs are chromosomally similar.

It took more than a decade, and better microscopes, before the same X–Y system was found in the tinier chromosomes of human cells. Today, we know that it determines sex in all mammals and many insects. A gene on the Y chromosome makes embryonic sex organs develop as male; without its influence, they are female. Yet this is not universal; in birds, females have unequal sex chromosomes, and males have exact pairs. In other animals, the sexes are differentiated only by environment. ■



A human karyotype is a collection of chromosomes containing 23 pairs. They include a pair of sex chromosomes, either XX (female) or XY (male).

See also: Fertilization 186–87 ▪ Embryological development 196–97 ▪ The laws of inheritance 208–215 ▪ Chromosomes 216–19 ▪ What are genes? 222–25

DNA IS THE TRANSFORMING PRINCIPLE

THE CHEMICALS OF INHERITANCE

IN CONTEXT

KEY FIGURE
Frederick Griffith (1877–1941)

BEFORE
1869 Friedrich Miescher isolates a chemical substance from the nuclei of cells that he calls nuclein (nucleic acid).

1909, 1929 Phoebus Levene analyzes the chemical composition of nucleic acids and identifies two kinds: RNA and DNA.

AFTER
1944 A team of American geneticists shows that nucleic acid, in the form of DNA, can transform the properties of cells, evidence that it is genetic material.

1953 American biologist James Watson and British physicist Francis Crick show that DNA has a double-helix structure, helping explain how genetic material self-replicates.

Swiss physician Friedrich Miescher pioneered the chemical study of genetics in 1869 when he discovered a new kind of substance in the nuclei of cells, which he called nuclein. He knew it was important to how the cell worked but did not understand why.

Miescher's nuclein was renamed nucleic acid in 1889. Early in the 20th century, American biochemist Phoebus Levene found that it contained sugars, phosphoric acid, and units called bases. He showed that it came in two different forms: ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).

Levene underestimated the potential of DNA, thinking it was too simplistic to be the genetic material that determines an organism's structure. Experiments to prove exactly what genes were made from began with British biologist Frederick Griffith. In the wake of the Spanish flu pandemic of 1918, Griffith was interested in how pneumonia could change from virulent to benign strains. He made a major breakthrough in 1928, when he found that a chemical "transforming principle," extracted from dead bacteria, could alter the strain. It looked as though this might be the genetic material.

> Nucleic acids … induce predictable and hereditary changes in cells.
> **Oswald Avery**

In 1944, at New York's Rockefeller Institute, geneticists Oswald Avery, Colin MacLeod, and Maclyn McCarty proved the transforming principle and nucleic acid were the same. By showing that the virulence from an infectious strain of pneumococcus could be transferred with pure DNA to a noninfectious bacterium, they uncovered the chemical identity of genes. ■

See also: The laws of inheritance 208–215 ▪ What are genes? 222–25 ▪ The double helix 228–31 ▪ The genetic code 232–33

ONE GENE–ONE ENZYME

WHAT ARE GENES?

IN CONTEXT

KEY FIGURES
George Beadle (1903–89),
Edward Tatum (1909–75)

BEFORE
1885 August Weismann proposes a theory of "hard" inheritance that involves fixed, indivisible particles passing from one generation to the next.

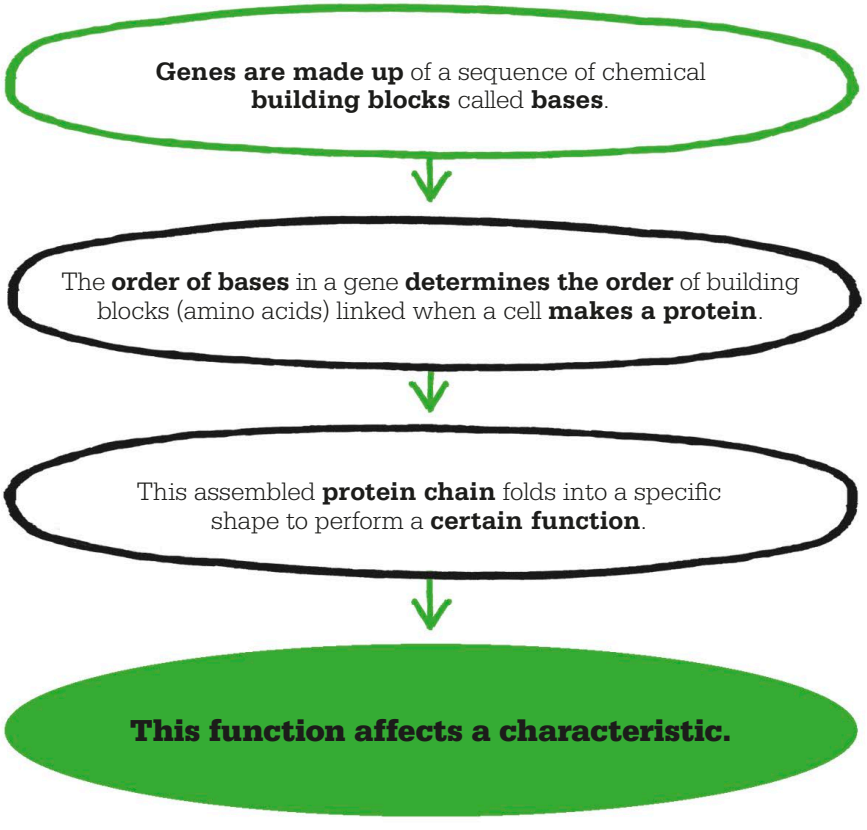
1902 British physician Archibald Garrod suggests that particles of inheritance can turn faulty, resulting in chemical imbalances.

1909 Wilhelm Johannsen calls particles of inheritance "genes"

AFTER
1961 American biochemists Marshall Nirenberg and Philip Leder and German biochemist Heinrich Matthaei establish how the base sequence "code" found in a gene "translates" into an amino acid sequence in a protein.

The idea that inherited characteristics are controlled by physical particles was developed in the 19th century. Biologists revealed not only that organisms were made up of minute living units called cells but that these, in turn, contained even tinier complex structures. By 1875, German zoologist Oscar Hertwig had established that fertilization involved a fusion of a single sperm cell with a single egg cell and that this provided the microscopic route for particles to pass from one generation to the next. In the 1940s, American biologists George Beadle and Edward Tatum would discover how these particles worked.

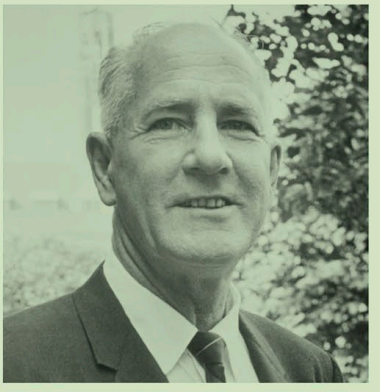
See also: How enzymes work 66–67 ▪ The laws of inheritance 208–15 ▪ The chemicals of inheritance 221 ▪ Jumping genes 226–27 ▪ The double helix 228–31



In 1868, British naturalist Charles Darwin argued that cells contained trait-forming corpuscles—that is, tiny particles—that divided with cells. These released products into circulation that would gather in the reproductive organs of parents, ready to be passed to their offspring. Yet Darwin also suggested that effects of the environment and use and disuse of body parts could alter the corpuscles to some extent. German biologist August Weismann disagreed. In 1885, he proposed a theory of "hard" inheritance with particles fixed between generations.

Weismann was closer to the truth than Darwin: genes, as we understand them today, are normally replicated faithfully from one generation to the next. Weismann thought that different kinds of cells somehow ended up with different kinds of particles. He thought this could explain different body parts—but he was wrong. Dutch botanist Hugo de Vries had a more accurate explanation. In his work of 1889, *Intracellular Pangenesis*, he argued that all cells—irrespective of where they are in the body—had the same complete set of particles needed for a species. But particles were only active, or "switched on," in some parts of the body and not others.

This is effectively true, and helps explain how cells can develop in different ways around the body, »



George Beadle

Born to farmers in Nebraska in 1903, George Beadle studied at the University of Nebraska, where he earned his Ph.D. studying the genetics of corn plants. While later working at the California Institute of Technology, Beadle developed an interest in the way genes worked at a biochemical level. He became a professor in genetics, first at Harvard, and then at Stanford University.

It was while he was at Stanford that he collaborated with Edward Tatum; this led to research on mold biochemistry that would show that genes work by making cells produce specific enzymes. For this, he and Tatum received the Nobel Prize in Physiology or Medicine in 1958. He received many other awards in his lifetime, including fellowship to the American Academy of Arts and Sciences in 1946. He died in 1989.

Key works

1930 "Genetical and Cytological Studies of Mendelian Asynapsis in *Zea mays*"
1945 "Biochemical Genetics"

despite them being genetically identical. De Vries called these particles "pangens," and in 1909 Danish botanist Wilhelm Johannsen coined the term genes.

Metabolic errors

In 1900, de Vries rediscovered the work of Austrian monk Gregor Mendel on inheritance in pea plants. In 1865, Mendel presented evidence to suggest that each inherited characteristic was caused by a pair of a single type of particle (or gene). But how did genes exert their influence? Organisms, and their cells, are made up of chemicals that react in complex ways. This is key to understanding how a body works. Genes are no different, so it should be possible to decipher what they do at a chemical level. Some of the first big clues would come from studies of inherited diseases. If these diseases were inherited in the way Mendel had described, then they could each be attributed to a single faulty gene, and their symptoms might help reveal what this faulty gene was, or was not, doing.

In 1902, Archibald Garrod, a British physician, published one such study on a human disease called alkaptonuria. From birth, sufferers produce urine that turns black, with serious complications, such as osteoarthritis, arising in adulthood. Garrod discovered that the disease was associated with an accumulated pigment and argued that this happens when the body is unable to perform a critical chemical reaction that processes the pigment and removes it.

Garrod knew that each reaction of the body's metabolism required a catalyst, in the form of an enzyme. He suggested that alkaptonuria was caused by a fault in a gene that controlled production of the pigment-processing enzyme. Garrod later attributed other inherited conditions, including albinism, to similar enzyme deficiencies; he called them "inborn errors of metabolism." Yet it took decades of research to prove he was right about alkaptonuria. Only in 1958 was the exact detail of the missing chemical reaction accepted.

Experimenting with genes

Garrod's link between genes and enzymes needed proof. It came in the 1940s, with the work of George Beadle and Edward Tatum, who had carried out tests on a bread mold called neurospora. Like other organisms, neurospora needs a certain set of nutrients, such as amino acids and vitamins, to grow properly, and it makes the rest by chemical reactions. By exposing the mold to X-rays, Beadle and Tatum could create mutated strains that lost their ability to make certain nutrients. If the X-rays damaged a gene, it was unable to make its enzyme. This blocked the chemical reaction for making a nutrient, and the mold no longer grew.

By studying one mutated strain after another, Beadle and Tatum were able to identify specific genes that were linked to the manufacture of certain nutrients. They confirmed that each gene worked by controlling the production of a specific enzyme.

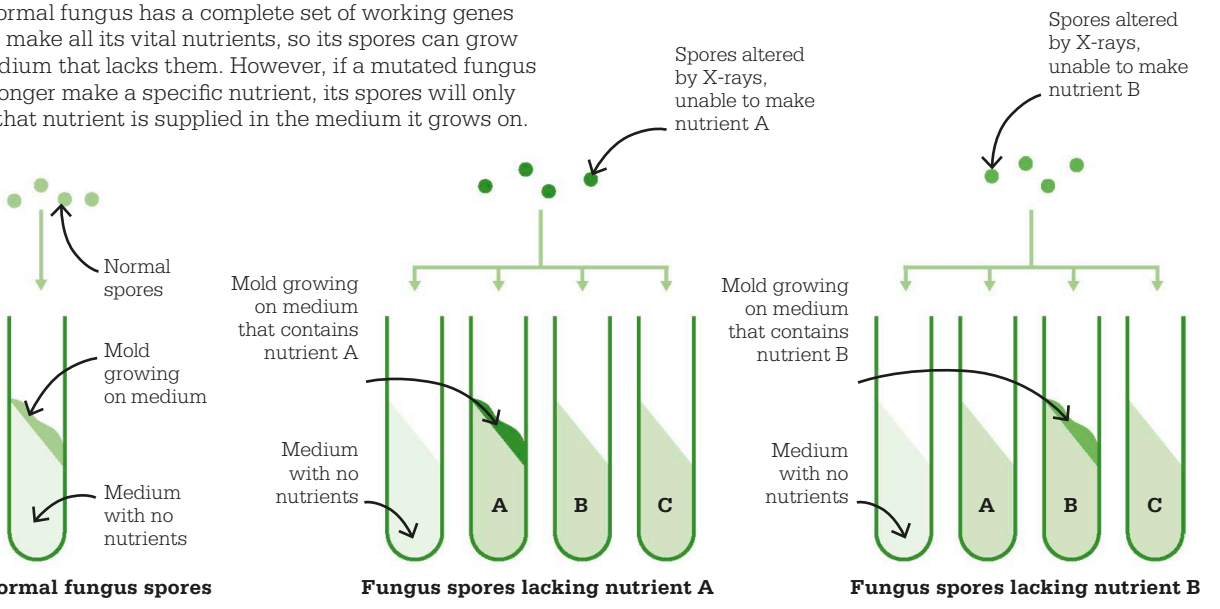
> "Genes are the atoms of heredity."
> **Seymour Benzer**
> **American physicist (1921–2007)**

One gene, one protein

The "one gene, one enzyme" idea was a big step in understanding the nature of genes. By the 1950s, rapid advances in biochemistry were piecing together the molecular building blocks of living things and showing just how central to

Albinism, as seen in this boy (center) with his schoolfriends in South Africa, is a genetic condition affecting the production of melanin, the pigment that colors skin, hair, and eyes.

Beadle and Tatum's mold experiment demonstrated that a normal fungus has a complete set of working genes and can make all its vital nutrients, so its spores can grow on a medium that lacks them. However, if a mutated fungus can no longer make a specific nutrient, its spores will only grow if that nutrient is supplied in the medium it grows on.



Normal fungus spores **Fungus spores lacking nutrient A** **Fungus spores lacking nutrient B**

their workings genes really were. Enzymes belong to a class of complex substances called proteins. Each type of organism produces thousands of different kinds of protein, each with its own role in the body's metabolism. Enzymes work by driving reactions, but other proteins work as signals, receptors, antibodies, and much more, and all originate as genes. Also, the growing acceptance that genes were made of DNA helped substantiate the connection between genes and proteins. A gene is a section of DNA that encodes to produce protein. DNA and proteins are both long-chain molecules assembled from sequences of smaller building blocks. This shared sequential arrangement is key. A cell effectively "reads" the order of building blocks (or bases) along a gene's DNA and translates this information into the order of amino acids along a protein. The folded shape of this protein chain depends directly on the sequence of amino acids, and the shape affects its function.

Back in 1865, Gregor Mendel had hypothesized that pea plant characteristics, such as seed color, were caused by inherited particles that could not be seen, even with the best microscopes at that time. We can now see and even understand how these genes are expressed (when a gene's coded information is converted into a protein). In 2010, biologists in New Zealand traced pea plant flower color to a gene that produces an enzyme. This drives a pigment-making reaction, and the pigment turns flowers purple. A change of just one building block in the gene's DNA prevents the enzyme from working, leaving the flowers white.

Rapid discoveries in the field of genetics have given key information about the makeup of living things. ■

Knockout experiments

Gene knockout is a type of experiment in which the genes of an organism are deliberately rendered non-workable in order to discover their effects. By comparing the results with normal organisms, biologists can make deductions about what the gene was doing when it was functional.

Initially, biologists relied on mutation-causing factors, such as X-rays, as Beadle and Tatum did when studying the effects of genes in bread mold. Today, genes can be targeted in more precise ways by genetic engineering techniques that either remove a gene or replace it in a living thing. Such knockout organisms are especially useful in medical studies, such as cancer research. Laboratory knockout mice have been used to help show how genes such as BRCA1 are naturally involved in suppressing cancerous tumors, helping find potential treatments for breast cancer and ovarian cancer.

I COULD TURN A DEVELOPING SNAIL'S EGG INTO AN ELEPHANT

JUMPING GENES

IN CONTEXT

KEY FIGURE
Barbara McClintock
(1902–92)

BEFORE
1902–04 Walter Sutton and Theodor Boveri independently publish their evidence that genetic material is carried by chromosomes.

1909 Frans Alfons Janssens notes that, during meiosis, maternal and paternal chromatids cross over each other and exchange segments.

1910s Studies of fruit flies, carried out by a research team led by Thomas Hunt Morgan, show how chromosome crossing-over affects patterns of inheritance.

AFTER
1961 Through their work with bacteria, François Jacob and Jacques Monod discover how genetic information is switched on or off, depending on whether or not it is needed.

The fact that genes are carried together on the same chromosome might suggest the characteristics they control should always get passed down together. But the chromosome makeup of a cell is not fixed. Chromosomes break naturally during cell division and even swap sections. The idea of chromosomes breaking first emerged in 1909, when Belgian biologist Frans Alfons Janssens noted that, during meiosis, chromosomes divided and maternal and paternal chromatids crossed over each other. Correctly, he suggested that they were exchanging sections of themselves by breaking in places and resealing with neighboring chromosome parts. This meant that the genes carried on those chromosomes would move position, separating those that were previously linked and creating chromosomes with new combinations.

Genetic shuffling

Between 1910 and 1915, American geneticist Thomas Hunt Morgan and his team of researchers at Columbia University studied the effects of this kind of genetic shuffling on the inheritance of characteristics among fruit flies. By the mid-1920s, another American geneticist, Barbara McClintock, was working on something similar with different varieties of corn plants. Cross-breeding plants that produced brown kernels with plants that had yellow kernels, she created offspring with mixed colors. Just as Morgan had tracked fruit flies, McClintock counted kernels on corn cobs to work out inheritance patterns.

McClintock combined her own breeding experiments with some microscopic studies of corn chromosomes and showed not

Crossing corn plants produces kernels with different colors, which are the result of changes in the way anthocyanin pigments behave in the cells of the kernel's food store.

See also: The laws of inheritance 208–15 ▪ Chromosomes 216–19 ▪ Sex determination 220 ▪ The chemicals of inheritance 221 ▪ What are genes? 222–25 ▪ The double helix 228–31 ▪ The genetic code 232–33 ▪ Genetic engineering 234–39

only that genes swapped position by conventional crossing-over but that some even moved to entirely different chromosomes. These "jumping genes"—later known as transposable elements—affected the inherited characteristics, indicating that the position on a chromosome could be just as important as the genes themselves.

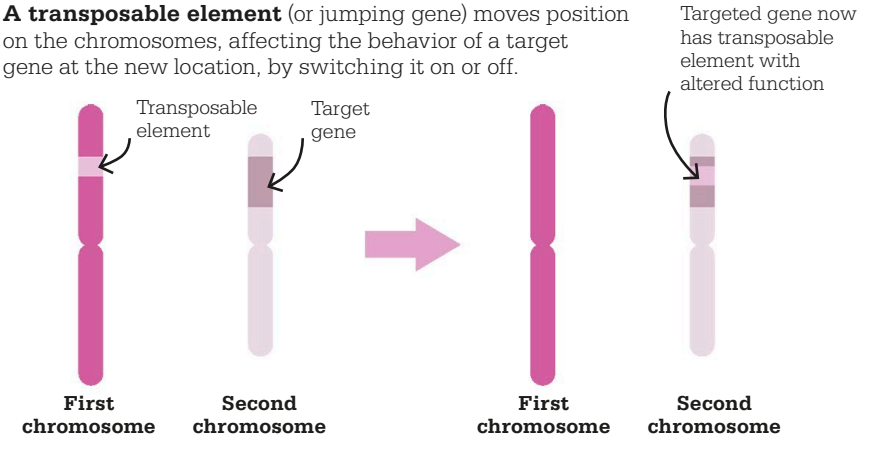
Controlling genes

McClintock worked out that some of these jumping genes were actually making the chromosomes break—so wherever they moved, they caused crossing-over. In this way, they helped shake up the genome, increasing the amount of genetic variety.

McClintock also showed that not all parts of chromosomes were involved directly in determining expressed characteristics. They could be more subtle than that—by affecting the ways other genes functioned. In particular, she discovered that some sections could effectively switch genes on or off. The idea that some genes may be activated by others helped answer another question: if all the cells in an embryo, copied from the original fertilized egg, were genetically identical, how was it possible for them to differentiate into organs and body parts? For instance, cells in a pancreas end up producing insulin, but those in the brain do not, even though they all contain the insulin gene.

Evidence that only certain genes get switched on—depending on where they are in a developing embryo—provides an explanation. In 1961, working with bacteria, French geneticists François Jacob and Jacques Monod published proof that genes can be switched on and off. They showed that a bacterium's gene produces an enzyme that metabolizes milk sugar—but only when milk sugar was supplied in the environment. Jacob and Monod identified a set of components—including the activator—that regulated the gene, depending on the surroundings. ■

A transposable element (or jumping gene) moves position on the chromosomes, affecting the behavior of a target gene at the new location, by switching it on or off.



Barbara McClintock

Born in 1902 in Hartford in Connecticut to a homeopathic physician, Barbara McClintock studied genetics and botany in the 1920s at Cornell University. She stayed on at Cornell until 1936 to carry out her research and collaborated with fellow geneticist Harriet Creighton on the way chromosomes can exchange segments by crossing over.

McClintock continued her research at the University of Missouri and then at Cold Spring Harbor Laboratory, where, during the 1940s, she discovered that parts of chromosomes—now called transposable elements—could shift position. The importance of McClintock's genetic work initially went unrecognized, but she was eventually awarded America's National Medal of Science in 1971, and the Nobel Prize in Physiology or Medicine in 1983. She died in 1992.

Key works

1931 "A Correlation of Cytological and Genetical Crossing-Over in *Zea mays*"
1950 "The Origin and Behavior of Mutable Loci in Maize"

TWO INTERWOVEN SPIRAL STAIRCASES

THE DOUBLE HELIX

IN CONTEXT

KEY FIGURES
James Watson (1928–),
Francis Crick (1916–2004)
Rosalind Franklin (1920–58)

BEFORE
1869 Friedrich Miescher isolates DNA, which he calls nuclein, suggesting that it might be involved in heredity.

1905–29 Phoebus Levene identifies the chemical components of RNA and DNA.

1944 Oswald Avery shows that genes are stretches of DNA in chromosomes.

AFTER
1973 American geneticists Herbert Boyer and Stanley N. Cohen show that it is possible to modify genetic material.

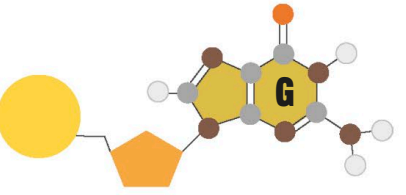
2000 The Human Genome Project publishes the complete sequence of DNA bases in a set of human chromosomes.

In the early 1950s, a major challenge in biology was to unravel the structure of deoxyribonucleic acid (DNA), a substance that many biologists believed must form the physical basis of genes, which are the units of heredity. Much was already understood about DNA. It was known that it forms a major part of structures called chromosomes, which reside in the nuclei of living cells, and that it is a very large molecule made up of subunits called nucleotides. Each nucleotide consists of a chemical group called a phosphate, linked to a sugar called deoxyribose, itself linked to a substance called a nitrogenous

See also: Viruses 160–63 ▪ The laws of inheritance 208–15 ▪ Chromosomes 216–19 ▪ What are genes? 222–25 ▪ The genetic code 232–33 ▪ Genetic engineering 234–39 ▪ Sequencing DNA 240–41 ▪ The Human Genome Project 242–43

Nucleotides are the building blocks of the DNA molecule. Each nucleotide consists of a phosphate group linked to a sugar (deoxyribose), which is itself linked to one of four nitrogen-containing bases: adenine (A), cytosine (C), guanine (G), or thymine (T). Watson and Crick discovered the 3D arrangement of the bases.

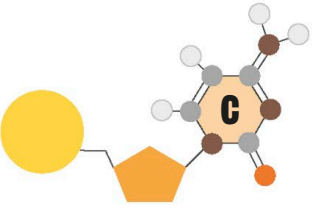
Adenine (A) nucleotide



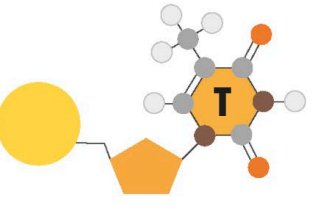
Guanine (G) nucleotide

Key

- Carbon atom
- Hydrogen atom
- Nitrogen atom
- Oxygen atom
- Sugar (deoxyribose)
- Phosphate



Cytosine (C) nucleotide



Thymine (T) nucleotide

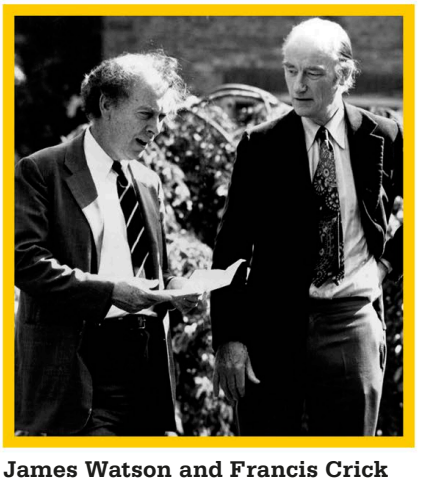
base. The last can be any one of four types: adenine (A), cytosine (C), guanine (G), or thymine (T).

It was also known that the phosphate and sugar parts of the nucleotides were linked in a chain (or chains) that was thought to form a "backbone" (or backbones) for the DNA molecule. What was not known was how the A, C, G, and T bases were positioned within the structure. One particular question that scientists wanted to answer was how the DNA in a cell replicates when a cell divides, so that each "daughter cell" receives an exact copy of the DNA in the original cell.

Competing teams

Between May 1950 and late 1951, several scientific teams were set up with the aim of trying to unravel the structure of DNA. One team, located at King's College London and led by British biophysicist Maurice Wilkins, concentrated on studying DNA through the technique of X-ray diffraction. This involved directing a beam of X-rays at a bundle of DNA fibers and measuring how the atoms in the DNA diffract (spread out) the X-rays. In 1950, Wilkins obtained a reasonable X-ray image of DNA fibers, demonstrating that the technique could yield useful data. In 1951, another expert in X-ray diffraction, British chemist Rosalind Franklin, joined the team, producing even better images. She later went on to use her X-ray skills on viruses.

From mid-1951, American chemist Linus Pauling led a group looking at DNA structure at the California Institute of Technology (Caltech). Earlier that year, Pauling had correctly proposed that protein molecules have, in part, a helical (spiral) structure. And by November 1951, Wilkins was postulating that DNA also had a helical structure. In a report published in February the following year, Franklin proposed that DNA had a closely packed helical structure probably containing two, three, or four chains of nucleotides. Meanwhile, two more scientists had joined the hunt to solve the puzzle, forming a team at the University of Cambridge in the UK. They were Francis Crick, a British physicist with expertise in X-ray diffraction techniques, and James Watson, an American biologist specializing in genetics. »



James Watson and Francis Crick worked together on finding DNA's structure at the Cavendish Laboratory in Cambridge, UK.

Rather than carrying out new experiments, Crick and Watson opted to collect the data that was already available about DNA, then apply their creativity to solve the mystery of its structure. Following the example of Pauling in his work on protein structure, they decided to try building a 3D model of part of a DNA molecule from its known subunits. Crick and Watson also maintained contact with Wilkins and Franklin.

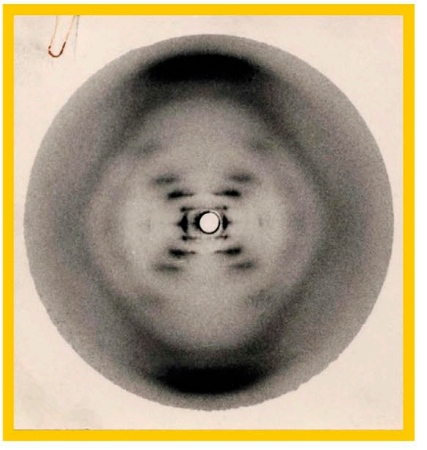
The solution to the puzzle

Watson and Crick's first attempt at constructing a DNA model was not a success. They built a three-stranded helical structure with the nitrogenous bases on the outside of the model, but when they showed this to Franklin, she pointed out inconsistencies with her findings from X-ray diffraction studies. In particular, she also suggested that the nitrogenous bases should be on the inside.

Early in 1953, Crick and Watson began to build a second model, this time with the phosphate-sugar groups on the outside. They also revisited all the data that had been discovered about DNA in the previous decade. One snippet of information they pondered was that DNA contains some relatively weak interatomic bonds called hydrogen bonds. Another clue that proved crucial was a feature of DNA's composition known as Chargaff's rule (see box). This states that the amount of adenine (A) in DNA is very similar to the amount of thymine (T), while the amounts of guanine (G) and cytosine (C) are also similar. This suggested that DNA might contain pairings of nitrogenous bases—A with T, and G with C.

Watson and Crick then had a stroke of luck. Wilkins showed them an X-ray diffraction image of DNA that had been taken by a student of Franklin's in May 1952. The image indicated that DNA contains two helical backbones made of sugar and phosphate. Using this, they were able to calculate crucial parameters for the helices' dimensions. This meant that the only thing left to be figured out was how the nitrogenous bases are arranged in the spaces between the backbones.

Watson made some cardboard cut-outs of the bases and shuffled them around, trying to establish if there was some revelatory way in which they might fit together in the DNA molecule. Initially, this approach proved fruitless, until a colleague pointed out that Watson's assumptions about the structure of two of the bases were out of date and probably wrong.



In Photo 51, an X-ray crystallography image of DNA taken in 1952 by Ray Gosling, a student of Rosalind Franklin, the striped cross shape indicates that DNA has a helical structure.

Pairing the bases

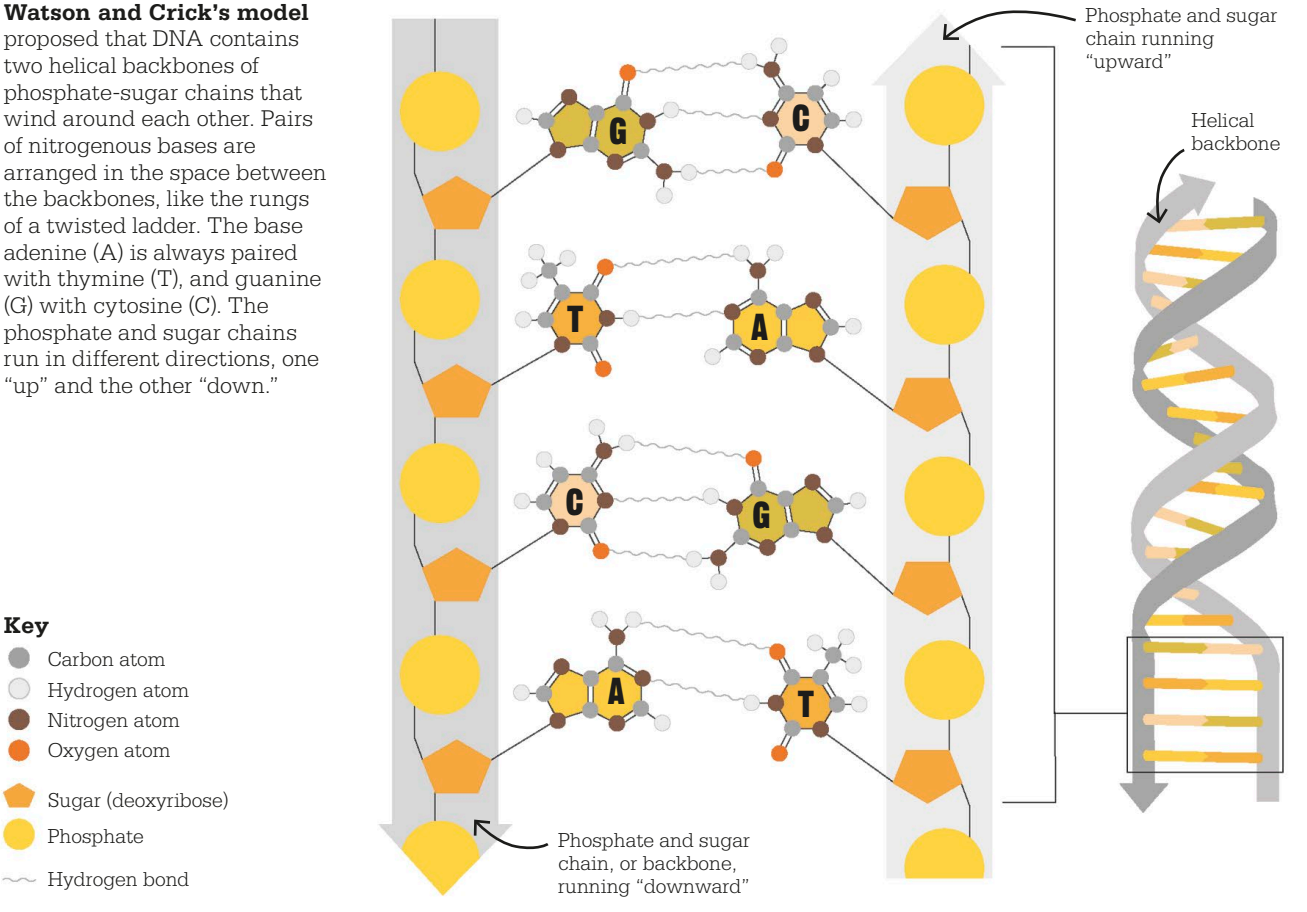
On February 28, 1953, Watson corrected the relevant cut-outs, shuffled them around again, and realized that when adenine (A) is joined by hydrogen bonds with thymine (T), it forms a shape that closely resembles the shape formed when combining guanine (G) and cytosine (C). If A always paired with T, and C with G, this not only accounted for Chargaff's rule, but the pairs could fit neatly in the space between the two helical phosphate-sugar backbones. The base pairs would be arranged like the rungs of a "twisted ladder."

Following the revelation about the base pairings, Watson and Crick completed their double helix model of DNA's structure in March 1953 and published their findings

Chargaff's rule

By the late 1940s, it was clear that DNA forms the hereditary material in animals and plants. American biochemist Erwin Chargaff decided to investigate whether there were any differences in DNA composition between various species. He found that the proportions of the different nucleotide bases—adenine (A), cytosine (C), guanine (G), and thymine (T)—varied significantly between species. Assuming the bases occur in some kind of stack or series within the DNA molecule, this means they do not repeat endlessly in the same order in every species, but exist in sequences that vary between species. Chargaff also noticed that the amount of A in the DNA of every species he studied is very similar to the amount of T, and the amount of G is about the same as the amount of C. This finding became known as Chargaff's rule and was vital to the work of Watson and Crick, since it suggested that A and T, and G and C, might exist as paired structures within DNA.

Watson and Crick's model proposed that DNA contains two helical backbones of phosphate-sugar chains that wind around each other. Pairs of nitrogenous bases are arranged in the space between the backbones, like the rungs of a twisted ladder. The base adenine (A) is always paired with thymine (T), and guanine (G) with cytosine (C). The phosphate and sugar chains run in different directions, one "up" and the other "down."



in the British journal *Nature* in April. A key aspect of their model—and one that strongly implied it was correct—derived from the fact that the base pairings clearly indicated a replication mechanism for DNA. Given the sequence of bases in one strand, the base sequence of the other was automatically determined—if the two strands unraveled, each could serve as a template for a complementary new strand.

In 1958, Caltech researchers Matthew Meselson and Franklin Stahl showed that when DNA replicates, each of the two new double helices formed consists of one strand from the original double helix and one strand that was newly synthesized. This observation proved that Crick and Watson's interpretation of how DNA replicates was correct.

Unanswered questions

The discovery of DNA's structure was clearly a major breakthrough in biology. However, it did not begin to answer how DNA controls the activities of cells and leads to the expression of inherited characteristics. Some scientists immediately speculated that the sequence of nucleotide bases (A, C, G, T) in DNA must play a role in these aspects, but the exact details of how they did this still had to be worked out and would come later, with the cracking of the genetic code. Even so, the discovery of DNA's structure fundamentally changed science's understanding of life—and the modern era of biology had begun. ■

> Jim Watson and I have probably made a most important discovery.
> **Francis Crick**

DNA EMBODIES THE GENETIC CODE OF ALL LIVING ORGANISMS

THE GENETIC CODE

IN CONTEXT

KEY FIGURE
Marshall Nirenberg
(1927–2010)

BEFORE
1941 American geneticists George Beadle and Edward Tatum demonstrate that genes cause an organism's cells to make specific enzymes.

1944 Canadian-American physician Oswald Avery shows that genes are sections of DNA in chromosomes.

1953 James Watson and Francis Crick discover the double-helix structure of DNA.

AFTER
1973 American scientists Herbert Boyer and Stanley Cohen show that it is possible to modify genetic material (genetic engineering).

2000 A first draft of the complete sequence of DNA bases in a human genome (a complete set of human chromosomes) is published.

In the early 1940s, American geneticists showed that genes (discrete units of heredity) exert their effects in a living organism by causing its cells to manufacture enzymes (types of protein). These enzymes affect the organism's characteristics. Later, this concept was generalized to the rule that the synthesis of a protein is directed by a particular gene.

By 1944, it was clear that genes are sections of DNA. Then, in 1953, molecular biologists Francis Crick and James Watson explained DNA's structure, proposing that it consists of two linked strands of substances called nucleotides. These are of four types, each containing one of the bases adenine (A), cytosine (C), guanine (G), or thymine (T). Experts in genetics quickly realized that the sequence of these four bases in a strand of DNA contains encoded instructions for cells to make proteins. But the details of the code were not known—and cracking this code was the next hurdle for scientists.

> Man may be able to program his own cells [before] he has sufficient wisdom to use this knowledge for the benefit of mankind.
> **Marshall Nirenberg, 1967**

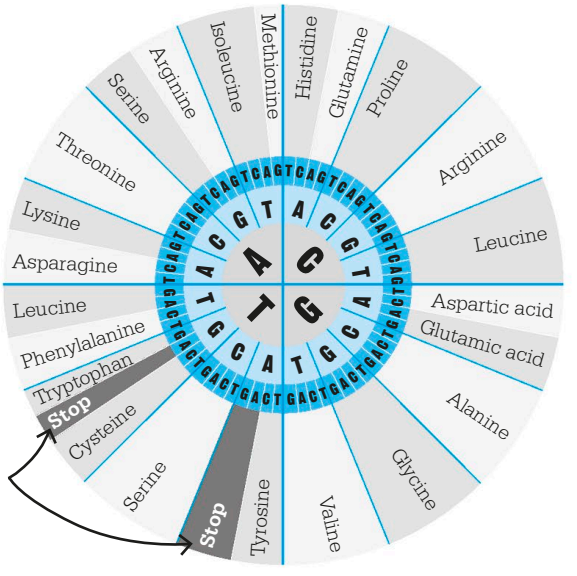
Cracking the code

The challenge was to work out how a long sequence of the four types of DNA bases—A, C, G, and T—encodes for a protein, which itself consists of a string of subunits called amino acids. Twenty different amino acids are used to make proteins, and biologists realized that short strings of DNA bases might code for specific amino acids. A string of two bases (with each base consisting of A, C, G, and T) can exist in only 16 (4 x 4) combinations, which would not be enough to code for 20 amino acids. A triplet of DNA bases, however, could exist in 64 (4 x 4 x 4) different combinations, which would be more than enough. In 1961, Crick and

See also: Making life 34–37 ▪ Enzymes as biological catalysts 64–65 ▪ What are genes? 222–25 ▪ The double helix 228–31 ▪ Genetic engineering 234–39 ▪ Sequencing DNA 240–41 ▪ The Human Genome Project 242–43 ▪ Gene editing 244–45

South African biologist Sydney Brenner tested this idea on a gene taken from a virus. What they found suggested that living cells do decode the sequence of bases in DNA in triplets, or three bases at a time.

The next step was to work out which triplets of bases in DNA code for which amino acids in a protein. Between 1961 and 1966, all 20 amino acids were decoded largely through the work of two American geneticists, Marshall Nirenberg and Philip Leder, and German biochemist Heinrich Matthaei. First, Nirenberg and Matthaei carried out some ingenious experiments on bacteria to try to find out what the various DNA base triplets consisting of just one type of base (such as TTT, CCC, and AAA) code for. From these experiments, they discovered that the DNA base triplet TTT codes for the amino acid phenylalanine, while CCC codes for proline. Nirenberg and Leder then carried out further experiments to establish which amino acids are coded for by most of the other base triplet combinations. Their work also confirmed that the base triplets are read in sequence, without any overlap between each triplet.

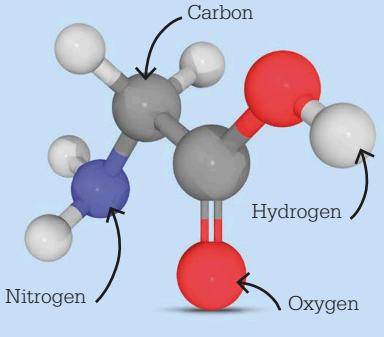


The DNA genetic code wheel shows which amino acids are coded for by each of the 64 possible DNA triplet combinations. To use the wheel, pick the first letter from the innermost circle, the second from the light blue ring, and the third from the adjacent part of the darker blue ring.

The DNA base triplets TAA, TAG, and TAA do not code for an amino acid. Instead, they signal for the synthesis of a protein to stop.

Importance of the code

The cracking of the genetic code has been crucial to later advances in genetics and biotechnology. It has made it possible to manufacture novel proteins—for testing as potential medicines—through inserting pieces of artificial DNA into microorganisms. The same genetic code is now known to be used by nearly all living organisms, with just a few differences in primitive life forms. This knowledge has provided powerful evidence of a common origin for all life on Earth. ■



The molecular structure of the amino acid glycine was discovered by French chemist Henri Braconnot in 1820. It is coded for by DNA base triplets such as GGC.

What are amino acids?

Amino acids are a class of organic (carbon-containing) compounds. They are the building blocks of proteins. Every amino acid contains a nitrogen atom attached to two hydrogen atoms (this is called an amino group), another group of atoms called a carboxyl group (containing one carbon, one hydrogen, and two oxygen atoms), and at least one other carbon atom.

Amino acids of 20 different types become linked in cells to form chainlike molecules called polypeptides. These are subunits of enzymes and other proteins. This linking process is carried out by the chemical machinery in a cell, with the sequence of amino acids in a polypeptide ultimately determined by a sequence of bases in DNA.

Many cells receive the amino acids that are necessary to build polypeptides and proteins mainly from the breakdown of proteins in their sources of nutrition, although some amino acids can be synthesized from other substances.

A CUT, PASTE, AND COPY OPERATION

GENETIC ENGINEERING

IN CONTEXT

KEY FIGURES
Stanley N. Cohen (1935–),
Herbert Boyer (1936–)

BEFORE
1968 Swiss geneticist Werner Arber hypothesizes that bacteria produce DNA-cutting enzymes, subsequently used as restriction enzymes in genetic engineering.

1971 Paul Berg successfully joins viral DNA molecules from two different species of virus.

AFTER
1975 Asilomar Hotel, California, hosts a conference to discuss ethical concerns about genetic engineering, leading to agreements that are still followed decades later.

1977 Herbert Boyer successfully uses genetically modified bacteria to produce growth hormone for potential therapeutic use.

For 10,000 years or so, since hunter-gatherers first began to domesticate wild plants and animals, humankind has deliberately altered living things to make them more useful. Selective breeding—choosing stock with the best characteristics, knowing that the process of inheritance would pass them on to the next generation—has produced higher yields in crops, meat, milk, and wool.

In the 20th century, as the physical basis of inherited genes was revealed at the cellular and chemical levels, biologists realized that there could be more specific, targeted ways to produce useful organisms—by directly altering their genetic makeup.

By the 1970s, biologists knew that genes were made up of an information-packed chemical called DNA. They also understood how this DNA replicated before cell division, and how genes were "read" inside cells to make proteins and affect characteristics.

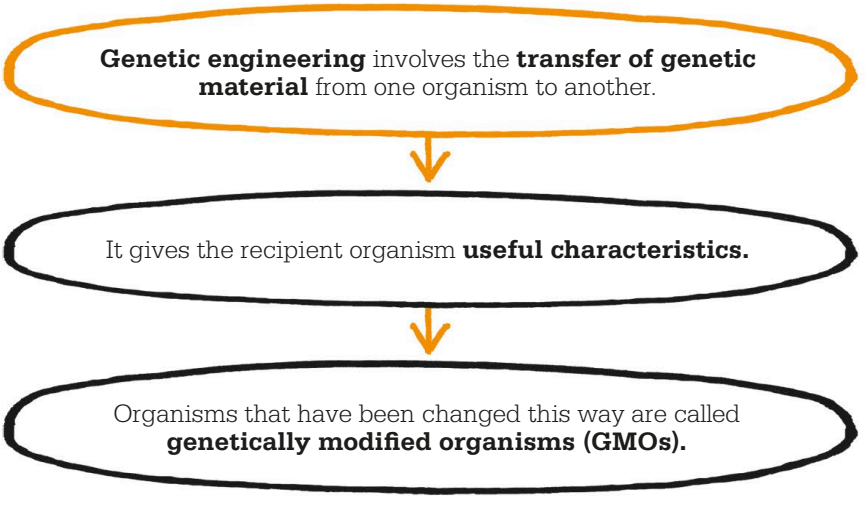
Like other metabolic chemical reactions, these processes were driven by catalysts called enzymes. Biologists thought it might be possible to use these enzymes to move genes from one organism to another. By cherry-picking specific genes for useful characteristics, they might be able to genetically modify organisms far more precisely—and quickly—than selective breeding, which could take many generations.

> Genetic engineers don't make new genes, they rearrange existing ones.
>
> **Thomas E. Lovejoy**
> **American biologist**

Modifying microbes

In their quest to see if genetic engineering worked, biologists initially targeted microbes. These single-celled organisms have fewer genes than plants and animals so their genetic systems are more easily controlled. Moreover, bacteria already have a way of swapping genes between their single cells—they exchange tiny, mobile, self-replicating rings of DNA called plasmids. This mixing of genes creates variety, which increases a species's chances of survival. The discovery of this process—called conjugation—in 1946 opened up an opportunity for scientists to genetically manipulate bacteria. In 1973, American geneticists Herbert Boyer and Stanley N. Cohen took the first step.

As well as having the usual enzymes that cells use to build and replicate their DNA, bacteria also have enzymes that cut DNA into



See also: What are genes? 222–25 ▪ The double helix 228–31 ▪ Sequencing DNA 240–41 ▪ The Human Genome Project 242–43 ▪ Gene editing 244–45

pieces. This helps them disable other invading microbes, especially viruses. These enzymes target very limited sites on DNA, cutting the double helix only where it carries a specific sequence of DNA bases. Boyer and Cohen realized that, in a purified form, these so-called restriction enzymes could be used to cut around useful genes and remove them from cells. They proposed using the DNA-building enzymes to stitch the genes into the genome of a target organism.

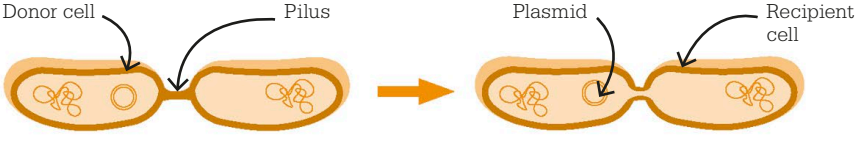
Two years earlier, American biochemist Paul Berg had used the enzymes to cut and splice DNA from different viruses—but no one had yet seen whether engineered DNA would work inside living cells. As a test, Boyer and Cohen used the enzymes to cut genes from plasmids responsible for antibiotic resistance in a strain of bacteria and inserted them into plasmids of bacteria that were not resistant. These bacteria thrived in the presence of the antibiotic, proving the technique worked.

Useful genes

Genetic modification of microbes already had exciting possibilities. Because genes work by instructing cells to make specific kinds of proteins, scientists realized that a large culture of bacteria carrying the right sort of genes could be used as a biological factory to make commercial amounts of the proteins used therapeutically in medicine as drugs.

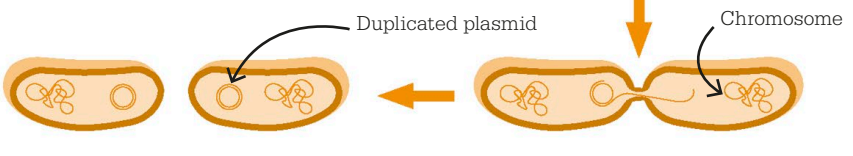
Insulin, for example, is used to treat diabetes. In the past, insulin had to be obtained from the pancreases of cows and pigs. This method is highly inefficient because it produces a low yield of usable insulin and risks transmission of infectious disease from animal to human. But scientists reasoned that if genetic engineering could be used to insert the genes for proteins, such as insulin and human growth hormones, into bacteria, their rapid division and simple separation would produce more of the protein and could also make it safer to use. »

The process of plasmid transfer in bacteria



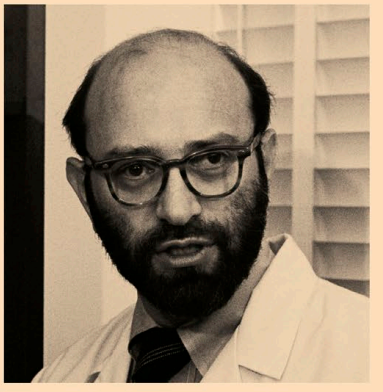
1. The donor cell attaches to the recipient cell with its pilus and pulls the two together.

2. The cells join up.



3. One strand of plasmid DNA transfers to the recipient.

4. After the cells separate, the donor makes a complementary strand to restore its plasmid. The recipient also makes a complementary strand and is now a new donor cell.



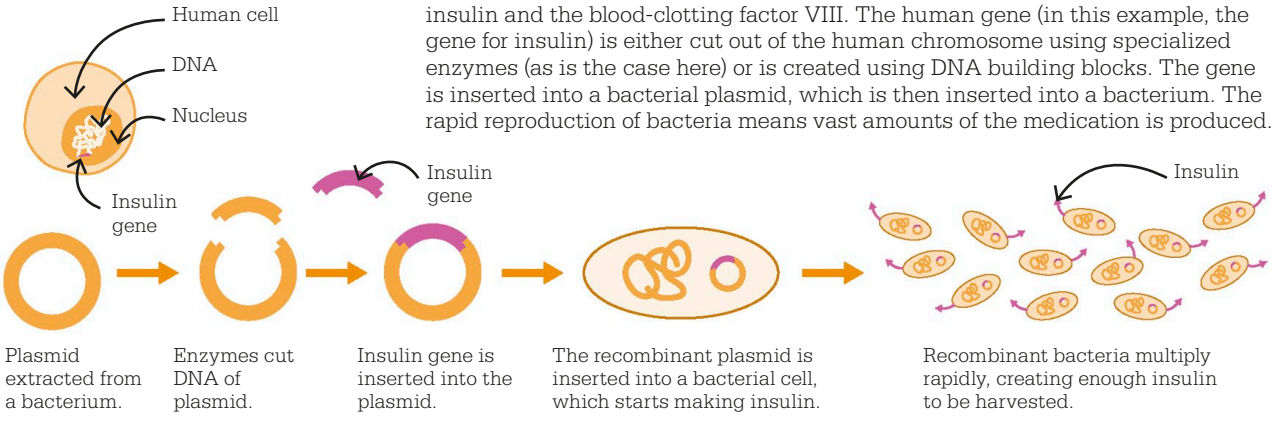
Stanley N. Cohen

Born in New Jersey in 1935, Stanley N. Cohen trained in medicine at the University of Pennsylvania before moving to Stanford University, California. Here he worked on plasmids, rings of DNA that can be exchanged between bacteria.

In 1972, at a conference on bacterial genetics, he met Herbert Boyer from the University of San Francisco, who had been working on DNA-cutting enzymes. They collaborated on experiments designed to alter DNA in bacteria and succeeded the following year, pioneering the field of genetic engineering. For this work, Cohen was awarded America's National Medal of Science in 1988 (Boyer was awarded it in 1990). Cohen and Boyer filed patents on their techniques in 1974—a move that benefited their universities but was regarded as controversial.

Key works

1973 "Construction of biologically functional bacterial plasmids in vitro"
1980 "Transposable Genetic Elements"



Genetically modified bacteria are used to make various medications including insulin and the blood-clotting factor VIII. The human gene (in this example, the gene for insulin) is either cut out of the human chromosome using specialized enzymes (as is the case here) or is created using DNA building blocks. The gene is inserted into a bacterial plasmid, which is then inserted into a bacterium. The rapid reproduction of bacteria means vast amounts of the medication is produced.

Boyer set up a company to do just that. At first, he aimed to make a simpler protein than insulin, the growth hormone somatostatin. But using a natural source of the gene—found in human cells—was a far more formidable prospect than using bacterial plasmids. So Boyer took the bold step of making the gene from scratch, using genetic engineering to link the DNA bases together in the correct order to make the somatostatin gene. He then inserted the gene into bacterial plasmids—just as he had done with the antibiotic gene.

> The most profound consequence of the recombinant DNA technology has been our increased knowledge of fundamental life processes.
>
> **Paul Berg**
> **American biochemist**

By 1977, Boyer's team had produced a bacterial culture that generated viable somatostatin, and a year later used the technology to do the same thing for insulin. All insulin used to treat diabetics is now made this way.

Bigger genes

The gene-manufacturing technique that was at the heart of Boyer's engineering process was possible because the genes involved were small and manageable. An insulin gene is made up of around 150 DNA base units. Each must be linked together in exactly the right order for cells to "read" the information and make insulin. But some genes are far bigger than this, and it is unrealistic to make them from scratch. For example, the gene for producing factor VIII—used to treat people with the blood-clotting disorder hemophilia—is 50 times larger than the insulin gene.

Boyer's company decided to use a different approach to make factor VIII. DNA-cutting restriction enzymes still offered the hope of removing big genes from a natural source such as human cells. But even if the gene could be properly located within the huge human genome, there was a technical problem that hindered putting such a gene into bacteria. Genes found in the complex cells of humans (and all other animals and plants) have patches of non-coding DNA called introns. These are removed when cells use the genes to generate proteins, but bacteria lack introns and the capacity to deal with them, so they cannot read DNA from complex cells. However, when any cell makes a protein from a gene, it first creates a copy of the gene, called messenger RNA, which has the introns removed.

Boyer's company isolated the messenger RNA, then used an enzyme from a virus to convert it into DNA—a form of the gene that bacteria could read. Conventional genetic engineering was then used to insert the gene into bacteria, and by 1983 bacteria-produced factor VIII was being used to treat people with hemophilia.

Modifying plants and animals

Today, genetic engineering is used to modify more complex targets – plants and animals. And plasmids or microbes can be used as vectors to carry a gene into the cells of a plant or animal to alter their characteristics.

One microbe, a plant-infecting bacterium called *Agrobacterium*, has proved especially useful. Its natural infection cycle involves inserting pieces of DNA into its host—a behavior that biologists can exploit by replacing the DNA with useful genes. In 2000, the technique was used to produce a genetically modified (GM) rice as a way of fighting vitamin A deficiency, a condition that causes childhood blindness. By infecting rice with *Agrobacterium* carrying a gene for the yellow beta-carotene pigment, a new variety, called golden rice, was created. It produces and stores the pigment in its grains. When eaten, the human body converts the beta-carotene into vitamin A.

Golden rice is a GM form of white *Oryza sativa* (above left). It is a source of vitamin A, which is important for vision, but also boosts the immune system and promotes healthy organs.

Uses in medical research

Some of the most ambitious uses of genetic engineering have been in medical research. One example is the creation of knockout mice—rodents that have been genetically modified at the embryonic stage to have certain genes "knocked out" so they no longer work. This allows researchers to study the effects of specific genes. On average, the protein-coding regions of the mouse and human genomes are about 85 percent identical, so researchers can use knockout mice to understand how a particular gene may be implicated in human diseases, such as various cancers, Parkinson's disease, and arthritis.

Today, genetic engineering goes far beyond modifying microbes to generate useful drugs or improve food sources. The techniques it offers have enabled scientists—including those involved with the Human Genome Project—to come full circle and better understand genes themselves. ■

Knockout mice are used as models for gene research in humans. The mouse on the left has been bred with a particular gene "knocked out," which has affected the color of its fur.

Amplifying DNA

In 1984, American biochemist Kary Mullis developed a technique that could rapidly copy (amplify) specific genes or strands of DNA for use in genetic engineering. This breakthrough transformed the pace of research and led to a whole new way of working with genes.

Mullis's technique, called polymerase chain reaction (PCR), mimics the way DNA replicates inside cells, but uses cycles of heat and cooling to achieve the result. First, the gene or a small fragment of DNA that is needed to be amplified is mixed with the DNA-assembling enzyme DNA polymerase and DNA base units. The mixture is heated to just below boiling point to separate the double helix strands. The system is then allowed to cool to an optimum temperature to enable the DNA base units to attach to the single strands of DNA. The enzyme then helps bind the base units, producing a replica of the gene or DNA fragment. By repeating this cycle again and again, the amount of the gene or DNA doubles continuously.

Mullis was awarded the Nobel Prize in Chemistry in 1993 for his invention. Today, PCR is used whenever tiny samples of DNA need to be amplified for analysis, such as in forensic science or the Human Genome Project, or to study ancient DNA from fossils or archaeological sites. PCR can also be used to detect tiny amounts of viral RNA that might indicate an infection. In 2020, it became widely used for testing samples for the COVID-19 virus.

THE SEQUENCE OF THE BEAST

SEQUENCING DNA

IN CONTEXT

KEY FIGURE
Frederick Sanger
(1918–2013)

BEFORE
1902 German chemists Emil Fischer and Franz Hofmeister independently suggest that protein molecules are chains of amino acids linked by peptide bonds.

1951–53 Frederick Sanger publishes the sequence of amino acids in each of the two chains of the protein insulin.

1953 British molecular biologist Francis Crick and American molecular biologist James Watson establish that a DNA molecule is a double helix consisting of two chains of bonded units paired together.

AFTER
2000 The Human Genome Project produces the first draft of the sequenced human genome.

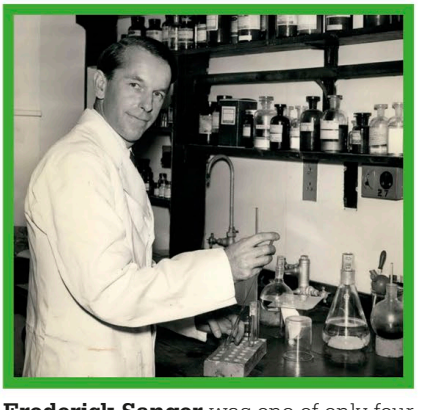
The biggest molecules in living organisms, such as proteins or DNA, are chains of smaller units bonded together in a certain order. This sequence of units running through the chain determines what the molecule does. Genes (sections of DNA) are the code for forming proteins, which determine your features, how your body survives, and how it behaves. Biologists interested in deciphering the mechanisms of life look for clues in the chemical sequences of proteins or the genes encoding them.

British biochemist Frederick Sanger pioneered the sequencing of long-chain biological molecules, and established that such molecules have a specific composition. Genes and proteins can be hundreds or thousands of units long. If just one unit is out of place, it can disrupt the functioning of the molecule.

Sanger began with a protein whose effects were well known: the hormone insulin. He split its two chains into their "building blocks"—amino acids—in a way that released these from the end of their chain one at a time. As each amino acid was isolated, it was identified. To make the process more efficient, Sanger used it on short sections of the molecule, then looked for areas of overlap to determine how the sections were pieced together. By 1953, he knew the exact sequence of amino acids that made up each insulin chain, and in 1955 he established how the two chains were linked. His method revolutionized the study of proteins.

Decoding DNA

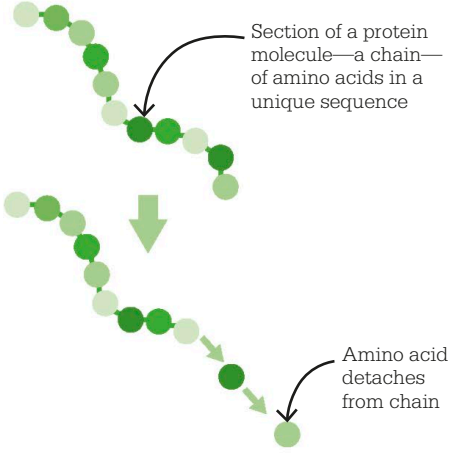
From 1962, Sanger focused on sequencing RNA (ribonucleic acid), before moving on to DNA, which was larger. These molecules are much bigger than insulin, so Sanger



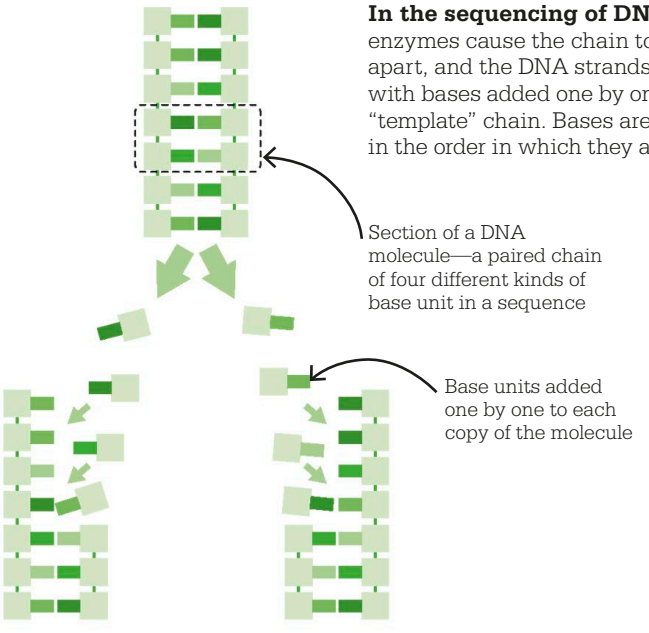
Frederick Sanger was one of only four people to be named a Nobel laureate more than once. He won the Nobel Prize in Chemistry in 1958 and in 1980 for his work on sequencing insulin and DNA.

See also: Hormones help regulate the body 92–97 ▪ The chemicals of inheritance 221 ▪ What are genes? 222–25 ▪ The double helix 228–31 ▪ The genetic code 232–33 ▪ Genetic engineering 234–39 ▪ The Human Genome Project 242–43

In the sequencing of protein, chemicals break off amino acids one by one from one end of the chain. Amino acids are identified in the order in which they come away.



In the sequencing of DNA, enzymes cause the chain to split apart, and the DNA strands replicate, with bases added one by one to each "template" chain. Bases are identified in the order in which they are added.



looked for the smallest naturally occurring DNA. He found it in a virus that infected bacteria—but even this was 5,386 units long. (By contrast, a human insulin molecule is made up of 51 amino acids.)

Sanger clearly needed a new, faster sequencing technique, so he looked to nature for inspiration. Cells constantly divide to make new cells, each time replicating their DNA. This is done at incredible speed, with around 50 base units added every second. Sanger wondered if there was a way to identify the base units as they were added during replication. Biologists had isolated the enzyme that drove replication, and this worked well in test tubes when mixed with the four kinds of DNA base units: adenine (A), cytosine (C), guanine (G), and thymine (T).

Sanger mixed a sample of virus DNA with the enzyme and doctored his mixture with a modified version of A, which had the effect of terminating the replication process at a given point in the chain. By repeating this with modified versions of C, G, and T, he was able to read the sequence of the whole DNA chain. In 1977, he became the first person to determine the complete genetic makeup, at chemical level, of any DNA. The Sanger method—the principle of interrupting DNA replication—became the basis for much more ambitious, computerized schemes for sequencing DNA, including the Human Genome Project. ■

Comparing DNA samples

While the objective of DNA sequencing is to compile a complete and unique set of information, other types of DNA analysis are used for purposes of identification. With such techniques, there is no need to determine complete sequences; instead, DNA samples are compared in order to assess their similarity—for example, "DNA barcoding" is used to identify species, while other methods are used to establish parentage or in forensic analysis.

In 1984, British geneticist Alec Jeffreys developed a method called DNA profiling, or DNA fingerprinting, for identification of individuals. It relies on the fact that DNA contains repeated sections (like stutters in speech) in its sequence. Some individuals have more than others, and by comparing the number of repeats from two samples, it is possible to assess the likelihood that they are genetically related or even—in the case of DNA samples left at a crime scene—a match.

THE FIRST DRAFT OF THE HUMAN BOOK OF LIFE

THE HUMAN GENOME PROJECT

IN CONTEXT

KEY FIGURES
Francis Collins (1950–)
Craig Venter (1946–)

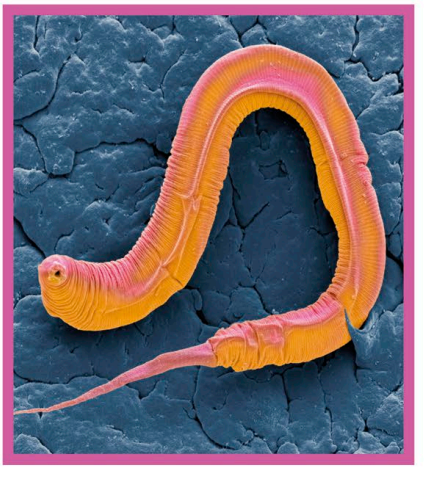
BEFORE
1977 Frederick Sanger publishes the sequence of base units in a virus called bacteriophage phi X174—the first published genome.

1995 Craig Venter sequences the genome of the bacterium *Haemophilus influenzae*, the first sequenced genome of a cellular organism.

AFTER
2004 The International Sequencing Consortium launches an online resource to detail ongoing genome projects for many species.

2016 Genome Project-Write is launched to investigate the synthesis of many plant and animal species' genomes.

The amount of genetic information in organisms is phenomenal. Even those with the simplest single cells, such as bacteria, can carry thousands of genes, each one made up of hundreds or thousands of base units. The complete sequence of bases and genes along the DNA of an organism is called its genome, and documenting this genetic makeup brings biologists closer to understanding how cells work and occasionally misfunction. After British biochemist Frederick Sanger sequenced the genome of a virus in 1977, other biologists set their sights on more complex targets.



The worm species *Caenorhabditis elegans* is easily cultured in the laboratory. This is one of the reasons that it makes an ideal target for genome studies.

American geneticist Craig Venter, armed with a computer to analyze tiny DNA fragments, sequenced the genome of the bacterium *Haemophilus influenzae* in 1995—a first for a cellular organism.

Bigger targets

Multicellular organisms, such as animals and plants, have vastly bigger genomes than single-celled bacteria. They need more genetic information to control the way their cells work, in order to make tissues and organs. In 1998, a millimeter-long worm called *Caenorhabditis elegans* became the first animal to have its genome sequenced. It was found to have almost 20,000 genes.

Geneticists began to envisage mapping the human genome as a serious possibility in the 1980s. It was predicted that such a project might cost $3 billion and, even with 1,000 technicians, could take up to 50 years to complete. Starting in 1989, it became a collaborative international effort guided by the

See also: Chromosomes 216–19 ▪ What are genes? 222–25 ▪ Genetic engineering 234–39 ▪ Sequencing DNA 240–41 ▪ Gene editing 244–45

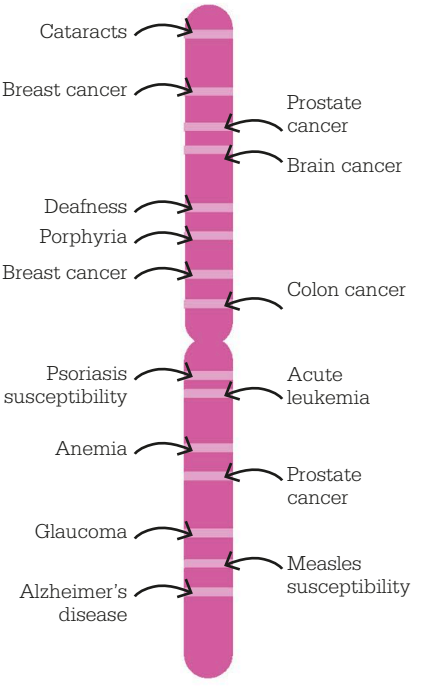
> It's hard to overstate the importance of reading our own instruction book—and that's what the Human Genome Project is all about.
> **Francis Collins**

US National Institutes of Health (NIH), ultimately to be directed by American geneticist Francis Collins. The team of scientists at NIH included American biochemist Craig Venter, who later set up his own genome-sequencing company. In the end, both parties, using slightly different approaches, worked in parallel. In June 2000, Collins and Venter announced a first draft in a presentation at the White House. Then, three years later but still ahead of schedule, a more comprehensive edition of the entire human genome was published.

The human genome

The complete human genome is 3.2 billion bases long. If these were represented by their letters (A, T, C, and G) and printed out in order, even using a tiny font, the genome would fill more than 100 books. According to current knowledge, humans have 20,687 genes—and they are arranged along 23 pairs of chromosomes. The first gene appearing on chromosome number one (so numbered because it is the biggest) helps control our sense of smell. The last gene on chromosome X helps control the immune system. In between, thousands of others are arranged in a way that looks random but is actually critical for life. The Human Genome Project supplied some surprises, too, with 98 percent of the genome's base sequence being made up of long, non-coding stretches between the functioning genes, or patches of "nonsense" DNA within the genes. Scientists now know that some non-coding DNA determines when coding genes are switched on and off.

Despite not being completely understood, the Human Genome Project is helping biologists carry out important research. A map of human DNA and its base sequence does more than help pinpoint the location of genes involved in diseases such as cystic fibrosis, hemophilia, and cancer. Through understanding exactly how genes are used by cells, and what happens when they go wrong, biologists can get one step closer to treating the symptoms of disease and even finding potential cures. ■



The effects of many genes are often revealed when they malfunction, which causes disease. This diagram shows some of the diseases caused by key genes on the first (and largest) chromosome of the human genome. Many diseases, such as cancers, can be caused by multiple genes.

The 100,000 Genomes Project

The publication of the first human genome sequence was only possible after more than a decade of international cooperation. The project was a great achievement but had its limitations, not least because the DNA samples came from a very small number of people, so it tells us little about genetic variation within a population.

In 2012, a company funded by the UK government launched the 100,000 Genomes Project, which aimed to sequence 100,000 genomes from patients suffering from genetic disorders, with the last of these genomes sequenced at the end of 2018. This impressive undertaking was only possible because of technological advances: sequencing an individual now takes just a few days and costs only about £1,000. Researchers are using its enormous wealth of information to establish how to tailor treatments for specific patients according to their genetic makeup.

GENETIC SCISSORS: A TOOL FOR REWRITING THE CODE OF LIFE

GENE EDITING

IN CONTEXT

KEY FIGURES
Jennifer Doudna (1964–), **Emmanuelle Charpentier** (1968–)

BEFORE
1980 Controversially, Martin Cline, an American geneticist, attempts the first gene therapy to treat an inherited blood disorder. The trial results are never published.

2003 China becomes the first country to approve a virus-based gene therapy, to treat a form of cancer.

2010 French biologists Philippe Horvath and Rodolphe Barrangou discover a genetic system in bacteria—called CRISPR-Cas9—that helps them attack viruses.

AFTER
2017 A modified version of CRISPR-Cas9 is successfully used to treat muscular dystrophy in laboratory mice.

Faulty genes are responsible for causing many kinds of inherited diseases, such as cystic fibrosis and muscular dystrophy. Traditionally, it has only been possible to alleviate symptoms, not cure the disease. Because the rogue gene responsible is endemic in the body—most cells carry it—a complete cure looked impossible. But once biologists understood how genes work at a chemical level, they moved closer to finding a cure.

Since genes are sections of DNA that encode for proteins, biologists realized that it might be possible to treat the body with a normal version of the gene—or even to correct (edit) the faulty one so that the body makes normal protein.

> … this unusually quick adoption of [CRISPR-Cas9] just shows how desperately biologists were in need of a better tool to manipulate genes.
> **Emmanuelle Charpentier**

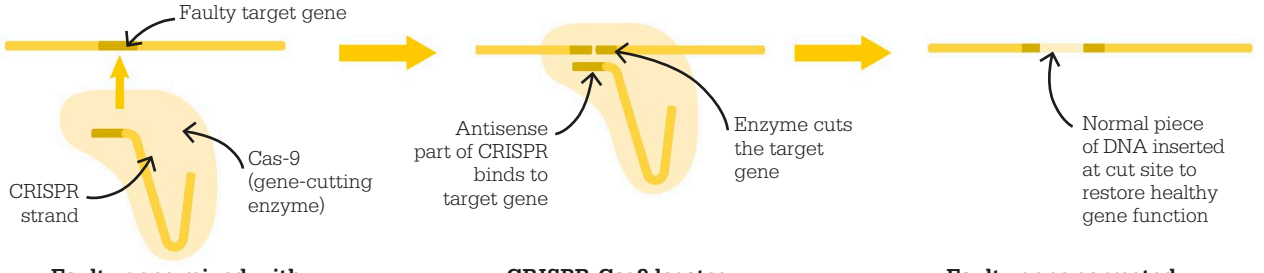
Gene therapy

Manipulating the genetic makeup to treat or cure genetic diseases is called gene therapy. Its origins lay in trials that started in the 1980s. These treated genetic blood disorders by transfusing therapeutic genes inside modified white blood cells or bone marrow stem cells. The normal gene is delivered to the nucleus of the cells by means of a genetically engineered virus. Despite early setbacks, by the turn of the millennium, virus-based gene therapy was successfully being used in trials to treat disease.

The obstacles to administering genes effectively and safely are as varied as the disorders themselves. The virus technique failed with cystic fibrosis because it could not penetrate the lungs' immune defenses. Another method involved using a nebulizer to inhale genes enveloped in fatty droplets. This worked slightly better—but only to a limited extent. Some conditions might be treatable if the faulty gene

See also: Enzymes as biological catalysts 64–65 ▪ How enzymes work 66–67 ▪ Cancer metastasis 154–55 ▪ Viruses 160–63 ▪ Meiosis 190–93 ▪ What are genes? 222–25 ▪ The genetic code 232–33 ▪ Genetic engineering 234–39

CRISPR-Cas9 gene-editing technique



could be blocked from affecting the cells, using what is called antisense therapy. Instead of treating patients with normal genes, this targets them with "antisense" versions. These have a base sequence that is opposite to that of the faulty gene. They bind to the gene and prevent it from working. Antisense therapy has proven effective in blocking some types of cancer-forming gene.

The ultimate goal is to correct the faulty gene. In 2012, biologists Jennifer Doudna (American) and Emmanuelle Charpentier (French) developed one such technique that was inspired by something that happens naturally in microbes. Bacteria are routinely attacked by viruses. To defend themselves, they deploy a kind of antisense strategy to fight back: first they have a DNA sequence that blocks the virus's genes, then they destroy them with a special gene-cutting enzyme called Cas9.

The bacteria's repetitive DNA sequence for doing this is known by the acronym CRISPR. Doudna and Charpentier saw the possibility of modifying the CRISPR-Cas9 system to target defective human genes instead of viral ones. This had the potential to stop these genes from working—but adding corrective DNA also offered the hope of fixing their mutated sequence. In 2020, the pair were awarded the Nobel Prize in Chemistry.

For the first time, biologists had a technology that could edit errors in genes. Initial experiments using CRISPR-Cas9 technology were promising. And human trials are currently underway to treat genetic disorders, such as childhood blindness, cancers, blood disorders, and even cystic fibrosis. ■

Germline therapy trials have been conducted in nearly 30 countries around the world. Most have been undertaken in China and the US.

Germline therapy

In the 1970s, Herbert Boyer and Stanley N. Cohen succeeded in using genetic engineering to transfer DNA from one strain of bacteria to another. Biologists then realized that similar gene modification techniques might one day be used to treat or even cure human genetic disorders. A complete cure—one that corrects the faulty gene throughout the body—is possible only if a body is genetically engineered from source, in the fertilized egg or embryo from which it grows.

The use of this technique, called germline gene therapy, is controversial since it raises fears of "designer babies" and so remains outlawed in many countries. But the potential of techniques such as CRISPR-Cas9 to correct faulty genes has resulted in a call for germline therapy regulation to be relaxed. Since 2015, researchers in China have used CRISPR-Cas9 technology in trials on human embryos. The reported successes include "corrections" to genes that are implicated in congenital heart disease and cancer.

DIVERSI
OF LIFE
EVOLUT

TY
AND
ION

Carl Linnaeus publishes *Plant Species*, followed by the 10th edition of *System of Nature* in 1758, introducing his **system** of binomial nomenclature for **classifying species**.

1753

A theory that evolutionary change occurs through **inheritance of acquired characteristics** is developed by Jean-Baptiste Lamarck.

1800s

Hugo de Vries sets out his **mutation theory**, proposing that evolutionary change happens **in sudden bursts** due to mutations.

1900–03

1796

From **fossil evidence**, Georges Cuvier identifies **extinct species** that are different from species alive today.

1859

On the Origin of Species is published, setting out Charles Darwin's **theory** that **evolution** occurs through a process of **natural selection**.

There is an extraordinarily large range of different life forms on Earth—from the simplest single-celled organisms to highly complex animals and plants. This diversity has been a source of wonder throughout the ages, and the question of how it came into existence has for much of history been answered by religion—that it is the work of a creator god.

The idea that life as we know it is a divine creation and therefore unchanging was a major influence on thinking about the diversity of life until the Enlightenment of the 17th and 18th centuries, when the first scientific theories hinting at a process of evolution emerged. Up to that point, the task was not to explain this diversity, but to classify all the species known to science. Carl Linnaeus, who in the 1750s developed a system of taxonomy (classification of species) still in use today, did so on the assumption that species are fixed, and variations found in them are accidental aberrations. However, by the end of the 18th century, new ideas were emerging. The accepted wisdom proved unsatisfactory in the face of evidence of evolutionary change, such as the discovery by Georges Cuvier of fossils of ancient species no longer in existence and very different from any alive.

Gradual change

The idea that species change over time began to take hold in the 19th century, and among the first to provide an explanation of how this came about was Jean-Baptiste Lamarck. He conjectured that evolutionary change in a species is a result of individuals acquiring characteristics through interaction with their environment, and that these acquired characteristics are inherited by subsequent generations.

While Lamarckism had its followers, it was only one step in developing a theory that would account for evolutionary change. Charles Darwin's insight into the subject was that evolutionary change is brought about by the process of natural selection—those individuals that are best suited to their environment will thrive, while those that are not will die out, and so variations will either survive and become established, or not. Darwin's *On the Origin of Species*, published in 1859, revolutionized the way that variations and diversity of species were thought about—and also undermined the

1918

Ronald Fisher shows that **Darwinian evolution** is compatible with **Mendelian genetics**, preparing the way for a new theory of evolution later known as **modern synthesis**.

1942

Ernst Mayr explains how **new species** appear when a population is isolated and its members evolve characteristics that **prevent** them from **breeding** with others.

1950

Willi Hennig devises **cladistics**, an alternative method of classification in which **species** are **grouped** according to their **evolutionary relationships**.

1960s

Emil Zuckerkandl and Linus Pauling discover the **rate** of **evolutionary change** of DNA sequences in similar species works as an effective "**molecular clock.**"

1976

In his book *The Selfish Gene*, Richard Dawkins proposes that the **gene** is the **fundamental unit** of selection in evolutionary change.

1980

Father and son Luis and Walter Alvarez propose that the **mass extinction** of the dinosaurs was caused by an **asteroid impact**.

religious idea of an unchanging creation with humans as God's greatest achievement.

Apparently in contradiction of Darwin's theory, Hugo de Vries proposed another explanation at the beginning of the next century. He maintained that variation was mostly brought about by genetic mutation, and not always the slow process of evolution that Darwin believed. De Vries thought that change occurred in sudden bursts when new varieties appeared spontaneously. Later research confirmed that mutation is a factor in genetic variation, but it occurs at a measurably constant rate.

Another factor affecting the rate of change, but an external one, was pointed out by Luis and Walter Alvarez in 1980. They had found evidence of the impact of a massive asteroid on Earth, which coincided with the sudden disappearance of all dinosaurs from the fossil record (except those that evolved into birds). They presumed the impact to be responsible for this mass extinction, raising the possibility of other environmental disasters causing similar events and bringing about sudden changes in the rate of evolution.

Combining ideas

The competing claims of Darwin's theory of natural selection and de Vries's mutation theory were, however, not incompatible. In fact, Ronald Fisher showed that they were complementary and, along with Mendel's idea of inheritance by particles, tied them together into a theory of evolutionary change that later became known as modern synthesis. The inclusion of Mendelian genetics in this theory was prescient, as Richard Dawkins later argued that the gene—which he refers to as *The Selfish Gene* in the title of his 1976 book on the subject—is the fundamental unit of selection in evolutionary change, rather than the organism.

In light of the overwhelming evidence supporting evolutionary change, there was a feeling in the mid-20th century that it was time to reexamine Linnaeus's system of taxonomy, based as it was on his assumptions of an unchanging order of life. One suggestion for an alternative was Willi Hennig's system of cladistics, where all species with a common ancestor—including that ancestor—are classified together in a group, known as clade. ■

THE FIRST STEP IS TO KNOW THE THINGS THEMSELVES

NAMING AND CLASSIFYING LIFE

IN CONTEXT

KEY FIGURE
Carl Linnaeus (1707–78)

BEFORE
***c.* 320 BCE** Aristotle groups organisms according to their position on a "ladder of life."

1551–58 Conrad Gesner divides the animal kingdom into five distinct groups.

1753 Carl Linnaeus produces a binomial system for naming plants in *Plant Species*.

AFTER
1866 Ernst Haeckel publishes a "tree of life" to illustrate the evolving lineages of animals, plants, and protists.

1969 American ecologist Robert Whittaker proposes a five-kingdom structure, adding fungi.

1990 Carl Woese devises a three-domain system now used by most taxonomists.

When Swedish naturalist Carl Linnaeus published the 10th edition of his *System of Nature* in 1758, it changed the way biologists classified organisms forever. It grouped the world's animals systematically by class, order, genus, and species, and it also gave each animal a Latin binomial (two-part name): a genus name followed by a species name. Previously, the names of organisms were often unwieldy descriptive terms that varied among countries. In contrast, Linnaeus's binomials acted as labels to allow universal recognition. By grouping species in genera, this classification also implicitly suggested the degree to

See also: Complex cells 38–41 ▪ Extinct species 254–55 ▪ Natural selection 258–63 ▪ Mutation 264–65 ▪ Speciation 272–73 ▪ Cladistics 274–75

Without knowing the names of living organisms, all **knowledge of them** is lost.

↓

All known living species are given a **two-part Latin name**, which places them in a **taxonomic hierarchy**.

↓

Within the hierarchy, species were originally grouped according to **basic shared physical characteristics**.

↓

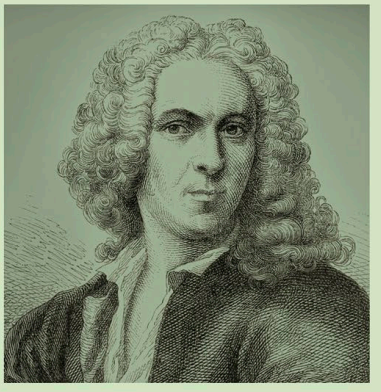
Living species are now arranged according to their genetic makeup, which indicates how closely related they are.

which various species were related. The International Commission on Zoological Nomenclature considers January 1, 1758, to be the starting point for the naming of animals; names from this point on take precedence over all previous ones.

Ancient roots

Taxonomy is the science of identifying, naming, and classifying organisms. Aristotle made the earliest attempts at this in the 4th century BCE. He divided living things into plants and animals. He classified approximately 500 species of animals according to anatomical features, including whether they had four legs or more, whether they laid eggs or gave birth to live offspring, and whether they were warm- or cold-blooded. Based on these studies, he devised a "ladder of life," with humans at the top, then a descending order of live-bearing tetrapods (four-legged animals), cetaceans (whales and dolphins), birds, egg-laying tetrapods, hard-shelled animals, insects, sponges, worms, plants, and minerals. Although flawed in many respects, it was generally accepted until the 16th century.

Conrad Gesner, a Swiss doctor, published his *History of Animals* in four volumes from 1551 to 1558; this was the first major catalog of animals since Aristotle's time. Gesner included descriptions from travelers who had visited many parts of the world. Different volumes covered egg-laying quadrupeds, live-bearing quadrupeds, birds, fish, and other aquatic animals. A fifth »



Carl Linnaeus

Considered the "father of taxonomy," Carl Linnaeus was born in southern Sweden in 1707. After studying medicine and botany at the Swedish universities of Lund and Uppsala, he spent three years in the Netherlands before returning to Uppsala. In 1741, he was appointed professor of medicine and botany, and he taught, organized botanical expeditions, and conducted research. Many of his students embarked on plant-finding expeditions, the most famous being Swedish naturalist Daniel Solander. The huge variety of specimens collected allowed Linnaeus to build his *System of Nature* into a multi-volume work that described more than 6,000 species of plants and some 4,000 animals.

After Linnaeus's death in 1778, he was buried in Uppsala Cathedral, where his remains are the type specimen (the representative of a species) for *Homo sapiens*.

Key works

1753 *Plant Species*
1758 *System of Nature* (10th edition)

volume on snakes was published after Gesner's death, and he had been preparing another on insects. Despite the odd inclusion of mythical unicorns and hydras, his work established a taxonomic benchmark.

Another major advance came in 1682, when English botanist John Ray published *Method of Plants*. This was the first book to stress the importance of the distinction between monocotyledons and dicotyledons (plants whose seeds germinate with one leaf and two leaves, respectively), and it also established the species as the ultimate unit of taxonomy. Ray catalogued species by arranging them into groups based on their appearance and characteristics. He followed up with three volumes of *History of Plants* between 1686 and 1704, containing descriptions of about 18,000 species from Europe, Asia, Africa, and the Americas.

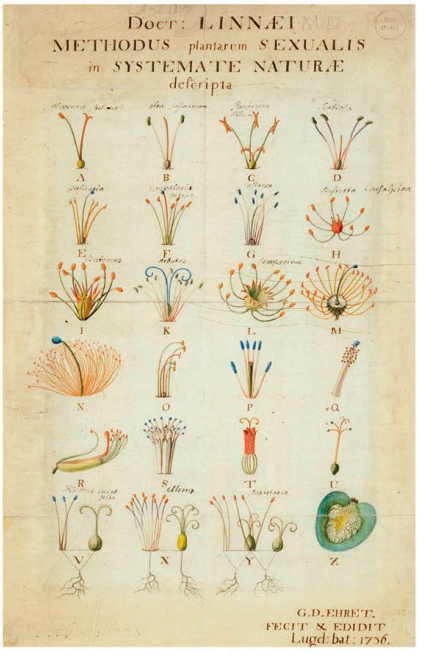
A new classification

Linnaeus's *System of Nature* groups the animal kingdom into six classes: mammals, amphibians, fish, birds, insects, and vermes (worms). The classes are differentiated by features of their anatomy—including the structure of their heart, lungs, gills, antennae, and tentacles—as well as their physical appearance. Many of the divisions, though not all, have stood the test of time. Within each class, Linnaeus listed a number of subgroups, or orders. For instance, he listed eight orders of mammals, including Primates, Ferae (dogs, cats, seals, and bears), and Bestiae (pigs, hedgehogs, moles, and shrews). He then divided each order into genera. His four primate genera were *Homo* (humans), *Simia* (monkeys and apes), *Lemur* (lemurs), and *Vespertilio* (bats). Linnaeus was the first to describe humans as primates, but zoologists now know that bats are not primates. His class of Amphibia incorrectly includes reptiles and sharks; he wrongly grouped spiders in the same class as insects; and his class Vermes is a strange mixture of animals of "soft substance" now known not to be related: worms, slugs, and jellyfish. Even so, Linnaeus's 1753 edition was impressive, describing more than 4,200 species.

> There are many species in nature which were never yet taken notice of by Man.
>
> **John Ray**
>
> **English botanist, 1691**

The following year, Linnaeus published a second volume, which covered all the plant species known to him. At a time when naturalists had not ventured into large parts of the world and did not have access to high-magnification microscopes, his classification was remarkable.

Zoologists and biologists readily accepted the Linnaean system. Although much modified since the 18th century, it still forms the basis for classifying life forms. Any organism has a specific place at several different levels of the classification hierarchy. For example, the Eurasian lynx, *Lynx lynx*, is a member of the kingdom Animalia, the phylum Chordata (it has a notochord during its development), the class Mammalia (females suckle their young), the order Carnivora (it is a meat-eater), the family Felidae, or cat (it is a specialist, mostly nocturnal hunter), and the genus *Lynx* (it is a short-tailed cat). Each of these categories is called a taxon. This system gives a lot of information about the animal without the need for a description. It also explains that the Eurasian lynx is closely related to the three other cats in the genus *Lynx*.



This watercolor illustration from Linnaeus's *System of Nature* shows his method for the classification of flowering plants, which was based on their reproductive organs.

The creation of new species

The question of why some species are anatomically very similar while others are completely different puzzled biologists until Charles Darwin's book *On the Origin of Species* (1859). His explanation of the evolution of new species as the result of natural selection, mutation, physical variation, and speciation fits well with Linnaeus's hierarchy—species with a recent common ancestor tend to be alike. It is now known, for example, that all four

The Eurasian lynx (*Lynx lynx*) is the third-largest predator in Europe. It lives in the deciduous forests of Europe and Asia and hunts deer and chamois.

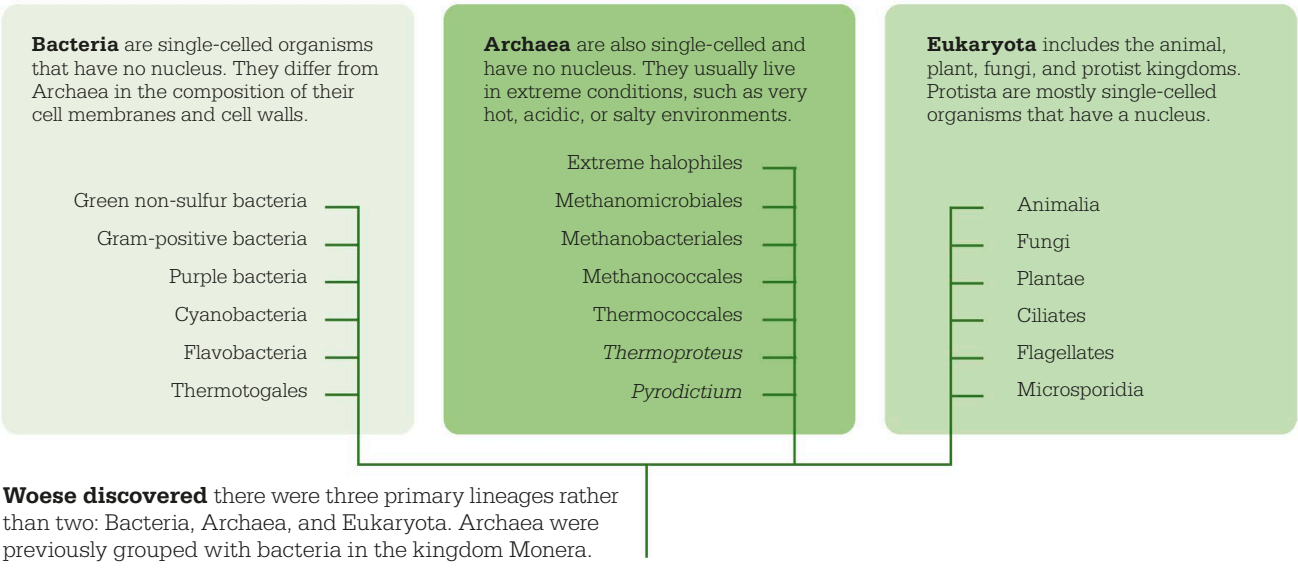
Lynx species are descendants of the extinct *Lynx issiodorensis*. Of course, animals or plants that look alike aren't necessarily closely related; convergent evolution means that species with different ancestors may have similar anatomical features if those have given them an evolutionary advantage.

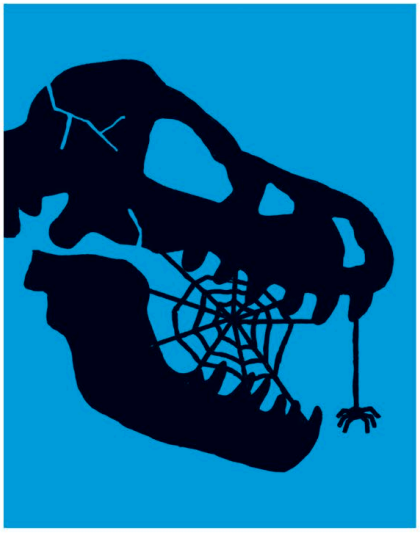
Inspired by Darwin, German biologist Ernst Haeckel pioneered the study of organisms' relatedness. In 1866, he drew an ancestral tree to show how surviving animals had descended from "lower" forms of life. He suggested a third kingdom for single-celled life, Protista, be added to the plant and animal kingdoms. In 1925, French biologist Edouard Chatton distinguished prokaryotes and eukaryotes.

The cladistic approach

In 1966, German biologist Willi Hennig proposed that life forms be classified strictly according to their evolutionary relationships. In this system, each group (or clade) of organisms contains every species known to have descended from a single ancestor, plus the single ancestor. This challenged many Linnaean assumptions.

Biologists' ability to classify life forms based on their relationships has been helped by improvements in microscopy and DNA analysis. More closely related species tend to have fewer differences in their DNA. Most taxonomists now use American microbiologist Carl Woese's three-domain system. This recognizes the huge diversity of microbial life that is found on Earth. ■





RELICS OF A PRIMEVAL WORLD

EXTINCT SPECIES

IN CONTEXT

KEY FIGURE
Georges Cuvier (1769–1832)

BEFORE
***c.* 500 BCE** In Ancient Greece, the philosopher Xenophanes of Colophon describes fossilized fish and mollusks.

1500–1600s Leonardo da Vinci, Danish geologist Nicolas Steno, and English polymath Robert Hooke realize that fossils are the remains of organisms.

AFTER
1815 William Smith's geological map of England and Wales, the first of its kind, identifies rock strata by the types of fossil they contain.

1859 Charles Darwin publishes *On the Origin of Species*, providing evidence for the evolution of life.

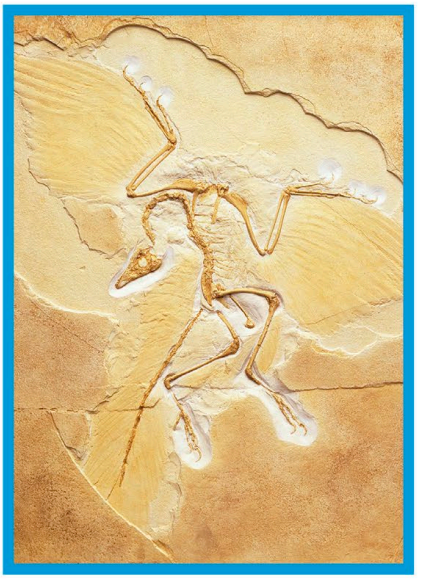
1907 American radiochemist Bertram Boltwood first uses radiometric dating to age rocks based on the radioactive impurities within them.

Evidence of prehistoric life is preserved in rocks, where bones and traces such as footprints, burrows, and even dung can leave lasting impressions. These fossils also show that many organisms that lived in the past were very different from those alive today. Paleontologists now interpret this in two ways: either the fossilized life forms became extinct—the population died out at a certain point in time—or they evolved, changing into other species.

Ancient Greek philosophers saw fossils as the remains of animals and plants, and they pondered over marine fossils found on land. But by medieval times, a common view was that fossils grew out of rocks and came to resemble living things by accident. When their organic origin became more widely accepted, the Christian Church taught that fossils were victims of the Biblical flood, even though some scholars, such as Italian polymath Leonardo da Vinci, pointed out that they had not all originated from a single catastrophe.

Fossil record

The rich diversity of life across prehistoric ages that span more than 4 billion years is far greater than that living today, but representatives of most of this diversity rotted away without becoming fossilized. As the science of geology developed and more fossils were discovered, researchers saw more discrepancies between their forms. Different fossils were also discovered in distinct rock strata—layers of sedimentary



This fossil archaeopteryx was discovered in a quarry in Germany in 1874. The species has features of birds and non-avian dinosaurs so it may be an evolutionary link between the two.

See also: Anatomy 20–25 ▪ Naming and classifying life 250–53 ▪ Life evolves 256–57 ▪ Natural selection 258–63 ▪ Speciation 272–73 ▪ Cladistics 274–75 ▪ Mass extinctions 278–79

rock deposited in different geological eras—with the deepest fossils being the oldest. The layering pattern was even repeated from place to place, suggesting that a record of the same prehistoric ages might be preserved everywhere.

In 1815, British geologist William Smith used the pattern of rock strata to produce the world's first geological map, for England and Wales. There were enormous implications for biology: if the kinds of fossils changed with depth in the ground, that indicated that life had changed through the ages, too.

How fossils form

Fossilization can happen in different ways. Sometimes, plants or animals have been reduced to dark films of carbon preserved in rock. Some of the best-preserved insects and small fossilized creatures were trapped in amber hardened from tree resin.

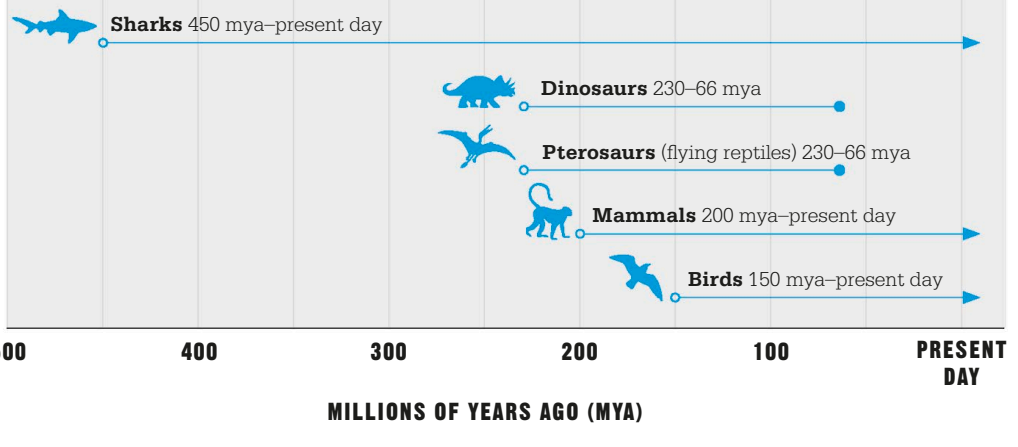
Many fossils formed by a process of mineralization. Dead organisms became buried by sediment, which slowed any decay and allowed time for the fossilization process to happen. In the thousands of years that followed, the minerals dissolved in water solidified and packed the microscopic spaces in bone, organs, or even individual cells. The result is a body fossil or cast made of rock that has kept much of the shape of the original life form. Such fossils only appear in sedimentary rocks. Their age can be estimated by radiometric dating of the volcanic rocks above or below, which involves analyzing the composition of radioactive elements that decay through time.

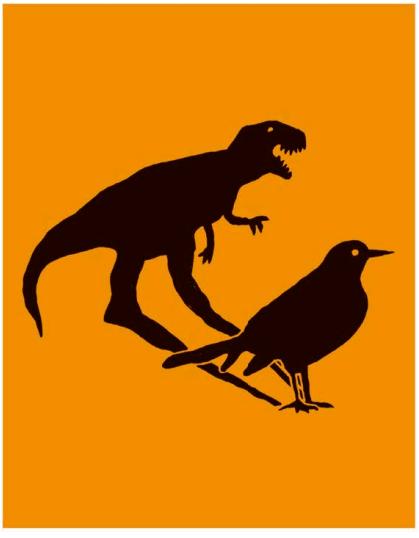
Catastrophic extinctions

In the early 19th century, one man dominated the study of fossils: French zoologist Georges Cuvier. His knowledge of anatomy helped him improve the scientific classification of animals—both living and dead. He became an expert on which fossil mammals could be found in different rock strata in the Paris area, and he saw abundant evidence that fossil species could differ greatly from living ones. He championed the idea that fossils were the remains of organisms that have become extinct. In 1812, Cuvier summarized these ideas in *Researches on the Bones of Fossil Vertebrates*. He believed that a series of catastrophic events had exterminated entire communities of species, which were then replaced by new ones.

Cuvier argued convincingly that extinction had shaped the history of life on Earth, although he was vague on the detail of where new species came from to replace the extinct ones. He refused to accept that species evolved, but evidence from other branches of biology—first articulated by Jean-Baptiste Lamarck and then by Charles Darwin—would ultimately support the idea of evolution. The history of biological organisms is a story of common descent. Cuvier was not wrong about catastrophes: events with global impact have caused mass extinctions periodically. But in every case, some species survived and evolved to produce new biological diversity. ■

The age of fossils can be determined by the knowledge of rock strata and radiometric dating. The data of such studies help establish when groups of organisms lived in the prehistoric past—and for how long.





ANIMALS HAVE IN COURSE OF TIME BEEN PROFOUNDLY ALTERED

LIFE EVOLVES

IN CONTEXT

KEY FIGURE
Jean Baptiste Lamarck (1744–1829)

BEFORE
***c.* 350–400 BCE** Plato argues that living things have a fixed, unchangeable essence. This view dominates thinking for the next two millennia.

1779 Comte de Buffon estimates that Earth is far older than suggested by Christian scripture.

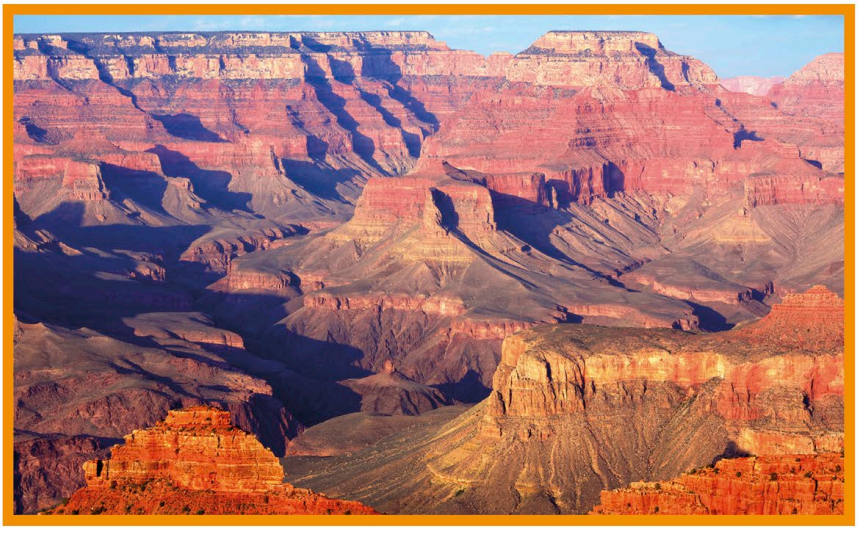
AFTER
1859 Charles Darwin publishes *On the Origin of Species*, which explains that evolution takes place by natural selection.

1930s Biologists reconcile Darwin's theory of natural selection with Gregor Mendel's explanation of inheritance. Together, these theories form the modern synthesis to explain the mechanics of evolution.

The premise of biological evolution—that life forms change over the course of many generations—is key to explaining why organisms are the way they are. For much of biology's history, this idea eluded even the world's greatest thinkers, for several reasons. Evolution seemed counterintuitive: each species produces more of its own kind, so how can that lead to change? Also, species were seen as unvarying products of a single act of creation. This notion can be traced back to Plato's theory of fixed, "ideal" forms, and it was reinforced by religious teachings. Additionally, according to Christian scripture, the world was not old enough for evolution to have happened.

Evidence against Creation

In the 17th century, geologists became aware of horizontal rock strata and the different types of fossils they contained, and some



Rock strata in the Grand Canyon, Arizona, represent six geological periods. They range from 270 million years old to 1.8 billion years old.

See also: Naming and classifying life 250–53 ▪ Extinct species 254–55 ▪ Natural selection 258–63 ▪ Mutation 264–65 ▪ Modern synthesis 266–71 ▪ Speciation 272–73

began to suspect that Earth's history was longer than had been previously thought. An increase in world travel led to the discovery of many new plants and animals that were not mentioned in the Bible, and microscopes revealed the existence of microbes.

In 18th-century France, Comte de Buffon, one of the most celebrated naturalists of his day, divided Earth's changing history into seven epochs—the planets were created in the first, and humankind appeared in the last. Buffon's private estimate of the age of Earth, based on his extensive knowledge of animals, was half a million years. That was hundreds of times older than the estimates derived from a literal interpretation of the Bible.

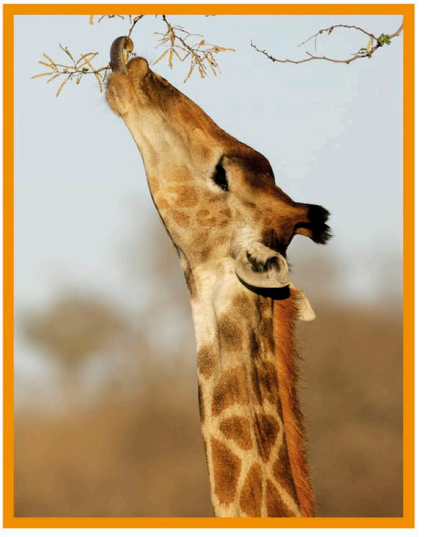
Buffon classified animals by region rather than structure, as Swedish botanist Carl Linnaeus had done. In doing so, he showed that species' distributions are not random: different regions have different animals and plants. This seemed to be at odds with the idea of a single garden of Creation.

Despite these insights, not even Buffon was an evolutionist. Although naturalists increasingly had to confront facts that conflicted with the concept of unchanging species, the religious convictions of most prevented them from drawing the conclusion that life continuously evolves.

An evolutionary theory

At the dawn of the 19th century, French naturalist Jean Baptiste Lamarck took the crucial step of departing from the Creationist world view. He was a dedicated taxonomist, with a detailed knowledge of invertebrate species. Impressed by similarities between living and extinct animals, he noticed that some fossils appeared to be transitional—intermediate forms between different species. This led him to abandon his view of constant species and conceive a theory of evolutionary change.

Lamarck's idea was that species' body parts change because they adapt to their environment. The newly acquired characteristics are then passed on to their offspring. He thought that the changes to an individual's body were caused by the effect of use or disuse on its physiology. For example, predators constantly chasing their quarry makes both predator and prey develop stronger muscles so they get faster, whereas if a body part is not used it becomes weak and diminished, and finally disappears.



Lamarck believed that the more an animal used a part of its body, the more developed that part became. So, if a giraffe constantly stretched its neck upward, its neck would become longer.

At the time, Lamarck's idea seemed plausible—and his theory was the first attempt to explain a mechanism for evolution. However, biologists soon recognized that characteristics acquired during life cannot be inherited. Lamarck was essentially right about the principle of species changing over time, but he was wrong about the means. It would be more than half a century before Charles Darwin came up with a better explanation: that evolution was driven by natural selection. ■

Jean Baptiste Lamarck

The youngest of 11 children, Jean Baptiste Lamarck was born into a poor family in Picardy, France, in 1744. Aged 17, he signed up to fight in the Seven Years' War between France and Germany, before spending some years as a writer. His passion for natural history motivated him to write a much-lauded book on French plants. Comte de Buffon secured Lamarck work at Paris's natural history museum, where he rose to become professor of the museum's "insects, worms, and microscopic animals" in 1793. During his time there, he developed his theory of evolution, which he first introduced in his Floreal lecture in 1800, before elaborating on it in several books. Later in life, Lamarck's failing eyesight hindered his work, and he died blind and in poverty in 1829.

Key works

1778 *French Flora*
1809 *Zoological Philosophy*
1815–22 *Natural History of Invertebrate Animals*

THE STRONGEST LIVE AND THE WEAKEST DIE

NATURAL SELECTION

IN CONTEXT

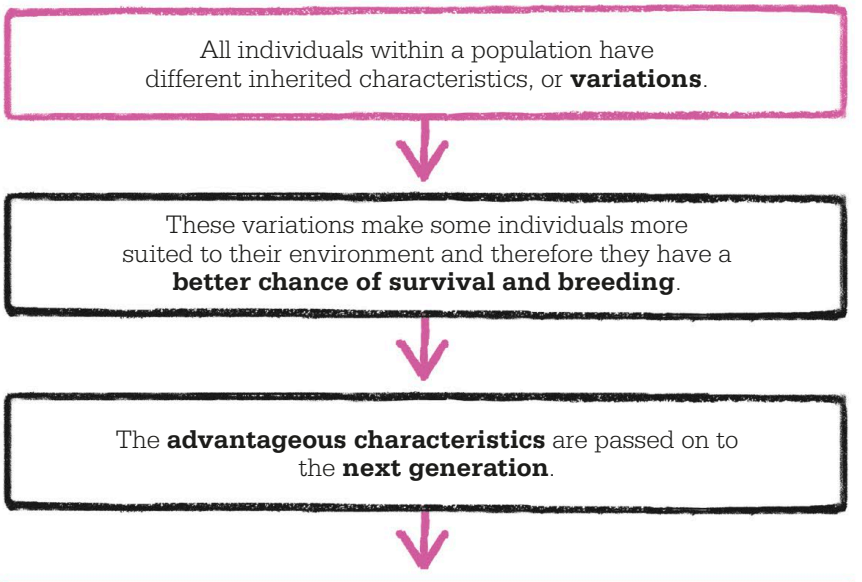
KEY FIGURES
Charles Darwin (1809–82), **Alfred Russel Wallace** (1823–1913)

BEFORE
1809 Jean Baptiste Lamarck elaborates on his theory of evolution through the inheritance of acquired characteristics in his book *Philosophie zoologique*, but is later shown to be wrong.

AFTER
1900 A number of biologists, including Hugo de Vries and William Bateson, rediscover the experimental studies of Gregor Mendel, who provided an explanation for the mechanism of inheritance.

1918 British statistician Ronald Fisher helps show how Darwinian evolution by natural selection is compatible with the Mendelian particulate nature of inheritance.

> … there is a tendency in nature to the continued progression of certain classes of varieties further and further from the original type…
> **Alfred Russel Wallace**



Over generations, the characteristics within a population change.

Charles Darwin was the first scientist to explain evolution in a way that is consistent with the facts of biology. His idea, natural selection, relies on the notion that a population of living organisms is made up of individuals that are not identical. Because of the variable characteristics they inherit, some individuals survive and breed better than others under certain conditions, passing their advantageous characteristics to the next generation. If conditions change, the best characteristics for surviving them change too. As a result, over time, the population continues to evolve and adapt to its surroundings. In effect, the surroundings select the organisms.

Natural selection remains the most powerful theory that explains why organisms are the way they are. However, general acceptance of Darwin's big theory took a long time. Not only was the idea of changeable species in conflict with the creationist views still widely held in the 19th century, Darwin's fellow naturalists believed each species had a non-varying "essence." It was an idea that stemmed from Plato's teachings in ancient Greece, and this notion of static, unvarying species was deeply entrenched.

A voyage of discovery

Like his Christian contemporaries, Darwin was initially a creationist. However, his views changed during his five-year expedition on HMS *Beagle,* which he joined in 1831 after graduating from Cambridge University. Captained by Robert Fitzroy, the ship's commission was to chart the coastline of South America, and the voyage proved to be a turning point in Darwin's life. It both secured his reputation as a naturalist and, ultimately, inspired him to reconsider his world view and build his theory of evolution.

See also: Chromosomes 216–19 ▪ Naming and classifying life 250–53 ▪ Life evolves 256–57 ▪ Mutation 264–65 ▪ Modern synthesis 266–71 ▪ Speciation 272–73

Darwin was struck by the fact that different parts of the world had their own unique communities of animals and plants. And his excavation of fossils—which received particular praise when he sent them back to England—also showed him how life changed over time. However, this was at odds with the biblical story of God creating the world and everything in it in six days.

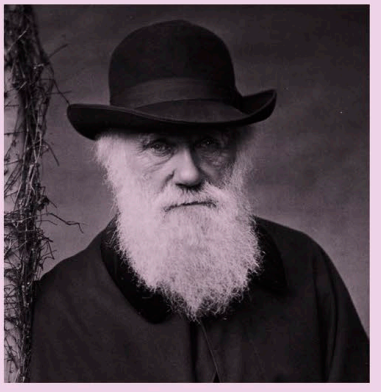
On his return to England in 1836, Darwin began to speculate that instead of all species remaining static, new ones might emerge from populations that were isolated, such as by a mountain range or by being on an island. Famously, the birds he collected from the Galápagos Islands looked like they had diversified from common ancestors. In 1837, British ornithologist John Gould pointed out that one group—with markedly different bills—were all interrelated species of finches that were evidently adapted in different ways to the islands' different habitats. It was a ground-breaking moment.

That same year, Darwin began a secret notebook on "transmutation" of species. His shift toward thinking in terms of populations helped him understand how species could evolve. He knew that plant and animal breeders had long appreciated the importance of identifying individuals with desirable characteristics for producing domesticated varieties. Darwin was beginning to see how wild species were variable too.

The struggle for existence

Darwin's study of barnacles, from 1846 to 1854, was another key component in his understanding of natural variation in populations. But its real significance first struck him in 1838, when he read *An Essay on the Principle of Population* by British economist Thomas Malthus. Malthus observed that, unchecked, a human population would swell, but since production of resources, such as food, would be unable to keep up with demand, starvation and disease were the inevitable consequence. »

The Galápagos Islands lie isolated in the Pacific Ocean. Darwin reached the islands in 1835, and his study of the organisms he found there laid the groundwork for his theory of evolution.



Charles Darwin

Born in 1809, Charles Darwin was, in his own words, "a born naturalist." Appalled by the trauma of 19th-century surgery, he gave up studying medicine at Edinburgh and transferred to Cambridge to study theology.

In 1831, Darwin was invited to join the voyage of HMS *Beagle* as a companion of the captain. His observations while traveling the Southern Hemisphere led him to reject the widely held belief that species were created and fixed. He continued to gather evidence for his theory of natural selection on his return to England, and published it 20 years later in his seminal work *On the Origin of Species*. This, and later publications, secured Darwin's place as one of the most famous naturalists of all time. After his death in 1882, he was honored by being buried in Westminster Abbey, London.

Key works

1839 *The Voyage of the Beagle*
1859 *On the Origin of Species by Means of Natural Selection*
1871 *The Descent of Man, and Selection in Relation to Sex*

In the previous century, naturalists Comte de Buffon (Georges-Louis Leclerc) and Carl Linnaeus had recognized the potential fertility of living things. The later research of German naturalist Christian Ehrenberg, who observed that successive doubling of single-celled microbes quickly produced vast numbers, also impressed Darwin. He realized that even the most complex plants and animals also had the potential to overpopulate.

Whereas naturalists with anti-evolution views saw species as being in harmony with their world, Darwin began to focus on the struggle for existence. If populations had the potential to grow so much, but finite resources kept them level, the weakest would lose out.

The weakest individuals are most likely to fall victim to predators, such as this young gazelle hunted by a lion. Stronger animals have a better chance of survival.

How species change

The idea that weak individuals die and strong ones survive was nothing new. Victorian hospitals and slums were witness to that. Some theologians and scientists used this observation to support their anti-evolution ideas, justifying why species stayed the same. One of Darwin's correspondents, British zoologist Edward Blyth, saw this as a way of reinforcing "type"—if weaker, "inferior" individuals died, surely this improved the perfection of the species.

Darwin, however, saw these struggles happening against the background of a changeable world. Geologists were seeing evidence that Earth itself was not a static place. Islands emerged, habitats changed, and fossils of different species were revealed in different rock strata. For Darwin, this was incompatible with the idea of fixed species in harmony with their surroundings.

Instead, Darwin proposed, when species find themselves living under new circumstances, only those individuals best adapted to cope will survive and breed. Over many generations, the predominant characteristics shift with changing circumstances—selection becomes directional, pushing a characteristic to one extreme or another (see box, left).

Publication

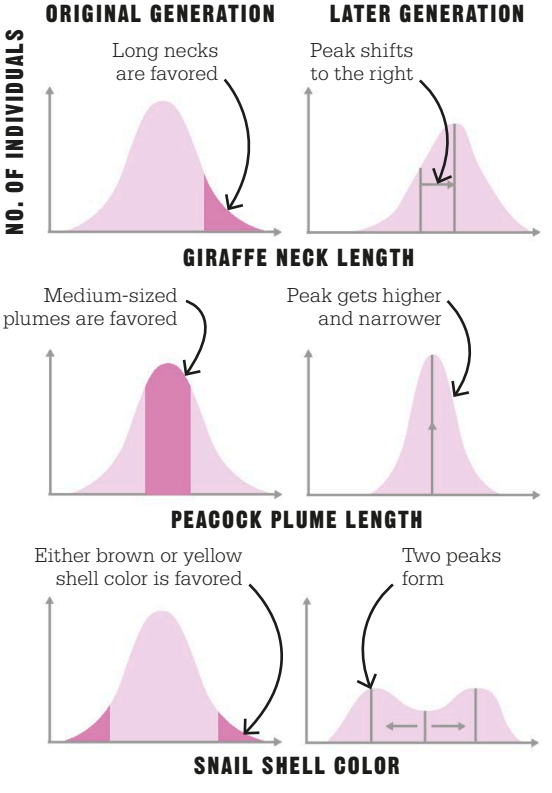
Darwin was painfully aware of the protests that would result from going public with these ideas in Victorian England, and he spent years prevaricating as he accumulated evidence. But, in 1858, another British naturalist forced his hand. Alfred Russel Wallace, while collecting specimens in Southeast Asia,

Modes of natural selection

Directional selection
There is a shift in a characteristic in a single direction. Longer and shorter-necked giraffes compete for food. Those with longer necks do better, so the peak shifts to the right.

Stabilizing selection
In wild peacocks, extremes of plume length have negative consequences. Peacocks burdened with the longest plumes are caught by tigers, but shorter plumes don't attract a mate. The range of plume length is reduced in later generations.

Diversifying selection
To avoid predation, the shell color of the brown-lipped snail diverges into two or more variants that are camouflaged against different backgrounds.



wrote to him with a theory that matched his own. Wallace's experience in the tropics of South America and Asia had led him to be an evolutionist, too, and—like Darwin—Malthus's notion of a struggle for existence was a turning point. Initially, Wallace had thought in terms of perfection of type—like Blyth—but he now saw selection resulting in changing species.

Darwin and Wallace agreed to submit their ideas as separate papers to a meeting of the Linnean Society, London, in July 1858. This prompted Darwin to expand his thesis in a book—*On the Origin of Species by Means of Natural Selection*—the following year. He intended this to be just an abstract of his theory, but it made him world famous and would seal his legacy.

Genetic evidence

Early in the 20th century, scientists helped to refine the understanding of natural selection in the light of discoveries about chromosomes, genes, and inheritance.

Biologists studying populations saw evidence of natural selection all around them, and could even study it happening in real time. In the US, biologist Theodosius Dobzhansky focused on fruit flies, complementing Thomas Hunt Morgan's work on the genetics of these insects. Through keeping large numbers in so-called population cages under different conditions, he saw how certain genes waxed and waned under the influence of natural selection.

In the 1950s, British geneticist Bernard Kettlewell used natural selection to explain how numbers of a black variety of the peppered moth (*Biston betularia*) increased in the soot-covered cities of the Industrial Revolution. Darker moths were less likely to be spotted by predatory birds. When pollution levels in British cities fell following the introduction of the Clean Air Act (1956), paler moths returned.

The peppered moth research shows the way selection can be directional, pushing characteristics to extremes. Other studies have revealed that selection can be stabilizing—extreme variations of a characteristic are eliminated (see box, left). British zoologists Arthur Cain and Philip Sheppard showed the diversifying potential of natural selection, whereby more than one variety is favored (selected) at the same time. Their study of the land snail *Cepaea nemoralis* proved that shell color strongly affected the chances of being eaten by a predator in different habitats and so different colors had evolved.

Brown-lipped snails (*Cepaea nemoralis*) have different shell colors and patterns. This is an example of divergent evolution.

Today, natural selection is seen as a cornerstone of biology. It is the only way that evolution produces adaptation in a changeable world. ■

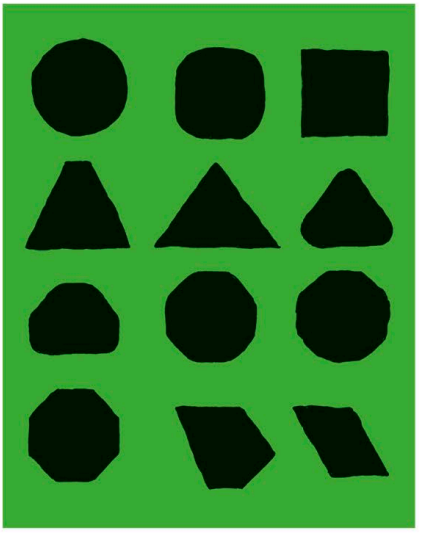
A male Victoria's riflebird (*Lophorina victoriae*), from Queensland, Australia, puffs up his feathers to get a female's attention.

Sexual selection

Darwin thought that, in addition to the struggle for survival, competition for mates could be a driving force for evolution. He saw this sexual selection as a different mechanism to natural selection, but in terms of evolutionary fitness, it is the same: individuals more successful in mating produce more offspring.

Sexual selection is thought to play an important role in the evolution of sexual differences. "Attractive" features that give an individual an advantage by being chosen by a mate more often will be passed on to their offspring. For instance, the showy plumes of male peafowl (peacocks) would not give an individual a better chance of survival, but could boost its reproductive chances. Showy males that have evaded predators might also be physically stronger.

Overall, females are usually the choosier sex, probably because their investment in the next generation—in terms of the physical cost of producing eggs or the risks of pregnancy—is usually greater.



MUTATIONS YIELD NEW AND CONSTANT FORMS

MUTATION

IN CONTEXT

KEY FIGURE
Hugo de Vries (1848–1935)

BEFORE
1859 Charles Darwin's *On the Origin of Species* explains evolution as a gradual process involving small changes by natural selection.

1900 Biologists, including Hugo de Vries, rediscover Gregor Mendel's work, published in 1866, explaining that inherited characteristics are due to particles, later called genes.

AFTER
1942 British biologist Julian Huxley compiles the ideas of Darwin's natural selection, Mendel's particulate inheritance, and de Vries's mutation in a unifying concept called "the modern synthesis."

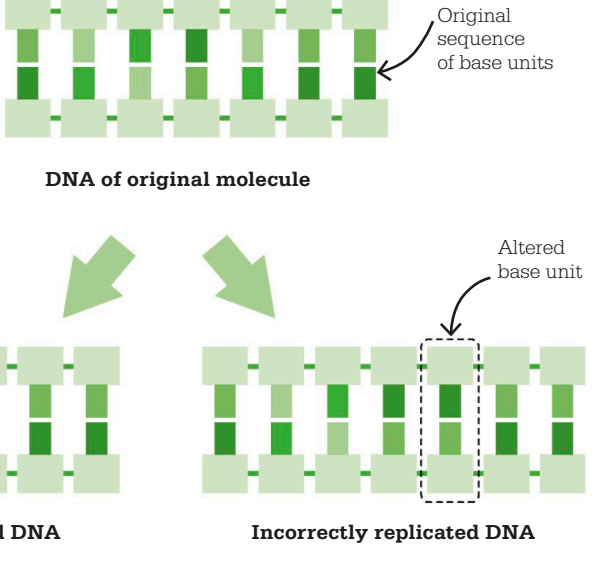
1953 Francis Crick and James Watson's discovery of the double helix offers a basis for the chemical makeup of inherited material.

For biological evolution to happen, there has to be variation, but what produces this variation in the first place?

Since ancient times, naturalists, including Britain's Charles Darwin, have been aware that "varieties" could suddenly appear, apparently spontaneously, and be inherited. This was especially well known among plant and animal breeders, who had been carrying out artificial selection in order to get better stock or varieties—a pigeon, for example, might grow up with lavender plumage instead of gray; brown mice could occasionally produce white ones; or a rose bush might suddenly sprout denser blooms. Dutch botanist Hugo de Vries was so impressed by the varieties that were growing among his evening primroses that in 1900–03 he published a theory of evolution based upon them.

De Vries called his varieties "mutations"—a term that has stuck ever since. He argued that there

In the original DNA molecule, there is a certain sequence of base units. Gene mutations occur when this existing DNA molecule is incorrectly replicated.



See also: The laws of inheritance 208–15 ▪ Chromosomes 216–19 ▪ What are genes? 222–25 ▪ The double helix 228–31 ▪ Modern synthesis 266–71

was a continual production of random mutations that not only accounted for the origin of life's diversity but even served as the driving force of evolution. Since his mutations were so sudden, de Vries suggested that evolution progressed in jumps—a process that became known as saltationism. This view of evolution contrasted sharply with the gradual change envisaged by Darwin's theory of natural selection.

De Vries saw support for his idea in the laws of heredity that had been published more than 30 years earlier by Gregor Mendel, an Austrian monk. Mendel had carried out breeding experiments on pea plants and suggested that inherited characteristics were determined by particles, later called genes. If mutations came in the form of discrete genes, then, de Vries argued, surely evolutionary change happened in discrete jumps, too.

Causes and effects

De Vries was partly right and partly wrong, but it would take another half-century for biologists to understand exactly how. As inheritance was studied in more detail, geneticists saw that many characteristics were caused by the particle-like genes and their mutated forms working together. This had the effect of smoothing out much of the variation, so it was continuous, rather than discrete—accounting for Darwin's gradual changes. At the same time, biologists scrutinizing cells and their contents were revealing the nature of mutations at the chemical level of their DNA.

Spontaneous mutations arise because DNA (the genetic material) gets miscopied. Mutations are rare,

> Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest.
> **Hugo de Vries**

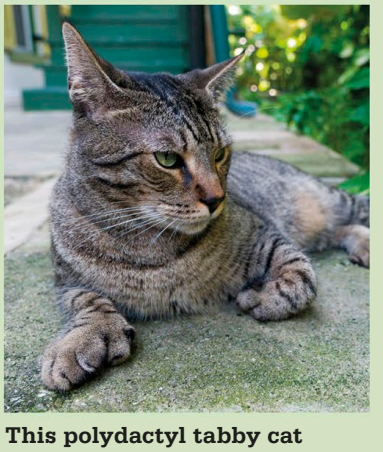
predicted to happen to any gene just once every million times a cell divides, but are the ultimate source of genetic diversity for life on Earth. Billions of years of miscopying, even at this low rate, explains how so much variation has come from a single common ancestor.

Different varieties of genes arising by mutation are called alleles, and they account for the familiar inherited variation, such as blue and brown eyes in humans, or green and yellow pods in Mendel's pea plants. Since they are random changes to an otherwise finely tuned living thing, many mutations end up being harmful. Others seem to have no effect on survival at all, while a small but significant number could be beneficial. Harmful mutations are kept low by natural selection, while the beneficial ones are increased by it—all depending on how the environment opposes some but favors others. De Vries was right that mutations produce variety, but then natural selection does the rest. And this alone explains how organisms become adapted to their surroundings, rather than randomly created. ■

Types of mutation

All mutations are random mistakes in the way genetic material—DNA—is passed on when cells divide. This may be a copying error in how DNA self-replicates, leaving a gene with an altered sequence of DNA base units—a gene mutation. Alternatively, entire strands of DNA may become misaligned or fractured and fail to separate evenly, creating chromosome mutations.

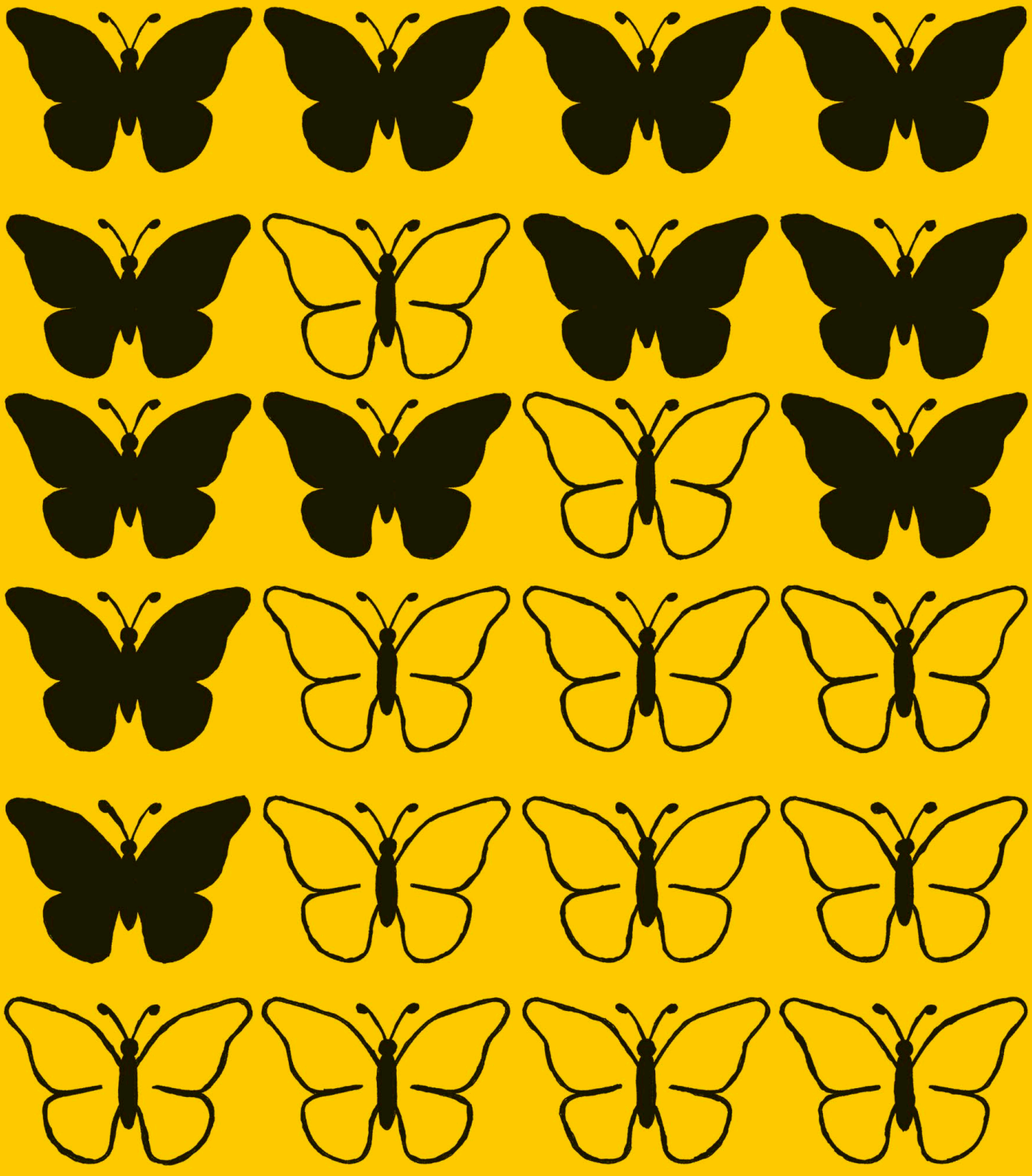
Although cells have natural "proofreading" systems that correct mistakes, some are inevitably missed, and certain harmful influences, such as X-rays, increase their rate. A mutation in sex organs might end up in sperm or eggs and then get copied into all of the cells of an offspring. Such "germ line" mutations are passed to future generations. Other mutations that appear in body cells are not part of the germ line. These somatic mutations affect localized patches of tissue, sometimes becoming cancerous, but are not passed on to offspring.



This polydactyl tabby cat has more than five toes on each foot as a result of an inherited genetic mutation.

NATURAL SELECTION SPREADS FAVORABLE MUTATIONS

MODERN SYNTHESIS



IN CONTEXT

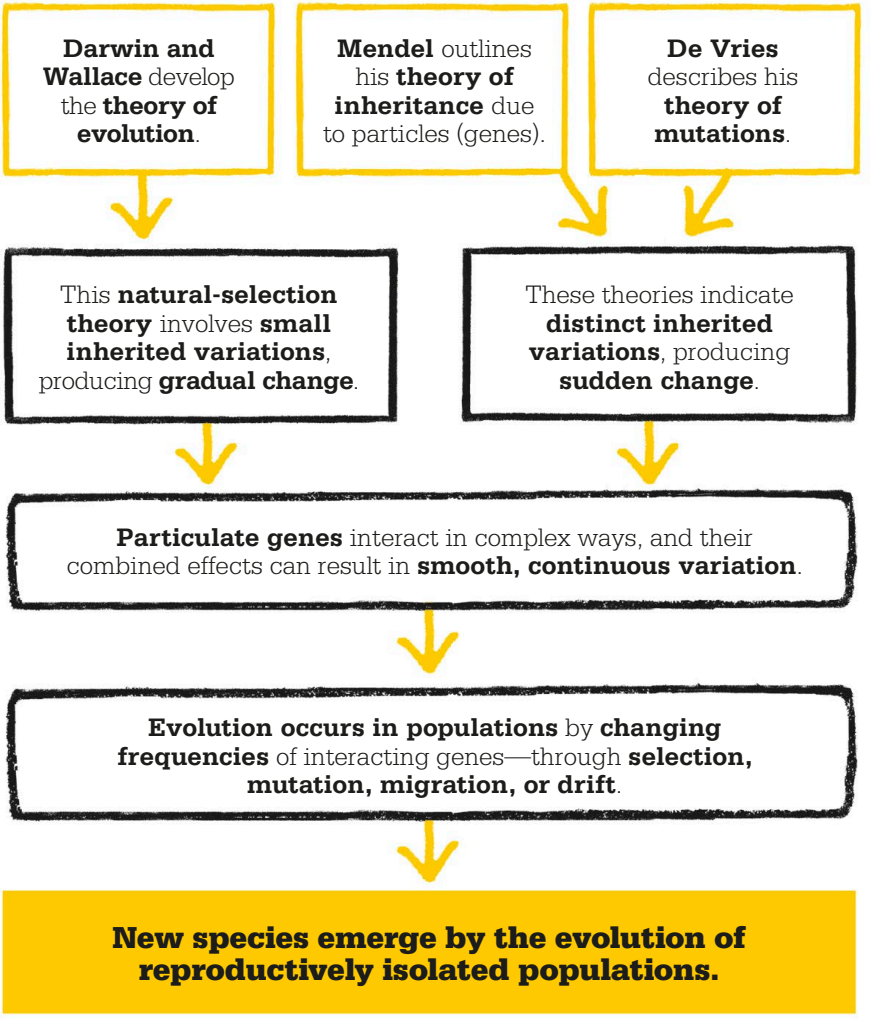
KEY FIGURES
Ronald Fisher (1890–1962), **Theodosius Dobzhansky** (1900–75)

BEFORE
1859 Charles Darwin describes the theory of evolution by natural selection in his book *On the Origin of Species*.

1865 Gregor Mendel delivers his lecture "Experiments in Plant Hybridization," detailing his pea-breeding research and three "laws of inheritance."

1900–03 In *The Mutation Theory*, Hugo de Vries argues that evolutionary change occurs in sudden large jumps.

AFTER
1942 Ernst Mayr publishes *Systematics and the Origin of Species* and defines a species as a group of organisms that is reproductively isolated—able to produce fertile offspring only among themselves.



> Evolution … is the most powerful and the most comprehensive idea that has ever arisen on Earth.
>
> **Julian Huxley**
> **(1887–1975)**

The 19th century witnessed the emergence of two of the most important ideas in biology: Charles Darwin's and Alfred Russel Wallace's theory of evolution by natural selection, and Gregor Mendel's theory that inheritance works via "particles," which we now call genes. Together, these concepts would eventually help explain the history of life on Earth. Initially, however, their respective supporters were in disagreement.

In the decades that followed the publication of Darwin's *On the Origin of Species*, most biologists came to accept the idea of evolving species linked by common descent, but few were convinced by the idea of natural selection. Darwin thought that evolution happened through the selection of very slight variations, which made it a gradual process. For him, sudden, big changes—such as occasional albinos—were aberrations and not significant. Others, however—even his formidable ally, British biologist Thomas Huxley—thought he was wrong to discount such phenomena. And when Mendel's theory of inheritance was "rediscovered"

See also: The laws of inheritance 208–15 ▪ What are genes? 222–25 ▪ Natural selection 258–63 ▪ Mutation 264–65 ▪ Speciation 272–73 ▪ Selfish genes 277

in 1900, after being ignored for decades, it was fuel for the opponents of Darwin. Mendel had demonstrated that discrete characteristics, such as the pod color of his pea plants, were caused by inherited units—persuading them that Darwin's theory of gradual selection was wrong.

Mutations

In 1894, British geneticist William Bateson published an in-depth study on what was then known about genetic variation, insisting that typical inherited variation materialized in a discontinuous way. He thought that smooth continuous variation—the sort favored by Darwin for natural selection to work—came instead from environmental influences. And while he was unaware of Mendel's work, Bateson also thought this discontinuity was therefore incompatible with Darwin's theory. Instead, he believed that evolution occurred in large jumps—a school of thought called saltationism. When Mendel's work resurfaced in 1900, Bateson saw it as proof of his view.

In Holland, fellow saltationist Hugo de Vries proposed that new species emerged by the spontaneous appearance of new variants, which he called mutations. His work, published between 1900 and 1903, was highly influential, even though his idea was based largely on evidence from just one plant species, the evening primrose. Saltationism appealed to those scientists trying to understand inheritance through breeding experiments. But field naturalists, in Darwin's tradition, saw gradual variation everywhere, and many perceived it as disproof of Mendelian inheritance.

Gene pools

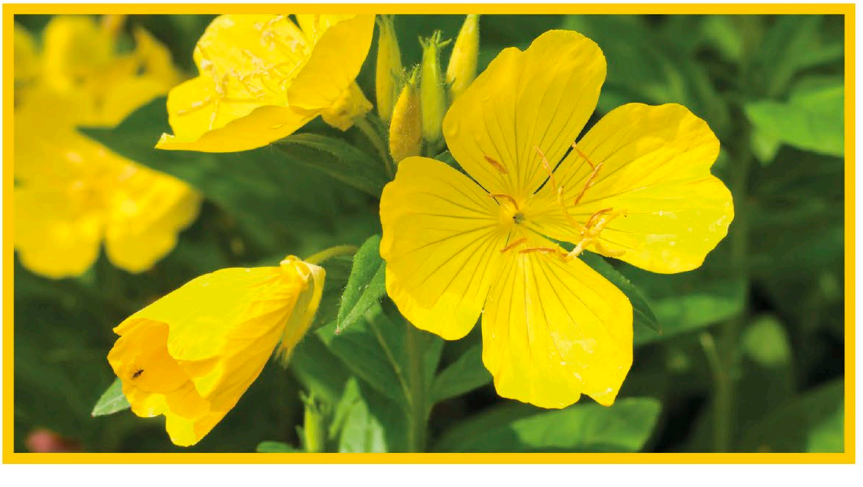
Evolution is a process that takes place in populations, when their genetic composition changes over the course of generations. It cannot happen to individuals, because an individual's genes stay largely fixed throughout its life. Although the members of a species share the same kinds of gene, there are different varieties, called alleles, of any gene for a given trait (such as for yellow or green pea pods). New alleles are produced when genes mutate. Populations with a large degree of genetic diversity—or lots of different alleles—are said to have a large gene pool. As a species evolves, the relative abundance, or frequency, of different alleles changes.

Scientists sometimes simulate a population's gene pool using a bag of colored beans, with the colors representing different alleles and a random sample of beans representing the next generation. Although this has been disparagingly described as "beanbag genetics," it is a useful way of modeling evolutionary change at the genetic level.

Population genetics

The biologists perhaps best placed to resolve the issue were geneticists who had a background in natural history. In Sweden, Herman Nilsson-Ehle started out researching plant taxonomy but later showed that individual genes—inherited as Mendel said—interact in complex ways, so the characteristics they control do not always emerge as discrete. Biologists were also appreciating that, to understand how evolution really worked, they needed to study genes in whole populations, not just in experiments.

Many geneticists used the mathematical approach of Mendel and began to look at genes in populations in a mathematical »



The evening primrose (*Oenothera* species) was seen by Hugo de Vries as evidence that evolution occurs in sudden jumps. Most evening primrose species are yellow, but *Oenothera rosea* is pink.

way, too. As soon as a gene for a characteristic had been identified, they were able to work out how abundant it was in a population—and to see how this changed from one generation to the next. Among the pioneers in this field were British mathematician Godfrey Hardy and German physician Wilhelm Weinberg. In 1908, while working independently, they proved mathematically that—in a large population—nothing in inheritance alone would cause the frequency of genes to change. Evolution would occur only if something disrupted the genetic equilibrium. The idea that genetic variation will remain constant in the absence of influencing factors became known as the Hardy–Weinberg equilibrium.

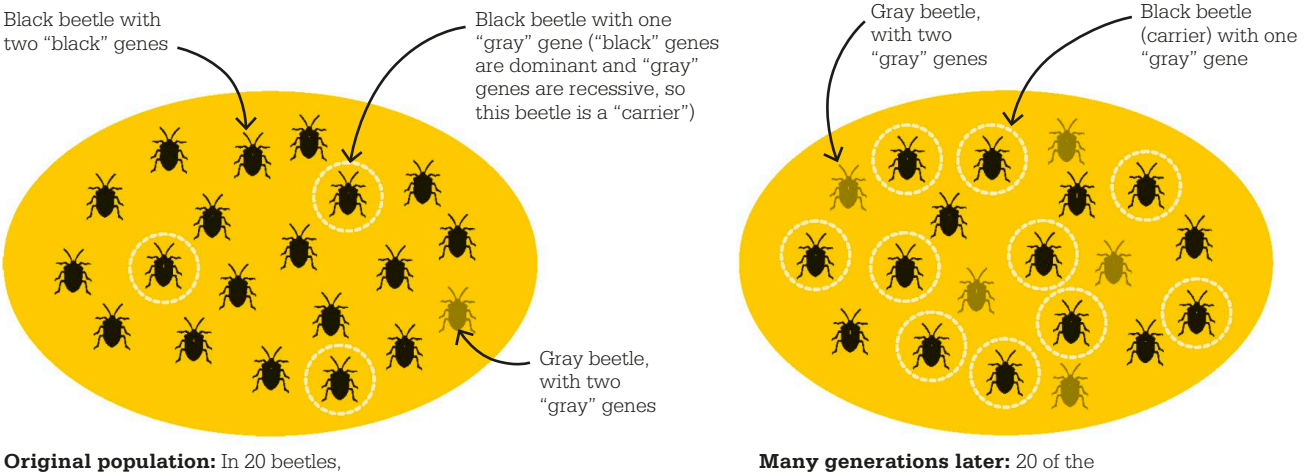
This principle made it possible to quantify the changes in gene frequency from one generation to the next. For example, a gene that determined fur color might have different forms (alleles) for brown or white fur. A population might start off with these in equal proportions: 50 percent for brown, 50 percent for white. After several generations, if the gene frequencies became 30 percent for brown and 70 for white, then the population had evolved. This could mean natural selection was favoring white fur.

The polar bear is a good illustration of the adaptation of a species to its environment. Its thick fur provides insulation and camouflage, conferring an advantage when hunting prey.

Combined effects

In 1915, British mathematician Harry Norton worked out that even a gene with a tiny advantage might bring about a big change in a population by natural selection. In 1918, British geneticist and statistician Ronald Fisher went a stage further. Knowing how genes interact in complex ways, he showed how the combined effect of many of them can account for smooth, continuous variation—in body size, for example, or in shades of pigment—thus creating the small differences needed for Darwin's natural selection to work. Fisher's work went a long way

Gene frequencies change over time, by selection or non-adaptive evolution



Original population: In 20 beetles, each with 2 color-determining genes, there are 5 "gray" genes.

Many generations later: 20 of the 40 color-determining genes in the population are now "gray".

> Natural selection depends on a succession of favorable chances.
> **Ronald Fisher**

toward revoking the belief that Mendel and Darwin's theories were incompatible.

Another key player in reconciling the two schools of thought was Russian biologist Sergei Chetverikov. He focused on the significance of genetic mutation—new genes resulting from, for example, errors in DNA replication—although he preferred the term "genovariation." He found that, while these did not automatically generate new species in the way de Vries had thought, mutations could exert an influence in more subtle ways. Some were beneficial or harmful, to greater or lesser degrees. Many were also recessive, a term coined by Mendel for alleles that, when combined with dominant alleles, do not manifest as characteristics, but when they happen to be paired up, their effect is expressed. The implication of all this was that genetic variation within populations was actually much wider than anyone—even Darwin—had realized. It made the potential for evolution much greater.

Non-adaptive evolution

Natural selection is not the only mechanism for genetic change in a population. Other factors have an impact, too, new mutations and migration (the transfer of genes from one population to another) among them. Another factor is genetic drift, a process described in 1931 by American geneticist Sewall Wright. Since each generation inherits a sample of genes from its parents, and whether an individual survives and reproduces is often due to chance, these factors can cause small changes in gene frequency. In very small populations, the change can be significant within a few generations. Tiny populations—such as on islands—can undergo rapid evolution by chance alone.

Migration, mutation, and drift are all random processes. In contrast, selection depends on both the characteristics of an organism and the environment in which it lives. It is the only evolutionary mechanism that satisfactorily accounts for adaptation—something that can be seen throughout the natural world. This in itself is powerful evidence for Darwinian natural selection.

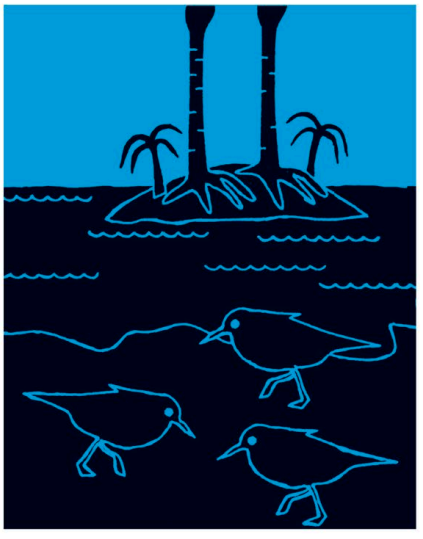
A new synthesis

Fresh perspectives on how evolution works culminated in 1937 with the publication of *Genetics and the Origin of Species* by Theodosius Dobzhansky, a Russian-American biologist. He synthesized the key concepts that were now understood: that evolution happened gradually with small genetic changes, largely driven by natural selection, and also that new species emerged because populations became reproductively isolated—so genetically distinct that they could breed only within their group. By the 1940s, the old idea of saltationism had been abandoned in favor of this broader theory. It became known—in a phrase coined by British biologist Julian Huxley in 1942—as the "modern synthesis." ■

The Galápagos giant tortoise is an example of rapid evolutionary change that can occur on small islands, at times resulting in extreme characteristics.

The unit of evolution

The work of Ronald Fisher and other population geneticists focused on the way that specific genes could be favored or depleted by natural selection, and they therefore took genes to be the significant units of evolution. This approach helps explain the complex way that the genetic makeup of an entire population changes from one generation to the next. It was taken to its extreme in the "selfish gene" theory of British evolutionary biologist Richard Dawkins in 1976, which argued that an organism's behavior was dictated by its genes. But some evolutionary biologists, like German-born American Ernst Mayr, argued that a gene-centered view of evolution may not be the best one. For them, the important unit of evolution is the individual organism. Genes do not function in isolation. It is the individual responding to the selective influences of its environment that contributes to the next generation.



DRASTIC CHANGE OCCURS IN AN ISOLATED POPULATION

SPECIATION

IN CONTEXT

KEY FIGURE
Ernst Mayr (1904–2005)

BEFORE
1859 Charles Darwin's *On the Origin of Species* introduces the idea that species evolve through natural selection.

1930s The modern synthesis theory explains evolution as a fusion of Darwin's natural selection and Gregor Mendel's explanation of inheritance.

1937 George Ledyard Stebbins Jr. describes how new plant species can emerge by chromosomal mutation.

AFTER
1951 American paleontologist George Simpson describes a species as an evolutionary lineage that is maintained through time.

1976 *The Selfish Gene* by British evolutionary biologist Richard Dawkins popularizes gene-centered evolution: natural selection at a genetic level.

Charles Darwin's theory of evolution by natural selection, as advanced in *On the Origin of Species*, is a powerful explanation of how life gradually changes across many generations. But it throws only limited light on the process of speciation—how new species emerge from old ones.

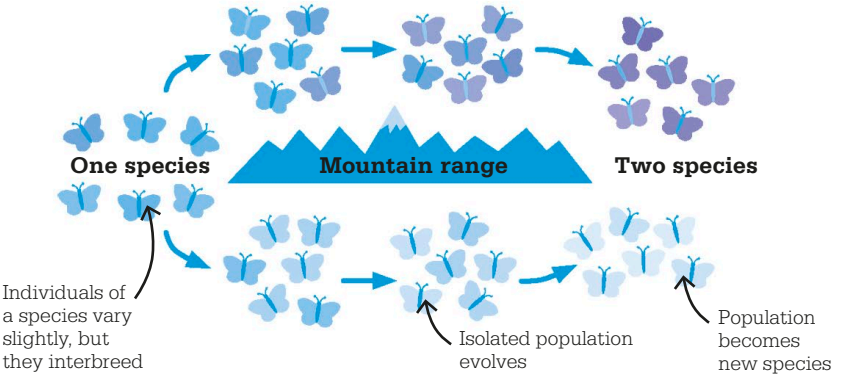
Small variations within species offer a clue to what might happen. In 1833, German zoologist Constantin Gloger noticed that bird species with large latitudinal ranges generally had darker feathers in the warm, humid tropics than in cooler, drier, temperate regions. This idea, which became known as Gloger's rule, raised the possibility that these geographical variants could be new species in the making. Both Darwin and British biogeographer Alfred Russel Wallace believed that geographical separation might be the key to producing new species but doubted whether this was always the case.

Darwin certainly thought that geographic isolation could be the reason for evolution on islands, and modern DNA analysis backs this up. For example, Galápagos finches have their closest kinship with

Arctic and timber wolves are two races of one species, the gray wolf. Despite physical differences, they are able to interbreed, although they may become separate species in the future.

See also: Asexual reproduction 178–79 ▪ The laws of inheritance 208–15 ▪ Chromosomes 216–19 ▪ Naming and classifying life 250–53 ▪ Natural selection 258–63 ▪ Mutation 264–65 ▪ Modern synthesis 266–71 ▪ Selfish genes 277

When the population of a species is divided by a physical barrier, the two newly separated populations evolve in different ways—such as by selection or drift—and so may end up becoming different species.



birds on mainland South America and in the Caribbean. At least 2 million years ago, members of an ancestral species flew out to sea, colonized the Galápagos Islands, and gradually evolved into the birds ornithologists described as Galápagos finches. DNA analysis has shown that animal populations divided by growing mountain ranges or other physical barriers also diverge into separate species over time.

Reproductive isolation

Geographic isolation alone is not enough to explain the emergence of new species. In 1942, German-born American biologist Ernst Mayr put forward the new idea of the biological species concept. This recognized that members of a species almost always breed only with their own kind, and only very rarely do they hybridize with others. He then explained that speciation must involve the evolution of new characteristics that prevent some individuals within a species from interbreeding with others. For example, a bird could evolve a slightly different courtship display that is not recognized by some members of its species as a reproductive isolation mechanism.

Mayr believed that this is most likely to happen when a population becomes divided along geographical lines. Once they are isolated on either side of the divide, the two new populations begin to evolve in separate ways. Eventually, they may become so different that, even if individuals from either side were to meet again, they would not breed with each other; they would have become two separate species.

Evolution in plants

Although the gradual effects of geographical separation are widely considered to play the dominant role in the emergence of new species in many well-studied groups, this is not the only reason for evolution. In the 1930s, American botanist George Ledyard Stebbins Jr. described how new plant species can emerge quickly through sudden mutations, and he developed the idea in his book *Variation and Evolution in Plants*, published in 1950.

Many plants experience spontaneous multiplications of their chromosome number, a process called polyploidy. In animals, this usually proves fatal, but some plants thrive on it. Polyploidy prevents them from interbreeding with their parental kinds within just one generation. It is so common among plants that at least a third of flowering plant species have probably evolved in this way. ■

Species concepts

For centuries, naturalists considered life forms to be of the same species if they shared certain physical characteristics (morphology). By the 17th century, biologists realized that this morphological concept has many limitations: the sexes may be different sizes and colors, and many animals change body shape as they metamorphose. In the 19th century, Gloger, Darwin, and others drew attention to natural variation in populations of animals that interbreed—and how it is key for evolution. Mayr's biological species concept—in which different species are reproductively isolated—went some way toward addressing this. However, even Mayr's concept does not work in all circumstances, such as for organisms that only reproduce asexually. Most biologists now use the phylogenetic species concept, which defines a species as a group of organisms that have a common ancestor with which they share certain traits.

ALL TRUE CLASSIFICATION IS GENEALOGICAL

CLADISTICS

IN CONTEXT

KEY FIGURE
Willi Hennig (1913–76)

BEFORE
1753, 1758 Carl Linnaeus's *Species of Plants* and *System of Nature* are the starting point for the hierarchical classifying and naming of species.

1859 Charles Darwin's *On the Origin of Species* provides evidence for evolutionary relationships between species.

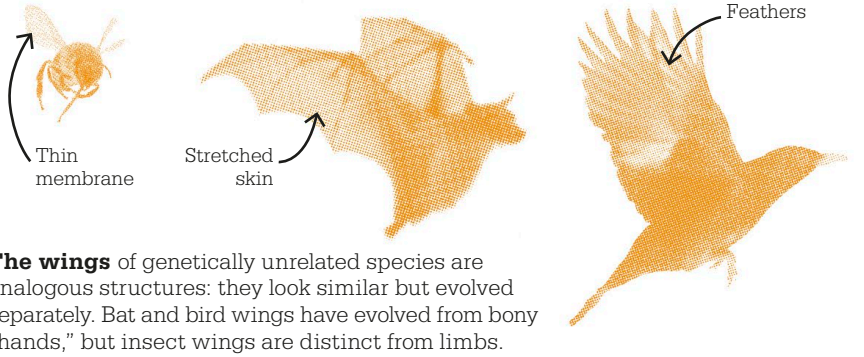
1939 Alfred Sturtevant's classification of fruit fly species according to multiple correlated characteristics is a forerunner of numerical taxonomy, which becomes popular in the 1950s and 1960s.

AFTER
1968 The neutral theory of molecular evolution, pioneered by Motoo Kimura, supports the idea that it could be possible to identify when species diverged in the evolutionary history of a group.

In his *On the Origin of Species*, Charles Darwin argued that species should be classified by evolutionary relationships. He thought that the best way to discover such relatedness was by comparing observable traits of different species, but he conceded that some characteristics were more important than others—and that some could be misleading. A bony spine unequivocally identifies vertebrates as descended from a common ancestor, but the same cannot be said of wings, which have evolved independently in different groups of species—for example, in birds, bats, and insects.

Biologists were aware that the choice of characteristics used in taxonomy (species classification), as well as their weighting, was subjective. Then, in 1939, American geneticist Alfred Sturtevant used a strictly numerical system to classify species of fruit flies. He analyzed 27 characteristics across 42 species to find which traits correlated with others, indicating likely genetic relationships. The 42 species divided clearly into three broad groups.

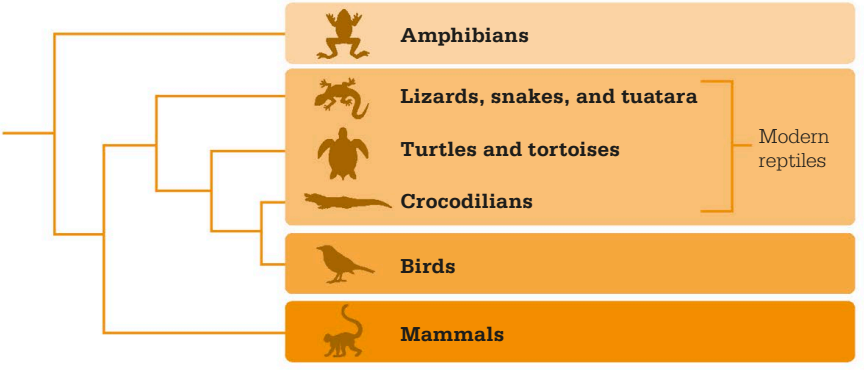
Supported by later studies, this quantitative approach to classification by overall similarity—known as phenetics—gained ground. With the invention of computers, biologists in the 1950s could tackle the enormous amount of data involved in bigger taxonomic groups. The technique culminated in 1963, when



The wings of genetically unrelated species are analogous structures: they look similar but evolved separately. Bat and bird wings have evolved from bony "hands," but insect wings are distinct from limbs.

See also: Naming and classifying life 250–253 ▪ Life evolves 256–57 ▪ Natural selection 258–63 ▪ Speciation 272–73 ▪ Mass extinctions 278–79

In this cladogram of living land vertebrates, birds are classified as a subgroup of reptiles, because birds are descended from reptilian dinosaurs and their closest living relatives are the crocodiles. However, the traditional class of modern reptiles does not include birds.



biologists Robert Sokal and Peter Sneath published their *Principles of Numerical Taxonomy*.

Classification by descent

While the statistical techniques of numerical taxonomy proved useful, the phenetic method does not explicitly consider evidence of evolutionary descent. However, a rival school of classification did just that. In 1950, German zoologist Willi Hennig published his work on what he called phylogenetic systematics. It began by assuming that evolution happens by dichotomous splitting, where one species branches into two. These branching points, which represent a hypothetical common ancestor, were inferred from the observation of heritable traits. According to Hennig, all species descended from a common ancestor—including that ancestor—should be classified together in a group, or "clade." The evolutionary history is shown diagrammatically in what is known as a phylogenetic tree, or cladogram.

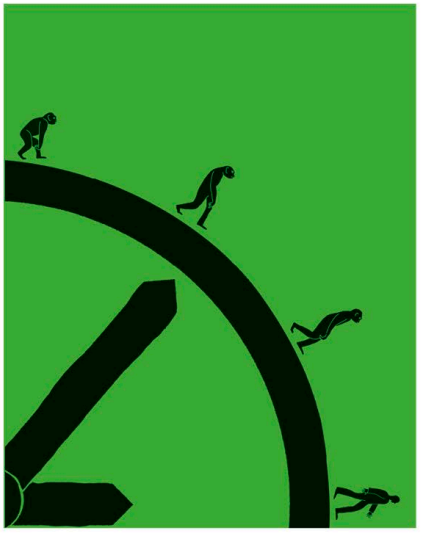
Hennig's method, cladistics, is the prevailing system used today, informed by the more sophisticated methods of data analysis that are now possible. For example, multiple DNA sequences are considered a more reliable indicator of descent than morphology (the form and structure of organisms) alone.

However, for all its purported objectivity, there are issues with the cladistic method. Species do not always split dichotomously, and some lineages evolve faster than others. For example, the branching point of origin for all birds occurs within the reptilian evolutionary tree, which, according to cladistic reasoning, makes birds a subgroup of reptiles. But some argue that the distinctive features that birds evolved within a comparatively short period of time—such as feathers and a toothless beak—justify classifying them as a group distinct from reptiles. Therefore, despite a shift in recent years toward cladistic groups, other, more traditional classification groups remain popular. ■

Cladistic terminology

When Willi Hennig described his system for classifying organisms, he invented a lot of new terminology. As cladistics gained wider acceptance, some of his terms were adopted by biologists and are now part of the taxonomist's lexicon. Two key terms are "apomorphy" and "plesiomorphy." The former is an evolutionary innovation—a characteristic (or trait) that is not found in ancestors, which is useful in defining groups. The latter is a characteristic retained from ancestors that therefore tells us little about relationships within a group. Taxonomists further define traits by looking at "out-groups"—that is, more distantly related species. Fingernails, for instance, are an apomorphy for primates, unique to species in that group. But hairy skin is a plesiomorphy for primates, because it is also found in mammalian out-groups, such as rodents or dogs.

> Cladistics was motivated by the [need] to eliminate subjectivity and arbitrariness from classifying.
>
> **Ernst Mayr**
> **American biologist, 1904–2005**



THE CLOCK-LIKE PROPERTY OF EVOLUTION

THE MOLECULAR CLOCK

IN CONTEXT

KEY FIGURES
Emile Zuckerkandl (1922–2013),
Linus Pauling (1901–94)

BEFORE
1905 New Zealand-born physicist Ernest Rutherford invents a technique to date rocks by analyzing their chemical isotopes; this is later adapted for dating fossils.

1950 Willi Hennig describes a method of classification by evolutionary trees (cladistics).

AFTER
1968 Japanese biologist Motoo Kimura introduces the neutral theory of molecular evolution, stating that much genetic variation arises by mutation at a constant rate.

2000 Biologists introduce the terms chronogram and timetree to describe evolutionary trees that have been calibrated to show the dates of branching points.

As life evolves, its DNA accumulates changes when it gets miscopied. These miscopies, or mutations, alter the sequence of the DNA's building blocks. In 1962, Austrian biologist Emil Zuckerkandl and American chemist Linus Pauling found—not unexpectedly—similar sequences in related species. In 1965, by fitting dated fossils into an evolutionary tree of the species studied, they could estimate just how fast sequences had changed. Later, Zuckerkandl and Pauling suggested that this kind of data could be used to show the rate of mutation in a given time period, and this could then be used as a "molecular clock" to work out when two species diverged.

> … one of the simplest and most powerful concepts in evolution.
> **Roger Lewin**
> ***Patterns in Evolution*, 1997**

Constancy of the clock

Estimating the length of time since divergence depends on the rate of change remaining constant, but biologists know that natural selection can make the rate increase. So the "clock" must be based on genes that change more randomly, rather than by selection.

In 1967, American biochemist Emanuel Margoliash found such a gene: it produces the protein cytochrome c, which is required for critical energy-releasing reactions in practically every life form, from bacteria to plants and animals. He produced evolutionary trees based on the mutation distances between the cytochrome c genes of different species. A refined version of this technique is still used and is crucial to understanding the timing of the branching of organisms' evolutionary trees. ■

See also: What are genes? 222–25 ▪ The genetic code 232–33 ▪ Sequencing DNA 240–41 ▪ Extinct species 254–55 ▪ Natural selection 258–63 ▪ Mutation 264–65

WE ARE SURVIVAL MACHINES

SELFISH GENES

IN CONTEXT

KEY FIGURE
Richard Dawkins (1941–)

BEFORE
1859 Charles Darwin unveils a theory of evolution by natural selection in which organisms behave in ways that benefit their species.

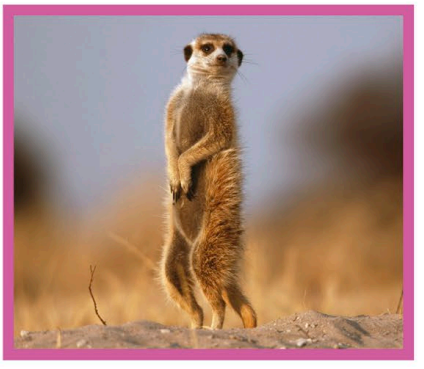
1930 British geneticist Ronald Fisher proposes a mechanism to explain kin selection, in which animals sacrifice their own chances of survival to aid the survival of their relatives.

AFTER
1980s The field of memetics, based on Richard Dawkins's description of memes, attempts to explain how cultural phenomena spread by natural selection.

1990s The new discipline of epigenetics is born. This studies those biochemical structures acquired in life that control gene expression, which may be inherited.

The concept of the "selfish gene" is a gene-centric view of evolution. It makes the gene—rather than the individual or species—the unit of selection in evolution. Darwin said that natural selection acted on individual organisms. Those well adapted to their environment survive, reproduce, and increase the prevalence of their useful traits in future populations. Less well-adapted individuals are less likely to survive and breed, so deleterious traits become less common.

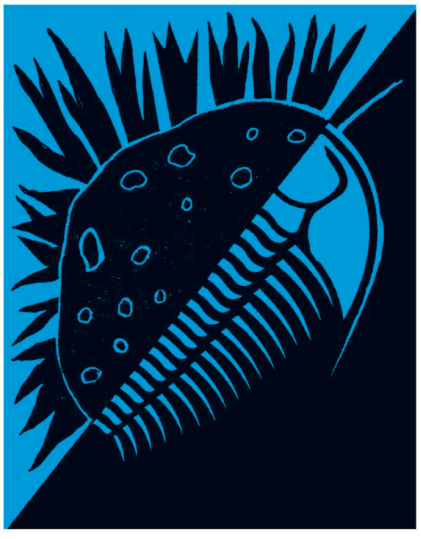
The gene-centered hypothesis challenges Darwin's original explanation of animal behaviors as evolving to benefit a group or a whole species. For example, when a sentinel meerkat sounds the alarm at the approach of a predator, it benefits its colony but runs less risk of being killed itself, since sentinels remain close to a burrow. If sentinels died as a result, natural selection would favor meerkats that do not raise the alarm. The gene-centered view is that behaviors such as that of sentinel meerkats evolve because members of the group share a high proportion of the same genes. The adaptations that are created by natural selection maximize the prevalence of genes, not of individuals nor of a species (although those are direct results).



Meerkats live in groups of up to 30 individuals. One or more members of each group remains alert, ready to sound an alarm if it sees a threat.

Richard Dawkins popularized this idea in his 1976 book *The Selfish Gene*—selfish, Dawkins posits, because biological activity of all kinds emerges from DNA's chemical imperative to replicate. ■

See also: The laws of inheritance 208–15 ▪ What are genes? 222–25 ▪ Natural selection 258–63 ▪ Mutation 264–65 ▪ Predator–prey relationships 292–93



THE EXTINCTION COINCIDES WITH THE IMPACT

MASS EXTINCTIONS

IN CONTEXT

KEY FIGURES
Luis Alvarez (1911–88),
Walter Alvarez (1940–)

BEFORE
1694 English astronomer Edmund Halley proposes that a comet's impact caused the Biblical flood but is pressured by the clergy to retract his idea.

1953 American geologists Allan O. Kelly and Frank Dachille suggest in a privately published book that the dinosaurs were wiped out by an asteroid impact.

AFTER
1990 Canadian geologist Alan Hildebrand finds that samples from the Chicxulub crater show "shock metamorphism," including glass crystals called tektites and "shocked" quartz.

2020 British planetary scientist Gareth Collins shows that the killer asteroid struck at a lethally steep angle, maximizing the possible size of the debris cloud.

During the history of life on Earth, there have been several major mass-extinction events, clearly evidenced by the fossil record. Each has been studied intensely, but the one that captures the imagination of scientists and non-scientists alike occurred about 66 million years ago, at the end of the Cretaceous period. In this event, three quarters of the species on Earth—including the dinosaurs, with the exception of those that evolved into birds—disappeared in the blink of a geological eye. The possible cause of the species destruction was debated without resolution for many years, due to an absence of physical evidence, until the publication of a paper in 1980 that presented new geological findings. American physicist Luis Alvarez and his son, geologist Walter Alvarez, argued

The asteroid that hit Earth 66 million years ago was about 6 miles (10 km) in diameter. The number of Earth-crossing asteroids of that size indicates an impact probability of once in 100 million years.

See also: Photosynthesis 50–55 ▪ Extinct species 254–55 ▪ Speciation 272–73 ▪ Food chains 284–85

Luis Alvarez won the Nobel Prize in Physics in 1968 for his work on subatomic particles. In 1979, he used a nuclear chemistry method to measure iridium levels in sedimentary clay.

that this mass-extinction event was the result of our planet being hit by an asteroid—a large, rocky object that orbits the Sun.

Iridium dust

The Alvarez hypothesis was based on the discovery in Gubbio, central Italy, of extremely high levels of the metal iridium in a clay layer of sedimentary rock corresponding to the time of the dinosaur extinction. The iridium was 30 times more concentrated than was usual, and further research found the same phenomenon in other parts of the world; in Denmark, iridium in the clay layer was 160 times the background level. Since platinum-group elements, such as iridium, are rare in Earth's crust, it was deduced that the clay resulted from dust from an extraterrestrial object.

One possibility was that it came from a supernova—the explosion of a star. However, the composition of the clay was found to be too similar to material from our own solar system, and a supernova would occur far beyond that. The most probable cause, therefore, was a large asteroid impact. Such a collision would generate a vast cloud of pulverized rock, 60 times the mass of the asteroid, which would prevent sunlight from reaching the planet's surface for several years. This would suppress photosynthesis, leading to a catastrophic collapse of food chains and a mass extinction.

The size of the asteroid was calculated from the iridium data to be about 6 miles (10 km) across. However, the impact crater had not yet been found. Then, in 1990, new evidence emerged of an immense crater near the town of Chicxulub in Mexico, which confirmed that it was of impact origin. It was just the right size and age to be the culprit.

Volcanic eruptions

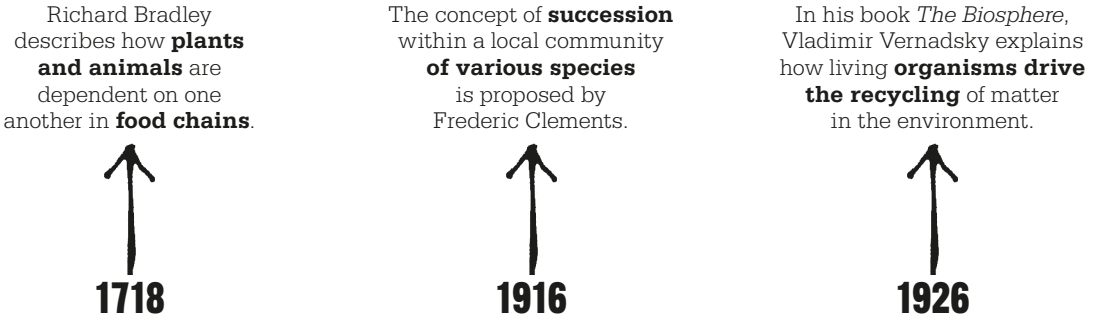
The asteroid hypothesis was met with scepticism by those who believed that the decline of the dinosaurs, as well as the change in land flora at the time, was too gradual to have been caused by a sudden event. An enduring rival theory is that the cause was the massive volcanic eruptions that occurred at the end of the Cretaceous period. These created one of the largest volcanic features in the world—the Deccan Traps in west-central India—and could have transformed living conditions on Earth. Volcanoes that were blasting sulfurous gases into the atmosphere could have turned the oceans acidic, and ejecting carbon dioxide could have caused a hike in global temperatures. Another theory is that the asteroid impact intensified the volcanic activity.

> … we dream of finding new secrets of nature as important and as exciting as those uncovered by our scientific heroes.
>
> **Luis Alvarez**
> **Nobel lecture, 1968**

The Chicxulub crater, created by the asteroid impact, extends into the Gulf of Mexico from the Yucatán Peninsula. Its edge is marked by a ring of sinkholes, or "cenotes" in the Mayan language.

However, climate and ecological modeling work supports the asteroid hypothesis. It shows the resulting long-winter scenario would have made Earth uninhabitable for dinosaurs, but climate-warming effects from the volcanism would have mitigated the cooling and may have supported ecological recovery. Without the volcanism, an even greater number of species would have become extinct. ■

ECOLOGY



While the greater part of biology is concerned with the study of living organisms themselves—their anatomy and physiology, and the process of life itself—an important area of study is ecology, which examines the complex relationships between living organisms and their external environment. Ecology emerged as a distinct subject during the Enlightenment period of the 17th and 18th centuries, at the peak of the scientific revolution when scientists and natural philosophers sought rational explanations of natural phenomena.

The idea of studying living things in their natural habitat was not a new one: naturalists had observed and commented on plants and animals and the world in which they lived since Aristotle in the 4th century BCE. But in the 18th century, the methodical scientific approach to such observation started to provide information about the interactions of organisms and their surroundings.

Among the first of the scientists to study this aspect of biology was Richard Bradley, who noted the interdependence of different organisms in what he described as food chains. The idea of studying living things not as individuals, but as participants in a community of organisms occupying a particular environment, was not immediately taken up by biologists, and its importance was not fully recognized until the 20th century.

The voyages of explorers such as Alexander von Humboldt, Alfred Russel Wallace, and Charles Darwin during the 19th century revived interest in the approach. These expeditions revealed a huge variety of life, and showed how different species have evolved to fit the geographical conditions—and particularly the climatic conditions—in which they live.

A new discipline

In establishing the link between species and their environment, the modern discipline of ecology was founded. By studying all the organisms in a particular place—in what he called a community—Frederick Clements showed how these organisms react to conditions and change over time. He also found that the composition of the community varies according to the physical nature of its surroundings. Alfred Lotka and Vito Volterra also examined the behavior of animals

Arthur Tansley introduces the concept of **ecosystems** and the **interaction** within them between living **organisms and their non-living** environment.

1935

The **niche** of a species—the **role it plays** in its environment—is defined by G. Evelyn Hutchinson in terms of **multiple factors** involving survival and reproduction.

1957

The theory of **island biogeography** by Robert MacArthur and Edward Wilson presents a **model of the balance** between the extinction rate and arrival rate of species in island **ecosystems**.

1967

1941

Raymond Lindeman describes how energy from **sunlight flows** through the various levels—**"trophic" levels** – of food chains.

1962

Rachel Carson's book *Silent Spring* warns of the **harmful impact of human activity** on ecosystems.

1974

James Lovelock's **Gaia hypothesis** proposes that planet Earth's ecosystem behaves as a self-regulating **superorganism**.

in a community, observing the relationship between predators and their prey, and how this symbiotic relationship caused their populations to fluctuate. Georgy Gause showed how the weaker of two competing species is forced to adapt, or die out. A balance is established in a community, G. Evelyn Hutchinson later argued, when each species occupies a particular niche, so that different species cohabit rather than compete in their environment.

Ecosystems

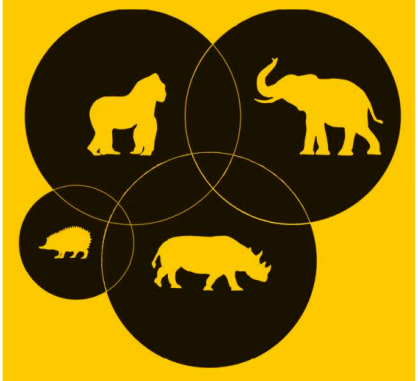
New concepts about the environment gradually emerged from this notion of communities of organisms. Vladimir Vernadsky referred to "the biosphere" in his writings to describe the total environment in which all living things exist on Earth, and in which organisms interact with the non-living world to continually recycle matter. A similar idea of the interaction between organisms and their non-living environment was described by Arthur Tansley, but on a much smaller scale. Rather than operating at a global level, he regarded these interactions as being divided into distinct areas, known as ecosystems.

With the idea of the ecosystem established, attention now turned to how these systems function as self-contained units, as well as the behaviour of the organisms within them. Joining the dots in 1941, Raymond Lindeman revisited the notion of food chains, explaining how energy from sunlight flows in these chains through all the organisms in an ecosystem.

Environmentalism

Perhaps the most comprehensive theory of an ecosystem was James Lovelock's Gaia hypothesis of the 1970s. This suggests that the whole Earth—not just the biosphere—is a self-contained ecosystem in which living organisms and the environment constantly interact, and that, when taken together, behave in some ways like an individual superorganism.

Lovelock's ideas were a major influence on the growing environmental movement that had begun in the 1960s. One of the pioneers was Rachel Carson, whose 1962 book *Silent Spring* describes the harmful impact human activity has had on the delicate balance of Earth's ecosystems. In this age of global climate change, her work continues to inspire. ■



ALL BODIES HAVE SOME DEPENDANCE UPON ONE ANOTHER

FOOD CHAINS

IN CONTEXT

KEY FIGURE
Richard Bradley (1688–1732)

BEFORE
9th century Arab scholar al-Jahiz describes food chains in his *Book of Animals*.

1717 Antonie van Leeuwenhoek notes that shrimps eat "animalcules," haddock eat shrimps, and cod consume haddock.

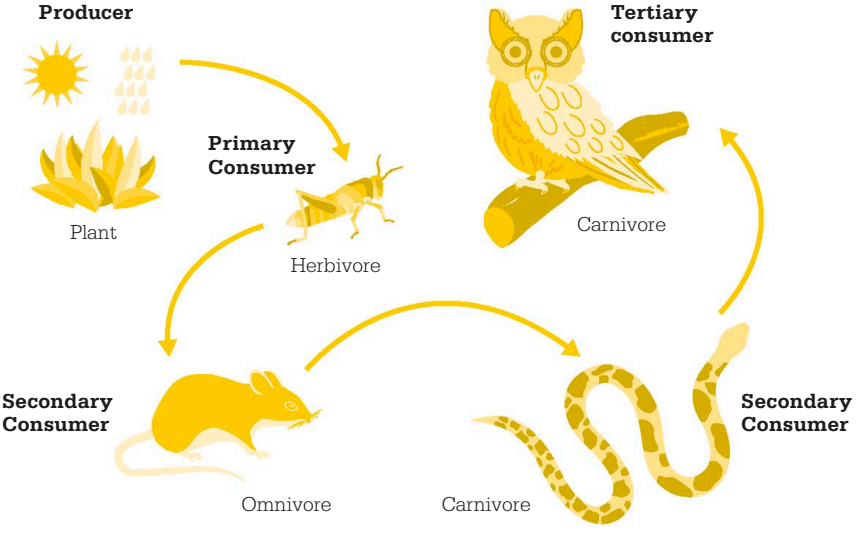
AFTER
1749 Swedish botanist Carl Linnaeus outlines two food chains in his concept the "economy of nature."

1927 English zoologist Charles Elton writes about food chains and food cycles in his book *Animal Ecology*.

2008 German paleobiologist Jürgen Kriwet shows how the stomach contents of an extinct shark revealed an ancient food chain: the shark ate amphibians that ate fish.

How does life interact with life in order to obtain food? The earliest ideas about food chains, which documented the feeding hierarchy of different animals in a habitat, appeared during the 9th century. However, the concept was first theorized in more detail by British botanist Richard Bradley during the Age of Enlightenment in the late 17th century. Bradley did not have a formal scientific education, but he had a fondness for plants and wrote extensively on horticulture. He noticed that insects or their larvae feed on garden plants, that each plant species has its own range of

The feeding hierarchy of different organisms in a habitat is shown in food chains. Organisms are grouped into categories including producers, consumers, and decomposers, which feed at all levels of the chain. Nearly all producers, also known as autotrophs, make their own food using photosynthesis.



See also: Photosynthesis 50–55 ▪ Community succession 290–91 ▪ Predator–prey relationships 292–93 ▪ Competitive exclusion principle 298 ▪ Ecosystems 299 ▪ Trophic levels 300–01 ▪ Niches 302–03

pests, and that these grazers in turn fall prey to predators, such as spiders and birds. In his 1719–20 book *New Improvements of Planting and Gardening*, he proposed that all animals rely on each other for food, in a continuous chain.

Producers and consumers

In modern food chains, plants are known as the producers and they are at the base of the food chain. They contain chlorophyll and use energy from the Sun to convert carbon dioxide and water into sugars, a process known as photosynthesis, with oxygen as a byproduct. These photosynthetic organisms, which include algae and bacteria as well as green plants, manufacture their own food, and without them very little else would exist. They are grazed, browsed, or otherwise consumed by herbivorous primary consumers, such as cattle, rabbits, and caterpillars. These primary consumers are the prey of the carnivores or meat-eaters—the secondary consumers—including foxes, owls, and snakes. Higher up the food chain, increasingly larger predators catch and consume the smaller ones, with animals without predators (but maybe with parasites) occupying the top level—the apex predators. At each stage, energy is transferred from one link to the next. The chain perpetuates itself when its plants and animals die. The decomposers break down the bodies and any waste, such as droppings, and recycle raw materials, making them available to the producers in the next generation of the chain.

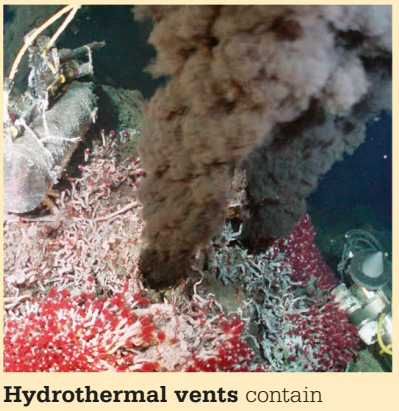
Food webs and symbiosis

In 1768, Dutch cleric and naturalist John Bruckner recognized that food chains do not exist in isolation, and that organisms in different food chains interact to form a "food web," later described by Charles Darwin as a "web of complex relationships."

Within a food chain or web, the number of individuals of a particular species in a geographic area is called its "population," and when two or more populations are tied to a particular area by, say, vegetation, they become part of a community.

> Mosquitoes remind us that we are not as high up on the food chain as we think.
>
> **Tom Wilson**
>
> **Canadian author and comedian**

Within the community, species in each food chain might interact in several ways. Some eat each other—predation—while others interact in other ways. This can be mutually beneficial to both parties—mutualism—or one organism might benefit from the relationship at the expense of the other, the host, and maybe even kill it, called parasitism. If one species obtains benefits from another without harming or helping it, it is known as commensalism. ■



Hydrothermal vents contain unique ecosystems. Organisms can survive lack of sunlight, extreme pressures, and hot mineral-rich water.

Food chain in the deep sea

In 1976, deep in the Pacific Ocean, an extraordinary food chain was discovered—one that gets its energy not from the Sun, but from inside Earth. Deep-sea hydrothermal vents are openings on the ocean floor, like geysers, where seawater is heated by magma. Some spew out water heated to more than 752°F (400°C). The two types of vents—black smokers and white smokers—are characterized by their mineral content. Black smokers contain sulfides, which are converted to energy by bacteria in a process called chemosynthesis. These organisms are at the base of an unusual deep-sea food chain that includes giant tubeworms, clams, and blind shrimps, all depending on the bacteria for food. One especially strange creature—the Pompeii worm—has its front end in water at a comfortable 72°F (22°C) and its rear end, protected by a fleece of symbiotic bacteria, in vent water at 176°F (80°C).

ANIMALS OF ONE CONTINENT ARE NOT FOUND IN ANOTHER

PLANT AND ANIMAL BIOGEOGRAPHY

IN CONTEXT

KEY FIGURES
Alexander von Humboldt (1769–1859), **Alfred Russel Wallace** (1823–1913)

BEFORE
4th century BCE Aristotle describes different plants and animals living in some places, but not in others.

1749–88 Comte de Buffon publishes his 36-volume *Histoire Naturelle* (*Natural History*), which includes his theory on variation of species.

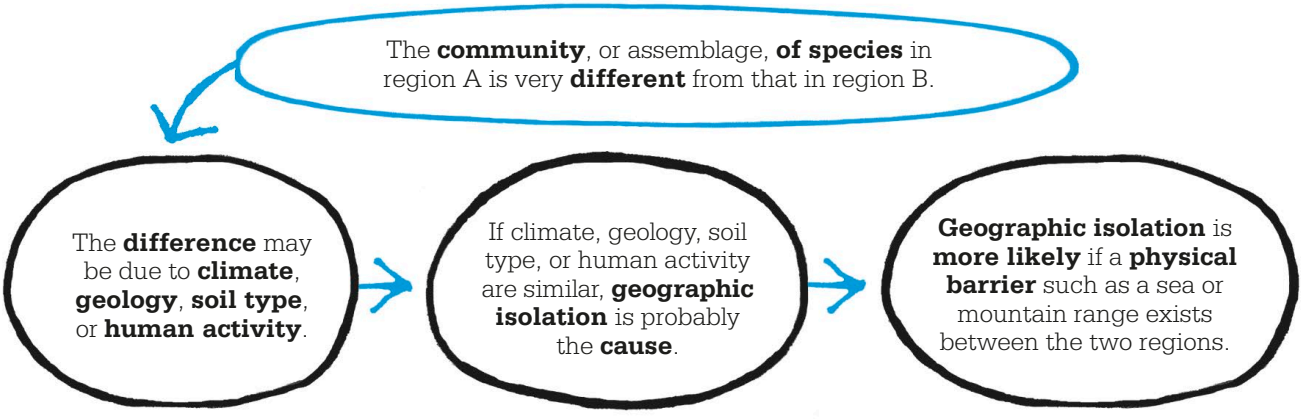
AFTER
1967 American ecologists Robert MacArthur and Edward O. Wilson develop their mathematical model of island biogeography.

1975 Hungarian biogeographer Miklos Udvardy proposes dividing biogeographic realms into smaller biogeographic provinces.

People had always known that not all life forms live in the same places but, before the 18th century, few had tried to explain why. In the 1780s, Swedish botanist and taxonomist Carl Linnaeus, heavily influenced by the Christian Bible, suggested that all life originated on a "paradisiacal island," where each species was adapted to a particular habitat. After a great flood receded, this diversity of plants and animals had spread to every corner of Earth.

French polymath the Comte de Buffon adopted scientific methods, studying distributions of fossils and animals. Buffon described how environmentally similar, but

See also: Naming and classifying life 250–53 ▪ Natural selection 258–63 ▪ Speciation 272–73 ▪ Competitive exclusion principle 298 ▪ Ecosystems 299 ▪ Human impact on ecosystems 304–11 ▪ Island biogeography 312–13



isolated, regions have comparable, but distinct, groups of mammals and birds (called Buffon's Law).

Buffon suggested environmental adaptation caused biogeographical variation over time. For example, he speculated that all elephants were descendants of furry Siberian mammoths that had migrated from northern Asia and adapted to new environmental conditions. So elephants in Indian forests lost their fur in adaptation to warm forests; African elephants evolved big ears to dissipate heat on hot savannas.

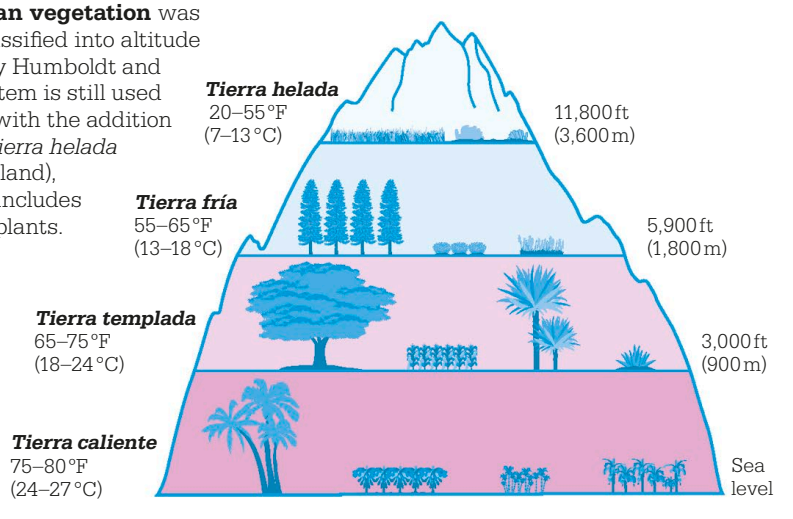
Humboldt's expedition

Prussian geographer and naturalist Alexander von Humboldt laid the foundations of biogeography (the study of geographic distributions of animals and plants) in 1799—1804 during an expedition to South America, Mexico, and the Caribbean. Together with French botanist Aimé Bonpland, Humboldt showed the interrelationship of geography, climate, living organisms, and human activity by analyzing a huge amount of data. They collected 5,800 plant species (3,600 of them previously unknown to Western science) and took countless measurements of location, altitude, temperature, humidity, and other geographical parameters to explain the factors that determine which plants grew where.

In 1807, Humboldt published his famed *Tableau Physique*, a cross-section diagram of the vegetation and climatic zones of the equatorial Andes Mountains, based on the expedition data he had collected from Mount Chimborazo and Mount Antisana in present-day Ecuador. In 1811, he also described and named three Mexican vegetation types: *tierra caliente* (hot land) with tropical evergreen or deciduous forest; *tierra templada* (temperate land) of temperate oak and pine-oak forest; and *tierra fría* (cold land) with pine and pine-fir forest. His definitions have been greatly refined, but reveal how Humboldt understood that the geographic distribution of plant communities varies according to factors such as elevation, soil, and climate.

Humboldt realized that similar zones, and plants, were found in different parts of the world. He »

Mexican vegetation was first classified into altitude belts by Humboldt and his system is still used today, with the addition of the *tierra helada* (frozen land), which includes alpine plants.



analyzed his data and wrote about his conclusions in his magnum opus, *Kosmos* (1845–62).

Since Humboldt, further study has examined factors such as latitude, isolation, aspect, evolution, and human activity that affect geographic distribution of plants (phytogeography). German botanist Adolf Engler highlighted geology as a factor. With German botanist Oscar Drude, Engler edited the multi-volume *Die Vegetation der Erde* (*The Vegetation of the Earth*) in 1896–1928; it was the first systematic, global phytogeography.

Zoogeography

After Humboldt's pioneering work on plant distributions, many contributed to the new field of zoogeography (the study of animal distributions). On his voyage on HMS *Beagle* in 1831–36, Charles Darwin studied the distribution of island species, research he would later use to develop his ideas on natural selection and evolution. He noted many animals were found in one place only and not in similar habitats elsewhere—for example, some Falkland Island birds and the Galapágos giant tortoises.

> I shall endeavor to find out how nature's forces act upon one another, and in what manner the geographic environment exerts its influence on animals and plants.
>
> **Alexander von Humboldt**
>
> **Letter to Karl Freiesleben (1799)**

In 1857, British ornithologist Philip Sclater presented a paper to the Linnean Society of London in which he divided the world into six biogeographical regions, based on their birdlife. He pointed out that there was more in common between bird species of distant corners of temperate Europe and Asia (which he called Palaearctica) than there was between this region and neighboring regions of sub-Saharan Africa or South Asia. This suggested that Palaearctica had a distinct fauna, which it did not share with the regions around it.

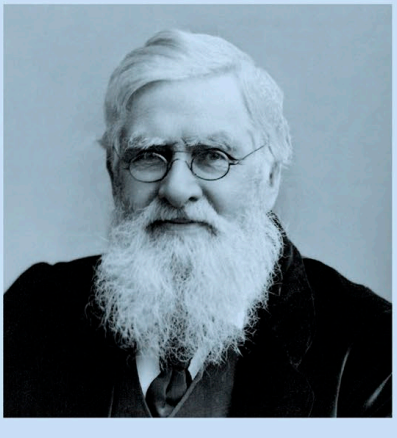
Wallace's contribution

The 19th century's leading authority on animal distributions was British biologist and geographer Alfred Russel Wallace. On his expeditions, he noted carefully each animal and plant species at every location he visited. On his second expedition, he collected over 125,000 animal specimens, describing more than 5,000 species new to science.

Wallace also observed animal feeding, breeding, and migratory behaviors. By the 1850s, he saw how biogeography could support his ideas on evolution, so sought out parallels and variances in life forms as he explored different areas.

In *The Malay Archipelago*, Wallace noted a sharp contrast between animals in the north-western and southeastern parts of the islands. Species on Sumatra and Java are more like those of mainland Asia, while those on Sulawesi and New Guinea are more similar to Australian animals. He found marsupials on Sulawesi, for example, but no further west than

Alfred Russel Wallace



Wallace was born in 1823 in Monmouthshire, UK. He left school aged 14 and performed a variety of jobs before embarking on two major expeditions: to the Amazon Basin in 1848–52, and to the Malay Archipelago (in present-day Indonesia and the Philippines) during 1854–62, where he studied and collected animals and plants.

During his Malay expedition, Wallace developed his theory of natural selection, independently of Charles Darwin, to explain evolution. He posted his paper in 1858 to Darwin, whose own paper on the subject was then presented, along with Wallace's, to the Linnean Society of London. As well as being an exceptional naturalist, Wallace was a keen environmentalist, social reformer, and advocate of women's rights and land reform. He died in 1913.

Key works

1869 *The Malay Archipelago*
1870 *Contributions to the Theory of Natural Selection*
1876 *The Geographical Distribution of Animals*
1880 *Island Life*

Wallace's six zoogeographic regions, with the modern additions of Oceania (the islands of the Pacific Ocean) and Antarctica, are today described as realms.

*Now called Afrotropical

that. Discoveries like these helped to shape Wallace's ideas about the origin of species: in particular, that new species arose where their ancestors' populations became separated by the emergence of mountain and ocean barriers.

In the first extensive publication on zoogeography, *The Geographical Distribution of Animals*, Wallace used his own explorations and the evidence of Sclater and others to draw the boundaries of the world's zoogeographic regions (see above).

Wallace's boundary (called the Wallace Line) between the Oriental and Australian regions winds from the Indian Ocean to the Philippine Sea—through the Lombok Strait between Lombok and Bali islands and the Makassar Strait between Borneo and Sulawesi islands. The line marks the sudden limit in distribution of many plants and animals that Wallace noted earlier.

Plate tectonics

In the early 20th century, German geophysicist Alfred Wegener noted the odd distributions of some plant and animal fossils. For instance, the Triassic reptile *Cynognathus* was found on the coasts of Brazil in South America and Angola, Central Africa, thousands of miles apart. A second example, described by Wallace, was the Early Permian seed fern *Glossopteris* in Uruguay, Namibia, Madagascar, southern India, Antarctica, and Australia.

Wegener believed that the continents were once joined in a super-continent, which he named Pangaea, and that they had broken apart and were slowly moving across Earth. His 1915 "continental drift" theory (now called plate tectonics) was not confirmed until the 1960s, but was a major advance in fossil biogeography (paleobiogeography).

Modern applications

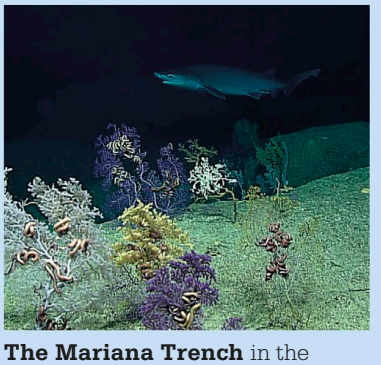
By indicating changes in species distribution, biogeography provides vital information about global climate change and other human activity on species. For example, botanists found that Humboldt's vegetation zones had moved 705–873 ft (215–266 m) higher up Mount Antisana's slopes by 2017, marking a major warming of the climate. Biogeography also reveals changes in animal migration or breeding dates. Such knowledge helps with species conservation measures. ■

Oceanic biogeography

The world's oceans present biogeographers with unique challenges. Scientists have struggled to overcome the technological challenges of exploring these vast spaces. At depths of 3,280 ft (1,000 m), there is no natural light and water pressure crushes all but the most sophisticated submersibles. Ocean water dynamism is also a problem: boundaries between warm and cool—and higher- and lower-salt—water shift from year to year and seasonally.

The most comprehensive zoning of all the oceans' biogeographic regions to date is UNESCO's 2009 Global Open Oceans and Deep Seabed (GOODS) biogeographical classification.

GOODS identifies 30 pelagic (open ocean), 38 benthic (seabed), and 10 hydrothermal-vent species communities, or assemblages. It aims to be a guide to safeguarding marine biodiversity, including designating marine protection areas and planning fisheries, but is a work in progress and will need to be refined.



The Mariana Trench in the Pacific Ocean, the deepest seabed on Earth, lies between two tectonic plates and has rarely been explored.

THE INTERACTION OF HABITAT, LIFE FORMS, AND SPECIES

COMMUNITY SUCCESSION

IN CONTEXT

KEY FIGURE
Frederic E. Clements
(1874–1945)

BEFORE
1863 Austrian botanist Anton Kerner publishes a study about the succession of plants in the river basin of the Danube.

AFTER
1916 US botanist William S. Cooper goes to Glacier Bay, Alaska, to study how plants colonize newly exposed ground following a glacier's retreat.

1926 Henry A. Gleason argues against the idea of climax communities, stating each species in a community responds individually to environmental conditions.

1939 British botanist Arthur Tansley proposes that rather than a single climax community, there are several "polyclimaxes," which are influenced by climate and other environmental factors.

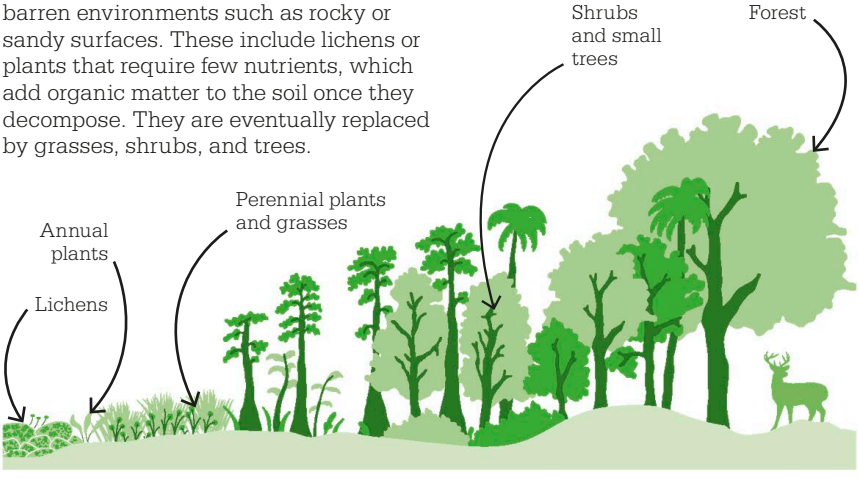
In ecology, a group of different species living in the same habitat is called a community. Succession refers to the process of change in a community over time, such as a bare volcanic island being colonized by life—as each species grows, it modifies the habitat to aid the growth of the subsequent species. In 1825, French naturalist Adolphe Dureau de la Malle was first to coin the term when he saw how a succession of plant species sprang up where a forest had been felled, and asked, "is succession a general law of nature?"

While succession tends to focus on plant communities and the way that they change their environment, the accompanying microorganisms, fungi, and animals also change during this process.

Primary succession

In 1899, American botanist Henry Chandler Cowles built on Dureau de la Malle's work with a study of sand dune communities on the shores of Lake Michigan, US. He proposed the notion of primary succession, which describes how plants arrive on land not previously

Pioneer species are the first to colonize barren environments such as rocky or sandy surfaces. These include lichens or plants that require few nutrients, which add organic matter to the soil once they decompose. They are eventually replaced by grasses, shrubs, and trees.



See also: Plant and animal biogeography 286–89 ▪ Recycling and natural cycles 294–97 ▪ Ecosystems 299 ▪ Human impact on ecosystems 304–11 ▪ Island biogeography 312–13 ▪ The Gaia hypothesis 314–15

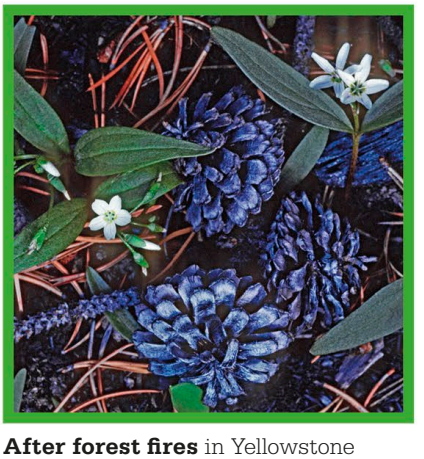
> The vegetation of an area is merely the resultant of two factors, the fluctuating and fortuitous immigration of plants and an equally fluctuating and variable environment.
>
> **Henry A. Gleason**
> **American ecologist (1882–1975)**

vegetated, and then change and develop in stages of increasing size and complexity, as a succession of new plant species outcompete older species, and soils change due to erosion and the actions of biota. If water accumulates to form a pond, for example, and it is undisturbed for many years, the habitat will gradually become a woodland through a series of stages—aquatic plants, bog plants, grasses, shrubs, and trees. The pond effectively transitions into soil that supports terrestrial vegetation.

The final stage of succession, first described by Clements, is the climax community. In 1916, he suggested that a climax community is composed of plants that are best adapted to the regional climate, such as an unlogged forest of ancient broadleaved trees in a temperate climate. It is tempting to consider climax vegetation as stable, but little in nature remains the same forever. Clements likened the plant community to a living organism, which grows, matures, and decays. He went on to describe the entire ecosystem as a "superorganism."

Secondary succession

When a community is disturbed or damaged, such as a forest cleared by fire or by felling, secondary succession kicks in, which by definition is the recolonizing of a community. When a forest tree falls, as Dureau de la Malle had noticed, the forest floor is suddenly bathed in light, so seeds that would normally be suppressed by the shade of the leafy canopy can germinate successfully, and the plants of the understory flourish, together with shrubs and sub-canopy trees; that is, until the trees take over once again. ■



After forest fires in Yellowstone National Park, US, secondary succession is seen. The lodgepole pine tree is adapted to fire, and its pine cone (above) opens and releases its seeds when its resin is melted.

The islands of Krakatoa

The three surviving islands of Krakatoa in Indonesia were effectively sterilized by the 1883 volcanic eruption, and their recolonization is an example of primary succession. Two months after the eruption, no life was visible, but soon after, blue-green algae grew in coastal areas, while there was still bare lava inland. After three years, the coast was covered with mosses, grasses, ferns, and tropical seashore plants, with a few grasses inland. After 13 years, coconut palms and horsetail trees appeared close to the shore, and grasses covered inland areas, with isolated horsetail trees. By the 23rd year, trees were growing in both locations, and after 47 years, dense forest was widespread.

It is thought it will take the three surviving islands more than 1,000 years to reach a similar diversity of climax vegetation to the nearby mainland. However, on the highly active volcanic island of Anak Krakatoa, frequent eruptions have partly destroyed the vegetation many times, so each recovery is an example of secondary succession.

A COMPETITION BETWEEN PREY AND A PREDATORY SPECIES

PREDATOR-PREY RELATIONSHIPS

IN CONTEXT

KEY FIGURE
Alfred J. Lotka (1880–1949), **Vito Volterra** (1860–1940)

BEFORE
1910 Alfred J. Lotka proposes one of the first mathematical models to help predict population fluctuations in predator–prey groups.

1920 Soviet mathematician Andrey Kolmogorov applies Lotka's original model to plant-herbivore interactions.

AFTER
1973 American biologist Leigh Van Valen proposes the Red Queen hypothesis to explain the constant "arms race" between predators and prey.

1989 Mathematical ecologists Roger Arditi and Lev R. Ginzburg introduce the Arditi-Ginzburg equations, which include the impact of the ratio between predator and prey.

A predator is a living organism that eats another living organism, and the prey is the organism that the predator eats. Their relationship, in which two species interact in the same environment, develops over time, as generations of each species impact each other. During the process, natural selection favors physical, physiological, and behavioral adaptations that make them more efficient predators or better-defended prey.

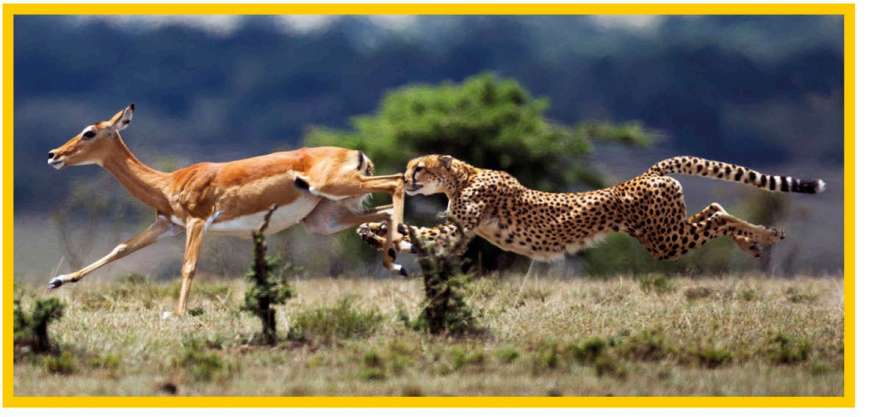
The two species are, in effect, in an "evolutionary arms race." This influences the success and therefore the survival of each species and the fitness of their populations. As prey numbers increase, there is more food for predators, so the population of predators increases too. The greater number of predators, however, means that the prey population then declines, and, after a short time, predator numbers drop as well. These fluctuations of predator and prey populations sometimes occur in recognizable cycles, which can be over months or even years.

> The Paradox of Sustenance: for an organism's life to be continued, another organism's life has to be discontinued.
>
> **Mokokoma Mokhonoana**
> **South African author**

Mathematics and ecology

Regular population fluctuations, known as oscillations, were first formalized in the 1920s by American mathematician Alfred J. Lotka and Italian mathematician Vito Volterra, who both came up with a pair of equations, almost simultaneously but independently, now known as the Lotka-Volterra equations. The equations were used to describe the changes in predator-prey populations in relation to each other and were first included by Lotka in his book *Elements of Physical Biology* in 1925. Volterra published his conclusions a year later. However, the Lotka-Volterra model assumed

See also: Extinct species 254–55 ▪ Natural selection 258–63 ▪ Food chains 284–85 ▪ Competitive exclusion principle 298 ▪ Community succession 290–91 ▪ Ecosystems 299 ▪ Niches 302–03



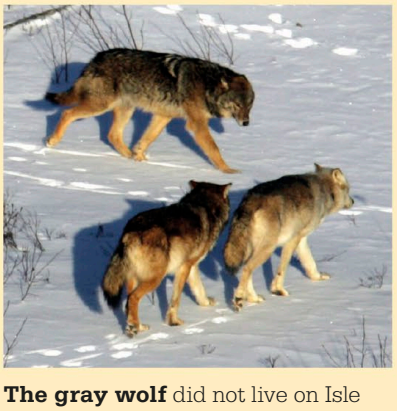
The cheetah and the gazelle are locked in an evolutionary arms race. Cheetahs have evolved to run extremely quickly to catch gazelles, which can swiftly change direction while running.

that the environment remained constant. It assumed the prey must find sufficient food all the time, predators must have an unlimited appetite and never stop hunting, and the environment has no impact on either species.

Testing the theory

Predator-prey cycles are based on a feeding relationship between two species. Because predators consume their prey, there is the danger that they kill off the resource that keeps them alive, but if predators are a little less efficient at catching their prey, then prey populations can recover, while predator numbers decline. The Lotka-Volterra equations suggested that although the predator-prey cycles are interrupted by random swings, they always return to their normal rhythm; and a new cycle begins. But how long these potentially endless cycles could last had not yet been clarified.

Led by German professor Bernd Blasius, a team of researchers at universities in Canada and Germany tested whether predator-prey cycles are sustained in a real community by observing tiny freshwater organisms called rotifers (the predator) feeding on algae (the prey). Previous research had been restricted to a few cycle periods, but in this experiment the team spent 10 years watching population oscillations over 50 cycles and approximately 300 generations of rotifers. In 2019, the team confirmed the concept of long-term, self-generated predator-prey cycles. However, despite the conditions being constant, the regular oscillations were interrupted by short, irregular periods where there were no discernable external influences. The research into how various external factors could be involved is ongoing, but the study proved the ability of predator-prey cycles to return to their original state after random distruptions. ■



The gray wolf did not live on Isle Royale prior to the late 1940s. It arrived by crossing the ice in winter or swimming at other times of the year.

Isle Royale wolves

Isle Royale, an island of the Great Lakes, US, is home to two species whose lives are inextricably linked: the gray wolf (predator) and the moose (prey). Since 1958, they have been watched closely; the longest continuous study of any predator-prey system in the world. The Lotka-Volterra model has been used to try to describe the population fluctuations of the two species, but the dynamic is too complicated. As well as wolf predation, other issues, such as harsh winters, poor food supplies, and an outbreak of moose ticks, have had an impact on the moose population. While this results in a decrease in the number of wolves, there are other factors. An aging wolf population, canine parvovirus, and a spine deformity caused by inbreeding, also resulted in their numbers' drastic decline.

In 2012, the gray wolf was on the brink of extinction, until a wolf crossed from Canada and refreshed the gene pool. In short, the rise and fall of wolf and moose populations on Isle Royale is unpredictable.

LIVING MATTER IS INCESSANTLY MOVING, DECOMPOSING, AND REFORMING

RECYCLING AND NATURAL CYCLES

IN CONTEXT

KEY FIGURE
Vladimir Vernadsky
(1863–1945)

BEFORE
1699 English naturalist John Woodward realizes that water contains "something" essential for plant growth.

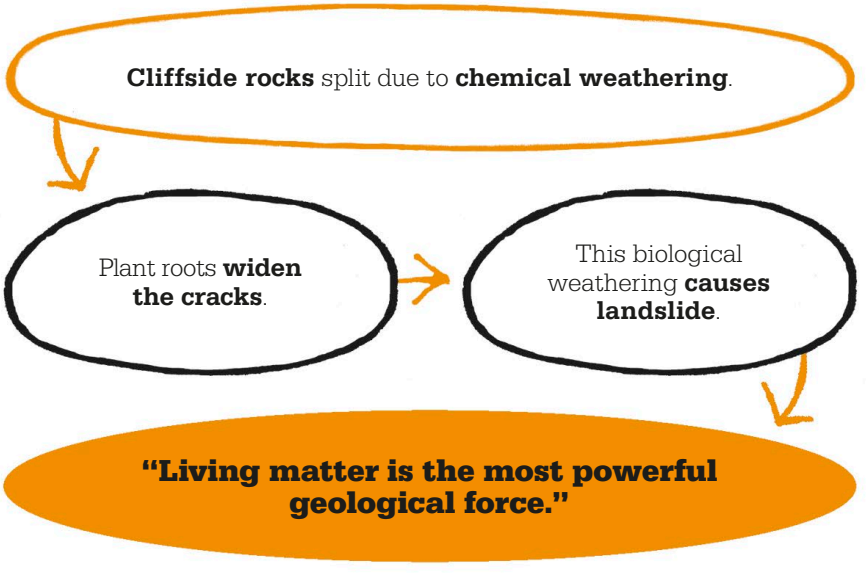
1875 Austrian geologist Eduard Suess introduces the term biosphere, to describe "the place on Earth's surface where life dwells."

AFTER
1928 Russian zoologist Vladimir Beklemishev warns that the future of the human race is linked to safeguarding the biosphere.

1974 British scientist James Lovelock and American biologist Lynn Margulis propose their Gaia hypothesis, the idea that Earth behaves like a living organism.

Earth contains two types of matter: living matter and non-living matter. Organisms, or living matter, do not exist in isolation from their environment. During their lifetime, they take in materials from their surroundings and release waste products, and at the end of their life they die and decay. Organisms are made up of the same types of atoms that exist in non-living matter and these components—such as atoms of carbon and nitrogen—are "recycled" between the living and non-living in chemical processes. The total amounts of each do not change, but are combined and recombined in a variety of ways.

See also: Respiration 68–69 ▪ Reactions of photosynthesis 70–71 ▪ Ecosystems 299 ▪ Human impact on ecosystems 304–11 ▪ The Gaia hypothesis 314–15



One of the first scientists to explore the nature of life in relation to Earth was Russian geochemist Vladimir Vernadsky, who coined the term biogeochemistry to describe the study of Earth's chemical cycles and how they are influenced by living things. His 1926 monograph *The Biosphere* attracted attention; its title refers to the area of Earth's surface where life exists, on land and in the oceans.

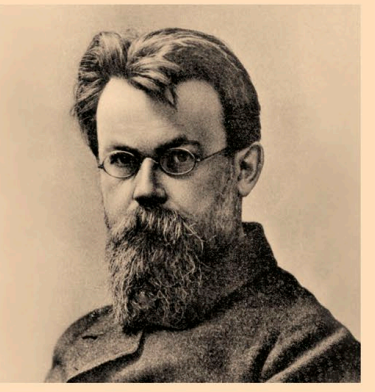
Earth is made up of four "spheres," or subsystems: the biosphere, the atmosphere (the surrounding gases), the hydrosphere (the water on Earth's surface, in its atmosphere, and underground), and the lithosphere (Earth's rocky outer shell). Vernadsky argued that the biosphere is shaped by living organisms, and key to this notion are several natural cycles.

The carbon cycle

Carbon is the fourth most abundant element in the Universe and the basic chemical backbone of life as we know it. On Earth, carbon is continually recycled, and the carbon cycle has two elements: fast and slow.

The slow carbon cycle involves the long-term storage of carbon in rocks, and one cycle can last 100–200 million years. Carbon moves from the atmosphere in the form of a weak carbonic acid, which falls as rain and chemically weathers rocks. Rivers carry the released carbonates to the ocean, where they are incorporated into the bodies of marine organisms, which drop to the seabed when they die. Over millions of years, the dead matter is compressed and forms carboniferous sedimentary rocks.

This process accounts for about 80 percent of the carbon in rocks; the other 20 percent occurs in the form of organic material in shale (fine-grained sedimentary rock) or as oil, coal, or gas created by heat and pressure. When these fossil fuels are extracted and burned, carbon returns to the atmosphere. »



Vladimir Vernadsky

Born in St Petersburg, Russia, in 1863, Vladimir Vernadsky studied at the city's university under Vasily Vasilyevich Dokuchaev, the founding father of soil science. He gained a masters degree in minerology, geology, and chemistry in 1887. He then spent three years in France, Italy, and Germany studying crystallography. From 1890 to 1911, Vernadsky lectured in crystallography and mineralogy at Moscow State University, becoming a professor in 1898.

After the Russian Revolution, Vernadsky investigated the potential of radioactivity as a source of energy, and studied the role of living organisms in shaping planet Earth. He founded and directed the Biogeochemical Laboratory of the Academy of Sciences in St Petersburg in 1928. Vernadsky died in Moscow in 1945, aged 81.

Key works

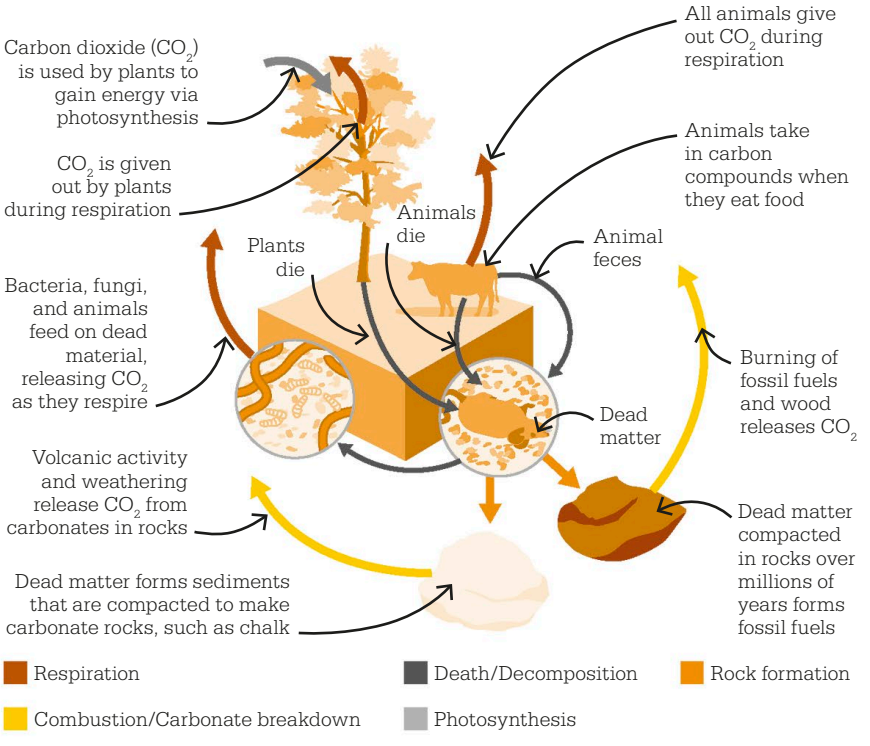
1924 *Geochemistry*
1926 *The Biosphere*
1943 "The Biosphere and the Noosphere"
1944 "Problems of Biochemistry"

The ocean both absorbs carbon dioxide and releases it into the atmosphere; it does so at a slightly faster rate than rocks.

The fast carbon cycle involves the movement of carbon through all of Earth's living organisms. It is measured not in millions of years, but in a lifespan. When living organisms respire, they absorb oxygen from the atmosphere and release energy, water, and carbon dioxide. Plants and phytoplankton (marine microorganisms) use carbon dioxide as a raw material for photosynthesis, the process of using energy from the Sun to create sugars for energy (plus oxygen as waste).

Animals eat phytoplankton, plants, and/or other animals, and die, providing food for some animals, fungi, and bacteria. Locked-in carbon is transferred to these decomposers, and then to the soil; some is lost via cellular respiration. Some stored carbon is burned in forest or bush fires, converting it to carbon dioxide and releasing it into the atmosphere.During fall and winter in the Northern Hemisphere, many plants lose their leaves and atmospheric carbon dioxide levels increase, due to a reduction in photosynthesis. In spring, the plants grow new leaves and the level drops. It is as if Earth's plants and phytoplankton are the planet's lungs.

The carbon cycle describes the way in which carbon atoms are continually cycled between the living and non-living parts of ecosystems, through a series of complex processes.



> You will die but the carbon will not; its career does not end with you. It will return to the soil, and there a plant may take it up again in time, sending it once more on a cycle of plant and animal life.
>
> **Jacob Bronowski**
> **British–Polish mathematician (1908–74)**

The nitrogen cycle

Discovered in 1772 by Scottish physician Daniel Rutherford and named in 1790 by French chemist Jean Antoine Chaptal, nitrogen constitutes around 78 percent of Earth's atmosphere and is essential for life. It is a key component of the building blocks of living organisms: DNA, RNA, and proteins. Nitrogen is an inert (non-reactive) gas, so it has to be converted to another form, such as ammonia, nitrates, or organic nitrogen (urea), for living organisms to be able to utilize it.

Nitrogen in the atmosphere can be "fixed" into more usable forms through the action of lightning or by nitrogen-fixing bacteria in soil and the roots of some plants (legumes; see opposite). Nitrogen can also be released into soils from underlying bedrock. Other plants can then obtain nitrogen from the soil through their roots, in the form of simple, inorganic nitrogen compounds called nitrates.

The cycle continues with animals obtaining nitrogen from the plants they eat and/or from other animals. When plants nd animals die and decay, decomposers, such as bacteria and fungi, convert a substantial amount of the nitrogen from dead organic matter into ammonia in the soil. The ammonia is converted to

nitrates in a process called nitrification discovered in 1877 by French chemists Jean-Jacque Schloesing and Achille Münz.

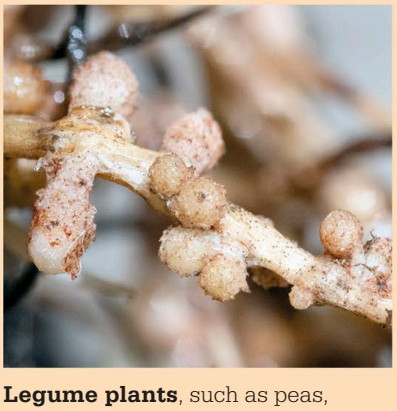
Nitrification requires oxygen, so it takes place in well-oxygenated streams, in the ocean, or in surface layers of the soil. The first step is carried out by two groups of microorganisms: ammonia-oxidizing bacteria and archaea, which convert ammonia to nitrites by combining it with oxygen. The second step is the oxidation of nitrites to nitrates by nitrite-oxidizing bacteria. Nitrogen can then be absorbed by plants in the form of nitrates in the soil.

The last stage in the nitrogen cycle, the process of denitrification, was revealed in 1886 by French chemists Ulysse Gayon and Gabriel Dupetit. They found that denitrifying bacteria in the soil convert nitrites and nitrates into atmospheric nitrogen that is released into the air. A small part of atmospheric nitrogen is in the form of nitrogen oxide, which forms smog (air pollution), and some is nitrous oxide, a greenhouse gas. The final stage of the nitrogen cycle removes fixed nitrogen from ecosystems and returns it to the atmosphere—the amount produced balancing roughly that which is fixed at the start of the cycle.

Nitrate fertilizer runoff creates high concentrations of nitrates in water sources, causing algae to proliferate. This depletes oxygen in the water, so other water organisms cannot survive.

Synthesizing ammonia

In 1563, French potter Bernard Palissy advocated the use of manure (a source of nitrogen) when growing crops, a practice that dates back to ancient times. But natural fertilizers are in limited supply and by 1913, German chemists Fritz Haber and Carl Bosch had developed the process to artificially fix atmospheric nitrogen and produce ammonia. The gas can be used to manufacture ammonium nitrate, one of the most common artificial fertilizers. These have been essential in helping to feed the world's growing population, but they have a downside. The runoff from artificial fertilizers causes nitrates to build up in water sources, contaminating drinking water and causing excessive growth of algae, which depletes oxygen and light in aquatic systems. American scientist John H. Ryther first drew attention to this phenomenon in 1954. The impact of this and other human activity on natural cycles has serious consequences for life on Earth. ■

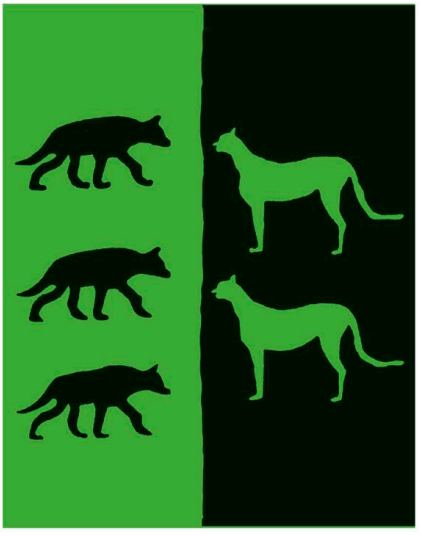


Legume plants, such as peas, broad or field beans, and clover, have root nodules that contain nitrogen-fixing bacteria.

Fixing nitrogen

Nitrogen must be reduced, or fixed, before it can be used by plants or animals. Lightning can fix nitrogen, but the greatest natural contribution is from microorganisms, especially soil bacteria. This was recognized in 1838, when French chemist Jean-Baptiste Boussingault established the first agricultural research station and found that legume plants could fix their own nitrogen, but he was at a loss to explain how. In 1901, Dutch microbiologist and botanist Martinus Beijerinck found that microorganisms in root nodules—specialized organs found mostly on legume plants—were responsible. Both soil bacteria and nodule bacteria produce ammonia, which the plant turns into nitrogen-containing organic molecules, such as amino acids and DNA.

The discovery explained the mechanism behind crop rotation, a farming practice in which a non-legume crop planted in a field that had previously grown legume plants results in a greater yield.



ONE WILL CROWD OUT THE OTHER

COMPETITIVE EXCLUSION PRINCIPLE

IN CONTEXT

KEY FIGURE
Georgy Gause (1910–86)

BEFORE
1904 Joseph Grinnell, an American field biologist, outlines the principle of competitive exclusion.

1925–26 Mathematicians Alfred Lotka and Vito Volterra use equations to analyze the dynamics of species competing for the same resources.

AFTER
1958 American ecologist Robert MacArthur explains the operation of competitive exclusion among a group of warbler species with similar feeding requirements.

1967 MacArthur and Richard Levins, an American ecologist, use probability theory and Lotka–Volterra equations to describe how coexisting species interact when factors like niche adaptation and immigration are involved.

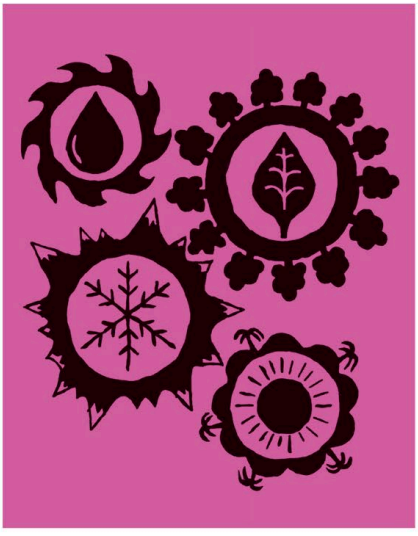
When two different species compete for identical resources, the one with a physical or behavioral advantage will outcompete the other. The disadvantaged species either dies out or adapts so that it no longer has to compete directly. This competitive exclusion principle became known as Gause's law after Russian microbiologist Georgy Gause, who conducted laboratory experiments in the 1930s to prove its validity. He grew cultures of two different species of the protozoan *Paramecium*, feeding them a constant amount of food. Both thrived when he grew them in separate containers, but when Gause put them together, the one that could gather food more quickly reproduced faster and came to dominate completely. Eventually, the other species starved.

Competition is the driving force behind selection. Those individuals and species best adapted to their environment thrive; those less well adapted do not. Although this idea was originally proposed by Charles Darwin and Alfred Russel Wallace in the mid-19th century, Gause's experiments were the first to prove that the principle was valid—at least in one situation.

It is difficult to demonstrate competitive exclusion in natural environments because there are so many variables. For example, predators may keep populations of competing prey species below the levels at which food resources become factors that limit their populations—so the competitors are able to coexist. ■

Red squirrels have been replaced by gray squirrels in most of Britain because the grays compete more successfully for food and habitat.

See also: Food chains 284–85 ▪ Predator–prey relationships 292–93 ▪ Trophic levels 300–01 ▪ Niches 302–03



THE BASIC UNITS OF NATURE ON EARTH

ECOSYSTEMS

IN CONTEXT

KEY FIGURE
Arthur Tansley (1871–1955)

BEFORE
1872 German botanist August Griesbach classifies the world's vegetation patterns in relation to climate.

1899 Henry Cowles proposes that vegetation develops in stages, later known as ecological succession.

1916 Frederic Clements proposes the idea of climax communities.

AFTER
1942 American ecologist Raymond Lindeman expands on Tansley's idea of an ecosystem to include all physical, chemical, and biological processes in a given space.

1969 American ecologist Robert Paine proposes the concept of a keystone species and its critical position in a natural food chain.

Ecosystem is the name given to a community of living organisms that interact with each other and the nonliving components of a specific environment that can be as small as a puddle or as large as an ocean. The idea was introduced by British botanist Arthur Tansley in 1935.

Botanists had long recognized patterns of vegetation around the world reflecting factors such as climate. In 1899, American botanist Henry Cowles described how plants colonize sand dunes in stages or successions of increasing size and complexity, and in 1916, fellow American Frederic Clements developed the idea of natural "communities." For him, all the plants in a particular environment were one complete organism.

However, Tansley argued that the plants and animals found in a particular place are not a community but simply a random association of individuals. Drawing inspiration from physics and thermodynamic systems, he proposed that what unifies them is energy flows.

> "… we cannot separate [the organisms] from their special environment, with which they form one physical system."
> **Arthur Tansley**

Nature, he believed, is a network of ecosystems that spread energy between living and nonliving things. For example, the Sun's energy enters the ecosystem through plants' photosynthesis then spreads as animals eat plants and each other. This concept provided ecologists with a method to study the complex, unpredictable variety of life. Tansley's ecosystem idea is now at the heart of modern ecology, further helping scientists understand the bewildering interconnectedness of nature. ■

See also: Plant and animal biogeography 286–89 ▪ Community succession 290–91 ▪ Trophic levels 300–01 ▪ Human impact on ecosystems 304–11

NETWORKS THROUGH WHICH ENERGY IS FLOWING

TROPHIC LEVELS

IN CONTEXT

KEY FIGURE
Raymond Lindeman
(1915–42)

BEFORE
1839 Charles Darwin describes an island food chain following a visit to St. Paul's Rocks, a small island in the Atlantic Ocean between Brazil and West Africa.

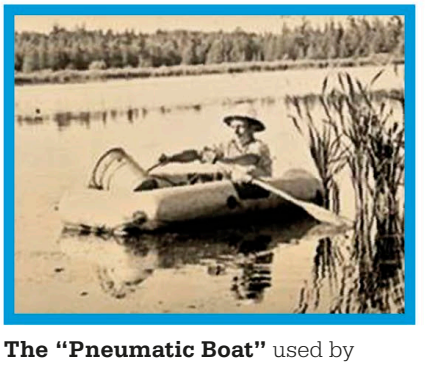
1913 American zoologist Victor Shelford produces one of the first illustrated food webs.

1926 Vladimir Vernadsky proposes that chemicals are recycled between living and non-living things.

1935 Arthur Tansley develops the concept of the ecosystem.

AFTER
1953 American ecologists Eugene and Howard Odum explore how the different levels of an ecosystem interact with each other in their book *The Fundamentals of Ecology*.

The chemical processes in living organisms that convert food into energy are known collectively as metabolism. Organisms need an original source of energy to power the metabolic process, and for most ecosystems this initial stream of energy comes from the Sun. Producers such as plants and algae use photosynthesis to capture energy from sunlight to make food, and this energy is passed to consumers that eat the producers, such as animals and fungi. There are exceptions to this rule, including organisms that oxidize iron, hydrogen, carbon monoxide, nitrite ammonium, and magnesium.



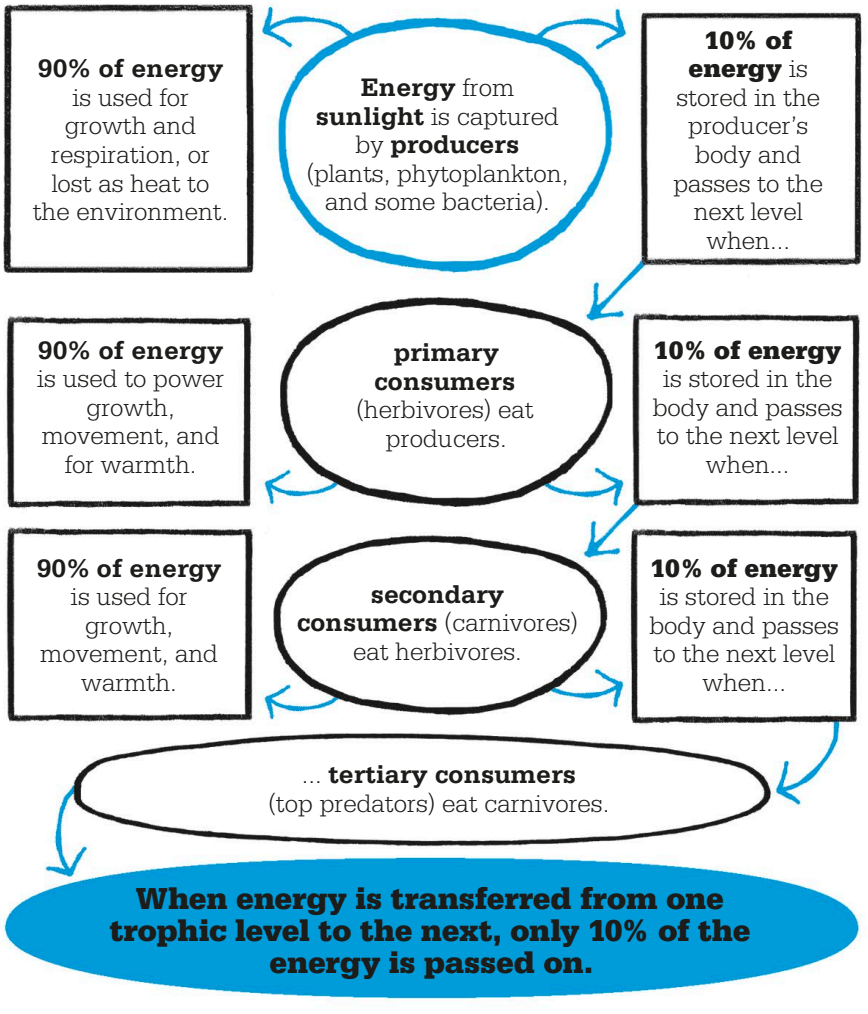
The "Pneumatic Boat" used by Raymond Lindeman and his colleagues to sample organisms in the Cedar Bog Lake, Minnesota. Data collected here provided the basis of his doctoral thesis.

Matter such as air, water, and soil minerals is recycled. In contrast, energy "flows" through organisms up the food chain in feeding levels called "trophic levels." This process was first demonstrated in a 1942 paper by American ecologist Raymond Lindeman.

Lindeman carried out much of his early fieldwork as part of his Ph.D. at Cedar Bog Lake, now the University of Minnesota's Cedar Creek Ecosystem Science Reserve. He was studying life in and around the aging lake as it underwent the classic stages of succession, changing gradually from a lake, through bog, to woodland. He described how the lake community could not be considered in isolation, but that everything—living organisms in different food chains and non-living components of the environment—is linked together by nutrient cycles and energy flows.

Lindeman's paper was initially rejected for being too theoretical, but his mentor, G. Evelyn Hutchinson of Yale University, was convinced it deserved a wider audience. He lobbied for Lindeman's work to be published, and his paper "The trophic-dynamic aspect of

See also: Metabolism 48–49 ▪ Photosynthesis 50–55 ▪ Food chains 284–85 ▪ Recycling and natural cycles 294–97 ▪ Ecosystems 299



ecology" appeared in *The Ecologist* in 1942 just a few months after Lindeman's premature death from cirrhosis of the liver at the age of 27.

In his paper, Lindeman demonstrated a means to evaluate the amount of energy accumulated at each trophic level in an ecosystem, now referred to as productivity. Using the Cedar Creek bog ecosystem as an example, he also revealed that as energy is transferred from one trophic level to the next, each organism receives a smaller amount. At each trophic level, some of the energy is lost as waste, or converted into heat when organisms respire. When an organism eats another, only about 10 percent of the energy is transferred from each trophic level to the next level up in the food chain. This led to the "10 percent law"—used as a guideline for understanding energy flow—and the view from ecologists worldwide that Lindeman's paper was of key importance in the rapidly expanding science of ecology. ■

Ecological pyramids

First developed by Lindeman and British-born zoologist G. Evelyn Hutchinson, ecological pyramids show the relationship between living organisms at different trophic levels. Generally, the broad base of the pyramid is occupied by producers, the next layer by primary consumers, and so on, up the pyramid.

The three types of pyramid are based on number, energy, or biomass (total quantity of an organism within a habitat, expressed as weight or volume). Some pyramids are inverted, such as an ocean biomass pyramid, in which zooplankton have a greater biomass than phytoplankton.

Pyramids work only for simple food chains, not more complex food webs. They do not take account of variations in climate and seasons, and decomposers are not included. But they do show how organisms are feeding in different ecosystems and the efficiency of energy transfer, and they help monitor the condition of the ecosystem.

A pyramid of numbers shows how many organisms exist at each trophic level, from producers at the bottom to apex predators at the top.

AN ORGANISM'S NICHE IS ITS PROFESSION

NICHES

IN CONTEXT

KEY FIGURE
G. Evelyn Hutchinson (1903–91)

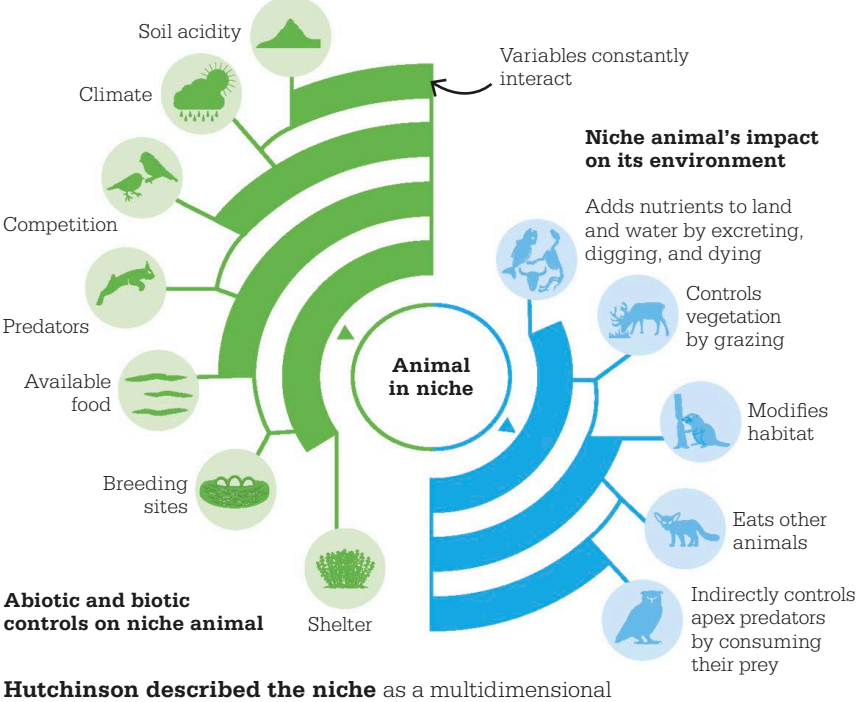
BEFORE
1917 Joseph Grinnell defines the niche as a habitat that allows a specific species to thrive. Habitats that might suit a species could be "vacant" due to geographical barriers.

1927 Charles Elton suggests that an organism's role in the food chain—both as predator and prey—is as important to its niche as its habitat.

AFTER
1968 David Klein, an American biologist, describes how niche changes caused a population crash of reindeer on an island.

1991 The term "niche conservatism," which explains how species tend to maintain similar niche needs over time, is coined by British ecologists Paul Harvey and Mark Pagel.

The concept of the niche, or a species' place in its ecosystem, is central to ecology. In the early 20th century, American biologist Joseph Grinnell explained the niche as the habitat in which a species was able to thrive. Then British ecologist Charles Elton expanded the niche idea to include an organism's role in its environment, or its "relations to food and enemies." Animals could occupy similar niches in different regions, for example spotted hyenas



Hutchinson described the niche as a multidimensional space, where a complex range of biotic (living) and abiotic (non-living) variables, or dimensions, interacts constantly with an organism, enabling it to thrive.

See also: Food chains 284–85 ▪ Predator–prey relationships 292–93 ▪ Competitive exclusion principle 298 ▪ Ecosystems 299

Hyacinth macaws of the Pantanal region in Brazil are specialists, depending on only three tree species for most of their food and nesting sites.

in tropical Africa and Arctic foxes occupy similar places in the food chain, being opportunistic feeders that both hunt and scavenge.

Multidimensional space

In 1957, American ecologist G. Evelyn Hutchinson pioneered a new understanding of niche complexity by studying an environment's chemical, physical, and geological, as well as biological features. American ecologist Lawrence Slobodkin summed up Hutchinson's concept of the niche as a "highly abstract multi-dimensional hyperspace." A niche is more than a location or a role: it is an attribute of the species, not its environment, involving complex interactions with other organisms and non-living variables, from climate, water acidity, geology, and soil, to nutrient flows.

If habitat conditions fall within a species' niche, a population of a species thrives. However, if conditions fall outside its niche, for example if the water it inhabits changes acidity or the area is colonized by a new predator, it faces extinction. Hutchinson also showed that a unique niche reduces competition with other species. Similar niches of different organisms in the same location cause competition for resources and may force species to adapt to occupy a different niche, or face extinction—as defined by the competitive exclusion principle.

Niches may be broad, occupied by generalists such as raccoons, brown rats, and pigeons, or narrow, occupied by specialists, such as the hyacinth macaw (*Anodorhynchus hyacinthinus*). This species would become extinct if the three tree species that are crucial to its niche were taken out of the ecosystem.

Niches as predictors

Any animal or plant occupying an ultra-specialized niche is extremely vulnerable to environmental change. Today, niches are even more crucial in predicting ecological responses to rapid environmental changes, especially those caused by habitat destruction or climate change. ■

> The niche of an animal can be defined to a large extent by its size and food habits.
> **Charles Elton**

G. Evelyn Hutchinson

Considered by many to be the father of modern ecology, Hutchinson was born in the UK in 1903 and took a degree in zoology at the University of Cambridge. After teaching in South Africa, from 1928 he spent the rest of his academic career at Yale University and became a US citizen in 1941.

Hutchinson's great interest was limnology, studying ecological systems of inland waters in Asia, Africa, and North America. He examined what determines the number of species in each specific ecosystem. With his students (including American ecologist Robert MacArthur), he created the first comprehensive mathematical model to predict species richness.

Hutchinson was a great field and theoretical biologist and teacher. He pioneered paleoecology, the study of the relationships between fossil animals and plants and their environments, and was an early predictor of climate warming. He died in 1991.

Key works

1957–93 *A Treatise on Limnology* (4 volumes)

MAN'S WAR AGAINST NATURE IS INEVITABLY WAR AGAINST HIMSELF

HUMAN IMPACT ON ECOSYSTEMS

IN CONTEXT

KEY FIGURE
Rachel Carson (1907–64)

BEFORE
1948 Swiss chemist Paul Müller receives the Nobel Prize for his work on DDT as an effective pesticide.

AFTER
1969 French toxicologist René Truhaut coins the term "ecotoxicology" for the study of the toxic effects of natural or synthetic pollutants.

1970 The US establishes the Environmental Protection Agency (EPA).

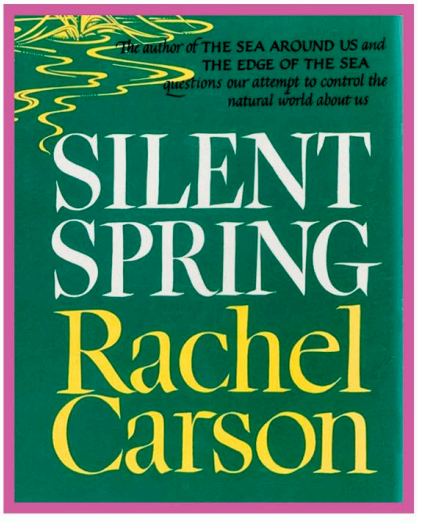
1988 In the US, zoologist Theo Colborn reveals that animals in the Great Lakes region pass on synthetic chemicals to their offspring.

2019 Danish scientist Frank Rigét studies the trends of persistent organic pollutants in Arctic marine and freshwater animal and plant life.

In 1962, a book was published that would draw attention to the way humans are negatively impacting the natural order of things. Initially serialized in three parts in *The New Yorker* magazine, it challenged established scientific views and values, and gave wings to a new environmental movement. Its title was *Silent Spring*, and its author an unassuming but scholarly American marine biologist with a flare for making science accessible and relevant to all.

The effects of pesticides

Rachel Carson had written extensively about the oceans and marine life, including her award-winning *The Sea Around Us* (1951), but in her penultimate book, *Silent Spring*, she was drawn to synthetic pesticides and their misuse. The inspiration was a letter in January 1958 from her friend Olga Huckins, whose bird sanctuary at Powder Point in Duxbury, Massachusetts, was next to farmland that was being sprayed with a mixture of fuel oil and the chemical compound dichlorodiphenyltrichloroethane (DDT). Many of the birds had died. Carson went to visit, and while she was a houseguest at Powder Point, a spray plane flew over. The next morning, she went along the estuary with Huckins in her boat, only to find dead and dying fish and shellfish, their nervous systems apparently compromised. This event led to Carson questioning the indiscriminate use of these chemicals, especially DDT.



Carson took inspiration for the title of *Silent Spring* from a poem by British poet John Keats in which "The sedge is wither'd from the lake, And no birds sing."

Rachel Carson

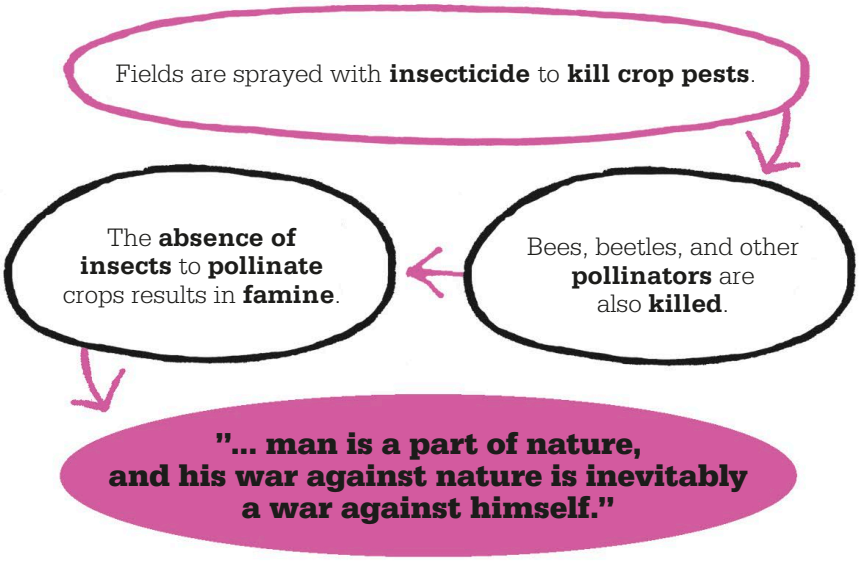
Born in 1907, Rachel Carson grew up in Springdale, Pennsylvania. She graduated in biology from the Pennsylvania College for Women in 1929, then studied at Woods Hole Marine Biological Laboratory and gained a masters in zoology at Johns Hopkins University. Carson was assigned to write radio scripts by the US Bureau of Fisheries, wrote feature articles for the *Baltimore Sun*, and later became editor-in-chief at the US Fish and Wildlife Service. She became a fulltime writer after the success of her three books on marine biology.

With *Silent Spring*, Carson's focus changed to warning the public about the long-term effects of pesticide use. Despite attacks by the chemical industry, she stood firm and laws were changed in the US. Carson died in 1964 after a long battle with cancer, but her work continues to inspire new generations of environmental scientists, campaigners, and legislators around the world.

Key work

1962 *Silent Spring*

See also: Pollination 180–83 ▪ Food chains 284–85 ▪ Predator–prey relationships 292–93 ▪ Recycling and natural cycles 294–97 ▪ Trophic levels 300–01 ▪ Island biogeography 312–13 ▪ The Gaia hypothesis 314–15



At this time, DDT was the most commonly applied pesticide for insect control worldwide. It was initially used to kill the insects transmitting malaria, typhus, bubonic plague, and other diseases to Allied troops and civilians during World War II. When hostilities ceased, it became the pesticide of choice for farmers and pest controllers because it was cheap to manufacture and remained active for a long time in the environment. DDT was later classified with other hazardous and long-lived pollutants as a persistent organic pollutant (POP). What Carson revealed was that this persistence had a profound effect not only on the target insects, but on other wildlife.

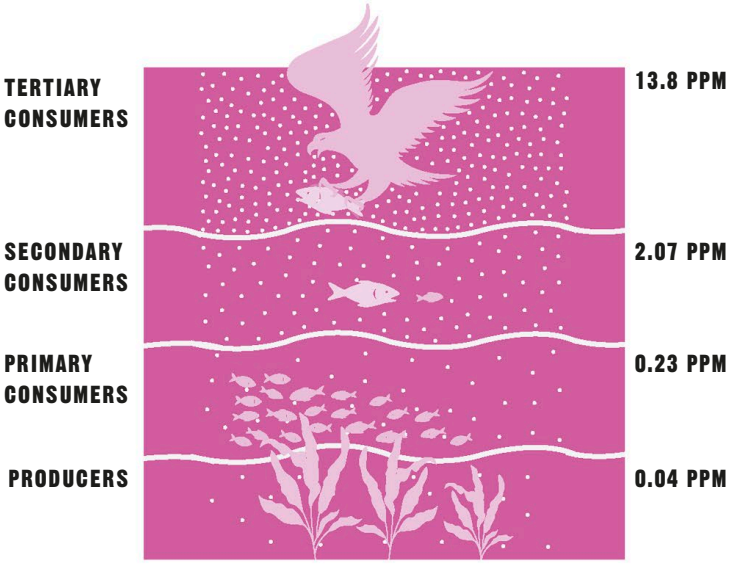
> The most alarming of all man's assaults upon the environment is the contamination of air, earth, rivers, and sea with dangerous and even lethal materials.
> **Rachel Carson**

DDT stays in the environment for years, sometimes decades. When ingested, the chemical is not broken down but remains in the animal's body, particularly in fatty tissues. As more DDT is ingested, the amount in the body fat increases—this is known as bioaccumulation. As the toxic chemical passes from one animal to the next up the food chain, its concentration increases—this is called biomagnification.

The pesticide DDT interferes with the calcium metabolism of birds of prey and therefore their ability to produce strong egg shells, causing shells to break during incubation.

Carson had not been the first person to question DDT's suitability as a safe pesticide. In 1945, American naturalist Edwin Way Teale warned of the indiscriminate use of DDT, and he later became a mentor of Carson. In the same year, Clarence Cottam, director of the US Fish and Wildlife Service, stated that caution was essential in its use because the effect of DDT on living things was not yet fully understood.

In 1958, the environmental consequences of DDT use began to be recognized, when British scientist Derek A. Ratcliffe, from Monks Wood Experimental Station in Cambridgeshire, recorded an abnormal number of broken eggs in peregrine nests. Surveys in the UK and US subsequently revealed that peregrine populations had plummeted since the end of World War II. Research in the 1960s by Canadian toxicologist David B. Peakall showed that DDT becomes so concentrated in the upper level of the food chain that birds of prey, such as peregrines, sparrowhawks, and golden eagles, suffer thinning of their egg shells, and that parent birds crushed their eggs when trying to incubate them. »



The concentration of DDT increases in each step up the food chain, with organisms higher in the chain suffering from the impact the most. In producers, the poison only represents 0.04 ppm (parts per million), but by the time tertiary consumers are involved, levels are high enough to have toxic effects.

This was a wake-up call, and Rachel Carson rang the bell. *Silent Spring* became a turning point in environmental awareness despite a significant backlash from the US chemical industry. However, it was not until a decade later that the politicians and administrators caught up with the scientists. In 1972 DDT was banned in the US, with many other countries following suit.

Organic mercury

In May 1956, a strange disease began to affect the central nervous system of people and animals in Minamata, Japan. Local cats had convulsions, nicknamed "cat dancing disease," and crows fell out of the sky. There were 2,265 human victims, most of whom have since died. The cause was a mystery until 1958, when visiting British neurologist Douglas McAlpine suggested the symptoms were similar to those of organic mercury poisoning. The scientific detective work that followed revealed the culprit to be methylmercury (an extremely poisonous form of mercury) from industrial waste poured into Minamata Bay by a chemical plant. The mercury had entered the food chain and was concentrated in the flesh of fish and shellfish eaten by local people.

In 1959, the Japanese government recognized the cause of "Minamata disease," but it was not until 1972 that the company responsible was reprimanded and eventually made to pay out more than $86 million ($87 million today) in compensation. Lawsuits and claims continued for decades.

Acid rain

In the 17th century, English writer John Evelyn wrote that London's air was so corrosive the Arundel marbles, a collection of ancient Greek sculptures, should be moved to Oxford. But it was Scottish chemist Robert Angus Smith who coined the term acid rain when he made the link between human activities and rainwater acidity in Britain's industrial cities and published his findings in 1872.

When fossil fuels burn in power stations and factories, or in car use, sulfur dioxide and nitrogen oxide are released into the atmosphere. These gases react with water and other substances to form sulfuric and nitric acid. When acid rain falls,

Karkonoski National Park in southwest Poland was significantly damaged by acid rain in the 1980s. A major source was air pollution from power plants burning fossil fuels.

Canadian polar bear populations have among the highest levels of mercury in the world, as revealed in a 2018 report by the Arctic Council.

it enters bodies of water, making them more acidic and toxic to many aquatic animals. It also affects soil pH. These effects eventually pass throughout the food chain.

In 1881, Norwegian geologist Waldemar Brøgger suggested that the nitric acid (a highly corrosive mineral acid) in contaminated snow could have originated in the UK. Only in 1968 did Swedish agricultural scientist Svante Odén make the connection between the emissions from the burning of fossil fuels in one country (the UK) to "dead" lakes and damaged forests in another (Sweden). In this case, acid rain did not eliminate just one part of the food chain, as with DDT killing birds of prey, but it annihilated the entire food chain, from the plankton (algae) in lakes to aquatic predators, such as salmon and Arctic char.

Arctic threats

Some scientists consider the Arctic to be a chemical sink, reporting that the area is increasingly contaminated with chemicals and pollutants from other regions. In 2006, researchers at the Norwegian Polar Institute (NPI) revealed that industrial flame retardants called polybrominated diphenyls (PBDEs) were present in the fatty tissues of polar bears. The chemicals reduce the flammability of soft furnishings, and about 95 percent of their global use at that time was in North America. It was found that PBDEs had a negative affect on the hormonal glands and brain function of polar bears. The report followed previous work that revealed deadly chemicals such as mercury from burning coal and polychlorinated biphenyls (PCBs)—used heavily from the 1950s to the 1970s as coolants and insulating fluids—had been found in polar bears, orcas, seals, and seabirds.

The pollutants are carried by ocean currents, northbound winds, or rivers flowing into the Arctic Ocean, where they are absorbed by plankton and then concentrated »

Biomagnification

Once a persistent organic pollutant (POP) enters a food chain, it builds up in the tissues of animals as it moves from one level to the next. This process is known as biomagnification.

The concentration of a pesticide such as DDT is measured in parts per million (ppm). If a pesticide washed into a lake has a concentration of 0.000003 ppm, for example, it could be absorbed or adsorbed (accumulate on the surface) by aquatic algae and concentrated to 0.04 ppm. Mayfly nymphs eat the algae, and the pesticide attains a level of 0.5 ppm in their tissues. Small fish eat many nymphs, so the figure rises to 2 ppm in each fish. A heron catches and eats several fish and so ends up with 25 ppm of pesticide in its tissues. From the bottom to the top of this freshwater food chain, the amount of pesticide has increased roughly 10 million times. By the time a POP reaches the top predators, the amount can become so toxic that those animals can experience reduced fertility or even die.

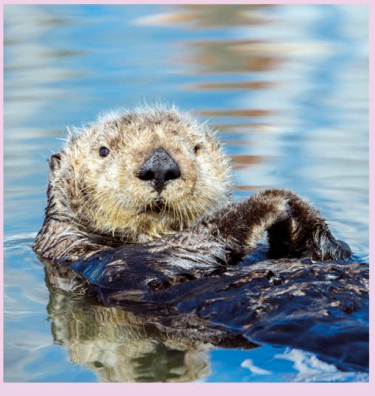
Notable examples of POPs include: organochlorine pesticides, such as DDT and chlordane; dioxins (highly toxic compounds) produced when municipal waste is burned; PCBs arising from the electrical and building industries; methylmercury from chemicals production; and tributyltin from paint on ships. All are dangerous to wildlife and to human health—humans are at the top of many food chains.

Keystone species

Some animals have such an impact on an ecosystem that its health is determined by their presence or absence. These are keystone species, a term introduced in 1969 by US ecologist Robert Paine, named after the wedge-shaped stone that holds up an arch.

Paine conducted his research in rocky tide pools on the Pacific Coast. He kept one area free of a species of starfish, which fed mainly on mollusks, by throwing them into the ocean. He left another area with the starfish as a control. Paine found that when the starfish were present, species diversity was much higher, so he named them a keystone species.

Paine also identified sea otters as a keystone species, noting that they keep sea urchin populations in check and therefore influence the populations of kelp (seaweed). His research showed that the elimination of certain species due to human impact can produce unexpected and profound consequences for the environment.



Sea otters were named by Paine as a keystone species when he studied their disappearance along the Pacific Coast due to fur trading.

Microplastics are created from the fragmentation of larger plastic products, which gradually break down into smaller pieces through natural weathering processes.

in the food chain to such an extent that some polar bears—the top, or apex, predator (they feed mainly on seals)—are exposed to dangerously high levels.

Research has revealed there to be about 150 dangerous compounds present in the Arctic food web, and, according to Canadian environmental scientist Robert Letcher, a lead author of an Arctic Council study published in 2018, "The number and types of contaminants continue to broaden."

Microplastics

First mass produced in the early 20th century, one of the most insidious pollutants has turned out to be plastic. The 2017 BBC television series *Blue Planet II* heightened public concern about the amount of plastic found in the ocean, especially the huge quantities concentrated in "garbage patches" at the centre of circular ocean currents called ocean gyres. These revelations became all the more poignant in 2019, when the crew of a record-breaking deep-sea dive in the Mariana Trench—the world's deepest ocean trench—found a plastic bag and sweet wrappers nearly 7 miles (11 km) below the surface of the Pacific Ocean. The biggest concern, however, is microplastics.

Microplastics—tiny fragments of plastic less than $^{1}/_{5}$ in (5 mm) across—include plastic beads added to health and beauty products, and synthetic fibers from fleeces and other clothing discharged from domestic washing machines. Sewage filtration systems fail to pick them up, and they are discharged into the sea then distributed throughout the water column, even reaching the ocean floor. In 2020, an Australian team reported that it had sent robot submarines 9,842 ft (3,000 m) deep to sample the seabed off the coast of South Australia. The team found that there could be as much as

15 million tons of microplastics being moved about by currents on sea floors all over the world. The currents are like conveyor belts, transporting the pollutants from estuaries and undersea canyons at the coast to the deep sea, where they become concentrated in "microplastic hotspots." However, not all of the particles remain on the sea floor.

In 2013, British ecotoxicologist Matthew Cole at the University of Exeter found that zooplankton (aquatic microscopic organisms) were ingesting the minute plastic particles. Thus microplastics enter the food chain, and prevent zooplankton from feeding properly. As yet, scientists do not know what the impact of microplastics will be on life further up the food chain, especially apex predators, such as orcas, sharks, and humans, yet they are now found virtually everywhere on Earth.

The air above large cities is polluted with microplastics, and they have also appeared in remote and largely untouched mountain regions, such as the Pyrenees between Spain and France. In 2018, researchers from France and Scotland analyzed rain, dust, and snow samples collected for five months at the Bernadouze meteorological station, 4,265 ft (1,300 m) up and 75 miles (120 km) from the nearest city. They found that an average of 365 tiny plastic particles fell each day on a 11-sq-ft (1-sq-m) collector. The researchers estimated that the particles came from at least 62 miles (100 km) away and probably much farther. Their findings indicate that wherever a person is in the world, they will be inhaling microplastics—including at the top of the world's highest mountain, Everest.

In 2020, researchers at the University of Plymouth in the UK described how they had analyzed snow and stream samples from different sites on Mount Everest and discovered microplastics at an altitude of 6 miles (9 km) on the "Balcony," a rest stop just below the summit. Most of them were from synthetic fibers from the clothes and gear used by climbers.

Ongoing concerns

Despite Rachel Carson's revelations in the early 1960s, the disturbing story of man-made pollutants and their impact on ecosystems and human health continues unabated. Even the story of DDT is far from over. Exposure to DDT has been linked to cancer, infertility, miscarriage, and diabetes in humans. Despite a global ban for all uses except malaria control in 2001, DDT or its breakdown products are still present in the environment. In 2016, the US Department of Agriculture found detectable levels in foods such as American cheese, carrots, celery, and salmon. ■

> Humans are certainly the overdominant keystones and will be the ultimate losers if the rules are not understood.
>
> **Robert Paine**
> **American ecologist**

Rat-tailed maggots can survive in polluted conditions. Their posterior siphon enables them to breathe air while feeding underwater.

Indicator species

Just as canaries were once used to warn coal miners of poisonous gases, ecologists observe indicator species in the wild to determine the degree of pollution in a habitat. Some lichens, for example, are sensitive to air pollution, and will only grow where the air is clean. Aquatic invertebrates, such as mayfly and caddisfly larvae, are sensitive to pollution in freshwater, whereas the rat-tailed maggot of the drone fly can thrive even in heavily polluted water, such as in sewage lagoons.

Bioaccumulator indicator species are organisms that accumulate pollutants in their tissues, but are resistant to their harmful effects. They can help reveal pollutants present at very low levels. Bivalve mollusks, such as clams and mussels, are often monitored by researchers because their wide geographical distribution but limited mobility makes they are good indicators of site-specific bioaccumulation. Several species of algae, such as green seaweeds, are also useful bioaccumulator indicator species for heavy metals and pesticides.

DIVISION OF AREA BY TEN DIVIDES THE FAUNA BY TWO

ISLAND BIOGEOGRAPHY

IN CONTEXT

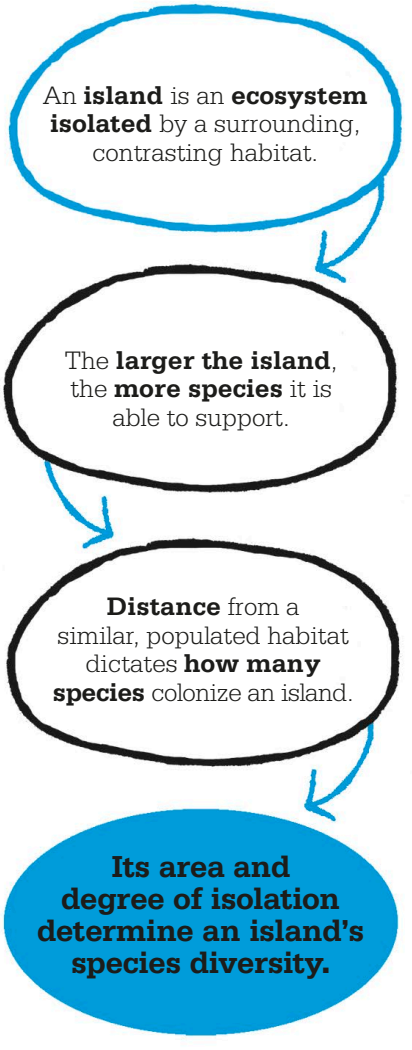
KEY FIGURES
Robert MacArthur (1930–72), **Edward O. Wilson** (1929–)

BEFORE
1835 Charles Darwin notes variations in giant tortoises and birds from island to island in the Galápagos archipelago.

1880 Alfred Russel Wallace realizes that isolated islands form natural laboratories for studying animal adaptation.

1948 Eugene Munroe, a Canadian lepidopterist working in the Caribbean, finds that butterfly diversity is related to island size.

AFTER
2006 A study of birds on 346 oceanic islands, by Canadian biologists Attila Kalmar and David Currie, shows climate, as well as island isolation and size, affects species diversity.

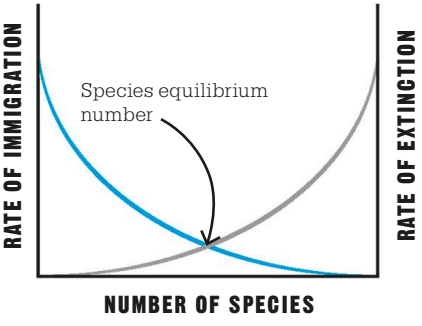


A habitat that is surrounded by another—usually less diverse—habitat is known as an "island," such as an oceanic island, a forest patch encircled by arable monoculture, or a desert oasis. Island biogeography examines the causes of variation in levels of species diversity on such islands.

In 1967, *The Theory of Island Biogeography* by American biologists Robert MacArthur and Edward O. Wilson offered a mathematical model of factors affecting the complexity of oceanic island ecosystems. The biologists suggested there was a balance on any island between the arrival rate (immigration) of new species and extinction rate of existing species.

Immigration is largely governed by an island's distance from the mainland, or other islands that could supply new life forms. If it is close to the mainland, new species arrive more often than if it is very distant. Immigration rate is also affected by the island's length of isolation, area, habitat suitability, relationship to ocean currents, and climate. New arrivals establish viable populations to a greater degree if the island has a diverse range of habitats or microhabitats.

See also: Food chains 284–85 ▪ Plant and animal biogeography 286–89 ▪ Predator–prey relationships 292–93 ▪ Competitive exclusion principle 298 ▪ Ecosystems 299 ▪ Trophic levels 300–01 ▪ Niches 302–03



Species equilibrium, or a stable number of species, on an island occurs when the immigration rate (affected by how close another species' habitat may be) and the extinction rate (affected by the size of the island) become equal.

MacArthur and Wilson argued that a habitable but fairly under-occupied island has a low extinction rate because there are fewer species to become extinct. As more species arrive, competition for resources builds until the immigration and extinction rates equalize.

Finally, MacArthur and Wilson explained the "species–area effect": larger islands, with more habitat variety, have lower extinction rates and a greater species mix than do small islands. This diversity will maintain its richness even if actual species in the mix vary over time.

Wilson and his student Daniel Simberloff in 1969 recorded the species on six mangrove islands in the Florida Keys, US. They fumigated the vegetation to remove all the invertebrates, chiefly insects, spiders, and crustaceans. Over one year, they logged returning species to chart the recolonization: the nearest islands to the mainland were recolonized more quickly, thereby confirming the main tenet of MacArthur and Wilson's theory.

The wood thrush often migrates to forest fragments or other "islands," such as Central Park in New York City.

Refining the model

Ecologists later applied island theory to terrestrial-island, or isolated, habitats. American biologist James Brown studied montane forest islands in the Great Basin of California and Utah in 1970–78. He showed flying species are more likely to colonize islands than other species. Canadian ecologists John Wylie and David Currie proposed their species–energy theory in 1993, in which available energy, such as solar energy, also affects diversity. The modified theory of MacArthur and Wilson still informs conservation of island habitats and their diversity today. ■

Barro Colorado Island

The damming of a Panamanian river in 1914 created Lake Gatun and, within it, Barro Colorado Island, an area of 6sq miles (15.6sq. km) covered by tropical forest. It is managed by the Smithsonian Institution as a nature reserve and is one of the most studied areas on Earth.

Biologists have collected invaluable data on the island's invertebrates, vertebrates, and plants, and their colonization and extinction. For example, 45 breeding pairs of birds were lost from the island by 1970. A likely factor in some disappearances of species was the island's size. It was too small to support its top predators—pumas and jaguars.

Without predators to keep them in check, the numbers of medium-sized omnivores such as coatis, howler monkeys, and possums boomed, and they ate more bird eggs and chicks. This "mesopredator release" affected some small forest birds, because many will not fly over even short distances of water, so they could not top up island numbers by immigration from the mainland.

GAIA IS THE SUPERORGANISM COMPOSED OF ALL LIFE

THE GAIA HYPOTHESIS

IN CONTEXT

KEY FIGURE
James Lovelock (1919–)

BEFORE
1789 Scottish geologist James Hutton coins the term superorganism.

1920s Vladimir Vernadsky describes how the composition of Earth's atmosphere was created and is maintained by biological processes.

1926 American physiologist Walter Cannon introduces the term homeostasis.

AFTER
2016 The Trace Gas Orbiter is sent to Mars to search for methane and other gases in its atmosphere that could be evidence of biological activity on the planet.

2019 The World Meteorological Association warns that Earth could warm by 5.4–9°F (3–5°C) by the end of the century if greenhouse gas emissions continue at their present rate.

The Gaia hypothesis is an ambitious proposal that seeks to show that Earth's biosphere—the region on or close to the planet's surface where all life exists—is self regulating. The biosphere maintains the conditions, such as temperature and chemical composition, that allow life to exist.

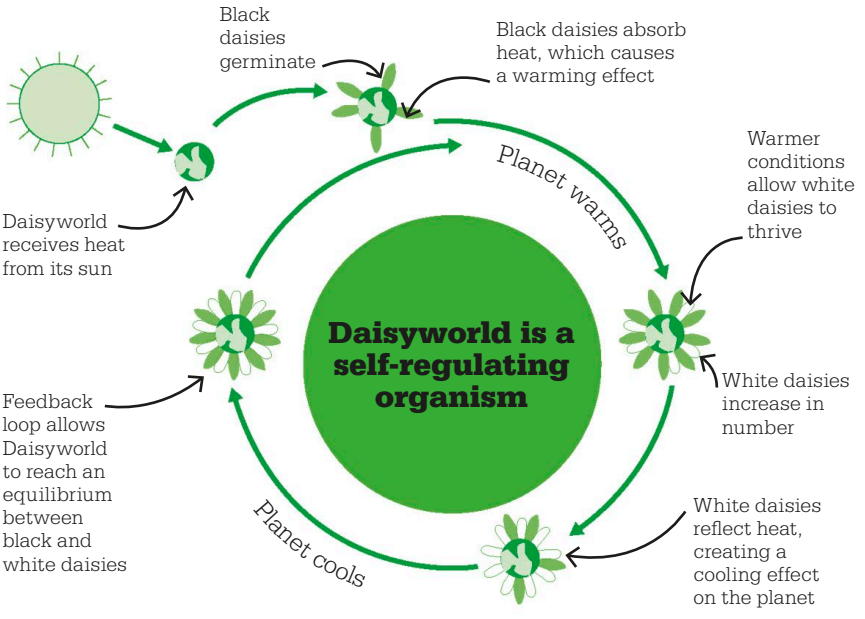
This theory was the brainchild of British scientist James Lovelock in the 1970s. He considered how, unlike that of a dead planet, Earth's atmosphere contains oxygen and small amounts of methane gas, and both of these gases are produced by biological processes. Not only had the composition of Earth's atmosphere been created by living organisms, it was also maintained by them via a feedback loop. In the carbon cycle, for example, as the biomass of plants increases, the amount of carbon dioxide in the air drops, and the amount of oxygen goes up. More plants to eat leads to a rise in animal biomass, which takes in more oxygen and gives out more carbon dioxide, so in the long term the amount of both gases in the air stays broadly stable.

Lovelock suggested that this kind of process was very similar to the feedback loops seen in homeostasis, the mechanism by which a body maintains an optimal internal temperature, water level, and chemical composition. Working with American biologist Lynn Margulis, he described several other feedback mechanisms where life interacts with rocks, minerals, and seawater, as well as the air, to keep the biosphere in homeostasis. This inspired the pair to describe the planet as a superorganism—a collection of interacting life forms

Earth's oceans, land masses, and atmosphere work together as a living organism, according to the Gaia hypothesis. This view of Earth was taken by the Galileo space probe.

See also: The beginnings of organic chemistry 61 ▪ Homeostasis 86–89 ▪ Recycling and natural cycles 294–97 ▪ Human impact on ecosystems 304–11

Equilibrium of Daisyworld



that, when taken together, behave in some ways like an individual organism. They called their hypothesis Gaia, after the ancient Greek Earth goddess, and their paper was published in 1974.

Daisyworld and beyond

Lovelock simplified the hypothesis with Daisyworld, a virtual planet that has a basic feedback loop. The planet is populated by two species of daisies. Black daisies grow in cold conditions, and their dark petals absorb the heat of the planet's sun. White daisies reflect the heat away and thrive where it is hot. Black daisies trap heat, making the planet warmer, while white ones do the opposite. Black daisies spread over Daisyworld's poles, while white ones form a belt around the warmer equatorial regions. If the number of white daisies increases, Daisyworld cools, creating conditions that allow black daisies to expand their range. This in turn warms Daisyworld, and white daisies increase once more. This cycle of warming and cooling repeats until eventually an equilibrium is reached, where Daisyworld's temperature fluctuates within a small range.

The Gaia hypothesis was embraced by many people, but scientists complained it lacked rigor or proof. Although Lovelock's theory never entered the scientific mainstream, its approach of looking at the planet as a whole is now very much part of research into climate change—with some arguing that the impact of humans burning fossil fuels and releasing vast amounts of carbon dioxide into the atmosphere is just a recent example of life affecting the planet. ■

James Lovelock (1919–)

Born in the UK in 1919, Lovelock began work at the National Institute for Medical Research in London in 1941 after earning a degree in chemistry. Two decades later, he worked with a research team at NASA to design instruments for space probes, including one tasked with detecting life on Mars. Later, in the 1960s and early 1970s, Lovelock began to develop the Gaia hypothesis.

First published in 1974, the Gaia hypothesis made Lovelock famous, and he refined the ideas for the next 20 years. In the 21st century, he turned his attention to climate science, becoming a reluctant advocate of nuclear power as a way of reducing carbon emissions, a move that put him at odds with many of the people who were drawn to his work on Gaia.

Key works

1974 *Atmospheric homeostasis by and for the biosphere: the Gaia hypothesis,* coauthored with L. Margulis
1984 *The Greening of Mars*
2019 *Novacene: The coming age of hyperintelligence*

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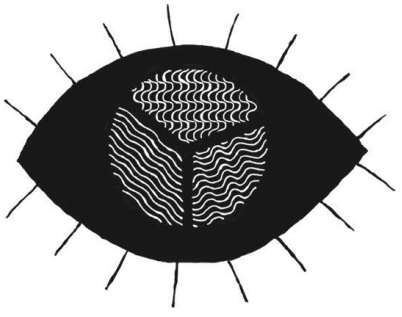

More men and women have contributed to the development of biology than could possibly be described in this book. The directory that follows lists some other figures who each played a crucial role. They include early pioneers such as Avicenna, Leonardo da Vinci, Robert Hooke, and Mary Anning, who—despite access to only basic technology—advanced their disciplines through scientific method. With the advent of good-quality microscopy in the 19th century, biologists such as Jan Purkinje, Sergei Winogradsky, and Dorothy Crowfoot Hodgkin developed microbiology. From the late 20th century, genetics was at the cutting edge of biological discovery, with Janaki Ammal, Flossie Wong-Staal, and Tak Wah Mak among those contributing to breakthroughs.

ARISTOTLE
*c.*384–322 BCE

Founder of comparative anatomy, Greek philosopher Aristotle keenly observed animal diets, habitats, and life cycles and used dissection to learn about anatomy. He described more than 500 animal species and produced the first classification of animals. Some of his 10 major categories were wrong, but his system was remarkable for its time and largely unchallenged until the 18th century.
See also: Experimental physiology 18–19 ▪ Anatomy 20–25 ▪ Naming and classifying life 250–53

AVICENNA
*c.*980–1037 CE

Avicenna (Arabic name, Ibn Sina) was a Persian polymath. He created a holistic system of medicine, which combined diet, medicine, and psychological and physical factors in the treatment of patients. His most influential work was *The Canon of Medicine*, a five-volume encyclopedia covering human anatomy, diagnosis of diseases and conditions, and medication. The book became the standard medical textbook in the Islamic world and in Europe until the 17th century.
See also: Anatomy 20–25 ▪ Drugs and disease 143

LEONARDO DA VINCI
1452–1519

Born in Italy, Renaissance polymath Leonardo da Vinci became a great artist, writer, mathematician, engineer, inventor, and anatomist. From 1507, da Vinci dissected about 30 human corpses. An unsurpassed anatomical illustrator and skilled dissector, da Vinci also investigated how parts of the body work. From an ox heart, he made a glass model of the heart's main blood vessel, the aorta, and showed how blood flows through the aortic valve, using a solution of water and grass seeds. He defined the ventricles (cavities) of the brain by pouring in molten wax. In 1513, he abandoned his anatomical project, despite having created hundreds of detailed and incredibly accurate, annotated drawings of the human body.
See also: Anatomy 20–25 ▪ Circulation of the blood 76–79

FRANCESCO REDI
1626–1697

Italian physician, parasitologist, and poet Francesco Redi was the first biologist to distinguish between ecto- and endoparasites (those living on and within their hosts, respectively) and described about 180 species of parasites. In the 17th century, it was believed that maggots arose from meat by spontaneous generation. In 1668, Redi debunked the theory with experiments that showed maggots grew from eggs laid by flies.
See also: Naming and classifying life 250–53 ▪ Food chains 284–85

ROBERT HOOKE
1635–1703

English polymath Robert Hooke was one of the greatest scientists of the 17th century and detailed many

crucial biological discoveries in his 1665 epoch-defining *Micrographia* (*Small Drawings*). A proficient microscopist, Hooke was one of the first to see microscopic organisms, and he described and named plant cells long before their function was understood. He deduced that plant cells in fossilized wood were once parts of living organisms whose cells had been preserved by being impregnated with minerals. Also, he speculated that some organisms must have become extinct—a radical view in the 17th century.

See also: Anatomy 20–25
- The cellular nature of life 28–31
- Extinct species 254–55

JAN SWAMMERDAM
1637–1680

In 1658, Dutch microscopist Jan Swammerdam was the first to describe red blood cells. He also employed innovative techniques to explore animal anatomy and found structures (now called imaginal discs) in caterpillars that grew into limbs and wings of adult butterflies and moths. It proved that insects undergo metamorphosis and that egg, larva, pupa, and adult are all developmental insect stages. He also used frogs to show that nerve stimulation causes muscles to contract. Many of his findings appeared in 1737–38, in the two-volume *The Book of Nature*.

See also: Anatomy 20–25
- Circulation of the blood 76–79

MARIA MERIAN
1647–1717

The work on insect development, including metamorphosis, of German naturalist Maria Merian greatly advanced entomology. In 1679–83, she published her two-volume *Caterpillars: their Wondrous Transformation and Strange Diet of Flowers*, in which scientifically accurate illustrations show each moth and butterfly beside its plant food source, along with descriptive text. In 1705, after a two-year expedition to South America, another significant work—*The Metamorphosis of the Insects of Suriname*—was published.

See also: Anatomy 20–25
- Naming and classifying life 250–53

GILBERT WHITE
1720–1793

One of the earliest ecologists, British curate White observed plants and animal behaviour and interactions in the natural world for more than 40 years. He pioneered the study of seasonal natural phenomena (phenology), recording the first dates that plants came into flower and migrant birds arrived. White understood the roles played by even humble organisms and explained food chains. He described some species for the first time, such as the willow warbler (*Phylloscopus trochilus*), wood warbler (*P. sibilatrix*), and chiffchaff (*P. collybita*), which he set apart by their distinct songs.

See also: Naming and classifying life 250–53 ▪ Food chains 284–85

JOSEPH BANKS
1743–1820

An expedition to Newfoundland and Labrador in 1766 allowed British botanist Sir Joseph Banks to collect and describe many plants and animals unknown to Western science, including the now-extinct great auk, which he believed to be a penguin. On Captain James Cook's 1768–71 expedition to South America, the South Pacific, and the Antipodes, Banks collected 30,000 plant specimens, including more than 1,000 undescribed species. For 41 years, Banks was president of the Royal Society, London's leading scientific body.

See also: Naming and classifying life 250–53 ▪ Plant and animal biogeography 286–89

ROBERT BROWN
1773–1858

Pioneering Scottish botanist Robert Brown collected nearly 4,000 plant species, in 1801 on an expedition to Australia. Brown's work included the earliest detailed description of the cell nucleus; contributions to understanding pollination and fertilization; and distinguishing gymnosperms (conifers and allied plants) and angiosperms (flowering plants). He discovered what is now called Brownian motion (random motion of microscopic particles while suspended in a gas or liquid). While examining pollen grains in water, he saw tiny particles, now known to be organelles ejected from pollen moving with a random, jittery motion. He showed that tiny, non-living particles, such as rock dust, also move in the same way.

See also: The discovery of gametes 176–77 ▪ Pollination 180–83 ▪ Fertilization 186–87

JAN PURKINJE
1787–1869

Czech physician Jan Purkinje was first to use a microtome, a device to make very thin slices of tissue

for microscopic examination. He described how the human eye perceives the color red fading faster than blue when light intensity decreases (the Purkinje effect). He discovered large nerve cells (Purkinje cells) in the brain's cerebellum, and the fibrous tissues (Purkinje fibers) that conduct electrical impulses to all parts of the heart. In 1839, he founded the world's first department and institute devoted to physiology.
See also: The heart muscle 81 ▪ Color vision 110–13 ▪ Nerve cells 124–25

MARY ANNING
1799–1847

Born into poverty, British self-taught paleontologist Mary Anning collected fossils from the Jurassic rock strata in local cliffs to earn money. In 1810, she excavated the first correctly described ichthyosaur and went on to find two almost complete plesiosaurs and to unearth the first pterosaur outside Germany. Her finds provided strong evidence for extinction theory and so helped to change views about Earth's history. In 2010, the Royal Society in London described her as one of 10 British women who most influenced the history of science.
See also: Naming and classifying life 250–53 ▪ Life evolves 256–57

JOSEPH HOOKER
1817–1911

A prolific collector and leading late 19th-century British botanist, Hooker took part in expeditions to the Antarctic, India, the Himalayas, New Zealand, Morocco, and California. The three-volume work, *Genera Plantarum* (1862–83), by Hooker and fellow British botanist George Bentham, was the most complete compilation of Earth's plants at the time. It has 7,569 genera and more than 97,000 species of seed-bearing plants.
See also: Naming and classifying life 250–53 ▪ Plant and animal biogeography 286–89

ILYA MECHNIKOV
1845–1916

In 1882, Mechnikov established a laboratory at Messina, Sicily. While studying starfish, the Russian immunologist discovered phagocytosis, the immune system's method of using mobile cells, such as white blood cells, to encapsulate and destroy harmful pathogens. For his work, he won the 1908 Nobel Prize in Physiology or Medicine.
See also: Germ theory 144–51 ▪ Viruses 160–63 ▪ Immune response 168–71

KARL VON FRISCH
1886–1982

Austrian zoologist Frisch shared the 1973 Nobel Prize in Physiology or Medicine with Konrad Lorenz and Nikolaas Tinbergen (see right) for explaining the "dances" performed by bees on their return to the hive, in which they convey to other bees the distance and direction of food sources. Over 50 years of studying bees, Frisch also demonstrated that they can be trained to distinguish different tastes and odors and that bees use the Sun as a compass.
See also: Color vision 110–13 ▪ Innate and learned behavior 118–23 ▪ Memory storage 134–35

JANAKI AMMAL
1897–1984

Indian botanist and conservationist Janaki Ammal worked with British cytologist Cyril Darlington to study the chromosomes of a wide range of plants. Their work threw light on plant evolution and in 1945, they published *The Chromosome Atlas of Cultivated Plants*. Indian prime minister Jawaharlal Nehru invited Ammal to reorganize the Botanical Survey of India (BSI) in 1951. She developed several hybrid crop species, including sugarcane that could grow in the Indian climate, so avoiding the need to import it.
See also: Chromosomes 216–19

NIKOLAAS TINBERGEN
1907–1988

Dutch-born, British biologist Tinbergen's main interest was ethology, the study of animal behavior. He conducted several pioneering behavioral studies of birds, wasps, and stickleback fish. In 1973, he, German ethologist Konrad Lorenz, and Karl von Frisch (see left) shared the Nobel Prize in Physiology or Medicine for their separate work on genetically programmed behaviour in animals.
See also: Innate and learned behavior 118–23 ▪ Memory storage 134–35

DOROTHY CROWFOOT HODGKIN
1910–1994

At the University of Cambridge, UK, British chemist Hodgkin pioneered ways of using X-rays to analyze the structure of biological

protein molecules, such as pepsin. She taught and researched from 1934 at the University of Oxford and was the first to describe the atomic structure of penicillin, in 1945, and vitamin B12, in 1955. Hodgkin won the Nobel Prize in Chemistry for her discoveries in 1964. Determining the structure of insulin proved to be a greater challenge, but she succeeded in 1969, 34 years after first seeing its X-ray image.

See also: Antibiotics 158–59 ▪ The double helix 228–31

NORMAN BORLAUG
1914–2009

At the Rockefeller Foundation's Mexican Agriculture Program in 1944–60, American agronomist Borlaug was charged with boosting crop yields for wheat farmers. He induced genetic mutations to create resilient crops, including a dwarf form of high-yielding, disease-resistant wheat that did not break under its heavy seed heads. Mexican wheat production increased three-fold. Borlaug's similar successes in South Asia with rice and wheat saved millions from starvation. He was dubbed "father of the green revolution" and won the 1970 Nobel Peace Prize for his work on global food supplies.

See also: Pollination 180–83 ▪ What are genes? 222–25 ▪ Mutation 264–65

GERTRUDE ELION
1918–1999

Working together with physician and medical researcher George Hitchings, pharmocologist Elion introduced a more modern, rational approach to developing drugs. In 1950, Elion made her first major discovery—a drug to treat leukemia. Later, she developed antiviral therapies to treat shingles and chickenpox, helping pave the way for the AIDS medication AZT. The patents for 45 life-saving or life-changing drugs bear Elion's name; she and Hitchings won the 1988 Nobel Prize in Physiology or Medicine for their work.

See also: Cancer metastasis 154–55 ▪ Viruses 160–63 ▪ Vaccination for preventing disease 164–67

JOE HIN TJIO
1919–2001

Indonesian agronomist Joe Hin Tjio researched plant chromosomes in Zaragoza, Spain, and at the Institute of Genetics, University of Lund, Sweden, where he invented a new way of counting chromosomes in 1955. It was believed that humans have 48 chromosomes, but Tjio proved the true number to be 46. Tjio's breakthrough made possible an understanding of the link between abnormal chromosomes and disease and led to the discovery that an additional chromosome causes Down syndrome.

See also: The laws of inheritance 208–15 ▪ Chromosomes 216–19

DAVID ATTENBOROUGH
1926–

A renowned broadcaster on the natural world, British naturalist Attenborough brought the world's flora and fauna to millions through documentaries, including *Life on Earth* in 1979 and *The Private Life of Plants* in 1995. He alerted his global audience to environmental destruction, species' extinction, and climate change through programs such as *Climate Change—The Facts* (2019). In 2003, he became a patron of the World Land Trust, which aims to preserve biodiversity and ecosystems.

See also: Predator–prey relationships 292–93 ▪ Human impact on ecosystems 304–11

SYDNEY BRENNER
1927–2019

Molecules in DNA, called nucleotides, each have one of four types of nitrogen bases. In the 1950s, South African molecular biologist Brenner proved in theory that instructions from DNA to the cell to build proteins are carried in a succession of codons (groups of three bases) and that each codon has a different combination of three bases. He, Francis Crick, and two others confirmed it experimentally in 1961.

With geneticists Robert Horvitz from the US and John Sulston from Britain, Brenner was awarded the 2002 Nobel Prize in Physiology or Medicine. They used roundworms to explain how genes program cell death to maintain the optimum number of cells in the body. Brenner also showed how genes could regulate organ development.

See also: What are genes? 222–25 ▪ The double helix 228–31

MARTHA CHASE
1927–2003

American biologist Chase worked with geneticist Alfred Hershey at Cold Spring Harbor Laboratory, New York. In 1952, in the Hershey-Chase experiments, they confirmed that DNA—not protein, as was

believed—is the genetic material of life. Hershey won the 1969 Nobel Prize in Physiology or Medicine for the discovery, but Chase was omitted despite being named as coauthor of the paper describing it.
See also: What are genes? 222–25 ▪ The genetic code 232–33

CARL WOESE
1928–2012

American microbiologist Woese redrew the taxonomic tree of life with his pioneering work on microorganisms. Until the 1970s, all life was thought to belong to two lineages: eukaryotes (including all plants, animals, and fungi) and prokaryotes (bacteria and other microscopic organisms). Woese and fellow American biologist George Fox analyzed the ribosomal RNA of microorganisms and discovered that prokaryotes consist of two distinct groups—true bacteria (eubacteria) and archaebacteria (archaea). They argued in 1977 that archaea are as distinct from bacteria as they are from plants and animals. In 1990, Woese proposed dividing all life into three domains: Archaea, Bacteria, and Eukarya.
See also: Naming and classifying life 250–53 ▪ Speciation 272–73 ▪ Cladistics 274–75

TU YOUYOU
1930–

Chinese pharmacologist Tu Youyou researched modern applications of traditional Chinese medicines at the Academy of Traditional Chinese Medicine. In 1971, she employed a nontoxic extract from sweet wormwood (*Artemisia*) to eliminate the parasites (*Plasmodium* spp.) responsible for malaria in animals. Tu named the chemical *Qinghaosu*, or artemisinin. In clinical trials of the extract in 1972, 21 human patients were cured of malaria. Drugs based on artemisinin led to the survival and improved health of countless sufferers of malaria. In 2015, Tu was awarded the Nobel Prize in Physiology or Medicine.
See also: Biochemicals can be made 27 ▪ Drugs and disease 143

SUSUMU TONEGAWA
1939–

In 1971, Japanese microbiologist and immunologist Tonegawa found that genes in the B-lymphocyte, a white blood cell that produces antibodies, are moved around, recombined, and deleted. In vertebrates, this enables a limited number of genes to form millions of antibody types that can fight pathogens in the immune system. Tonegawa was awarded the 1987 Nobel Prize in Physiology or Medicine for his work.
See also: Immune response 168–71 ▪ What are genes? 222–25

STEPHEN JAY GOULD
1941–2002

The theory of punctuated equilibria was developed by American paleontologist and evolutionary biologist Gould, with American paleontologist Niles Eldredge. They proposed that most evolution of species (speciation) occurs in rapid bursts between long periods of extremely slow evolutionary change. Gould and Eldredge cited as evidence of explosive speciation the fossils from the Burgess Shale—fossil beds of fauna in Canada from the Cambrian period. Their theory divided opinion among evolutionary biologists.
See also: Naming and classifying life 250–53 ▪ Extinct species 254–55 ▪ Life evolves 256–57

CHRISTIANE NÜSSLEIN-VOLHARD
1942–

German developmental geneticist Nüsslein-Volhard helped solve one of biology's great mysteries: how the genes in a fertilized egg form an embryo. She used fruit flies (*Drosophila* spp.), whose embryos develop very rapidly, and worked with American developmental geneticist Eric Wieschaus. They invented saturation mutagenesis: a process of producing mutations in adult genes and observing the impact on the offspring. By 1980, Nüsslein-Volhard and Wieschaus had identified the genes that tell fly cells to form embryos. They won the 1995 Nobel Prize in Physiology or Medicine for their work.
See also: Embryological development 196–97

LARRY BRILLIANT
1944–

American epidemiologist Larry Brilliant contributed to major health projects in the developing world, including the WHO Intensified National Smallpox Eradication Program in India during 1972–76. In 1978, he co-founded the Seva Foundation to treat visual impairment in developing nations. By 2020, its doctors had restored the sight of five million people.
See also: Vaccination for preventing disease 164–67

TAK WAH MAK
1946–

The "holy grail of immunology" was discovered by Chinese-Canadian immunologist Mak in 1983, when he identified the DNA that coded for human T-cell receptors. These receptors are the protein complexes on the surfaces of T-lymphocytes (a type of white blood cell and part of the acquired immune system). Each receptor recognizes and binds to a specific foreign substance (antigen) in the body. Mak's discovery enabled the genetic modification of T-cells for use in immunotherapy.
See also: Cancer metastasis 154–55 ▪ Immune response 168–71 ▪ Genetic engineering 234–39

FLOSSIE WONG-STAAL
1946–2020

Chinese-American molecular biologist Wong-Staal in 1985 led the team that cloned the human immunodeficiency virus (HIV), the retrovirus that caused acquired immunodeficiency syndrome (AIDS). She determined the function of the HIV genes, helping understand how it evades the immune system and enabling the development of a blood test to detect the virus—a significant step in combating AIDS.
See also: Viruses 160–63 ▪ Immune response 168–71 ▪ The genetic code 232–33

ELIZABETH BLACKBURN
1948–

Australian-American molecular biologist and biochemist Blackburn became interested in telomeres, the "caps" that prevent damage to the ends of chromosomes when a cell divides. In 1982, with British-American geneticist Jack Szostak, she proved that the distinct DNA of a telomere stops its breaking down. In 1984, with American molecular biologist Carol Greider, Blackburn discovered the enzyme telomerase, which is crucial in replenishing telomeres, thereby protecting chromosomes and slowing aging of cells. Blackburn, Greider, and Szostak won the 2009 Nobel Prize in Physiology or Medicine.
See also: Enzymes as biological catalysts 64–65 ▪ Chromosomes 216–19 ▪ Sequencing DNA 240–41

LAP-CHEE TSUI
1950–

In 1989, with colleagues American geneticist Francis Collins and Canadian biochemist Jack Riordan, Chinese-Canadian geneticist Tsui isolated the gene on chromosome 7 that is partly responsible for cystic fibrosis (CF). The gene produces a protein called cystic fibrosis transmembrane conductance regular (CFTR). Once the gene's location was known, pre- and prenatal screening strategies for the mutation that causes cystic fibrosis could be developed.
See also: Chromosomes 216–19 ▪ What are genes? 222–25 ▪ Mutation 264–65

SUSAN GREENFIELD
1950–

British neuroscientist Greenfield researched brain functions and disorders, including Alzheimer's and Parkinson's diseases. In 2013, she co-founded a biotech company that discovered a neurotoxin that might cause Alzheimer's disease. She also warned that overuse of screen technologies could modify brain structure in young people.
See also: Innate and learned behavior 118–23 ▪ Organization of the brain cortex 126–29

FRANCES ARNOLD
1956–

In 1993, American biochemist Arnold developed the directed evolution technique, which accelerates natural selection of enzymes by introducing many mutations. Among the mutations, she found new enzymes that could be used to speed up or bring about chemical reactions. The technique has applications ranging from pharmaceuticals to renewable fuels. For her work, in 2018, Arnold became the fifth woman to receive the Nobel Prize in Chemistry.
See also: Enzymes as biological catalysts 64–65 ▪ How enzymes work 66–67

SARA SEAGER
1971–

Canadian astrophysicist Seager developed theoretical models of atmospheric conditions on exoplanets (planets that orbit stars other than the Sun). In 2013, Seager developed a mathematical model to estimate the number of habitable planets. Now known as the Seager equation, her model incorporates data on the presence or absence of biosignature gases (gases produced by life forms) in planetary atmospheres.
See also: Respiration 68–69 ▪ Life evolves 256-57

GLOSSARY

Abiotic Non-living; often used to refer to the non-living components of an ecosystem (such as climate and temperature).

Abscisic acid A hormone that regulates processes, including seed dormancy, in a plant's life cycle.

Active transport The transport of molecules or ions across a cell membrane that uses energy from respiration.

Agar A gelatinous substance extracted from red seaweed.

Air chemistry Also known as pneumatic or atmospheric chemistry; the study of the composition of the atmosphere (of Earth or other planets).

Amino acids The building blocks of protein molecules.

Anther The part of a flower's stamen that produces pollen.

Antibody A chemical produced by the body's immune system that binds to a specific target molecule (antigen) on foreign cells, helping the body destroy them.

Antigen A cell surface molecule that an antibody binds to.

Antiviral In medicine, a type of medication used to treat viral infections.

Apex predator A predator at the top of a food chain, which is not prey for any other species.

Assemblage Also known as a community; all the species that are found in a particular habitat.

Atom The smallest part of an element that has the chemical properties of that element.

Auxin A plant hormone that controls the way shoots and roots grow, such as in response to light or gravity.

Bacterium (pl. bacteria) A type of single-celled microorganism.

Benthic Related to the bottom of a body of water.

Biogeography The study of how plants and animals are distributed geographically, and the changes to this distribution over time.

Biosynthesis The production of complex molecules within the cells of living organisms.

Biotic Living organisms, or resulting from living organisms.

Calyx (pl. calyces) The outer part of a flower, made up of a ring of sepals. The calyx forms a cover that encloses the petals while in bud.

Carbon The main chemical element that makes up organic molecules, the basic components of organisms.

Carbon fixation The process in which living organisms convert carbon dioxide into organic compounds.

Carnivore Any animal that eats meat. Also used to describe mammals of the order Carnivora.

Carpel The female reproductive part of a flower, consisting of an ovary, style, and stigma. Also called pistil.

Carrier protein Protein molecule embedded in a cell's membrane that carries out active transport.

Cell The smallest unit of an organism that can exist on its own.

Channel protein A protein that forms a channel in a cell membrane that allows molecules and ions to pass across the membrane.

Chemical energy Energy stored in substances and released through a chemical reaction. For example, energy stored in food is released by the body's metabolism.

Chlorophyll Green pigment found in chloroplasts that enables them to absorb light energy and carry out photosynthesis.

Chloroplasts The chlorophyll-containing organelles inside plant cells, where sugars are formed during photosynthesis.

Cholesterol A fatlike substance found in every animal cell. It is vital for normal body function, but if too much builds up in the blood it can cause problems, such as heart disease.

Circadian rhythm The 24-hour biological cycle that governs the body's day/night processes. Informally, the body clock.

Cohesion The process of sticking together of like molecules.

Corolla A ring of petals on the head of a flower.

Cross-pollination The transfer of pollen from the anthers of a flower on one plant to the stigma of a bloom on another plant.

Culture A collection of cells grown in a controlled environment for the purposes of study or analysis, such as bacteria grown in a laboratory.

Cuticle The outer layer or part of an organism that comes in contact with the environment. In plants, a protective, waxy, water-repellent coating of the outer cell surface of the epidermis.

Cytokinin A type of plant hormone that is involved in cell growth in plant roots and shoots.

Dark reaction The light-independent chemical processes of photosynthesis that involve fixation of carbon dioxide into organic molecules.

Dichogamy When male and female reproductive cells on a flower mature at different times to ensure cross-pollination.

Diffusion The movement of particles from a region of high concentration to a region of low concentration.

Dioecious A plant that bears unisexual flowers, with male and female blooms occurring on separate plants.

Diversity A measure of the variety of species within a biological community or ecosystem.

DNA Deoxyribonucleic acid is a large molecule in the shape of a double helix that carries genetic information.

Dormancy A state in which an organism's physical processes are slowed down or suspended for a period of time, usually to conserve energy until conditions are favorable for growth and development.

Ecosystem A community of animals and plants and the physical environment they share.

Electron A subatomic particle with a negative electric charge.

Endosperm Food-storing tissue that surrounds the embryo in the seeds of flowering plants.

Enzyme A molecule, usually a protein, that accelerates a chemical reaction in a living organism.

Ethylene A colorless hydrocarbon (an organic compound of hydrogen and carbon) gas, used in the manufacture of polyethylene.

Exobiology The branch of biology that deals with the possibility, origin, and nature of life in space and on other planets.

Fermentation A type of chemical respiration that is anaerobic (does not use oxygen), and may produce acids, alcohol, or carbon dioxide as waste products.

Filament The stalk that bears the anther in a flower.

Food chain A series of organisms, each of which is eaten by the next.

Gametes The sexual reproductive cells of organisms—the male sperm or pollen and female egg.

Genome The full set of genes, or hereditary information, for a living organism.

Geotropism The response of plants to gravity. For example, a plant shoot growing upward (against gravity) is negative geotropism.

Gibberellins Plant hormones involved in controlling many aspects of growth and development, such as triggering the end of dormancy in seeds and flower buds.

Humor In ancient medicine, a liquid in the body that was thought to determine a person's health and temperament. The four humors were blood, phlegm, yellow bile, and black bile.

Hydrophilic Material with an affinity to water.

Hydrophobic Material that repels water.

Hydrothermal vent An opening in Earth's crust at the bottom of an ocean, which is an outlet for superheated water, rich in a variety of minerals.

Immigration The movement of a species or organism into a new ecosystem, or geographical region.

Interstitial fluid Fluid in the body that occupies the spaces between cells.

Inorganic A chemical substance that is not a complex carbon-containing molecule

Invertebrate An animal without a backbone.

Ion An atom, or group of atoms, that has lost or gained one or more of its electrons to become electrically charged.

Lepidopterist One who studies or collects butterflies and moths.

Limnology The study of inland water ecosystems.

Lipid Fatty or oily substance, insoluble in water, with varied roles in the body, including formation of adipose tissue, cell membranes (phospholipid), and steroid hormones.

Mesopredator A mid-level predator, which is both a predator and preyed upon.

Mesopredator release An ecological theory that describes the boom in population numbers of mesopredators when there is a decline in the number of apex predators in an ecosystem.

Metabolism The sum of all the chemical processes that take place in the body.

Microbe A microscopic organism, or microorganism.

Molecule A group of two or more atoms joined by strong chemical bonds.

Monoculture A method of farming that involves growing a single crop, often over a large area.

Monoecious A plant with separate male and female flowers that are borne on the same plant.

Montane Of a forest: a type of woodland in mountainous areas.

Nectar guides Markings or patterns on a flower that guide pollinators to the nectar.

Nectary A gland in a plant that secretes nectar.

Niche The specific space and role that a species occupies within an ecosystem. The different species in an ecosystem will never occupy the same niche.

Niche conservatism The degree to which species retain their niche over time.

Nucleotide Building-block subunit of a nucleic acid (DNA, RNA) consisting of a sugar, phosphate, and a nitrogen-containing base.

Nucleus The control center of a eukaryotic cell, where the cell's genes arestored in DNA molecules. The word "nucleus" can also refer to the central part of an atom.

Omnivore An animal that eats both plants and animals.

Organelle A structure inside a cell that performs a specific task, such as making protein molecules or releasing energy from sugar.

Organic Derived from living organisms, or a compound based on carbon and hydrogen atoms.

Organism A living thing.

Osmosis The movement of water through a partially permeable membrane from a low to high solute concentration.

Paleoecology The study of past ecosystems using geological and fossil records.

Pandemic An outbreak of a disease that affects a very large number of people worldwide.

Pasteurization A process of mildly heating foods, such as milk or wine, to eliminate pathogens, such as bacteria, without altering the taste of the food.

Pathogen Any microorganism that causes disease.

Pelagic Relating to or living in the waters of the open ocean, without immediate contact with the shore or ocean floor.

Phospholipid A type of lipid (fatty) substance that forms cell membranes.

Photoreceptor A type of specialized, light-sensitive cell that forms the retinal layer at the back of animals' eyes.

Photosynthesis The process by which plants use the Sun's energy to make food molecules from water and carbon dioxide, producing oxygen as a waste product.

Phototropism The growth of part of a plant towards or away from light. Positive phototropism means growing toward the light.

Phytochrome A type of light-detecting substance found in plants, fungi, and bacteria.

Phytogeography Branch of botany that studies the geographical distribution of plants.

Plant growth regulator (PGR) A compounds that benefits and influences plant growth.

Plasma The fluid part of the blood from which all cells have been removed; contains proteins, salts, and various other nutrients and waste products.

Plate tectonics The study of continental drift and the way in which the ocean floor spreads.

Pollen Small grains, formed in the anther of seed-bearing plants, which contain the male reproductive cells of the flower.

Pollinium (pl. pollinia) A mass of pollen grains within a flower.

Predator An animal that hunts other animals for food.

Prey An animal hunted by other animals.

Protein A complex substance composed of chains of amino acids that is found in all living organisms and needed for growth and repair, and many other vital processes.

Protocell A complex molecule with self-copying abilities, wrapped in a membrane.

Protozoa Typically microscopic, single-celled organisms with a clearly defined nucleus encased within a membrane.

Pseudocopulation In flowers, pollination that occurs when male insects are tricked into copulating with a part of a flower that mimics a female insect.

Rain forest A forest characterized by evergreen trees and a high annual rainfall. Most commonly found in the tropics.

Reduction A chemical reaction in which a substance loses oxygen. During reduction, atoms gain electrons.

Respiration A chemical process in cells that involves the release of energy from food molecules.

RNA Ribonucleic acid is a molecule similar to DNA. RNA molecules copy the genetic information in DNA so that it can be used to make protein molecules.

Ribozyme A molecule of RNA that acts as an enzyme.

Self-incompatibility Of flowers, unable to pollinate themselves in order to reproduce.

Semipermeable Allows some substances to pass through but blocks others. Cell membranes are semipermeable. Also called partially permeable.

Sepal Part of the calyx.

Species A group of organisms with similar characteristics that can breed with each other to produce fertile offspring.

Species richness The number of different species represented in a particular location or ecological community.

Stamen The male reproductive part of a flower comprising the pollen-producing anther and usually its supporting filament or stalk.

Stigma The female part of a flower that receives pollen before fertilization. The stigma is situated at the tip of the style.

Stoma (pl. stomata) A microscopic pore in the surface of aerial parts of plants (leaves and stems), allowing transpiration to take place.

Style The stalk that connects the stigma to the ovary in flowers.

Vaccine A dead, modified, or inactive part of a pathogen that is deliberately introduced into the body to trigger immunity to that pathogen.

Vertebrate An animal with a backbone (vertebral column).

Virus A parasitic, non-cellular, particle containing DNA or RNA that infects the cells of living organisms. Viruses reproduce by making the host cells manufacture more copies of the virus. Some viruses cause disease, but most do not.

Xylem Plant tissue made up of microscopic vessels that carry water and minerals from roots to leaves and may become woody for support.

Zoogeography Branch of zoology that studies the geographical distribution of animals.

Zoology Branch of biology that studies the animal kingdom.

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