Within days, Watson and Crick had built a new model of DNA from metal parts. Wilkins immediately accepted that it was correct. It was agreed between the two groups that they would publish three papers simultaneously in *Nature*, with the King's researchers commenting on the fit of Watson and Crick's structure to the experimental data, and Franklin and Gosling publishing Photograph 51 for the first time[7,8].

The Cambridge pair acknowledged in their paper that they knew of "the general nature of the unpublished experimental results and ideas" of the King's workers, but it wasn't until *The Double Helix*, Watson's explosive account of the discovery, was published in 1968 that it became clear how they obtained access to those results. Franklin had died of cancer a decade previously; her death prevented her from sharing the Nobel prize awarded to Watson, Crick and Wilkins in 1962.

The immediate reception of the double-helix model was surprisingly muted[9], perhaps because there was no obvious mechanism to explain its role in protein synthesis. In a landmark talk in 1957, Crick proposed that the base sequence encoded the sequence of amino acids in a protein, and that protein production involved RNA both as a template and as an 'adaptor' that would enable amino acids to be attached to one another in the right order. He also supported the suggestion — originally made informally by the physicist George Gamow to the members of the 'RNA Tie Club' convened by Gamow and Watson, but also independently proposed by biologist Sydney Brenner[10] — that triplets of bases (which Brenner called codons) encode the 20 amino acids commonly found in proteins. Finally, Crick expounded what he called the 'central dogma' of biology: that information can flow from nucleic acids to proteins, but not the other way round[11].

These predictions were confirmed by experiment in the next few years. In 1958, the biochemists Matthew Meselson and Franklin Stahl showed that one DNA strand acts as a template for the formation of a new strand[12]. The same year, Arthur Kornberg and his colleagues published their discovery of the enzyme DNA polymerase[13], which adds bases to newly forming strands. Messenger RNA, transfer RNA and ribosomal RNA were all quickly identified.

In 1961, Marshall Nirenberg and Heinrich Matthaei were the first to crack part of the genetic code, demonstrating that bacterial extracts synthesize only the amino acid phenylalanine from RNA that contains just one type of RNA base[14] (uracil; U). The same year, Crick, his indispensable female technician Leslie Barnett and their co-workers reported mutation studies that confirmed the existence of the triplet-based code[15], and which therefore suggested that the codon for phenylalanine was UUU. The race to identify the full set of codons was completed by 1966, with Har Gobind Khorana contributing the sequences of bases in several codons from his experiments with synthetic polynucleotides (see go.nature.com/2hebk3k).

With Fred Sanger and colleagues' publication[16] of an efficient method for sequencing DNA in 1977, the way was open for the complete reading of the genetic information in any species. The task was completed for the human genome by 2003, another milestone in the history of DNA.

Watson devoted most of the rest of his career to education and scientific administration as head of the Cold Spring Harbor Laboratory in Long Island, New York, and serving (briefly) as the first head of the US National Center for Human Genome Research, now the National Human Genome Research Institute. Always outspoken, he was eventually removed from his emeritus position at Cold Spring Harbor when he repeatedly aired controversial opinions about genetics, race and intelligence.

Crick continued to tackle hard problems in science, moving in 1977 from Cambridge to the Salk Institute in La Jolla, California, where he spent the rest of his life working on the neural basis of consciousness[17] and, specifically, of visual perception. He died in 2004, aged 88.

The double helix put genetics on a physical footing that would shed light on almost every aspect of modern biology and medicine. Examples include the migration of human populations throughout history; ecology and biodiversity; cancer-causing mutations in tumours and their drug treatment; surveillance of microbial drug resistance in hospitals and the global population; and the diagnosis and treatment of rare congenital diseases. DNA analysis has long been established in forensics, and research into more-futuristic applications, such as DNA-based computing, is well advanced.

Paradoxically, Watson and Crick's iconic structure has also made it possible to recognize the shortcomings of the central dogma, with the discovery of small RNAs that can regulate gene expression, and of environmental factors that induce heritable epigenetic change. No doubt, the concept of the double helix will continue to underpin discoveries in biology for decades to come.

**Georgina Ferry** is a science writer based in Oxford, UK. A revised edition of her biography *Dorothy Crowfoot Hodgkin* has just been published by Bloomsbury Reader.

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High-energy physics

# Detection of a strange particle

**Taku Yamanaka**

In 1947, scientists found a previously unseen particle, which is now called a neutral kaon. This work led to the discovery of elementary particles known as quarks, and ultimately to the establishment of the standard model of particle physics.

In the late 1940s, the physicists George Rochester and Clifford Butler[1] observed something unusual in their charged-particle detector. They were studying the interactions between high-energy cosmic rays and a lead plate in the detector when they spotted V-shaped particle tracks (Fig. 1a). The small gap between the lead plate and the vertex of the tracks indicated that an invisible neutral particle had been produced in the plate, had travelled for a short distance and had then decayed into two visible charged particles. The mass of the neutral particle was about 1,000 times that of an electron, implying

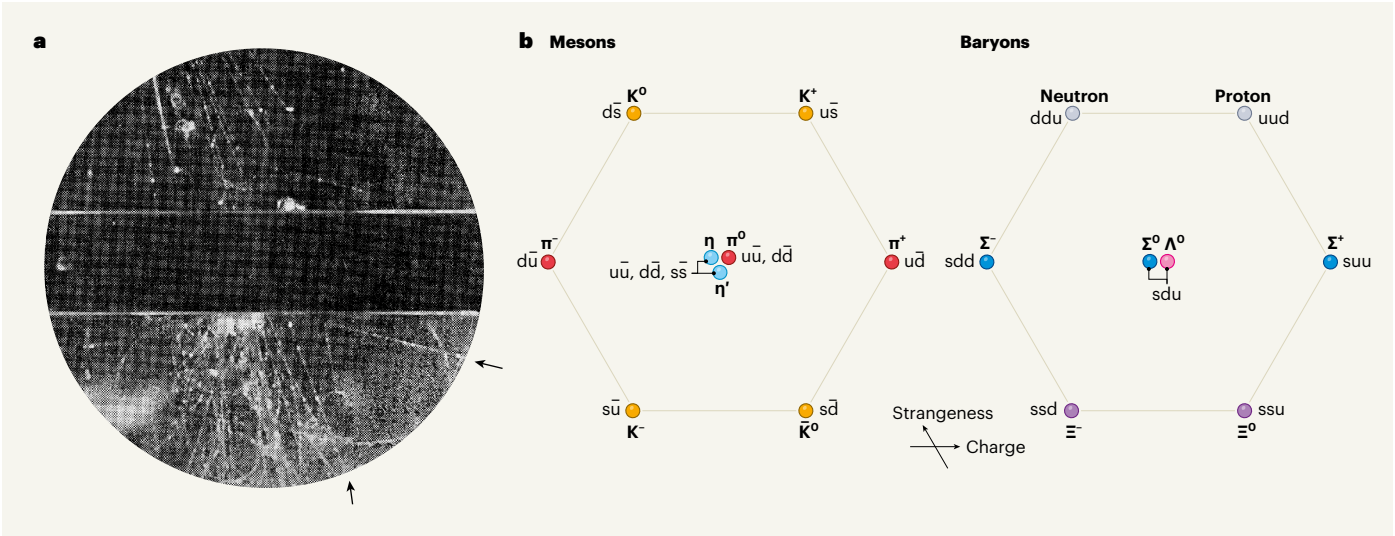


**Figure 1 | Particle detection that led to a better understanding of fundamental physics. a**, In 1947, Rochester and Butler[1] analysed the particles produced when high-energy cosmic rays hit a lead plate (the broad central stripe) in a charged-particle detector. In certain photographs, they spotted evidence of a previously undetected, invisible neutral particle decaying into two visible charged particles, which were identified by tracks (labelled with arrows). **b**, The discovery of many more particles following Rochester and Butler's work led to a model[12,13] in which all of the known mesons and baryons (two classes of particle) consist of elementary particles called up (u), down (d) and strange (s) quarks, along with their antiparticles (denoted by overbars). The η, η′ and $\pi^0$ mesons comprise mixtures of quark pairs. The mesons and baryons are arranged by their strangeness (a quantity that is related to the presence of strange quarks) and electric charge.

that it must be a previously unreported type of particle. This discovery paved the way for many puzzles and surprises in particle physics in the decades that followed.

At the time of Rochester and Butler's work, protons, neutrons, electrons and particles called pions (short for π mesons) had been identified, and were known to be sufficient to form atoms. Pions were proposed[2] in 1935 to explain how protons and neutrons are held together in small atomic nuclei by the strong nuclear force, and were found experimentally[3,4] in 1947.

While searching for a pion in cosmic rays, scientists discovered a different particle[5], which is now called a muon. A heavy charged particle was then found[6] in 1944, followed by Rochester and Butler's unstable neutral particle. But the discovery of unexpected particles did not stop there. Then came the τ meson, which decays into three pions; the θ meson, decaying into two pions; the κ meson, decaying into a muon and an invisible particle; the $\Lambda^0$ particle, decaying into a proton and a pion; and the list goes on.

In the early 1950s, researchers began producing these rare particles in large quantities by firing protons at targets in particle accelerators. The τ, θ and κ mesons and $\Lambda^0$ particle were peculiar, because, although they were generated by the strong force, their decay times were much longer than those expected for this force. To explain these observations, physicists proposed a quantity, known as strangeness ($S$), that is conserved by the strong force[7,8].

Protons and neutrons have $S = 0$, and through the strong force, can produce a pair of strange particles that have $S = -1$ and $S = +1$, so that total strangeness is conserved. However, a strange particle that has $S = -1$, for example, cannot decay into particles that have $S = 0$ through the strong force, because strangeness would not be conserved. Instead, this decay must occur much more slowly through the weak nuclear force, which allows total strangeness to change.

As the accuracy of accelerator-based measurements increased, it became clear that the τ and θ mesons had extremely similar masses and lifetimes. Scientists concluded that these mesons must be the same particle, which is able to decay into two or three pions. The mess of strange mesons was finally cleaned up into four particles dubbed kaons (short for K mesons): $K^+$ and $K^0$ and their antiparticles $K^-$ and $\bar{K}^0$.

However, accepting that the τ and θ mesons were the same particle raised another problem. A state of two pions has even parity, which means that its wavefunction does not change sign under a parity transformation (in which spatial coordinates are flipped). By contrast, a state of three pions has odd parity. If the same particle could decay into two or three pions, did that mean that, contrary to all conventional wisdom, parity is not conserved by the weak force? This question, known as the τ–θ puzzle, led to the discovery, in 1957, of such parity-symmetry breaking in cobalt-60 decays[9] and in pion decays[10].

A consequence of parity-symmetry breaking by the weak force is that elementary particles called neutrinos can be only left-handed, which means that their motion and intrinsic angular momentum are in opposite directions. Under a parity transformation, a left-handed neutrino becomes a right-handed neutrino, which does not exist. However, if one then applies a charge-conjugation transformation (in which particles are replaced by their antiparticles), the right-handed neutrino becomes a right-handed antineutrino, which does exist. The weak force therefore seemed to conserve CP symmetry (symmetry under a combined charge-conjugation and parity transformation), until such symmetry was found to be broken in neutral-kaon decays.

A neutral kaon is a mixture of $K^0$ and $\bar{K}^0$ states, and can exist as the CP-even state $K_{even}$ or the CP-odd state $K_{odd}$. The lifetime of $K_{odd}$ is much longer than that of $K_{even}$, so these particles were named $K_L$ (for 'K-long') and $K_S$ (for 'K-short'), respectively. A useful consequence of such lifetimes is that, if neutral kaons are produced by firing protons at a target, the CP-even $K_S$ component quickly decays, leaving only the CP-odd $K_L$ component. In 1964, such $K_L$ particles were observed[11] to decay into the CP-even state of two oppositely charged pions ($\pi^+\pi^-$). Therefore, despite expectations, CP symmetry was shown to be broken.

In that same year, physicists proposed a model[12,13] to explain all of the known mesons and baryons — a family that includes protons, neutrons and the $\Lambda^0$ particle. In the model, these mesons and baryons consist of elementary particles known as quarks, which come in three types: up, down and strange (Fig. 1b).

In 1973, a theoretical model[14] showed that the breaking of CP symmetry could be explained by introducing three more quarks: charm, top and bottom. In this framework, $K_L$ can have a small component of $K_{even}$ that can decay into the CP-even $\pi^+\pi^-$ state. But unlike other theoretical models, this framework also allows $K_{odd}$ to decay into the CP-even state (direct CP violation).

Many generations of experiments then were carried out to see whether direct CP violation exists. The measurement required extremely high precision, and after many improvements over 25 years, direct CP violation was finally confirmed[15,16]. Together with the observation of CP-symmetry breaking in B mesons (mesons that contain a bottom quark)[17,18], the theoretical model was confirmed, and helped to establish the standard model of particle physics, which is the current explanation of the Universe's particles and forces.

However, the standard model is not complete. For instance, it cannot explain why the Universe contains so little antimatter, nor what the mysterious substance called dark matter is. Researchers are therefore trying to search for a hint of particle physics beyond that of the standard model. For example, experiments in Japan[19] and Europe[20] are using extremely rare kaon decays to search for such a hint.

In retrospect, Rochester and Butler's V-shaped particle tracks are thought to have been caused by a $K_S$, produced in the lead plate, decaying into the $\pi^+\pi^-$ state. Since their work, kaons have been used to discover strangeness and the breaking of parity and CP symmetries, to build the quark model and the standard model, and now to search for previously unseen particle physics. Could Rochester and Butler have ever imagined that they had opened such a treasure chest?

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Neuroscience

# Neuronal signals thoroughly recorded

**Alexander D. Reyes**

Originally developed to record currents of ions flowing through channel proteins in the membranes of cells, the patch-clamp technique has become a true stalwart of the neuroscience toolbox.

Information in the brain is thought to be encoded as complex patterns of electrical impulses generated by thousands of neuronal cells. Each impulse, known as an action potential, is mediated by currents of charged ions flowing through a neuron's membrane. But how the ions pass through the insulated membrane of the neuron remained a puzzle for many years. In 1976, Erwin Neher and Bert Sakmann developed the patch-clamp technique, which showed definitively that currents result from the opening of many channel proteins in the membrane[1]. Although the technique was originally designed to record tiny currents, it has since become one of the most important tools in neuroscience for studying electrical signals — from those at the molecular scale to the level of networks of neurons.

By the 1970s, current flowing through the cell was generally accepted to result from the opening of many channels in the membrane, although the underlying mechanism was unknown. At that time, current was commonly recorded by impaling tissue with a sharp electrode — a pipette with a very fine point. Unfortunately, however, the signal recorded in this way was excessively noisy, and so only the large, 'macroscopic' current — the collective current mediated by many different types of channel — that flows through the tissue could be resolved.

In 1972, Bernard Katz and Ricardo Miledi[2], pioneers of the biology of the synaptic connections between cells, managed to infer from the macroscopic current certain properties of the membrane channels, but only after a heroic effort to exclude all possible confounding factors. The problem was that the macroscopic current could be influenced by factors not directly related to channel activity, such as cell geometry and modulatory processes that regulate cell excitability. Also troublesome was that interpretations of macroscopic-current features were based on unverified assumptions about the statistics of individual channel activity[2,3]. Despite Katz and Miledi's careful analyses, there was a lingering doubt about whether their conclusions were correct. The crucial data were obtained by Neher and Sakmann using patch clamp.

The patch-clamp technique is conceptually rather simple. Instead of impaling the cells, a pipette with a relatively large diameter is pressed against the cell membrane. Under the right conditions, the pipette tip 'bonds' with the membrane, forming a tight seal. This substantially reduces the noise compared with that encountered using sharp electrodes, because the small patch of membrane encompassed by the pipette tip is electrically isolated from the rest of the cell's membrane and from the environment surrounding the cell (Fig. 1).

The tiny currents passing through the few channels in the patch were thus observed for the first time. The recording confirmed key channel properties: when channels open, there is a step-like jump in the current trace and, when they close, a step-like drop back to baseline. It was now possible to determine details such as the statistics of the opening and closing of channels, the amplitude of the currents they mediate and the optimal stimuli that trigger their opening. For this work, Neher and Sakmann were awarded the 1991 Nobel Prize in Physiology or Medicine.

Improvements in patch clamp made it feasible to study channels in various preparations[4] to finally address long-standing questions. There was particular interest in verifying a model for action-potential generation[5] proposed by Nobel laureates Alan Hodgkin and Andrew Huxley in the 1950s. Specific predictions of the model could now be tested directly by examining the current through individual channels and by observing the changes in current that occur when the molecular structure of the channel is modified[6]. Ultimately, the model was shown to be mostly correct and remains the gold standard for computational neuroscientists today.

One of the several variants of patch clamp[4] — the whole-cell configuration — found an audience with neuroscientists studying electrical phenomena in neurons beyond the channel level. To achieve whole-cell recording, the