

# Frederick Sanger

Frederick Sanger, 1993. **Frederick Sanger** (born August 13, 1918, Rendcombe, Gloucestershire, England—died November 19, 2013, Cambridge) was an English biochemist who was twice the recipient of the Nobel Prize for Chemistry. He was awarded the prize in 1958 for his determination of the structure of the insulin molecule. He shared the prize (with Paul Berg and Walter Gilbert) in 1980 for his determination of base sequences in nucleic acids. Sanger was the fourth two-time recipient of the Nobel Prize.

## Education

Sanger was the middle child of Frederick Sanger, a medical practitioner, and Cicely Crewsdon Sanger, the daughter of a wealthy cotton manufacturer. The family expected him to follow in his father's footsteps and become a medical doctor. After much thought, he decided to become a scientist. In 1936 Sanger entered St. John's College, Cambridge. He initially concentrated on chemistry and physics, but he was later attracted to the new field of biochemistry. He received a bachelor's degree in 1939 and stayed at Cambridge an additional year to take an advanced course in biochemistry. He and Joan Howe married in 1940 and subsequently had three children.

Because of his Quaker upbringing, Sanger was a conscientious objector and was assigned as an orderly to a hospital near Bristol when World War II began. He soon decided to visit Cambridge to see if he could enter the doctoral program in biochemistry. Several researchers there were interested in having a student, especially one who did not need money. He studied lysine metabolism with biochemist Albert Neuberger. They also had a project in support of the war effort, analyzing nitrogen from potatoes. Sanger received a doctorate in 1943.

## Insulin research

Biochemist Albert C. Chibnall and his protein research group moved from Imperial College in London to the safer wartime environment of the biochemistry department at Cambridge. Two schools of thought existed among protein researchers at the time. One group thought proteins were complex mixtures that would not readily lend themselves to chemical analysis. Chibnall was in the other group, which considered a given protein to be a distinct chemical compound.

Chibnall was studying insulin when Sanger joined the group. At Chibnall's suggestion, Sanger set out to identify and quantify the free-amino groups of insulin. Sanger developed a method using dinitrofluorobenzene to produce yellow-coloured derivatives of amino groups (*see* amino acid). Information about a new separation technique, partition chromatography, had recently been published. In a pattern that typified Sanger's career, he immediately recognized the utility of the new technique in separating the hydrolysis products of the treated protein. He identified two terminal amino groups for insulin, phenylalanine and glycine, suggesting that insulin is composed of two types of chains. Working with his first graduate student, Rodney Porter, Sanger used the method to study the amino terminal groups of several other proteins. (Porter later shared the 1972 Nobel Prize for Physiology or Medicine for his work in determining the chemical structure of antibodies.)

On the assumption that insulin chains are held together by disulphide linkages, Sanger oxidized the chains and separated two fractions. One fraction had phenylalanine at its amino terminus; the other had glycine. Whereas complete acid hydrolysis degraded insulin to its constituent amino acids, partial acid hydrolysis generated insulin peptides composed of several amino acids. Using another recently introduced technique, paper chromatography, Sanger was able to sequence the amino-terminal peptides of each chain, demonstrating for the first time that a protein has a specific sequence at a specific site. A combination of partial acid hydrolysis and enzymatic hydrolysis allowed Sanger and the Austrian biochemist Hans Tuppy to determine the complete sequence of amino acids in the phenylalanine chain of insulin. Similarly, Sanger and the Australian biochemist E.O.P. Thompson determined the sequence of the glycine chain.

Two problems remained: the distribution of the amide groups and the location of the disulphide linkages. With the completion of those two puzzles in 1954, Sanger had deduced the structure of insulin. For being the first person to sequence a protein, Sanger was awarded the 1958 Nobel Prize for Chemistry.

Sanger and his coworkers continued their studies of insulin, sequencing insulin from several other species and comparing the results. Utilizing newly introduced radiolabeling techniques, Sanger mapped the amino acid sequences of the active centres from several enzymes. One of these studies was conducted with another graduate student, Argentine-born immunologist César Milstein. (Milstein later shared the 1984 Nobel Prize for Physiology or Medicine for discovering the principle for the production of monoclonal antibodies.)

## **RNA research**

In 1962 the Medical Research Council opened its new laboratory of molecular biology in Cambridge. The Austrian-born British biochemist Max Perutz, British biochemist John Kendrew, and British biophysicist Francis Crick moved to the new laboratory. Sanger joined them as head of the protein division. It was a banner year for the group, as Perutz and Kendrew shared the 1962 Nobel Prize for Chemistry and Crick shared the 1962 Nobel Prize for Physiology or Medicine with the American geneticist James D. Watson and the New Zealand-born British biophysicist Maurice Wilkins for the discovery of DNA (deoxyribonucleic acid).

Sanger's interaction with nucleic acid groups at the new laboratory led to his pursuing studies on ribonucleic acid (RNA). RNA molecules are much larger than proteins, so obtaining molecules small enough for technique development was difficult. The American biochemist Robert W. Holley and his coworkers were the first to sequence RNA when they sequenced alanine-transfer RNA. They used partial hydrolysis methods somewhat like those Sanger had used for insulin. Unlike other RNA types, transfer RNAs have many unusual nucleotides. This partial hydrolysis method would not work well with other RNA molecules, which contain only four types of nucleotides, so a new strategy was needed.

The goal of Sanger's lab was to sequence a messenger RNA and determine the genetic code, thereby solving the puzzle of how groups of nucleotides code for amino acids. Working with British biochemists George G. Brownlee and Bart G. Barrell, Sanger developed a two-dimensional electrophoresis method for sequencing RNA. By the time the sequence methods were worked out, the code had been broken by other researchers, mainly the

American biochemist Marshall Nirenberg and the Indian-born American biochemist Har Gobind Khorana, using in vitro protein synthesis techniques. The RNA sequence work of Sanger's group did confirm the genetic code.

## **DNA research**

By the early 1970s Sanger was interested in deoxyribonucleic acid (DNA). DNA sequence studies had not developed because of the immense size of DNA molecules and the lack of suitable enzymes to cleave DNA into smaller pieces. Building on the enzyme copying approach used by the Swiss chemist Charles Weissmann in his studies on bacteriophage RNA, Sanger began using the enzyme DNA polymerase to make new strands of DNA from single-strand templates, introducing radioactive nucleotides into the new DNA. DNA polymerase requires a primer that can bind to a known region of the template strand. Early success was limited by the lack of suitable primers. Sanger and British colleague Alan R. Coulson developed the "plus and minus" method for rapid DNA sequencing. It represented a radical departure from earlier methods in that it did not utilize partial hydrolysis. Instead, it generated a series of DNA molecules of varying lengths that could be separated by using polyacrylamide gel electrophoresis. For both plus and minus systems, DNA was synthesized from templates to generate random sets of DNA molecules from very short to very long. When both plus and minus sets were separated on the same gel, the sequence could be read from either system, one confirming the other. In 1977 Sanger's group used this system to deduce most of the DNA sequence of bacteriophage  $\Phi$ X174, the first complete genome to be sequenced.

A few problems remained with the plus and minus system. Sanger, Coulson, and British colleague Steve Nicklen developed a similar procedure using dideoxynucleotide chain-terminating inhibitors. DNA was synthesized until an inhibitor molecule was incorporated into the growing DNA chain. Using four reactions, each with a different inhibitor, sets of DNA fragments were generated ending in every nucleotide. For example, in the A reaction, a series of DNA fragments ending in A (adenine) was generated. In the C reaction, a series of DNA fragments ending in C (cytosine) was generated, and so on for G (guanine) and T (thymine). When the four reactions were separated side by side on a gel and an autoradiograph developed, the sequence was read from the film. Sanger and his coworkers used the dideoxy method to sequence human mitochondrial DNA. For his contributions to DNA sequencing methods, Sanger shared the 1980 Nobel Prize for Chemistry. He retired in 1983.

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