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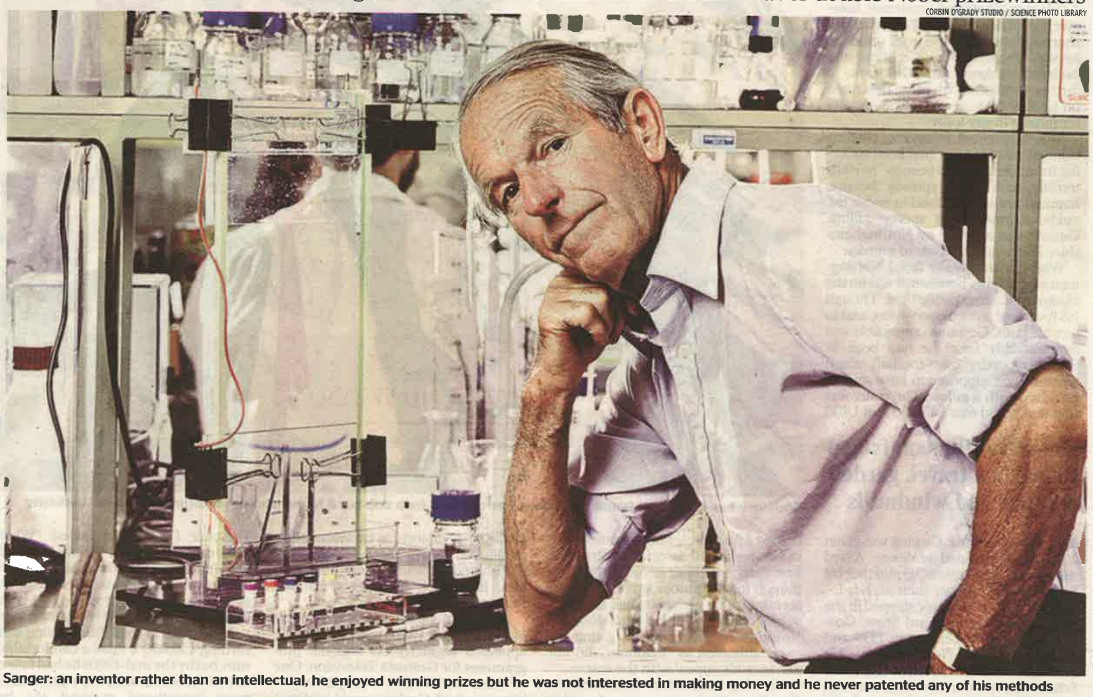
Obituaries

Frederick Sanger

Unassuming British biochemist whose pivotal and far-reaching discoveries made him one of the handful of double Nobel prizewinners



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Sanger: an inventor rather than an intellectual, he enjoyed winning prizes but he was not interested in making money and he never patented any of his methods

"It happens only once in one's life," said Fred Sanger after the King of Sweden had presented him with the Nobel Prize for Chemistry in 1958. This was one of the few occasions when Sanger was to be proved wrong — he won the Nobel Prize for Chemistry a second time in 1980.

Only four individuals have won the prize twice, and of these only Sanger won two prizes in chemistry. He received the prizes for his work on determining the sequences of amino acids in proteins and in DNA.

The impact of his discoveries was immense, and they continue to reverberate today. A famously and disarmingly modest man who once described himself as "just a chap who messed about in his lab", Sanger is regarded as no less than the father of the genomic era, and his work threw open whole scientific fields of molecular biology and genetics.

By laying the foundations for our ability to read and understand the genetic code he revolutionised many branches of biology and medicine, with the promise of curing many of humanity's gravest illnesses. And despite the dizzying speed of scientific advance, the Sanger method of DNA sequencing — for which he was awarded the 1980 Nobel Prize — is still used today. It is not fanciful to say that the effect on science of his discoveries over the past 50 years resembles that of computers on society in the same period.

Though garlanded with the highest honours and academic distinctions, Sanger was an inventor, not an intellectual. He shunned the corridors of power. Outside biochemistry his views were naive. When he was elected a Fellow of King's College he hardly ever bothered to go there. He was averse to reading and especially to writing, which he confined to the minimum needed for publication of his work. He disliked teaching and administration, so he was never tempted to accept a professorship. He enjoyed winning his many prizes, but was not interested in making money in other ways — he never patented any of his methods.

Sanger was extremely courteous and charming. He was a keen gardener but had few other interests apart from messing about in boats. He lived quietly and happily at home with his family. He invited no one to his home, not because he could not make friends, but because he did not need any. He had absorbed the Quaker virtues of honesty, industry, perseverance, modesty and good nature from his schooling and his childhood roaming the Gloucestershire countryside.

He was born in 1918 in the village of Rendcombe, and was sent to a Quaker school when he was 9. From there he moved to Bryanston School in Dorset and then, in 1936, St John's College, Cambridge. He had thought to follow his physician father — who had taken a medical degree at Cambridge , done research in immunology and served in China as a Quaker medical missionary — but decided to opt for the sciences.

He took physics and chemistry as his main subjects and biochemistry as a subsidiary. He soon found physics too difficult and gave it up in favour of biochemistry. His teacher, Ernest Baldwin, inspired him with the vision of explaining the workings of the living body in terms of the laws of physics and chemistry and he became passionate about biochemistry.

He graduated in 1939, on the eve of the war. When hostilities broke out he decided, on the strength of his Quaker beliefs, to register as a conscientious objector. To help alleviate the suffering caused by the war, he learnt farming, building and first aid, and then took a job as a hospital cleaner, but soon felt that he was not really helping anyone. He therefore arranged to do a PhD at

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Cambridge. He wrote his thesis on the metabolism of the amino acid lysine — it was criticised for poor spelling — and received his PhD in 1943.

In 1943 a new Professor of Biochemistry at Cambridge, A. C. Chibnall, suggested to Sanger that he should determine the nature of the amino acids that start the polypeptide chains in insulin, and got him support from the Medical Research Council.

Sanger's inventiveness first showed in a new method of labelling the amino acids at the start of the protein chains with a yellow dye. When the protein chains were split up with acid, the labelled amino acids could be separated from the others and identified. In 1945, when Sanger published his first results, little was known about the chemical structure of insulin, or, for that matter, of any other protein, beyond their amino acid compositions.

To determine the order in which the amino acids are arranged was beyond the power of existing chemical methods but within a decade Sanger had worked out methods that allowed him and his collaborators to show that insulin was made up of two chains, one containing 21 amino acids and the other 30. It was the first time the chemical formula of a protein had been determined.

The impact of Sanger's results was immense. They proved for the first time that pure proteins were definite chemical individuals possessing unique formulae. They showed that each position in the chain is occupied by one and only one amino acid, and that the order of amino acids along the chain, though unique, is devoid of regularity. The order varied in the insulins of different animals, showing that it was genetically determined and posing the question of the nature of the genetic information that determined it.

In 1944 this work — done in a crammed basement room of the Biochemistry Department in Tennis Court Road, Cambridge — won Sanger a Beit Memorial Fellowship for Medical Research and in 1951 an appointment to the staff of the Medical Research Council (MRC). It also won him his first Nobel Prize.

In 1957 Max Perutz, head of a MRC unit at the Cavendish Laboratory, Cambridge, invited Sanger to join a Laboratory of Molecular Biology that Perutz hoped the council would build. Sanger accepted. The merger of Perutz's and Sanger's teams assured the MRC that the proposed lab would be scientifically well balanced and was crucial for its approval of Perutz's plan.

In 1962, when the Queen opened the new laboratory, Sanger was trying to develop micro methods for determining amino acid sequences. He was sceptical at first of the new concepts of molecular biology such as the role of ribonucleic acid (RNA) and the genetic code. He decided to develop faster and more sensitive methods of determining the sequences of amino acids, based on labelling nucleic acids with radioactive atoms. His methods needed only one thousandth of the amount of material required by the earlier methods and were much quicker.

In most organisms the genetic information is laid down in DNA, but since no enzymes existed to split it at specific bases the prospects of deciphering it seemed remote. Undeterred, Sanger invented methods that allowed portions of a gene to be copied on to a newly synthesised strand of DNA that he labelled with radioactive phosphorus. He produced such copies in four different samples of the same strand and arranged it so that in each sample growth of the chain was terminated at random at a different one of the four nucleotide bases — the four types of amino acid that make up DNA.

Sanger's first success was the complete deciphering of the DNA of a small virus, 5,386 nucleotides long. Next he and his colleagues deciphered the DNA of mitochondrion. This showed that the genetic code is not universal as had been believed, but has local dialects.

These ingenious methods of deciphering genes opened new worlds. Together with the novel methods of gene cutting, splicing and cloning, they revolutionised genetics. Now analysis of genetic differences between individuals does not have to rely any longer on the results of crosses but can be done by direct reading of their genes. And antenatal diagnosis of inherited diseases can be done on minute samples of foetal DNA.

These discoveries earned Sanger his second Nobel Prize in Chemistry in 1980, which he shared with Paul Berg and Walter Gilbert. The award did not affect his simple lifestyle. To him experimentation remained the best form of thinking; he invented his new methods with his own hands, not by directing juniors. He retired in 1985.

In 1992 the Wellcome Trust and the MRC established the Sanger Institute at Hinxton, near Cambridge, to study the function of genes in disease.

Sanger was elected a Fellow of the Royal Society in 1954, was awarded the Royal Medal of the Society in 1969, and the Copley Medal, the Society's highest honour, in 1977.

He was appointed CBE in 1963, a Companion of Honour in 1981 and was made a member of the Order of Merit in 1986. He was a member of several foreign academies.

In 1940 he married Joan Howe; they had two sons and one daughter.

Frederick Sanger, OM, CH, CBE, FRS, biochemist and double Nobel prizewinner, was born on August 13, 1918. He died on November 19, 2013, aged 95