RETROSPECTIVE

Frederick Sanger (1918–2013)

Twice awarded the Nobel Prize, a biochemist's work on protein and DNA structure opened the door to modern biomedical science.

Sydney Brenner

Fred Sanger was a remarkable and unique scientist, and with his passing on 19 November 2013 we have lost one of the founders of molecular biology. He won two Nobel Prizes for chemistry, but we claim him for molecular biology because the methods he developed for sequencing proteins and nucleic acids provide the basis for much of what we do today.

Fred was born in Gloucestershire, UK, in 1918. He was educated at the University of Cambridge where he received his bachelor's degree in 1939 and his doctorate in 1943. In 1953, I attended the lecture he gave to the Alembic Club in Oxford on insulin. The meeting has remained in my mind for two reasons. One was the way he explained his work. He had a set of triangular blocks with the blank face turned to the audience, and as he went through the characterization of the peptide fragments, he turned the blocks around to display the amino acid, until he had assembled the sequences of the A and B chains of insulin. He would receive the Nobel Prize in Chemistry 5 years later for deciphering insulin's sequence. The other reason was a comment made by Nobel laureate Sir Robert Robinson in which he pointed out that chemists had viewed proteins as amorphous polymers, but Sanger had now proved that they had a definite chemical structure in the form of their amino acid sequences. This was an essential requirement for what the Nobel laureate Francis Crick later called the sequence hypothesis—that proteins were specified by the conversion of the one-dimensional sequence of nucleotides in DNA into the one-dimensional sequence of amino acids in the polypeptide chain; the conversion table was the genetic code. Proving this became the central problem of the early phase of molecular biology.

The geneticist Seymour Benzer had shown that recombination between mutations could be measured at single-nucleotide resolution, and combining this with chemical mutagenesis might allow us to compare a gene with its protein product—"sequencing" the gene by genetics and the protein product by Fred Sanger's techniques. When I came to the University of Cambridge in 1956, I went to see Fred in the Biochemistry Department. I found him developing methods for sequencing small amounts of proteins using radioactive techniques. He was synthesizing ovalbumin, labeling it with radioactive amino acids, digesting the protein, and separating peptides by a "fingerprinting" method that combined high-voltage electrophoresis and chromatography (he had invented this procedure for his insulin work). We were later to use this method on bacteriophage T4 head protein, the first of the many examples of exploiting Fred's approaches to solve biological problems.

After Fred joined the Medical Research Council (MRC) Laboratory of Molecular Biology in 1962, he began to develop methods to sequence RNA because the small RNAs could be purified. Although the Nobel laureate Robert Holley was the first to sequence a transfer RNA (tRNA), Fred and his colleagues published the sequence of the 5*S* ribosomal RNA in 1967. Again, his methods were used to sequence and study suppressor tRNAs and their mutants.

Fred then turned his attention to DNA and developed the "plus-minus" method that produced fragments with defined ends. By 1975, he had sequenced most of the 5-kb genome of bacteriophage phiX178. He published the dideoxy method in 1977 and used it to sequence the 17-kb DNA of human mitochondria and the 46.5-kb genome of bacteriophage lambda. With the advent of cloning techniques in 1974, it had become clear to most molecular biologists that a new era of research was beginning. Fred would share the 1980 Nobel Prize for chemistry with Walter Gilbert and Paul Berg for leading the way. Certainly, genetics would be different; we were no longer tied to the reproductive cycles of organism and could study the DNA directly, even of organisms long extinct. And biochemistry would change as well, because the nucleic acid can be used to produce any amount of the protein we require. Being able to sequence DNA turned embryology into a science and provided insights into physiology that we could not have acquired so easily. It will continue to give us an understanding into the most interesting organism on this planet—ourselves.

Fred has often been called a modest person, but his objectives were far from modest. He combined a singularity of purpose with a mastery of the laconic understatement. He often referred to his scientific work as "messing around in a lab," and Seymour Benzer told me that when he met Fred in 1954, he asked Fred whether he knew Francis Crick. "Yes," said Fred, "the fellow who is rather keen on genes." When we met in Cambridge in 1961 to discuss how we would organize the new lab, Nobel laureate Max Perutz was worried that Fred might be chosen to be chairman, but Fred said "I don't do that sort of thing."

A Fred Sanger would not survive today's world of science. With continuous reporting and appraisals, some committee would note that he published little of import between insulin in 1952 and his first paper on RNA sequencing in 1967 with another long gap until DNA sequencing in 1977. He would be labeled as unproductive, and his modest personal support would be denied. We no longer have a culture that allows individuals to embark on long-term—and what would be considered today extremely risky—projects.

Fred retired in 1983. Although the MRC wanted directors to move on after retirement, an exception was made for Max Perutz. I asked Fred whether he would like to keep his small office and laboratory and stay on. In a characteristic way he said: "No. I have had enough. I want to build a boat and spend some time messing about in my garden." On the afternoon of his retirement, he put down his pipette, went to a small farewell party, and walked out of the lab and science.

10.1126/science.1249912

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Published by AAAS