

Obituary*

Max Perutz (1914–2002)

A young Viennese chemist from a Jewish family who arrived in Cambridge in 1936 to study molecular structure, Max Perutz became the leader of the movement which created molecular biology, and the head of the most successful research laboratory in Britain.

Throughout his life, his personal research focused on haemoglobin, a familiar protein molecule whose extraordinary range of properties illuminated every stage of the scientific development leading from spectroscopy and protein chemistry through three-dimensional structure of molecular genetics and medical application.

His achievements followed from a combination of several outstanding qualities, not all intellectual. His irresistible powers of gentle persuasion brought him long-term support from the Cavendish Professor of Physics at Cambridge, Sir Lawrence Bragg, and from the Secretary of the Medical Research Council, Sir Edward Mellanby, in setting up a Medical Research Council Unit in 1947 for his work. He communicated ideas with extraordinary clarity and simplicity. Though he retained a strong Austrian accent, his written English was always elegant, compelling and stimulating. He seemed to write with a golden pen. He had a wonderful way of leading research, leaving his staff with the feeling they were free to decide their own way forward, while he created a vision of the long-term goals. And he had uncanny insight into the potential of young researchers seeking to work with him.

By the early 1950s he had drawn together an extraordinary group of people. His senior colleague was John Kendrew, like Perutz a chemist trained in crystallography, but in personality utterly different. Kendrew was a precise organiser, a gifted computer programmer, a man who knew exactly where he was going and how to get there. His research began by following Perutz's, but by brilliant organisation it later overtook him (by working on myoglobin, the much smaller brother of haemoglobin). There was also a PhD student with a degree in physics, whose dazzling intellect constantly darted from problem to problem. This man was Francis Crick. A postdoctoral researcher, a 22-year-old whizz kid named Jim Watson, turned up from Chicago.

Only 10 years later, Max Perutz and these three colleagues were all Nobel prizewinners – he shared the Chemistry prize with Kendrew for their structural analyses of haemoglobin and myoglobin, in the same year that Crick and Watson (with Maurice Wilkins) won the prize for Medicine – but in the early 1950s all these men were unknown, achievements unrecognised, seeking how to use the techniques of physics and chemistry to understand the nature of biological matter.

There were other remarkable people in the group. Hugh Huxley studied under Perutz using the primitive electron microscopes then in existence. With brilliant insight, they decided Huxley should study muscle, an object ideally matched to the powers of the microscope. In his doctoral thesis in 1954, Huxley laid out the basic mechanism of muscle contraction. And Perutz's biochemical assistant, Vernon Ingram, was to discover the precise

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molecular nature of sickle-cell disease a couple of years later – a change of one amino-acid in haemoglobin which we now recognise as the consequence of a single mutation.

The group first came to prominence with the achievement of the two young rebels – Crick and Watson's analysis of DNA in 1953 revealed an exquisite structure whose fascinating implications caught the imagination immediately. Meanwhile Perutz's own research (and that of Kendrew) had got stuck. The methods of X-ray crystallography had been used to picture the molecular structure of many small molecules, up to the size of penicillin. Perutz and Kendrew wanted to use these methods on haemoglobin (and its partner in muscle, myoglobin). But the methods that worked for the smaller molecules seemed hopeless for these much larger structures.

While the DNA structure was being worked out, Perutz had a shattering insight for his own work. If he could attach a heavy atom to a specific site in the haemoglobin molecule, and if it didn't disrupt the structure of the molecule, and if he could make it crystallise in just the same way as ordinary haemoglobin, and if it made changes big enough to measure – if all these things were true, he could see a way to use the methods of X-ray crystallography to image the haemoglobin molecule. He later wrote:

As I developed my first X-ray photograph of mercury haemoglobin my mood altered between sanguine hopes of immediate success and desperate forebodings of all possible causes of failure. I was jubilant when the diffraction spots appeared in exactly the same position as in the mercury-free protein, but with slightly altered intensity, exactly as I had hoped.

The rest, as they say, is history. Crick and Watson's work led to the discovery of the genetic code, development of molecular genetics, methods to make bacteria produce large quantities of useful proteins such as specific antibodies, towards ways to clone stem cells. The work of Max Perutz led to an understanding of proteins themselves. These are the molecules which DNA specifies. They are also the molecules which control all chemical processes in a living cell and organise its structure. His methods have now been applied to tens of thousands of different proteins, giving clear insights into their mode of action.

In the late 1950s, after Bragg's retirement, Perutz's unit was based in a small asbestos hut in the car park outside the Cavendish Laboratory in Cambridge. As the research group continued to grow, every empty room and disused shed on the site (including the building which was originally Lord Rutherford's stable) was converted to a laboratory for a different facet of molecular biology. Long before the Nobel Prizes, a report by Perutz convinced the Medical Research Council, then led by Sir Harold Himsworth, to build a large new laboratory for Perutz, Crick, Fred Sanger and others. The new building, known as the Laboratory of Molecular Biology, was completed in 1962 on the new site of Addenbrooke's Hospital, at the edge of Cambridge – just in time before over-population of the Cavendish site led to any serious dispute.

The Laboratory of Molecular Biology has been an outstanding and continuous success, a breeding-ground for scientific achievement. In addition to the four Nobel Prizes awarded in 1962, which set the laboratory off to a splendid start, it has appeared in the Nobel lists again and again: for the creation of monoclonal antibodies by César Milstein and Georges Köhler with immediate application to medicine, for Aaron Klug's deep analysis of the organisation of nucleic acids in chromatin and other types of nucleic acid structure, John Walker's long study of a beautiful protein (ATP synthase) which acts as a rotary motor powered by a biochemical energy source, and above all Fred Sanger's second Nobel Prize for inventing ways to find the sequence of bases in nucleic acids.

These are only the most visible of the laboratory's successes. Perutz has left some clues to its achievements:

I persuaded the Medical Research Council to appoint me Chairman of a Governing Board, rather than as Director ... This arrangement reserved major decisions of scientific policy to the board, and left their execution to me ... The board met only rarely ... This worked smoothly and left me free to pursue my own research. Seeing the Chairman standing at the laboratory bench or the X-ray tube, rather than sitting at his desk, set a good example and raised morale. The board never directed the laboratory's research but tried to attract, or to keep, talented young people and gave them a free hand.

He always recognised the importance of new instrumental developments, and maintained large mechanical and electronic workshops, to which research workers had full access, directly passing their enthusiasm to the technical staff. The most characteristic feature was the tearoom, open to all, visited three times a day by most, an important centre for exchange of ideas and scientific news, which was managed for over 20 years by Max Perutz's wife, Gisela.

Meanwhile Perutz continued his own lifetime study of haemoglobin, 'the molecular lung', and showed how concerted structural changes follow from its absorption of oxygen, causing it to be either fully oxygenated or fully reduced, and making it an ideal oxygen transporter. This demonstrated a general principle, since many enzymes and other proteins exploit a similar 'allosteric' structural change to switch a process on or off. By collecting abnormal haemoglobins discovered throughout the world, he opened up 'molecular pathology', relating a structural abnormality to disease. Long before mutant proteins could be created in the laboratory, he had a large collection of single-site mutants of haemoglobin.

The Medical Research Council had an inflexible rule that, when a Director of one of its institutions reached retirement age, he must not continue to work in the same laboratory. Adroitly, Perutz announced that he had never been the Director, and after retirement he would continue to pursue his research as usual. This arrangement, warmly welcomed by the staff, allowed Perutz to continue as he pleased. In retirement he wrote a lot, including book reviews on a wide range of topics from Karl Popper's view of Darwinism, and Fritz Haber's fanatical obsession with poison gases, to the social revolution caused by Carl Djerassi's synthesis of a contraceptive steroid, as well as several books of his own. He continued to travel, to collaborate with scientists from many nations. Above all, he pursued the endless ramifications of his deep understanding of haemoglobin and the many human diseases linked to it. He helped to design a useful drug to deliver oxygen to tumours and to damaged tissues.

In his scientific autobiography *Science is Not a Quiet Life* (1997) Max Perutz describes a number of scientific controversies surrounding his work, and how they were resolved. One of these involved a mutant haemoglobin, analysed incorrectly by its Japanese discoverers, suggesting a total conflict with his results. Perutz and his collaborators identified the mistake:

I worried that, if our Japanese colleagues learned of this disproof of their findings, a poor student who blamed himself for their mistake might commit suicide. To avoid such a tragedy, I invited them to publish a joint paper, a gesture which earned me their lifelong friendship.

Max Perutz was a deeply humane man, loved and admired by his colleagues, who combined that gift with exceptional powers of analysis, planning and leadership. His domed forehead suggested a mighty brain, but his small fingers were neat and dextrous. A robust and confident mountaineer, he studied glacier flow early in his career, so as to work in the Alps. A back injury in middle life ended his skiing, but he retained his love of mountains.

While his achievements were crowned with many honours, they rode lightly on his shoulders. He refused any honour that would give him a title, and was known, and invariably

addressed by colleagues, as 'Max'. He lived a quite and unostentatious life, walking from his home to the laboratory almost daily until a few months before his death. His brain remained razor-sharp, he gave thrilling lectures, and his research continued. Within the last year he had made important contributions to the understanding of Huntington's disease.

He and his wife, Gisela, who survives him, were devoted to each other and to their two children, Robin and Vivien.

DAVID BLOW

Max Ferdinand Perutz, molecular biologist; born Vienna 19 May 1914; Director, MRC Unit for Molecular Biology 1947–62; FRS 1954; Reader, Davy Faraday Research Laboratory, Royal Institution 1954–68, Fullerian Professor of Physiology 1973–79; Chairman, MRC Laboratory of Molecular Biology 1962–79; Nobel Prize for Chemistry (jointly) 1962; CBE 1963; Chairman, European Molecular Biology Organisation 1963–69; CH 1975; OM 1988; married 1942 Gisela Peiser (one son, one daughter); died Cambridge 6 February 2002.