Climbing mountains

A profile of Max Perutz 1914–2002: a life in science • by Daniela Rhodes

This year, the biological community mourned the loss of a great man. Max Perutz, who died of cancer on February 6, 2002, aged 87, was one of the scientific giants of the 20th Century. His life's work on the structure of the oxygen-carrying blood protein haemoglobin created the field of structural biology. He was also one of the founding fathers of molecular biology in Europe, not least by instigating the spectacularly successful Medical Research Council (MRC) Laboratory of Molecular Biology (LMB) in Cambridge. In his extensive writings, he argued for the importance of science and instructed and amused us with stories of how great science is done. But he was much more than all of this—he was also a great human being.

Max, as he was called by all who knew him, was born in Vienna in 1914 into a family of wealthy textile manufacturers. Although his parents had planned for him to study law, a schoolmaster awakened his interest in chemistry, which he went on to study at the University of Vienna. He then decided to leave Austria for the Cavendish Laboratory in Cambridge in 1936, to work towards his PhD with the brilliant and controversial Desmond Bernal. Max, inspired by Bernal's vision that the structure of large and complex molecules such as proteins could be solved using X-ray diffraction, embarked on scaling a mountain in biology—solving the structure of haemoglobin. This was to take him more than 20 years.

Max was influenced in his choice of studying haemoglobin by a family connection. The husband of one of his

cousins had shown that the morphology of deoxyhaemoglobin crystals changes upon exposure to oxygen, suggesting that the conformation of haemoglobin may

proteins containing many thousands of atoms using X-ray crystallography, although the structure of small molecules with ~100 atoms and of known chemical composition had been derived previously. Furthermore, the method of obtaining the amino acid sequence of a protein, and hence its chemical formula, was yet to be invented. After he obtained his PhD in 1940, his work was interrupted for several years. At the outbreak of the Second World War, he was interned as an 'enemy alien' and deported to Canada. Although his release was secured soon after, he was then enlisted by Earl Mountbatten in a scheme, which was later abandoned, to build airbases out of reinforced ice to refuel aeroplanes in the mid North Atlantic. It was not until towards the end of the war that Max was able to resume

Max and his group outside the hut at the Cavendish Laboratory, 1958. (Courtesy of the LMB.)

also alter upon oxygenation. Max set out to find the mechanism for this change. In addition, haemoglobin was a practical choice because it is very abundant and easy to crystallise. In 1938, he obtained

Max embarked on scaling a mountain in biology—solving the structure of haemoglobin, which was to take him more than 20 years

very encouraging X-ray diffraction patterns consisting of thousands of reflections extending to 2.0 Å resolution. But, at the time, Max did not realise that it was not possible to determine the structure of

his work on haemoglobin. In 1946 he was joined by John Kendrew, who would work on the structure of myoglobin, a much smaller oxygen-carrying muscle protein. Max and Kendrew spent several years laboriously collecting huge amounts of data and using the intensities of the reflections to calculate contour maps, hoping that these would allow prominent structural features such as α -helices to be identified. But Francis Crick, by then a graduate student with Max, proved that this approach was hopeless, as the arrangement of secondary structure elements in the proteins was irregular. In desperation, and encouraged by Sir Lawrence Bragg, the head of the Cavendish Laboratory, Max realised that, to solve the structure of a protein,

information on the phase angle of the reflections would be needed—the so-called ‘phase problem’.

The fundamental breakthrough came in 1953. In fact, that year turned out to be the dawn of molecular biology: Max cracked the phase problem, and Francis Crick and Jim Watson, a postdoctoral visitor in Max’s group, proposed the double helical model of DNA. Max discovered that attaching a heavy metal, in this case mercury, to haemoglobin changed the relative intensities of the diffraction spots measurably—and this, in principle, meant that the phase problem was solved and the isomorphous replacement method for determining crystal structures had been invented (Bragg and Perutz, 1954). This method is still the cornerstone of structural biology and has since been used to determine the structures of thousands of proteins.

However, even with this new method, there were many more obstacles to overcome before the three-dimensional structure of proteins could be visualised. Methods for measuring accurately the intensities of tens of thousands of reflections had to be devised; to assign the phases reliably, several heavy metal derivatives of the same crystal form were

describes the moment of discovery as: ‘It felt like falling in love and reaching the top of a high mountain after a hard climb all in one, an ecstasy induced not by

an interest in the development of clinically useful drugs. This interest in human disease led him, in his later years, to investigate the structure of glutamine repeats that give rise to the inherited neurodegenerative disease Huntington’s chorea (Perutz, 1999). During the latter part of 2001, Max was very excited by his latest ideas and submitted two manuscripts minutes before he was admitted to Addenbrooke’s Hospital for an emergency operation. That was the spirit of the man!

Max’s legacy is not only his Nobel Prize-winning research, but also the MRC LMB. The success of the LMB, where the research undertaken has resulted in nine Nobel Prizes and many other important discoveries, is well known. The origins of the LMB go back to 1947 when, with great foresight,

the MRC created ‘The MRC Unit for Research of the Molecular Structure of Biological Systems’ to enable Max and Kendrew to continue their work, even before they had any definitive results. Max was always grateful to the MRC for realising the potential of his work. Shortly afterwards, the unit was joined by Francis Crick; Jim Watson arrived in 1951, and the two soon started to work together on the structure of DNA—the rest is history.

Max on the canteen terrace of the LMB, 1995.
(Courtesy of the LMB.)

drugs but by finding the answer to one of life’s great riddles.’

In 1962, Max and Kendrew were awarded the Nobel Prize for Chemistry; in the same year, Crick, Watson and Maurice Wilkins shared the Nobel Prize for Medicine. Max went on to solve the structure of both deoxy- and oxy-haemoglobin to higher resolution. In 1970, based on the conformational changes observed in the structure of the two forms of haemoglobin, which had first attracted him to the subject, Max provided a stereochemical explanation for the allosteric mechanism proposed by Jacques Monod and colleagues (Perutz, 1970) and hence a detailed understanding of how haemoglobin functions in binding oxygen in the lungs and releasing it in oxygen-depleted tissues. Over the years, almost every aspect of his proposed mechanism was disputed, but he battled on until, finally, almost two decades later—50 years after he first started working on haemoglobin—he was vindicated by more accurate data (Perutz *et al.*, 1998). Fittingly, or perhaps as a consequence of his struggle, Max’s motto was: ‘In science truth always wins.’ He became the first person to use structural information to provide a molecular explanation for how naturally occurring mutations can lead to disease (Morimoto *et al.*, 1971), and he also took

Fittingly, or perhaps as a consequence of his struggle, Max’s motto was: ‘In science truth always wins’

required; and a way of displaying the results in terms of a physical model had to be invented. This was to take another 6 years. Finally, in 1960, the paper in which Max and his colleagues described the three-dimensional structure of haemoglobin to 5.5 Å resolution was published in *Nature* (Perutz *et al.*, 1960). Meanwhile, Kendrew and his colleagues had determined the atomic structure of the smaller myoglobin to 2 Å resolution, and their paper was published in the same issue (Kendrew *et al.*, 1960). Max

Max insisted that young scientists should be given full responsibility and credit for their work

Two other members of the unit were Hugh Huxley and Sidney Brenner. Huxley went on to discover that muscles contract by a sliding filament mechanism, and Brenner discovered mRNA and, together with Crick, unravelled the triplet nature of the genetic code. As the unit outgrew its location within the Cavendish Laboratory, the MRC decided to build a new laboratory on the site of the new Addenbrooke’s Hospital, on the outskirts of town. The LMB opened in 1962 with Max as its chairman until 1979. Max, Kendrew, Crick, Huxley and Brenner

were soon joined by several other scientists at the forefront of molecular biology: Fred Sanger, who had invented a method for sequencing proteins, would go on to develop techniques for sequencing both RNA and DNA; Aaron Klug developed crystallographic electron micro-

scopy and later determined the structure of tRNA and chromatin and discovered zinc fingers; César Milstein and Georges Köhler invented a technique for producing monoclonal antibodies; and John Walker solved the structure of mitochondrial ATP synthase. From its modest origins in a hut at the Cavendish Laboratory, the LMB has grown to house over 50 research groups and, 40 years on, continues to be a leading research institute. And Max's interest in establishing molecular biology in Europe extended beyond Britain: in addition to founding the LMB, Max and John Kendrew were also instrumental in the creation of the European Molecular Biology Organization (EMBO).

Max had a captivating way of speaking, a benevolent smile and penetrating brown eyes that, like his mind, never grew old

As evidenced by the success of the LMB, Max had the knack of picking extraordinary talent. But he also had the vision of creating a working environment where talented people were left alone to pursue their ideas. This philosophy lives on in the LMB and has been adopted by other research institutes as well. Max insisted that young scientists should be given full responsibility and credit for their work. There was to be no hierarchy, and everybody from the kitchen ladies to the director were on first-name terms. The groups were and still are small, and senior scientists work at the bench. Although I never worked with Max directly, I had the great privilege of sharing a laboratory with him for many years. The slight irritation of forever being taken to be his secretary when answering the telephone—the fate of females—was amply repaid by being able to watch him work and to talk with him. He would come into the laboratory in the morning, put on his lab-coat and proceed to do his experiments. He did everything himself, from making up solutions, to using the spectrophotometer and growing crystals. Max led by example and carried out his own experiments well into his 80s.

Many interactions were fostered by the marvellous atmosphere of the laboratory—the excitement of doing science was in the air. The canteen on the top floor of the LMB building, for many years managed without pay by Max's wife Gisela, still acts as the central station for meeting people to discuss the latest results or, more often, to ask for advice from a colleague working in a different part of the building. On being asked what made the LMB such a remarkable place, Max answered: 'Creativity in science, as in art [referring to the Renaissance in Florence], cannot be organised. It arises spontaneously from individual talent. Well-run laboratories can foster it, but hierarchical organisations, inflexible bureaucratic rules, and mountains of futile paperwork can kill it. Discoveries cannot be planned, they pop up, like Puck, in unexpected corners.'

Max was an unassuming, warm and deeply cultured man. Literature, classical music and art were subjects about which he loved to converse almost as much as science. Max had a captivating way of speaking, a benevolent smile and penetrating brown eyes that, like his mind, never grew old. Having lunch with him in the canteen was always interesting and enriching; sometimes, on returning to my desk, I would find a book from Max by some writer or on a subject we had discussed. Many honours were bestowed on him, and he was a member of many learned societies and academies, but he took the greatest pleasure from his interactions with young scientists. He would seek them out in the canteen, joining them for lunch or tea, to find out what they were doing.

Max was a great communicator, gave excellent seminars and would instruct us on how to present science and write papers. In his latter years he became a prolific writer, contributing regularly to the *New York Review of Books*. He produced a number of wonderful collections of essays and books that extended their scope beyond pure science: *Is Science Necessary?: Essays on Science and Scientists* (1989); *Protein Structure: New Approaches to Disease*

and *Therapy* (1992); *Science is not a Quiet Life: Unravelling the Atomic Mechanism of Haemoglobin* (1996); *I wish I made you angry earlier: Essays on Science, Scientists and Humanity* (1998). These books should be read by everybody involved in scientific research. They are a pleasure to read not only because of the elegant style of writing, but also because Max knew how to tell a good story. Most of all, his love for science and people shines through every page.

Max will be remembered by colleagues and friends with great affection and deep admiration. He loved the mountains and had been a keen mountaineer in his earlier days, which might give some insight into Max's ability to stay with a problem until it was conquered. Certainly, the enormous scientific heritage he has left will continue to influence research in molecular biology and medicine for years to come. He had a long and productive life and died a fulfilled man. He once said that his only regret was never to have climbed the Matterhorn!

References

- Bragg, W.L. and Perutz, M.F. (1954) The structure of haemoglobin: Fourier projections on the 010 plane. *Proc. R. Soc. Lond. A*, **225**, 315–329.
- Kendrew, J.C., Dickerson, R.E., Strandberg, B.E., Hart, R.G., Davies, R.D., Phillips, D.C. and Shore, V.C. (1960) Structure of myoglobin: a three-dimensional Fourier synthesis at 2.0 Å resolution. *Nature*, **185**, 422–427.
- Morimoto, H., Lehmann, H. and Perutz, M.F. (1971) Molecular pathology of human haemoglobin: stereochemical interpretation of abnormal oxygen affinities. *Nature*, **232**, 408–413.
- Perutz, M.F. (1970) Stereochemistry of cooperative effects in haemoglobin. *Nature*, **228**, 726–739.
- Perutz, M.F. (1999) Glutamine repeats and neurodegenerative diseases: molecular aspects. *Trends Biochem. Sci.*, **24**, 58–63.
- Perutz, M.F., Rossman, M.G., Cullis, A.F., Muirhead, H., Will, G. and North, A.C.T. (1960) Structure of haemoglobin: a three-dimensional Fourier synthesis at 5.5 Å resolution, obtained by X-ray analysis. *Nature*, **185**, 416–422.
- Perutz, M.F., Wilkinson, A.J., Paoli, M. and Dodson, G.G. (1998) The stereochemical mechanism of the cooperative effect in haemoglobin revisited. *Ann. Rev. Biophys. Biomol. Struct.*, **27**, 1–34.

Daniela Rhodes is at the MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK.
E-mail: rhodes@mrc-lmb.cam.ac.uk

DOI: 10.1093/embo-reports/kvf103