Max Perutz (1914–2002)

Max Perutz died on 6 February 2002. He won the Nobel Prize for Chemistry in 1962 after determining the molecular structure of haemoglobin, the red protein in blood that carries oxygen from the lungs to the body tissues. Perutz attempted to understand the riddle of life in the structure of proteins and peptides. He founded one of Britain's most successful research institutes, the Medical Research Council Laboratory of Molecular Biology (LMB) in Cambridge.

Max Perutz was born in Vienna in 1914. He came from a family of textile manufacturers and went to the Theresium School, named after Empress Maria Theresa. His parents wanted him to study law after school and later take over the family business. A schoolmaster kindled his interest in chemistry, which he took up as a subject of study in the University of Vienna. He specialized in organic chemistry, biochemistry and glaciology (because he was madly interested in skiing). With financial help from his father he went to the Cavendish Laboratory, Cambridge and joined Peterhouse College. He became a research student of J. D. Bernal, whom Perutz described as 'a restless genius, always searching for some of the very important things to do rather than the work he was doing at that moment'.

By then Bernal, along with Dorothy Crowfoot Hodgkin, had already taken X-ray diffraction photographs of the proteins, pepsin and insulin. Bernal taught him that 'the riddle of life was to be found in the structure of proteins and X-ray crystallography was the only way to solve it'.

Perutz, on Bernal's advice, first learnt the techniques of X-ray crystallography analysis in the Department of Mineralogy and Petrology, where he tried his hand on some silicate structures. After this, he turned his attention to proteins and chose to study the structure of haemoglobin as it is a protein abundantly found in the human body and was extremely easy to crystallize.

Perutz was the first Chairman (1962–79) of the Medical Research Council Laboratory for Molecular Biology, Cambridge. He was Reader of Chemistry at the Davy Faraday Research Laboratory, London (1956–67). Perutz shared the Nobel Prize for Chemistry in 1962 with his colleague and his first student John Kendrew for their work on the structure of haemoglobin (Perutz) and myoglobin (Kendrew). He was one of the greatest ambassadors of science, scientific method and philosophy. Apart from being a great scientist, he was a very kindly and tolerant person who loved young people and was passionately committed towards societal problems, social justice and intellectual honesty. His passion was to communicate science to the public and he continuously lectured to scientists both young and old, in schools, colleges, universities and research institutes. On his death, George Radda of the Medical Research Council said: 'The world will be mourning the loss of one of the 20th century's scientific giants. Perutz's achievements paved the way for others to unravel the shape of other large, complex proteins. His role in the development of the science of molecular biology was pivotal, and led directly to the emergence of the modern biotechnology sector and more efficient ways of creating and testing new drugs. Perutz undertook his work at the Cavendish Laboratories in Cambridge, UK, before moving to the newly set-up Laboratory of Molecular Biology (LMB), which he chaired until 1979. The LMB became a hotbed of research, producing nine Nobel laureates since the 1950s. The impact of Perutz's work remains a foundation on which science is being undertaken today. His Nobel prize-winning work on protein structure is more relevant now than ever as we turn attention to the smallest building blocks of life to make sense of the human genome and mechanisms of disease.'

Perutz described his work thus: 'Between September 1936 and May 1937 Zwicky took 300 or more photographs in which he scanned between 5000 and 10,000 nebular images for new stars. This led him to the discovery of one supernova, revealing the final dramatic moment in the death of a star. Zwicky could say, like Ferdinand in *The Tempest* when he had to hew wood:

For some sports are painful
    and the labour
Delight in them sets off;
    some kinds of baseness
Are nobly undergone, and
    most poor matters
Point to rich ends. This my mean task
Would be as heavy to me as odious; but
The mistress which I serve
    quickens what's dead
And makes my labours pleasures.

The heavens were Zwicky's mistress, and mine was haemoglobin, the protein of the red blood cells. As part of my attempt to solve its structure, I took several hundred X-ray diffraction pictures of haemoglobin crystals, each taking two hours' exposure. I took some of the pictures during World War II, when I had to spend nights in the laboratory to be prepared to extinguish incendiary bombs in the event of a German air raid. I used these nights to get up every two hours, turn my crystal by a few degrees, develop the exposed films and insert a new pack of films into the cassette. When all the photographs had been taken, the real labour began. Each of them contained several hundred little black spots whose degree of blackness I had to measure by eye, one by one. After six years of this labour, when the data were finally complete, a London firm processed them with a prehistoric, mechanical punch card computer that produced an output of thousands of numbers. These numbers outlined not a picture of the structure I was trying to solve, but a mathematical abstraction of it: the directions and lengths of all the 25 million lines between the 5000 atoms in the haemoglobin molecule radiating from a common origin. I scanned the maps eagerly for interpretable features and was elated when they seemed to tell me that the molecule consists simply of bundles of parallel chains of atoms spaced apart at equal intervals.'

'Shortly after my results appeared in print, a new graduate student joined me. As his first job, he performed a calculation which proved that no more than a small fraction of the haemoglobin molecule was made up of the bundles of parallel chains that I had persuaded myself to see, and that my results, the fruits of years of tedious labour, provided no other clue to its structure. It was a heartbreaking instance of patience wasted, an ever-present risk in scientific research. That graduate student was Francis Crick, later famous for his part in the solution of the structure of DNA.'

Perutz communicated ideas with extraordinary clarity and simplicity. Though he retained a strong accent when speaking, 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, who like Perutz, was a chemist trained in crystallography, but in personality utterly different. Kendrew was a precise organizer, 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 organization it later overtook him (by working on myoglobin, the much smaller brother of haemoglobin). There was also a Ph D 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 whiz-kid named Jim Watson, also turned up from Chicago.

Only ten years later, Max Perutz and these three colleagues were all Nobel Prize winners – he shared the chemistry prize with Kendrew for their structural analyses of haemoglobin (Perutz) and myoglobin (Kendrew), 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 unrecognized, 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 that Huxley should study the 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 molecular nature of sickle-cell disease a couple of years later – a change of one amino acid in haemoglobin which we now recognize as the consequence of a single mutation.

The group first came into 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 had a rather beautiful idea of introducing a heavy atom in haemoglobin in order to see whether the methods used in small molecule crystals would work. He was able to introduce mercury atoms in his haemoglobin crystal. This was isomorphous replacement and from this he was able to phase reflections. Then he says, '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'.

With these two photographs, he felt that he could determine phases of some of the reflections. He mentioned this to Dorothy Hodgkin, who was overjoyed. Many years later Perutz told me in London that Dorothy Hodgkin had pointed out to him that now it was just a question of time if he used the other idea of Bijvoet, who had also suggested that structures could be solved using the multi-isomorphous replacement method. Perutz frankly admitted to her that he had missed this in Bijvoet's paper and he was roundly chided by Dorothy Hodgkin that 'when a paper is written by a person like Bijvoet, you must read each word and sentence very very carefully'. Using the multiple isomorphous replacement method and also the anomalous scattering method (also suggested by Bijvoet), Perutz and his group could solve the structure of haemoglobin.

When Lawrence Bragg was in Chennai I had invited him home for dinner and I asked how he had started protein crystallography and molecular biology in Cambridge. He said: 'Once a young man with balding head and high domed forehead came in with a film in his hand. He said, "I would like you to see the X-ray photograph that I have taken of haemoglobin". It was an extraordinary photograph with clear spots. He also told me that he had introduced a heavy atom of mercury into haemoglobin and crystallized it and he was at present taking X-ray photographs. It looked as if the mercury haemoglobin was isomorphous with ordinary haemoglobin. It was then I made up my mind that we should go in for protein crystallography in a very big way. So I met Edward Mellanby the Secretary of the Medical Research Council and asked him "Mellanby, I want 100,000 pounds for the next two years for doing protein crystallography". Mellanby asked me what would be the returns that the Medical Research Council would get. I told him, "Probably, one or two Nobel Prizes". (I had underestimated, there were 4 or 5 Nobel Prizes.) I was sure that Max Perutz, the young man who brought me the photograph would solve the structure of the haemoglobin as he had done much of the work himself (J. D. Bernal had gone on to advise the war office). When Mellanby said that I would get the money, I found that we were not even paying Max Perutz a fellowship and he was being supported by his father, a textile manufacturer from Vienna. When Hitler invaded Austria, his family business collapsed and Perutz's financial support from his father was withdrawn. I also found that Perutz's parents were refugees and I talked to the refugee organization and arranged for Perutz's parents to come to Cambridge and for the first time in his life, Perutz's father who had never done any manual work became a lathe operator. I also wrote to the Rockefeller Foundation and got a fellowship for Perutz.'

Perutz was indeed very grateful to Lawrence Bragg for having given him a life-time assistantship in the Cavendish Laboratory and also for saving the lives of his parents and bringing them to England.

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 into a laboratory for different facets of molecular biology. Long before the Nobel Prizes, a report by Perutz convinced the Medical Research Council, then led by 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 (LMB), 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 LMB 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 Cesar Milstein and Georges Kohler with immediate application to medicine, for Aaron Klug's deep analysis of the organization 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 by Fred Sanger's second Nobel Prize for inventing ways to find the sequence of bases in nucleic acids.

Perutz says: '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.'

Some of the most important molecular biologists of the world spent the formative periods of their earlier careers at this institute. Perutz ensured that the laboratory had a canteen where scientists could discuss their problems over coffee, tea or lunch. This canteen was supervised by Perutz's charming wife Gisela for more than 20 years.

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 Harber'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. In his words: '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, crazy about skiing, 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 the mountains.

His authority was derived from his passionate belief in enabling others of supreme talent to pursue curiosity-driven research, and from his own epic achievement. The politicians were struck by Perutz's skill in explaining to laymen, in general terms, the most complex scientific developments. Most were especially moved when, in response to a direct question from Edmund Dell MP, he said: 'Had I remained in Austria, I could never possibly have got so far. Being brutally uprooted is a spur to achieve scientific goals. Cambridge made me'.

In Perutz's room when Chairman of the laboratory in the 1960s, and in the small office which he was allocated and to which he went daily after his retirement, there hung the same sepia, slightly tattered photograph in a frame – the looming presence of Lawrence Bragg. Perutz would recall the story of how, as a young visiting research student at the Cavendish Laboratory, he took courage into his hands, knocked on Bragg's door, and asked him to look at his X-ray crystallography pictures of haemoglobin.

Perutz was committed deeply to his science till the very end. A few years ago, he wrote to me saying that he had not yet found the crucial crystallographic evidence for the cause of Huntington's disease. I understand that a few days before he died, he completed a manuscript of a paper on the causes of Huntington's disease and sent it to the *Proceedings of the National Academy of Sciences, USA*. (Obviously he had got the crucial evidence he was looking for.)

But this was also the man who could contribute a major essay, 'By What Right Do We Invoke Human Rights?', to the *Proceedings of the American Philosophical Society* in June 1996. His opening reveals a lot about Perutz:

'Scientists the world over are united by a common purpose, ideally to discover Nature's secrets and put them to use for human benefit. Albert Szent-Gyorgyi, the discoverer of vitamin C, has said, "I feel closer to a Chinese colleague than to my own postman".'

When a scientist who has committed no crime is imprisoned, we feel like the minister freeing the prisoners when he says, 'Es sucht der Bruder seine Bruder' – he or she is one of our brothers or sisters, and we feel a duty to appeal for his or her release. In doing so, we are now on strong legal grounds established by the United Nations Universal Declaration of Human Rights of 1948 and the conventions and covenants that followed it. They have the force of international law and are backed by courts and commissions to which individuals can appeal.

Perutz in the last decade, through contact with people in public office and many letters to the broadsheet press, campaigned for international law to be upheld in Bosnia, Kosovo, the Gulf and latterly Afghanistan. He was deeply interested in military matters and was very well-informed. This may be partly because his first research student, a then young Wing Commander came into his office in uniform and asked if he could work for him. This was John Kendrew, with whom he was to share a Nobel Prize sixteen years later.

I will give you an example of how Perutz, whenever he undertook a job did it extraordinarily well. When America joined the war, American planes could not cross Atlantic at one go. So an idea was proposed by Geoffrey Pyke, one of the minor scientific advisors of Lord Mountbatten, who was the Commander of the joint operation, that an island of ice carved from the Arctic could be set-up in the middle of the Atlantic, which could be used for fuelling the planes. Unfortunately a big lacuna was found, because if the ice is bombarded by a torpedo or by bombs, it will shatter and the refuelling island will collapse. The only solution was to make ice shatter-proof. When Lord Mountbatten consulted J. D. Bernal, his chief advisor, he said the only person who knew intricacies of the structure of ice was Max Perutz, because of his craze for skiing. So Perutz was summoned by the Allied Commander to attempt to make ice shatter-proof. In 1942 he was abruptly summoned to London at the request of Lord Mountbatten. Geoffrey Pyke told him advice was needed on tunnelling glaciers and on low-cost ways of transforming ice – into a material tough enough to serve as armour which does not shatter when hit by a bullet. Perutz set-up a refrigerated laboratory in the caverns beneath the Smithfield meat market and leading a team clad in airmen's heated suits, produced an ice-fibre composite he appropriately called pykrete, which when frozen was tougher than steel. Fortunately, by that time American planes had become better and could cross the Atlantic in one hop and the whole idea was dropped. Pyke was very enthusiastic and wanted to show the American command the qualities of pykrete. Unfortunately, Perutz could not go to America as it was reported that he had liberal views and was a very close friend of avowed communists. The communist was J. D. Bernal who had recommended Perutz do this job. Many years later when I was in Brooklyn, I heard that Pyke put up a wall of pykrete and invited a large number of senior naval and army officers, to shoot at the pykrete wall. The bullets rebounded and one wounded the shoulder of a General.

Max Perutz gave a very beautiful lecture when the *Collected Works of Dorothy Crowfoot Hodgkin*, published by the Indian Academy of Sciences, Bangalore, was released by the British Crystallographic Association at the Royal Society, London. At the end of the lecture he came and met me and congratulated me and said that the Indian Academy of Sciences and I had done a great service to crystallography by publishing the above mentioned book, as her papers are models of how crystallography should be done. I felt greatly flattered. I noticed that he spoke English with an European continental accent, which he had not shed even after three decades of being in England. I also noticed that he had beautiful hands like an artist, as though they had been designed to mount crystals of haemoglobin. His achievements followed from a combination of several outstanding qualities, not all intellectual. His irresistible powers of gentle persuasion brought him long-term support and affection from all those he met. He also excused himself and said that he would not be able to be present at my after-dinner-speech.

When I came back to India, I wrote him a letter thanking him for speaking at the seminar and asked him whether he had any special secret in the organization of the LMB, such that so much excellent world-class work could be produced there. He sent me a copy of a book that he had written *I Wish I'd Made You Angry Earlier* (Cold Spring Harbor Laboratory Press) and he most graciously inscribed it to me with the words, 'To Siv, with kind regards and best wishes, Max'. This is one of the most remarkable books written by a scientist that I have ever read. He convinces us in this book that science is a passionate enterprise and the pursuit of knowledge a sortie into the unknown. There can be no more persuasive advocate than Perutz in this regard. These pages are filled with portraits of twentieth-century giants, Pauling, Meitner, Bragg, Haber, Medawar, Szilard, Jacob, Krebs, and others. There are entertaining glimpses of Perutz's own long and exceptional life: his flight from Vienna in the thirties and internment in Britain as an enemy alien in World War II, rescue from the sea after a U-boat attack, involvement in a scheme to make ships of ice for refuelling aircraft in the North Atlantic, and after the war his intense, ten-year struggle to perfect a new way of understanding protein structure and function. Perutz is an eloquent spokesman for humanitarian causes, and his observations on abortion issues, nuclear fuel reprocessing and human rights reflect a life-long concern for both social justice and scientific integrity.

It was in this book that I read his famous essay on Fritz Haber entitled 'The friend or foe of mankind', which provoked me to write an article on Haber in *Current Science*. I think the very first sentence of the book gave me the answer to the question I asked.

'Every now and then I receive visits from earnest men and women armed with questionnaires and tape recorders who want to find out what made the Laboratory of Molecular Biology in Cambridge (where I work) so remarkably creative. They come from the social sciences and seek their Holy Grail in interdisciplinary organization. I feel tempted to draw their attention to 15th century Florence with a population of less than 50,000, from which emerged Leonardo da Vinci, Michelangelo, Raphael, Ghiberti, Brunelleschi, Alberti, and other great artists. Had my questioners investigated whether the rulers of Florence had created an interdisciplinary organization of painters, sculptors, architects, and poets to bring to life this flowering of great art? Or had they found out how the 19th century municipality of Paris had planned Impressionism, so as to produce Renoir, Cezanne, Monet, Manet, Toulouse-Lautrec, and Seurat? My questions are not as absurd as they seem, because creativity in science, as in the arts, cannot be organized. It arises spontaneously from individual talent. Well-run laboratories can foster it, but hierarchical organization, inflexible bureaucratic rules and mountains of futile paperwork can kill it. Discoveries cannot be planned; they pop up, like Puck, in unexpected corners.

'In the past, most scientists were poorly paid; only few became famous and even fewer rich. One of the characters in Fred Hoyle's novel *The Black Cloud* remarks that scientists are always wrong, yet they always go on. What makes them continue? Often it is addiction to puzzle-solving and ambition to be recognized by their peers.

'Science has changed the world, but the scientists who changed it rarely foresaw the revolutions to which their research would lead. Oswald Avery never set out to discover what genes are made of; Hahn and Meitner never intended to split the uranium nucleus; Watson and Crick were taken by surprise when their atomic model of the DNA told them how the genetic information replicates itself; and when Jean Wiggle and Werner Arbor wondered why a bacterial virus infected one strain of coli bacteria and not another, they could not foresee that some 40 years on, their enquiry would lead to the cloning of a sheep named Dolly. Like children out on a treasure hunt, scientists do not know what they will find.

'According to Paul Ehrlich, the father of immunology, scientists need the four Gs: Geschick, Geduld, Geld, und Gluck (skill, patience, money and luck). Patience may or may not reap its own reward.'

When Perutz was asked, if he were on a lonely desert island, what he would have liked to have, he said that he would like to have Darwin's book *Origin of Species* and other works and if possible a pair of skis. 'A pair of skis?' 'Yes. One never knows whether it will snow or not on this desert island' – the eternal optimist.

As I said before, Perutz's command of English was extraordinary. When Dorothy Hodgkin died, he wrote a memorable and touching obituary. 'Dorothy Hodgkin's uncanny knack of solving difficult structures came from a combination of manual skill, mathematical ability and profound knowledge of crystallography and chemistry. It often led her and her alone to recognize what the initially blurred maps emerging from X-ray analysis were trying to tell. She will be remembered as a great chemist, a saintly, gentle and tolerant lover of people and a devoted protagonist of peace.'

Max Perutz's description of his great friend Dorothy Hodgkin fits himself perfectly.

When Max Perutz, one of the greatest scientists of the twentieth century, died, his demise attracted a lot of media attention and many tributes were paid to him. This obituary has been written culling information and quoting extensively from these tributes. I consider it a great privilege that I have had the honour of having known Max Perutz during my lifetime and that he had written so many friendly and affectionate letters to me.

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