The Scientific and Humane Legacy of Max Perutz (1914–2002)**

John Meurig Thomas*

The son of a prosperous Viennese textile manufacturer, educated first at the Theresianum (a grammar school derived from an officers' academy from the days of the Empress Maria Theresa) and then at the University of Vienna, Max Perutz was to have studied law in preparation for entering the family business. At the Theresianum, he was a small, dreamy, and sleepy boy; and many years later he said: "*I owe my first step to popularity to scarlet fever which I caught when I was fourteen. To disinfect the classroom, my schoolmates got three days off, for which they thanked me solemnly in a letter signed by the entire class*". At sixteen, he, plus two of his colleagues, won the cup for their school in the skiing competition of the Vienna High Schools, and as a result of that victory his standing at school was transformed. "*For the first time in my life I was treated with a certain degree of respect. From then on our gym teacher always gave me top marks, but they happened to be the only ones in my otherwise mediocre school reports*".

A good schoolmaster kindled his interest in chemistry, and he made this the subject of his studies at university. Although largely disappointed with the way in which the subject (especially inorganic analysis) was taught, he acquired a special interest in organic biochemistry and heard about the work of the Nobel Prizewinner (and discoverer of vitamins) Sir Gowland Hopkins at Cambridge. His teacher, Herman Mark, the polymer specialist, visited Cambridge and had planned to pave the way for Perutz to join Hopkins' group. But Mark met J. D. Bernal, who said that he would take Perutz as his student.

Writing in the *Scientific American* in 1978, Max Perutz said:

> *"When I was a student, I wanted to solve a great problem in biochemistry. One day I set out from Vienna, my home town, to find the Great Sage at Cambridge. He taught me that the riddle of life was hidden in the structure of proteins, and that X-ray crystallography was the only method capable of solving it. The sage was John Desmond Bernal, who had just discovered the rich X-ray diffraction patterns given by crystalline proteins. We really did call him Sage,*[1] *because he knew everything, and I became his disciple*".

Perutz was admitted as a graduate student[2] at the oldest college in Cambridge, Peterhouse, on 1 October 1936 and had already begun as a researcher in the Cavendish Laboratory (where Bernal taught and researched in physics) some days earlier. It is hardly necessary to recall that Max Perutz found out how to solve the structure of proteins and used his method for the solution of the structure and mode of action of haemoglobin. However, it is instructive and inspirational for scientists and nonscientists alike to trace the trajectory of his life and to ponder the ingredients of his greatness as a researcher, as a communicator, and as a human being.

A Summary of His Achievements

At the memorial meeting in honour of Sir John Kendrew held in Cambridge, 5 November 1997, Perutz said:

> *"John and I shared three great scientific adventures: founding the MRC Unit for Molecular Biology,*[3] *solving the first protein structure and founding the European Organization for Molecular Biology (EMBO)*".

Perutz and Kendrew, who shared the Chemistry Nobel Prize in 1962, for their pioneering work on the elucidation of the structure of the biological macromolecules haemoglobin and myoglobin, the respiratory proteins of red blood cells and of muscles, respectively, were very different from one another. They were phenomenally able and perspicacious individuals (Figure 1), among the greatest scientists ever to be members of their small Cambridge college, Peterhouse,[4] which boasts as its former students Henry Cavendish, William Thomson (Lord Kelvin), Charles Babbage,[5] Clerk Maxwell, James Dewar, and Frank Whittle.[6] Kendrew was a precise organiser and a gifted computer programmer, at a time when that breed of scientist was very rare. He was a man who knew exactly where he was going and how to get there. Although possessed of urbane charm, linguistic fluency, a love of music, and a great sense of humour, Kendrew was always a more distant,

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Figure 1. Max Perutz (right) constructing a model of the first ever protein structure determined by X-ray crystallography, with John Kendrew looking on (1959).

detached character than Perutz. Perutz was a gentle, kindly, and tolerant lover of people (particularly the young), passionately committed to social justice and intellectual honesty; the warmth of his personality radiated a sense of human goodness and decency which induced others to behave sanely, especially because he exuded an inner excitement that stems from a love of knowledge for its own sake. A distinguished American molecular biologist who worked in the Perutz–Kendrew team as Kendrew's postdoctoral assistant (1957–1958), in a reflective article published in *Protein Science*,[7] wrote:

> *"Max and John were utterly different in personality. Kendrew came in two or three mornings a week to discuss the progress of the research, and to give help where help was needed. He was a great mentor for someone who wanted to learn how to be an independent investigator. At other times he was busy as a science advisor to the British government (on the Polaris missile system as I recall), as an administrator of Peterhouse (college), and on other affairs. In contrast, Max was never so happy as when in the laboratory at the bench, doing science. One learned by talking with John, but by watching Max".*

Perutz's inspirational scientific leadership, more than that of any other, made it possible to unite structural crystallography and molecular pathology and helped to unfold the vast ramifying fields of present day molecular biology. In communicating knowledge to other scientists and the general public—and as an ambassador for science, its methods and philosophy—few of his contemporaries rivaled him. So central were his interests in the vast corpus of scientific endeavor that he was regularly called upon to address biochemists, physicists, physiologists, pathologists, geneticists, and medical scientists of several other kinds. For the last forty years of his life he maintained a punishing round of lecture commitments: one week it was to school sixth formers or to a University of the Third Age[8] audience; another it might be to the assembled researchers at places such as Rockefeller University, New York; the next to frontier scientists in the California Institute of Technology—or in Rome (lecturing in Italian), Berlin (in German, Figure 2), or Paris (in French).

Figure 2. Max Perutz lecturing in Berlin, 1999. An enlarged photo of "Sage" (J. D. Bernal) is seen on the screen behind him.

The Road to Haemoglobin

Perutz, on Bernal's advice, first learned of X-ray crystal-structure analysis in the Department of Mineralogy and Petrology, Cambridge, where he was handed—as he later put it—"*a nasty crystalline flake of a silicate mineral picked off a slag heap*" to investigate.[9] This training proved crucial, for he became adept at X-ray crystallography and he set out to pursue his "great problem in biochemistry". Guided a little later by a cousin, who lived in Prague, he soon convinced himself that an appropriate target for his ambitions was the structure of haemoglobin, especially since it was the protein that was most abundant and easiest to crystallize. It was not until the late 1950s that he finally reached his target of elucidating the structure of haemoglobin; when he did, it made him famous. But his path to success was frequently thwarted by scientific, personal, and political obstacles.

Perutz had obtained tantalizing X-ray diffraction patterns, published in 1938—just as Dorothy Crowfoot (later Hodgkin) and Bernal had earlier with crystals of the enzyme pepsin—and it could then be seen that the thousands of reflections he had obtained could, in principle, lead to the atomically resolved structure of haemoglobin. Unfortunately there was

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no way of interpreting these data, because the so-called phase angles of the reflections could not be evaluated. Previous X-ray structural determinations had been limited to molecular entities possessing a small number of atoms, and often with a known chemical composition. The analytical techniques then available in the solution of the structure of, for example, polynuclear aromatic hydrocarbons, carbohydrates, and other "small" molecules, simply could not be applied to proteins with thousands of atoms and an unknown chemical composition. Perutz, however, felt that proteins had to take up well-defined structures within their crystals, as, otherwise, those sharp spots that he, Crowfoot, and Bernal had obtained were altogether inexplicable.

As Bernal's research student, Perutz was disappointed that Lord Rutherford, then the Head of the Cavendish Laboratory, never looked in to find out what the crystallographers were doing. Perutz later discovered that it was not because of any antipathy towards the X-ray crystallography that Rutherford kept his distance. According to Perutz, "*The conservative and puritanical Rutherford detested the undisciplined Bernal, who was a communist and a woman chaser and let his scientific imagination run wild*".[10] Perutz was cleary disappointed when Rutherford died before he had a chance of attending his lectures or getting to know him. After his death, graduate students could help themselves to left-over reprints of Rutherford's classic scientific papers. Their clarity and rigor, Rutherford's imaginatively conceived experiments, and his determination to prove every one of his results experimentally beyond any possible doubt convinced Perutz that this was the way to do science.

Perutz finished his PhD in 1940, working with Sir Lawrence Bragg, who succeeded Rutherford as the Cavendish Professor, and who had obtained a small grant for him from the Rockefeller Foundation to enable his research to continue. However, the project was interrupted by Perutz's internment in 1940, along with several hundred German and Austrian refugee scholars, mostly Jewish and all anti-nazi.[11] They were rounded up and sent to an internment camp in Quebec, Canada. Fortunately, Perutz's academic friends rallied round and tried to secure his release. He returned to his studies and to work of national importance, which involved him in an unsuccessful scheme to make ships of ice for refueling aircraft in the North Atlantic.

Perutz returned to Cambridge in 1944, and he was joined in 1945 by Kendrew (whose PhD had started with the physical chemist, E. A. Moelwyn Hughes, and whose interest in protein structure had been kindled first by meeting Bernal during war service in operational research and later reinforced by discussions with Linus Pauling in Pasadena on his return journey to the UK). Bragg continued his enthusiastic support, and in 1947 he approached the secretary of the Medical Research Council (MRC), who made the crucial decision to back this small group despite the continuing lack of tangible results—a far cry from present-day attitudes! Francis Crick, a physicist, joined the group as Perutz's PhD student in 1948. Jim Watson, a geneticist, came later, in 1951, and was soon working with Crick on DNA.

As Hugh Huxley,[12] the distinguished muscle biophysicist and molecular biologist, has recently written:[13]

> "*Because there was no direct way of calculating protein structure, Perutz and Kendrew used the huge amounts of data (the intensities of all the X-ray reflections) to produce contour maps, known as Pattersons, to display the most frequently occurring distances between high-density regions in a structure. It was hoped that these might enable prominent features of the structure to be identified. To this end, Perutz and Kendrew, aided by Bragg, enumerated various helical configurations into which polypeptide chains might fold, based on stereochemical data*".

However, they made what seemed then the plausible—later found to be erroneous—assumption that the helices would contain an integral number of residues per turn. They also did not take into consideration that the chemical bonds on either side of the peptide bond are coplanar. (Pauling, working independently, made no such assumptions, and it was he who first arrived, in 1951, at the now well-known non-integral α-helical structure of proteins).

In early 1951, Crick showed that the Patterson maps for haemoglobin and myoglobin did not provide support for the view that there was some regular packing arrangement of polypeptide chains. Indeed he demonstrated that any such arrangement must be extremely irregular. This conclusion, in particular that no useful information was extractable from the Patterson maps, made Crick unpopular, and, for a while, depressed Perutz.[14] However, his resourcefulness as a scientist knew no limits—and it remained thus to the very end of his life.

Just as his two colleagues Watson and Crick were constructing what was later to become their monumental model for the structure of DNA in early 1953, Perutz ruminated on the potential of the heavy-atom substitution method of determining the phases of diffracted X-ray waves. This had its origins in the work of Robertson at the University of Glasgow and that of the Dutch crystallographer Bijvoet in Utrecht; Bernal had suggested in 1939 that it might work for proteins. Crick also made this suggestion somewhat later. Perutz argued that if he could attach a heavy atom to a specific site in the haemoglobin molecule, and if it did not disrupt the structure of the molecule, and if he could make it crystallize in just the same way as ordinary haemoglobin, and if it made changes large enough to be measurable, then if all these conditions were met, Perutz could see a way to use the methods of X-ray crystallography to image the haemoglobin molecule.

What Perutz realized, with increasing clarity and conviction, was that the X-ray diffraction (scattering) intensities from haemoglobin and other proteins were very weak, despite the large number of electrons contributing to them, and that this arose as an inevitable consequence of the fact that the scattering matter was distributed over a relatively large volume. As Huxley recently remarked,[13]

> "*Perutz also realized that scattering from a single heavy atom—mercury, say, with its 80 electrons, or gold with its 79 electrons within a single atomic diameter—would be relatively strong. So if such a marker (heavy atom) were*

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attached at a specific position on each protein molecule in a crystal, it would produce a measurable change in the intensities of the reflections (diffraction spots), and this could be used to obtain (X-ray) phase information necessary for the determination of the structure (the imaging) of the haemoglobin molecule. His peers and contemporaries had wrongly assumed that any such change (to the intensities of X-ray patterns) would be immeasurably small; but Perutz did the experiment carefully, using haemoglobin labelled with mercury, and he found quite measurable changes".

This constituted a major breakthrough in the methodological approach to the structure of proteins.[16] When the world's experts on proteins, assembled by Pauling at the California Institute of Technology in September 1953 (Figure 3), heard Perutz adumbrate his method, they were conscious that a major breakthrough in protein science was imminent. Perutz 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 positions as in the mercury-free protein, but with slightly altered intensity, exactly as I had hoped".

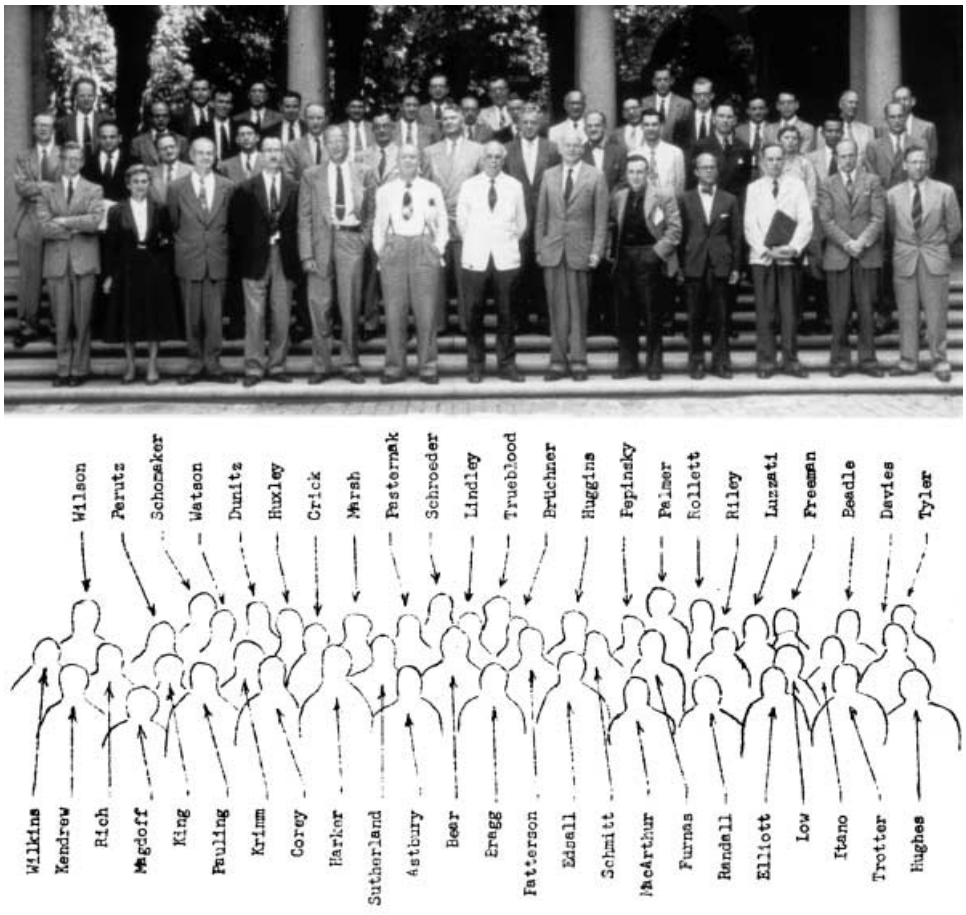

Figure 3. Group photograph taken at the Pasadena Conference on the Structure of Proteins in California, organized by Linus Pauling, 21–25 September 1953.

For Perutz and Kendrew (who also adopted the heavy-atom approach to the determination of the structure of myoglobin), great difficulties still lay ahead before the new method could lead to an interpretable structure.[13, 17] First, it was necessary to have several different heavy-atom derivatives before the phases of all the reflections could be reliably assigned. Second, all these derivatives had to crystallize with exactly the same (unit cell) dimensions. Third, appropriate mathematical procedures had to be devised for calculating the phases. Numerous assistants had to make intensity comparisons (using relatively primitive microdensitometers) on hundreds of thousands of diffraction spots; and, in turn, the electron-density distributions had to be calculated on very early—and by present-day standards extremely primitive—computers in the University of Cambridge Mathematics Department.

Kendrew, assisted by two visiting American scientists (Dickerson and Dintzis) who came to the Perutz–Kendrew unit in the Cavendish Laboratory succeeded in obtaining crystals of gold- and palladium-substituted myoglobin. With their resulting X-ray diffraction patterns, Kendrew, who possessed formidable quantitative skills and who took advantage of the emergence in Cambridge of the EDSAC-1 and EDSAC-2 (programable) digital computers, which he exploited for the Fourier analysis of his diffraction data, solved the structure of myoglobin in 1957.[19] But within two years, Perutz, along with his MRC associates Ann Cullis, Hilary Muirhead, Michael Rossmann, and Tony North, had unraveled the architecture of the haemoglobin molecule, which contains four times as many non-hydrogen atoms (10000) as myoglobin.[20]

Here were two quite independent structural determinations of related proteins, done by pure physics, without any assumptions about the chemical nature of haemoglobin and myoglobin or the relation between them. This exhilarating information revealed that the intrinsic structures of the two proteins, replete with haem groups, numerous folds, and (Pauling's) α-helices, were essentially similar. The inescapable conclusion was that each had to be right. This galvanized activity in molecular biology worldwide. Adolf Butenandt, the eminent German Nobel Laureate, set his colleagues in Munich the task of using chemical methods (such as those pioneered by Frederick Sanger) to trace the sequence of amino acids in the proteins studied by Perutz and Kendrew. The chem-

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ical results harmonized beautifully with those of X-ray crystallography. (Butenandt, among others, nominated Perutz and Kendrew for the Nobel Prize[21].)

The Nobel Prize and Beyond

By 1962, the number of staff of the Perutz – Kendrew MRC unit devoted to molecular biology had grown to ninety. It had long been apparent that the Cavendish Laboratory (now led by Sir Nevill Mott) could no longer satisfactorily house this thriving, expanding community. It seemed eminently sensible that the new breed of biologists, spawned by Perutz's and Kendrew's work, should be accommodated within one of the many existing departments of pure or applied biology of the University of Cambridge. However, cogent though his arguments were, there was little or no enthusiasm in these departments or among the central authorities of the University to welcome Perutz and his colleagues into their fold. Fortunately, the pertinacious and far-sighted Perutz found a ready ally in Sir Harold Himsworth at the MRC Headquarters in London, and, largely through the latter's advocacy, the MRC built the Laboratory of Molecular Biology (LMB) with Perutz as its Chairman on the site of the new Addenbrooke's hospital on the outskirts of the city of Cambridge. This allowed several different aspects of molecular biology to be brought together in one place, along with all the necessary technology. Sanger, who had already won[22] his first Nobel Prize (in 1958), was invited to join the new laboratory, and he brought with him two bright stars, Brian Hartley and Ieuan Harris (the latter in turn also brought along his outstanding young colleague John (later Sir John) Walker, who was to win the Nobel Prize in Chemistry in 1997).[23] In 1961, Huxley of University College, London, who had been Kendrew's first research student, came to join the Structural Studies Division of which Kendrew was head. In 1958, with Bernal's retirement looming at Birkbeck College, London, Perutz had invited Aaron Klug and Rosalind Franklin to join the planned new laboratory when their National Institutes of Health (USA) grant ran out. Klug, who also joined Kendrew's Division, came in 1961, bringing Kenneth Holmes (now of the Max-Plank-Institute for Medical Science, Heidelberg) and the expert electron microscopist and all-rounder, John Finch, with him. (Rosalind Franklin, who died in 1958, never came back to Cambridge, from where she had graduated in chemistry many years earlier.)

The LMB was duly opened by Her Majesty Queen Elizabeth one fine day in May, 1962 (Figure 4), and on that occasion Max Perutz took particular pleasure in explaining the significance of the structure of DNA to his Sovereign. In October of that year, the Swedish Academy announced that Perutz and Kendrew were to share the Nobel Prize in Chemistry, and that their two associates, Watson and Crick, along with Maurice Wilkins of King's College, London, were to share the Prize in Medicine and Physiology (Figures 5 and 6).

The unique success of the LMB, measured, for example, by the numerous awards gained by members of this one laboratory—nine Nobel Prizes, four Orders of Merit (the highest civil honour that the British Sovereign can bestow), eight Copley medals (the highest honour of the Royal

Figure 4. Official opening of the Laboratory of Molecular Biology, at which Max Perutz (extreme right) explains the double helix to H.M. Queen Elizabeth II, May 1962.

Figure 5. Photograph taken after the Nobel Prize ceremony, Stockholm: M. F. H. Wilkins, M. F. Perutz, F. H. C. Crick, J. Steinbeck, J. D. Watson, J. C. Kendrew.

Figure 6. Informal photograph (Dec 1962) of Max Perutz (left), Gisela Perutz, and John Kendrew.

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Society), and over a hundred Fellowships of the Royal Society conferred upon its staff—merits closer enquiry. An overwhelmingly important factor in all this is the way that Perutz organized the Laboratory and his own role within it.

Perutz, from the outset, adopted a new style of management. Thus he once wrote:

> *"I persuaded the MRC 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".*

As his former PhD student and distinguished molecular biophysicist, Professor David Blow,[24] who was a member of the LMB in its early days, said recently of Perutz:

> *"He always recognized 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".*

However, over and above these technical features of running a laboratory, Perutz, ably assisted by his devoted and shrewd wife Gisela, made the canteen at the LMB a focal point for intellectual stimulus. It was—and still is—visited three times a day by most scientists and associated staff, and it remains an important center for the exchange of ideas and scientific news. One American molecular biologist[25] on sabbatical leave in 1985 at the LMB commented that, because the canteen was the intellectual center of the laboratory, one could not stray off course in one's research work for more than a period of three hours! Perutz himself kept abreast of everybody's work, by making a habit of sitting with different groups of people at coffee time, lunch, or tea. (He did likewise whenever he came to lunch at his college, Peterhouse.)

Perutz led by example,[26] he aimed to spend some 90 % or more of his time working at the bench, and he expected others to do likewise. But he recognized and could cope with differences in individual style. In reflective mood, he once wrote:

> *"When Crick and Watson lounged around, arguing about problems for which there existed as yet no firm experimental data instead of getting down to the bench and doing experiments, I thought they were wasting their time. However, like Leonardo, they sometimes achieved most when they seemed to be working least, and their apparent idleness led them to solve the greatest of all biological problems, the structure of DNA. There is more than one way of doing good science".*
>
> *Every now and then,* Max Perutz wrote in one of his recent books (*I Wish I'd Made You Angry Earlier: Essays on Science, Scientists, and Humanity*), *I receive visits from earnest men and women armed with questionnaires and tape recorders who want to find out what made the LMB (where I work) so remarkably creative… I feel tempted to draw their attention to 15th century Florence with a population of less than 50000, from which emerged Leonardo, Michelangelo, Ghiberti, Brunelleschi, Alberti, and other great artists. Had my questioners investigated whether the rulers of Florence had created an interdisciplinary organisation of painters, sculptors, architects, and poets to bring to life this flowering of great art?… My question is not as absurd as it seems, because creativity in science, as in the arts, cannot be organised. It arises spontaneously from individual talent. Well-run laboratories can foster it, but hierarchical organisation, inflexible, bureaucratic rules, and mountains of futile paperwork can kill it. Discoveries cannot be planned; they pop up, like Puck, in unexpected corners".*

In an age when the Paladins of accountability and the Funding Councils persist in preaching the necessity for all academic research centers to have a Mission Statement and Strategic Plans, it is prudent to recall how Perutz set about founding and running the extraordinarily successful LMB. The principles he used were: choose outstanding people and give them intellectual freedom; show genuine interest in everyone's work, and give younger colleagues public credit; enlist skilled support staff who can design and build sophisticated and advanced new apparatus and instruments; facilitate the interchange of ideas, in the canteen as much as in seminars; have no secrecy; be in the laboratory most of the time and accessible to everybody where possible; and engender a happy environment where people's morale is kept high.

However, the LMB in Cambridge is not the only major laboratory in which Perutz had a hand in creating. Shortly after the Nobel ceremony in Stockholm in 1962, Leo Szilard and Victor Weisskopf of the United States called to see Watson, Kendrew, and Perutz to discuss the prospects of establishing a European Molecular Biology Organisation (EMBO) like the Nuclear Science Centre (CERN) in Geneva. All three responded enthusiastically. Supported by other European molecular biologists, notably Francois Jacob (France), Friedrich Freska (Germany), Ole Maalo (Denmark), Jeffries Wyman (USA), and, crucially, Ephraim Katchalski-Kazir (Israel), Kendrew led the way, and soon EMBO came into being with Perutz as its Chairman from 1963–1969. In due course, the European Molecular Biology Laboratory (EMBL) at Heidelberg, of which John Kendrew was the founding Director (for ten years), also came into being.[27]

Haemoglobin and its Impact on Medicine

In 1959 when Perutz and his colleagues first unraveled the architecture of the haemoglobin molecule in outline, it was appreciated by all concerned that it was not the end of their journey. As Perutz put it:

> *"…our much-admired model (of haemoglobin) did not reveal its inner workings—it provided no hint about the molecular mechanism of respiratory transport. Why not? Well-intentioned colleagues were quick to suggest that our hard-won structure was merely an artefact of crystallisation*

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and might be quite different from the structure of haemoglobin in its living environment, which is the red blood cell".

For a long time after Perutz solved the structure of haemoglobin (Figure 7), he zealously pursued the secret of its mode of action. How was it that, in effect, haemoglobin functions as a molecular lung? It was not until early in the 1970s that a satisfactory answer to this question came and the fundamentals of the mechanism were elucidated.[28]

The firm experimental evidence on which the now accepted (Perutz) mechanism for the so-called allosteric change that accompanies the reaction of haemoglobin with oxygen—an allosteric protein[29] is one that changes from one conformation to another when it binds another molecule (such as oxygen)—came not only from detailed X-ray crystallographic work but also from Perutz's imaginative use of other techniques, such as spectroscopy and magnetic measurements. First he recalled the significant earlier work of Faraday (in the 1840s) and Pauling (in 1936) who showed that when haemoglobin binds oxygen it loses its paramagnetism. Then he found that the structural changes in haemoglobin accompanying oxygenation were large. In the "deoxy" form the iron atom of the heme is displaced a little from the plane of the heme group, whereas in the "oxy" structure it lies almost in the plane (Figure 8). Perutz recognized that this is so because of a change in the (electronic) spin state of the iron atom—from so-called "high spin" in the deoxy to "low spin" in the oxy state—and hence to a diminuation in the radius of the iron. (This was independently established for heme groups by Leroy Hood.) When the iron center moves closer to the plane of the heme in the oxy state it drags with it the α-helix of the protein to which it is connected; this is the trigger that initiates a sequence of "molecular levers" that loosen and rearrange the subunits in the (tense) deoxy structure into a new (relaxed) oxy structure. This is the basis of the molecular mechanism—"*infinitely rewarding in its simple beauty*" as Perutz used to say—that governs the oxygen affinity of haemoglobin in response to physiological needs, and the release of bound oxygen when it is needed under conditions of oxygen scarcity.

This mechanism was to lead in due course, through work on haemoglobin mutants, to a fuller understanding of several inherited diseases and it opened up the new field of molecular pathology, a subject which relates a structural abnormality to a particular disease. Perutz gained new insights into molecular evolution,[31] and into the delicate (sometimes major) differences exhibited by haemoglobin in a wide range of living species. For example, the frogs of Lake Titicaca, high in the mountains of Bolivia, have evolved a form of haemoglobin that can absorb oxygen better than that in the frogs of Lake Michigan, at a lower altitude. This enhanced absorbability of oxygen is also a feature of the haemoglobin of migrating geese that fly at high altitudes. Crocodiles are able to remain under water for more than an hour without surfacing to breathe[32] and often kill their prey by drowning it. How do crocodiles stay under water for so long? Perutz's colleague, Kiyoshi Nagai, and his associates found that when crocodiles hold their breath, bicarbonate ions—the final products of respiration—accumulate and drastically reduce the oxygen affinity of their haemoglobin, thereby releasing a large fraction of the oxygen bound to the globin into the tissues of the mammal.[33] (In collaboration with an American company, Nagai (at the LMB) laid the groundwork for an engineered haemoglobin

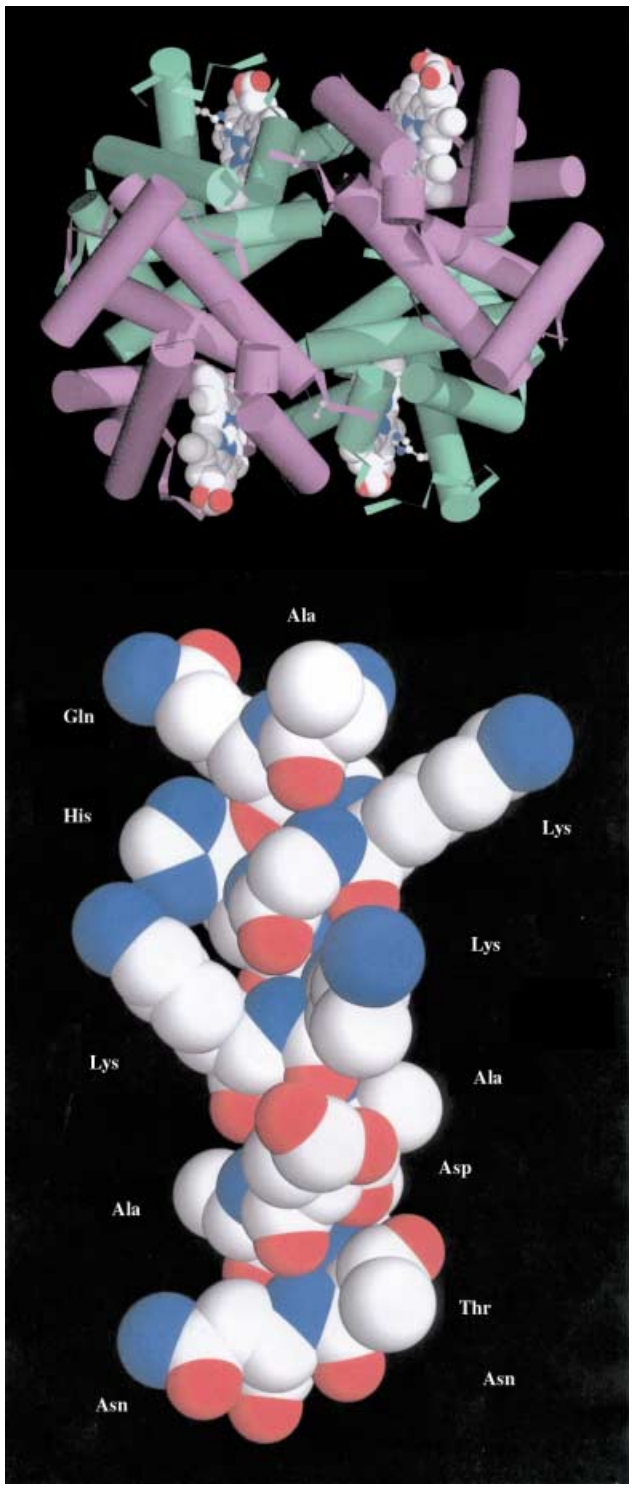

Figure 7. Top: Representation of a molecule of haemoglobin, with the four heme groups shown in atomic detail, and the two pairs (the so-called α and β subunits) of helically arranged amino acid residues shown as colored cylinders: α unit, green; β unit, purple. Bottom: Atomic representation of the amino acid residues that constitute the subunits shown as green and purple cylinders in the top picture. Carbon atoms are in white, nitrogen atoms in blue, and oxygen atoms in red).

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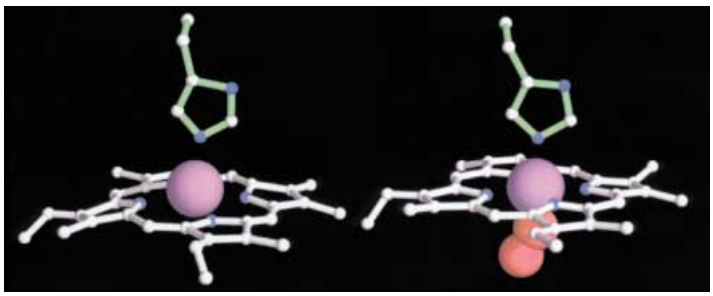

Figure 8. Left: In human deoxy haemoglobin the Fe^{2+} ion, attached to histidine (above), lies slightly above the plane of the heme group. Right: When the Fe^{2+} ion binds oxygen, as in the oxyform, it moves into the plane of the heme. This process is what initiates the sequence of resulting structural changes, see text for further information.

likely to be suitable for use as a cell-free blood substitute. The need to develop a blood substitute is now urgent because of the increasing concern over blood-transmitted viral and bacterial pathogens.)

Earlier, Perutz's pioneering work offered a deeper appreciation of such tragic diseases as thalassemia, which arises because of defective synthesis of haemoglobin, and of sickle-cell anaemia. His colleagues at Cambridge, Vernon Ingram and John Hunt, showed that sickle-cell haemoglobin differed from the normal protein merely by a change of a single amino acid residue, in fact the replacement of glutamic acid by valine.

The Exponential Growth of Protein-Structure Determination

In 1953, when Perutz discovered that the so-called X-ray phase problem of protein crystallography could be solved by the method of isomorphous replacement with heavy atoms, he expected that the structures, not only of haemoglobin, but also of many other proteins, would presently be solved;[34] but this did not happen. Only three protein structures had been solved by 1965, and only eleven by 1970. The practical difficulties of crystallization, of preparing isomorphous heavy-atom derivatives, and of recording the X-ray diffraction data were so great that determination of each new structure took many years. Besides, most professional crystallographers were reluctant to enter this risky new field. However, the situation has now been fundamentally transformed. Since 1975 there has been an exponential rise in the annual number of protein structures solved (Figure 9). In 1990 over 100 new structures came to light; but by 2000 approximately 16000 structures were known, and very many of these are of direct practical interest to medicine. If one knows the structure of a protein in atomic detail, then the precise architecture, shape, and dimensions of receptor centers and catalytically active sites are also known. This situation enables the protein engineer to improve the performance of existing proteins by using various modern methods. This is now one of the major growth areas of enzymology.

It is interesting to note that most, but not all, of the first generation protein crystallographers (1960–1980) came out of British laboratories in Cambridge, Oxford, and the Royal Institution, London. (The migration of D. C. Phillips and his former student Louise Johnson to Oxford in the mid-1960s, after they had solved the structure of lysozyme and explained its mode of action, accounts for a shift of the center of excellence in protein crystallography outside Cambridge from London to Oxford, although the towering presence and achievements of Dorothy Hodgkin at Oxford had already established it as a world-renowned X-ray structural laboratory.) It is also interesting to reflect, with the benefit of hindsight, how wrong-headed the eminent biochemist and Nobel Prizewinner Sir Ernst Chain was when, some thirty years ago, he advised the MRC in London that medical research involving crystal-structure analysis was a profligate waste.[35] Such is the unpredictability of science.

From Glaciers to Huntington Disease: Perutz's Earliest and Latest Research

As a teenager Perutz gained distinction in his school in Vienna as an expert downhill skier. He was also, at that time, an accomplished mountaineer, and his love of mountains and glaciers never left him. He claims to have barged into Sir Lawrence Bragg's office one day in the Cavendish making the untypical claim: "*I've had an honour that you can't match—I've had a glacier named after me!*" to which Sir Lawrence retorted "*I've had a cuttlefish named after me*".[36]

From his early twenties Perutz had a deep interest in glaciers, particularly how they flowed. Did this occur like

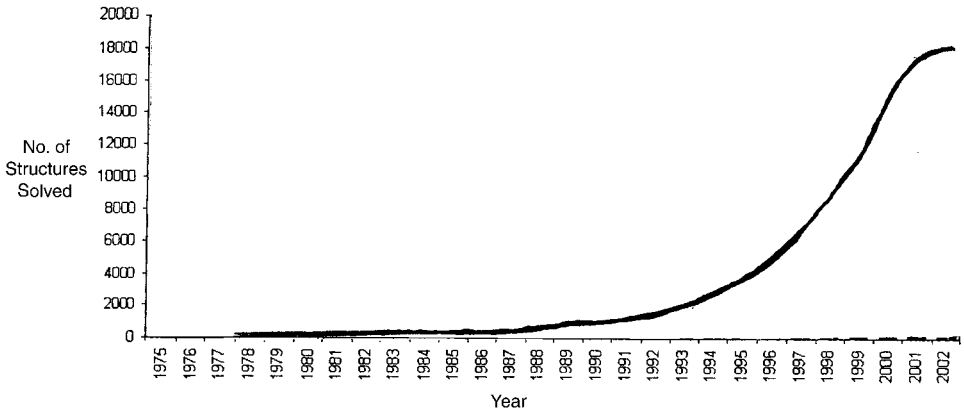

Figure 9. Exponential growth of the number of protein structures determined since 1975. (Adapted from the web site of the Research Collaboratory of Structural Bioinformatics (RCSB).)

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treacle or honey flowing out of a tilted container, or was there some other mechanism? More or less as a hobby, Perutz, after conducting measurements perched inside his Alpine igloo on the Jungfrau (Figure 10) for several months in 1938 and again

Figure 10. Max Perutz with a polarizing microscope examining thin sections of glacier ice on the Jungfraujoch in 1938 (Photograph by G. Seligman).

ten years later in a grotto in Eigergletscher, solved the problem of how a glacier flows. It moves, not like treacle, but more like a ductile metal (such as aluminum when it is rolled into a sheet). The process of slip, in the metallurgical sense of the term, is what occurs here. Perutz gave a Friday Evening Discourse on *The Flow of Glaciers* at the Royal Institution on 5 June, 1953, and a summary of his lecture/demonstration appeared in *Nature* later that year.[37]

In the dining Hall at Peterhouse in October 1936, Perutz made friends (at the research students' table) with a highly gifted, modest, gentle young man named John Carter, whose father, a retired Indian Civil Servant in Budleigh Salterton (a seaside town in Devon), had made a strange discovery. Could Perutz help to explain it? When walking under the red sandstone cliffs to the west of Budleigh Salterton, Carter senior had noticed gray balls of rock of ranging size protruding from the walls of the cliff. They looked like cannon balls and were surrounded by sharply drawn, circular white halos where the red sandstone had been bleached. Carter senior had himself decided that the bleached halos must have arisen from intrinsic radioactivity. In a fascinating account entitled *My First Great Discovery*, published in the *Peterhouse Annual Record* eight years ago,[38] Perutz describes how, notwithstanding the obstructionism of the wily old Lincoln (Rutherford's Sergeant Major-like, miserly lab steward), he established that the nodules contained about 0.5 % uranium, concentrated at the borders of dark and light material in the sandstone. Bernal, Perutz's supervisor, thought that the nodules were intriguing enough to be exhibited at the Royal Society Conversazione in June 1937.

Approaching his eightieth birthday, Perutz took an interest in Huntington disease, a neurodegenerative disorder caused by abnormal expansions of glutamine repeats in the mutant protein (later called huntingtin).[39] In 1994, Perutz and his colleagues showed that polyglutamine polymers could form β sheets in which glutamine residues of neighboring strands are linked by hydrogen bonds between the main chain and side-chain amides. Perutz proposed that proteins with long runs of glutamine residues would form aggregates harmful to the cell. Indeed, aggregates of huntingtin have by now been observed as intranuclear inclusions in the brain of patients suffering from Huntington disease. It has not yet, however, been incontrovertibly established that they are themselves the cause of neuronal deaths. Perutz, in a promising collaboration (started in 2000) with A. H. Windle (a materials scientist), drew parallels between the rates of nucleation of crystals with the random occurrence of neuron deaths.[40] Their model explains the finding that the age of the patient at the outset of the disease is related exponentially to the length of the glutamine repeats in the pathological protein. Perutz's very last paper,[41] was finished just ten minutes before he was admitted to Addenbrooke's Hospital for emergency surgery.

A memorable incident took place in the Henry Cavendish dining room at Perutz's College, Peterhouse, on 31st October 2001. At the instigation of the President of the Royal Society of Chemistry, Professor Stephen V. Ley, I organized a small lunch party (Figure 11) to celebrate the award to Perutz of Honorary Fellowship of the Society. Around the table all of us were chemists of various backgrounds. Just as coffee was being served, I asked Max, in a rather public manner, to outline his present research. Those who were privileged to listen to his impromptu, ten-minute exposition of the problems that cause neurodegenerative diseases (Huntington and Alzheimer) will never forget it. First he told us that certain clues were known to some scientists in the early 1930s; then he said that it was less that ten years ago that he himself had tumbled (via so-called "polar zippers") to the enigma of the amyloid proteins. Then he proceeded to proffer the hard experimental evidence that had led him to the structure of amyloid fibres. We listened in awe and exhilaration. Here was this gentle, patriarchal, sparkling, eighty-seven-year-old, who had won his Nobel Prize forty years earlier, flanked by his octogenarian friend Sanger (a double Nobel Laureate), telling us not only a scientifically important, but an absolutely fascinating story—a story which, fortunately for posterity, constitutes his last scientific paper.

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Figure 11. Photograph taken at Peterhouse, Cambridge, 31 October 2001, to celebrate Max Perutz's election as Honorary Fellow of the Royal Society of Chemistry (RSC) in which Max Perutz is flanked by Frederick Sanger (right) and John Meurig Thomas (left).

Some fourteen weeks later he passed away, having been visited by a succession of his friends and colleagues, lovingly supported by Gisela his wife (to whom he had been married for sixty years) and by his devoted children—Vivien, a historian of art, and Robin, Head of the Department of Chemistry, University of York—grandchildren, and neighbors.

The Expositor and Critic

Max Perutz was an excellent lecturer, with a gift of perceiving how to put his points so that they would be readily grasped by an audience which was not expert in his own line. His lectures had a wonderful lightness of touch and a mesmeric charm, partly because they were interspersed with unforgettable human incidents involving his friends and scientific adversaries. In a memorable lecture, entitled *Science is No Quiet Life*, (organized by the Kelvin Club, the students' scientific society at Peterhouse at which he was a frequent and highly popular speaker, to mark the 60th anniversary of his arrival at the College), he related how a pugnacious American physicist "*burst into my room at the LMB, like a gladiator entering the arena in Rome, telling me that the Perutz picture of haemoglobin is wrong*".

Perutz was also a deeply cultured individual, the breadth and depth of whose knowledge was extraordinary. These qualities, along with his magnanimity and generosity to friends and strangers, and his implacable opposition to any unfairness, were particularly evident in the many popular articles that he wrote in limpid prose for the *New York Review of Books* and the *London Review of Books*, with their frequent allusions to characters, incidents, and poems in the works of George Eliot, Tolstoy, Dickens, Shakespeare, Bacon, Donne, Rilke, Hugo, Iris Origo, Lampedusa, and Manzoni.

William Blake claimed that only through three human pursuits could one be brought to the edge of eternity: music, poetry, and painting. With any one of these, said Blake, one could acquire an ineffable sense of ecstasy. Judging by what Perutz has written over the years, I am sure that he would have wished to add science as a fourth such pursuit. He used to say that: *"Scientific research is an exhilarating and imaginative activity depending on qualities of the human mind that are beyond our comprehension"*.

The pursuit of science frequently entails the fusion of the aesthetic and the intellectual. Like music, poetry and painting its prosecution demands single-minded devotion. In this context two of Max Perutz other favorite sayings are pertinent:

> *"Haydn rose early each morning to compose; if ideas failed him, he clasped his rosary and prayed until Heaven sent him fresh inspiration"*;

and

> *"Renoir painted every day of his life, and, when old age had made his fingers too arthritic to hold a brush, he got someone to tie his brush to his hand*".

Max Perutz spoke with the same respect to young students, and to college and laboratory staff, as he did to Prime Ministers and Royalty. He was a citizen of the world, endowed with a great sense of history and of the continuity of existence. It is easy to appreciate why he so much admired the following passage from the *Memoirs* of the ballerina Dame Margot Fonteyn:

> *"I cannot imagine feeling lackadaisical about a performance. I treat each encounter as a matter of life and death. The important thing I have learned over the years is the difference between taking one*'s *work seriously and taking oneself seriously. The first is imperative and the second disastrous*".

Max Perutz was a wonderful human being: the great can also be good.

[1] Sage was J. D. Bernal (1901 – 1971), Anglo-Irish crystallographer, who graduated from the University of Cambridge before proceeding to work as a research student of W. H. Bragg at the Davy Faraday Research Laboratory of The Royal Institution, London, where he solved the structure of graphite. He was later appointed Assistant Director of Research at the Cavendish Laboratory, Cambridge (where Dorothy Crowfoot (later Hodgkin), and A. F. Wells of Oxford, Isadore Fankuchen, of Brooklyn Polytechnic, and Max Perutz, joined him). He later became Professor of Physics at Birkbeck College, University of London. During World War II he led a team of operational research and other work of national importance. John Kendrew rubbed shoulders with him during duties in the jungles of Sri Lanka. Max Perutz said that Bernal was the most brilliant conversationalist he had ever met, and that he was a restless genius always searching for something more important to do than the work of the moment. A lifelong member of the British Communist Party, he was much admired by an enormous circle of influential people. Earl Mountbatten of Burma, to whom he reported in the war years, said of him: "*Desmond Bernal was one of the most engaging personalities I have ever known… his most pleasant quality was his generosity. He never minded slaving away at other people*'s *ideas, helping to decide what could or could not be done, without himself being the originator of any of the major ideas on which he actually worked*". Bernal gave

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laboratory space to Aaron (later Sir Aaron) Klug, Nobel Laureate in Chemistry, 1982, and Rosalind Franklin, while at Birkbeck College. Bernal is widely acknowledged as one of the major pioneers of molecular biology. He and Dorothy Crowfoot published in 1934 (D. Bernal, D. Crowfoot, *Nature*, 1934, *130*, 794) the X-ray diffraction photographs of crystals of the enzyme pepsin (in its wet state). Up to then, many felt that large biological molecules had no well-defined structure, certainly not in solution, and believed that they resembled spaghetti with intertwined strands of variable length, bent and folded so as to be difficult to disentangle physically and to defy structural description. Bernal and Crowfoot, however, pointed out that "*from the intensity of the more distant (X-ray diffraction) spots, it can be inferred that the arrangement of atoms inside the protein molecules is also of a perfectly defined kind*".

[2] Perutz sought entry as a graduate student to Trinity, King's, Gonville and Caius, and St John's Colleges, but he was turned down. In desperation he asked the crystallographer, W. A. Wooster, an associate of Bernal, for advice. He told him: "*Why not choose the college with the best food, which is the college of which I am a member*?". And that is how he came to join Peterhouse (where the food is still among the best in Cambridge).

[3] The Medical Research Council (MRC) is one of Britain's most successful scientific seedbeds. It was set up for practical reasons as a consequence of the 1911 National Insurance Act, when David Lloyd George, as Chancellor of the Exchequer, singled out tuberculosis (TB) as a problem needing special attention. In Great Britain and Ireland this dreadful disease was responsible for one in three deaths among males aged between 15 and 44, and half the deaths among females aged 15 to 24. Germany was making great strides through the building of TB institutions. The Chancellor of the Exchequer felt that something had to be done in Britain. The First World War brought out many other pressing medical problems as well—wound infections (especially tetanus and gangrene), typhoid, cholera, dysentery, civilian malnutrition, and even TNT poisoning in munitions factories. The MRC worked successfully on many of these problems, and when the war ended the first Secretary of the MRC, Sir Walter Fletcher, was able to argue that its work should not be restricted to any particular area such as TB, for which the funds were originally committed. Fletcher defined the primary function of the MRC as promoting fundamental scientific research, since this was essential to the development of clinical treatment. He found a ready ally in the Prime Minister of the day, David Lloyd George, who had been the original architect of the National Insurance Act. The MRC has become one of the great jewels in the crown of British science.

[4] Of which they were each Honorary Fellows. Perutz, although a member of Peterhouse, with dining rights and some other privileges ever since he entered as a graduate student in 1936, was not made a Fellow until he won the Nobel Prize in 1962. Kendrew, on the other hand, from the time he entered the college in 1947 as a College Lecturer, Official Fellow, and Director of Studies in Natural Sciences, played a leading part in the academic, social, and administrative life of the College for 27 years. He served successively as Librarian, Wine Steward, Steward, and Curator of the College's paintings and portraits.

[5] Charles Babbage (1792 – 1871) is best known as the inventor of the so-called "Difference Engine", a calculating machine that is accepted as the first computer, see Doron Swade, *Charles Babbage and his Calculating Engines*, Science Museum, London, **1991**. The inventive Babbage once remarked: *"All of chemistry, and with it crystallography, would become a branch of mathematical analysis which, like astronomy taking its constants from observation, would enable us to predict the character of any new compound and possibly the source from which its formation may be anticipated"*.

[6] Inventor of the jet engine. Other distinguished living members include the Nobel Laureates A. J. P. Martin (Chemistry, 1952) and Aaron Klug (Chemistry, 1982).

[7] R. E. Dickerson, *Protein Sci.* **1992**, *1*, 182 – 186.

[8] The University of the Third Age (U3A), an organization that began in France, caters for retired people, and there are now branches in many British (especially university) towns and cities.

[9] Rhodonite is a manganese-rich silicate of the pyroxeroid family $(Mn,Ca,Fe)SiO_3$.

[10] Perutz subsequently discovered that Rutherford wanted to throw Bernal out of the Cavendish but was restrained from doing so by W. L. (later Sir Lawrence) Bragg, who became Rutherford's successor at Manchester and at Cambridge. Perutz used to say that "*Had Bragg not intervened, Bernal's pioneering work in molecular biology would not have started, John Kendrew and I would not have solved the structure of proteins, and Watson and Crick would never have met*".

[11] When Hitler invaded Austria, the family business was expropriated, and his parents became refugees. Perutz brought his parents to Britain, but he and his father were interned in 1940. After his release, his father, who had never worked with his hands before, took a manual job (as a lathe operator in Letchworth) to help the war effort.

[12] Who also joined the Perutz – Kendrew team in 1948.

[13] H. E. Huxley, *Nature* **2002**, *415*, 851 – 852.

[14] Perutz, after six years of labor extracting Patterson maps (which consisted of some 25 million lines between the thousands of atoms in the haemoglobin molecule, felt:[15] "*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 heart-breaking 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*".

[15] M. F. Perutz, *I Wish I'd Made You Angry Earlier*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, **1998**, p. XI.

[16] It is a fortunate fact that complex molecules such as haemoglobin take no more notice of the isomorphous attachment of a heavy atom than (to use Sir Lawrence Bragg's words) "*a Maharaja's elephant would of the gold star painted on its forehead*".

[17] The picture was crude, but two years later, by using the linear diffractometer devised and built by Arndt and Phillips[18] at the Davy Faraday Research Laboratory, London (where Perutz and Kendrew were Honorary Readers, 1954 – 1968), a much sharper picture of myoglobin, in all its glorious complexity, was obtained, with the identities of the amino acid residues clearly discernible.

[18] Arndt later moved from the Davy Faraday Laboratory to the LMB in Cambridge, and Phillips (later Sir David, then Lord Phillips of Ellesmere, 1925 – 1999) was appointed Professor of Molecular Biophysics in the University of Oxford.

[19] J. C. Kendrew, G. Bodo, H. M. Dintzis, R. G. Parrish, H. W. Wyckoff, D. C. Phillips, *Nature* **1958**, *181*, 662 – 666.

[20] M. F. Perutz, M. G. Rossman, A. F. Cullis, H. Muirhead, G. Will, A. C. T. North, *Nature* **1960**, *185*, 416 – 422.

[21] Perutz loved telling the story of how, on hearing so many people predict that he and Kendrew would be awarded the Nobel Prize, one day an excited secretary brought in to them an important-looking envelope bearing an unusual stamp, and they each thought: "This is it, news of the Prize". But the letter had been sent from the Pontifical Academy urgently requesting their reprint order forms, duly completed!

[22] For his work on the primary structure of proteins, especially that of insulin.

[23] For elucidating the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP).

[24] D. M. Blow, *The Independent* (London), 7 February **2002**.

[25] D. Eisenberg, *Protein Sci.* **1994**, *3*, 1625.

[26] In his *Commonplace Book*, Perutz has enumerated his own: "*People are best judged by their actions*", and that of Albert Schweitzer: "*Example is not the main thing in influencing others; it is the only thing*".

[27] K. C. Holmes, *Biogr. Mem. Fellows R. Soc.* **2001**, *47*, 311 – 332. Kendrew's own interest in fundamental research began to wane in the mid 1960s as he gradually turned his brilliant mind to matters of policy. He had already served as Deputy Chief Scientific Advisor to the Ministry of Defence (1960 – 1965); and then he became Chairman and Secretary General of the International Council of Scientific Unions (ICSU), centred in Paris, a body of which he became President (1988 – 1990). From 1969 to 1975, Kendrew was Secretary-General of

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the EMBO, and in 1974 he became the (first) Director General of EMBL at Heidelberg, where a splendid new building was opened in May 1978.
[28] M. F. Perutz, *New Sci.* **1971**, *49*, 676 – 679.
[29] In some cases, the binding of a molecule to the protein produces little conformational change. Sperm whale myoglobin[30] is a good example: the oxy and deoxy structures may be superimposed almost exactly.
[30] A. M. Lesk, *Protein Architecture: A Practical Approach*, Oxford University Press, Oxford, **1991**, p. 121.
[31] G. Fermi, M. F. Perutz, *Atlas of Molecular Structures in Biology: Haemoglobin and Myoglobin*, Clarendon Press, Oxford, **1981**. The aminoacid sequences in the α and β subunits of the haemoglobin in the following creatures are enumerated in this Atlas: man, rhesus monkey, orang-utan, slow loris, tupai, savannah monkey, capuchin monkey, hanuman langur, spider monkey, rabbit, dog, horse, cat, pig, camel, llama, Indian elephant, opossum, rat, chicken, grey lag goose, carp, goldfish, caiman, Nile and Mississippi crocodile, tadpole, and shark.
[32] H. T. Andersen, *Acta Physiol. Scand.* **1961**, *53*, 24 – 45.
[33] N. Hennakas, G. Miyazaki, J. Jame, K. Nagai, *Nature* **1995**, *373*, 244 – 246.
[34] M. F. Perutz, *Faraday Discuss.* **1992**, *93*, 1 – 11.
[35] Private communication from Max Perutz to Sir Aaron Klug, July **1993**.
[36] Neither of these two scientists was given to boasting, idle or otherwise. But the story is undoubtedly true and was told in Perutz's Royal Institution Discourse in 1990 entitled *How W. L. Bragg invented X-ray Analysis* published in M. F. Perutz, *The Legacy of Lawrence Bragg* (Eds.: J. M. Thomas, D. C. Phillips), Science Reviews Ltd, London, **1990**.
[37] M. F. Perutz, *Nature* **1953**, *172*, 929 – 932.
[38] M. F. Perutz, *Peterhouse Annual Record*, **1994** – **1995**, p. 15.
[39] A. Klug, *Science* **2002**, *295*, 2382 – 2383.
[40] M. F. Perutz, A. H. Windle, *Nature* **2001**, *412*, 143 – 144.
[41] M. F. Perutz, J. T. Finch, J. Berriman, A. Lesk, *Proc. Natl. Acad. Sci. USA*, **2002**, *99*, 5591 – 5595.

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