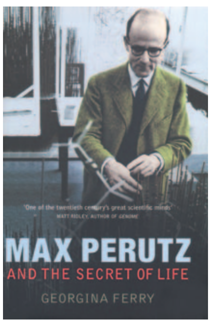
Max Perutz and the Secret of Life

Anyone who has ever climbed a challenging mountain or hill, or has ever contemplated trying to do so, will appreciate that such an adventure requires foresight, planning, motivation, innovation, and a good deal of perseverance. Max Perutz (1914–2002), the pioneer of protein crystallography and molecular biology, climbed many mountains in his lifetime, both figuratively and literally. Investing more than two decades in an effort to achieve the first-ever glimpse of a protein structure, he surmounted many experimental and personal difficulties throughout this and many other endeavors. In the course of achieving that scientific landmark, Max established and nurtured a research laboratory that blossomed with a creative energy that few places have matched outside of the artistic centers of the Renaissance. His biographer Georgina Ferry has written an engaging and scholarly book that describes Max's personal and scientific lives, and places these within the context of scientific and geopolitical histories. Mountains are a key unifying theme throughout the book.

Ferry describes Max's formative years in Vienna, where he developed a passion for challenging mountain expeditions and, as an undergraduate, first became aware of the work of F. G. Hopkins and J. D. Bernal in Cambridge to understand biological molecules at the level of chemistry and structure. She traces his path from Austria to Cambridge in 1936 to join Bernal's group as a PhD student, where he was provided with little guidance but much inspiration. A lifetime's supply of remarkable events soon followed his arrival. First, there was Max's quest to identify a feasible and important PhD project, leading him to haemoglobin, which was to remain the key research focus of much of his life. Work in Cambridge was interspersed with alpine expeditions to do glacier research. However, in 1939 tumultuous political change transformed Max from a foreign student to a stateless refugee left scrambling to rescue his parents from the menace of racial persecution in Austria; and this was followed soon afterwards by his unjust and incomprehensible internment in the UK, and deportation to Canada as an "enemy alien". Released after nearly a year, Max was soon recruited by Bernal into a bizarre secret project to construct floating airbases from ice, using his experience of glaciers. With the collapse of that project after a year, Max quietly returned to the bench full-time to pursue the crystal structure of haemoglobin.

When Max entered the field of crystallography as a PhD student, it was unclear whether solving a protein structure was a tractable problem. The proof of principle that proteins could be coaxed into diffracting crystals had only been recently established by Bernal and Dorothy Hodgkin. However, it was unclear how to go about determining the phases of thousands of diffraction maxima needed to elucidate the structure of a protein molecule. Ferry follows the crucial but painstakingly slow developments by Max and his team to crack the phase problem, and the key breakthrough when they showed that mercury could be covalently attached to the protein to prepare an isomorphous derivative. To appreciate the visionary aspect of the crystallographic work, one only needs to reflect on the extent of current international efforts to solve protein structures and the massive investment in crystallographic tools for structure elucidation: particle accelerators that are intense sources of well-focused monochromatic X-rays; robotics; and extensive computational developments. These efforts are motivated by the anticipation that they will be rewarded with the understanding of biological function at the level of detailed stereochemistry and the ability to design drugs and chemical switches. The current flood of scientific activity can be traced back half a century to a semi-dilapidated shed situated just outside the main building of the Cavendish Laboratory in Cambridge, where the structures of haemoglobin and myoglobin were solved by Max and his colleague, John Kendrew, respectively.

These first crystal structures revealed that proteins have complex folds. Further, in a key moment in the study of molecular evolution, the four subunits of haemoglobin were recognized as structural homologues of the stand-alone myoglobin, which demonstrated that structure is more highly conserved than sequence. One of Max's visionary aims in studying haemoglobin was to understand its cooperativity, whereby the binding of the first oxygen molecule boosts the affinity for others. However, the first crystal structure of haemoglobin did not provide the answer to that riddle. After another decade of effort, the details of the mechanism became clear; and this allowed Max to formulate a model proposing that quaternary structure affects the affinity of the oxygen-binding haem, and that the mesoscopic switch between two quaternary structures is triggered by amplification of a sub-atomic movement of the iron atom with respect to the haem–porphyin plane. One very minor criticism of the book is that it gives little sense of the valuable contribution made by J. Monod, F. Jacob, and J. Wyman in understanding cooperativity at the molecular level. Their two-state model was simple and yet very powerful for explaining cooperativity in haemoglobin and other proteins, with only three adjustable parameters that correspond to experimentally measurable physical



Max Perutz and the Secret of Life
By Georgina Ferry. Cold Spring Harbor Laboratory Press, 2008. 352 pp., hardcover $ 39.00.—ISBN 978-0879697853

parameters, and their two states interpreted as the different quaternary structures identified by Max.

Ferry describes many other scientific highlights of Max's studies of proteins. Noteworthy is the section on the α helix, which describes the puzzle presented by the 5.1 Å repeat seen in diffraction patterns from keratin fibers measured by W. Astbury at the University of Leeds. A conventional α helix was expected to have a longer repeat of 5.3 Å. Max's colleague Francis Crick proposed that the shorter repeat of keratin and similar proteins could arise from the super-coiling of helices. Max once described how Crick provided an intuitive demonstration of this solution by using models of α helices constructed from rubber tubing around which side chains, represented by small corks, spiraled with a repeat of about 3.6 corks in a turn. The cork knobs prevented the close approach of two of these tubes, but if a small left-handed twist was introduced, the knobs intermeshed. Max witnessed many other exciting developments in his laboratory, such as the evolution of Crick and J. Watson's model for DNA structure. Ferry also explores some awkward topics, such as the handling of a progress report on DNA structural studies by the groups of M. Wilkins and R. Franklin in London, which contained information previously disclosed in seminars. There is also an evaluation of the somewhat grumpy debates on the mechanism of haemoglobin.

Ferry captures well Max's passion for science, his character, and his slightly mischievous sense of humour. As an anecdotal example, on one of his frequent visits to the US, Max confessed to the Customs official at the airport that he had raw tomatoes in his baggage. The official went off to seek advice, and when he returned to Max after some delay, he was flabbergasted when Max explained that he had eaten all of the contraband. There is also an occasion when Max went to the lab in the late evening to develop with eager anticipation a precession photograph which would reveal whether or not his cocrystal of haemoglobin and a candidate druglike compound would be suitable for structure determination. Sadly, it was not. Although this was only a minor setback, it led Max to lament "It's a hard life in science."

Never at rest, Max continued working well past the official retirement age; and indeed he was correcting proofs of his final scientific publication while suffering from terminal illness. Driven with the determination that must have seen him reach many mountain tops, he spent his last days energetically writing notes and receiving many visitors, whom he always greeted with a warmth and charm that belied the pain he must have been feeling. The book conveys well a sense of Max's personal strength, as well as his compassion and concern about injustice and suffering in the world. It is reassuring that a spokesperson of that period could see broadly and could provide a humane voice of reason to caution against the capacity of mankind for senseless cruelty. Capturing well the achievements, character, humanity, and warmth of the man, the biography will help preserve a window onto a remarkable life and creative nexus of scientific history.

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DOI: 10.1002/anie.200805655