Max Perutz, a Nobel Prize winner, and Alain Marengo-Rowe

PATRICIA WILLIAMS, MT(ASCP)SBB

In 1962, Watson and Crick received the Nobel Prize in Physiology or Medicine for discovering the molecular structure of nucleic acids. That same year Max Perutz (1914–2002) received the Nobel Prize in Chemistry *(Figure 1)*. Born in Vienna, Austria, Perutz was expected to study law and to join the family textile business. He was enthralled, however, with organic biochemistry and began those studies with a thought of tackling a key problem in biology. He wrote:

> In 1936, when I joined J. D. Bernal's Crystallographic Laboratory as a graduate student, it was a small, dingy sub-department of the famous Cavendish Laboratory headed by Ernest Rutherford, the discoverer of the atomic nucleus, who was regarded as the world's greatest experimental physicist. On the other hand, I was trained as a chemist, and my interests grew in another direction. It had just been discovered that all chemical reactions in living cells are catalysed by enzymes and that all enzymes are proteins. Genes were also believed to be made of proteins, but next to nothing was known about the structure of proteins, let alone their mechanism of action. They were black boxes. Protein structure therefore seemed to be the central problem of biology, and x-ray crystallography was the only method in principle capable of solving it (1).

Figure 1. Max Perutz building the first atomic model of hemoglobin. Reprinted with permission from Perutz M. *Science is Not a Quiet Life.* Singapore: World Scientific Publishing Co. Pte. Ltd., 1997.

Perutz started his doctoral studies at Cambridge in the United Kingdom and remained there his entire career—except for a brief period during World War II in which he was interned and then deported to Canada. He reflected, "I was desperately unhappy. Having been rejected by my own country as a Jew, I now found myself rejected in my adopted country as an enemy" (2). Upon returning to Cambridge, Perutz worked with Sir Lawrence Bragg, the winner of the 1915 Nobel Prize in Physics. Perutz's work was funded by a Rockefeller grant.

Soon afterwards, Perutz formed his own laboratory: the Medical Research Council Laboratory for Molecular Biology. In 1947, the unit was staffed only with Perutz and John Kendrew, a doctoral student who later shared the Nobel Prize with him. By 1950, Perutz had a group of 4 and by 1960, 40. Perutz retired as director in 1979, and the laboratory today has >400 scientists. Francis Crick was a graduate student of Perutz; James Watson was a postdoctoral visitor in Perutz's laboratory. Together, Watson, Crick, and Perutz were players in the dawn of molecular biology.

Perutz made several contributions. He cracked the "phase" problem in protein structure:

> Max discovered that attaching a heavy metal, in this case mercury, to haemoglobin changed the relative intensities of the diffraction spots measurably—and this, in principle, meant that the phase problem was solved and the isomorphous replacement method for determining crystal structures had been invented. This method is still the cornerstone of structural biology and has since been used to determine the structures of thousands of proteins (3).

Perutz was also the first person to use structural information to provide a molecular explanation for how naturally occurring mutations lead to disease. Perutz's 25+-year study of hemoglobin still serves scientists today. He described a molecule of hemoglobin with four subunits, each of which consists of one polypeptide chain and one heme *(Figure 2)*. In the model, the two kinds of subunits—alpha and beta—have different sequences of amino acid residues but similar three-dimensional structures. The beta chain also has one short extra helix. The four subunits are arranged at the vertices of a tetrahedron around an axis of twofold

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Corresponding author: Patricia Williams, BS, MT(ASCP)SBB, Department of Pathology, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246 (e-mail: patw@BaylorHealth.edu).

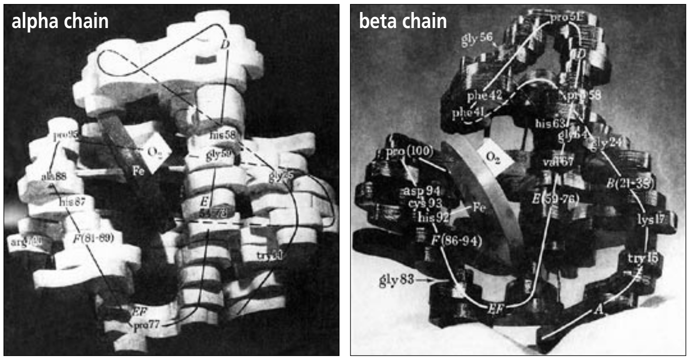

Figure 2. The three-dimensional structure of normal hemoglobin (back view). The large gray disks represent heme. Figure from Dr. Alain Marengo-Rowe.

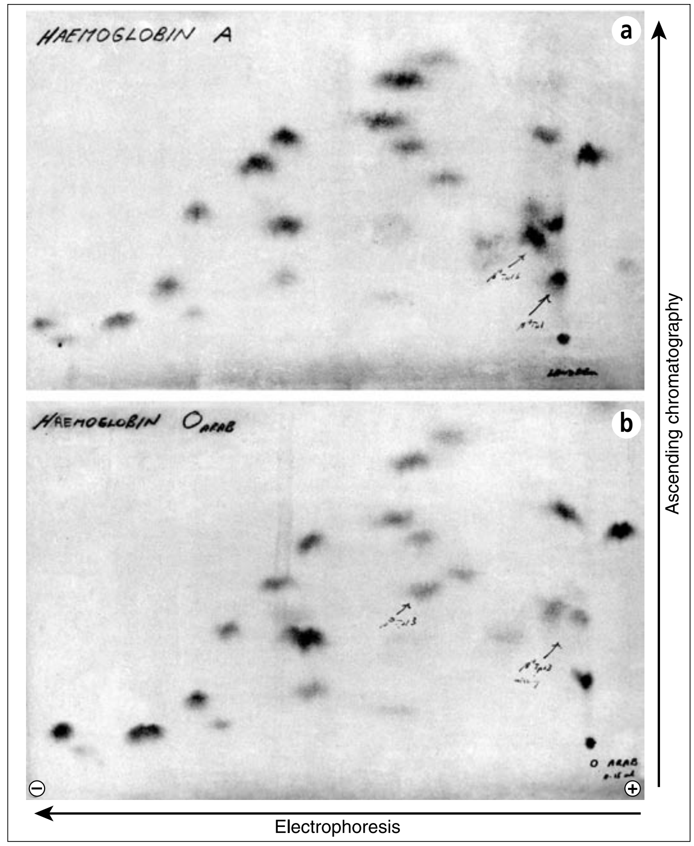

Figure 3. "Fingerprint" patterns of hemoglobin: **(a)** normal hemoglobin A; **(b)** hemoglobin O Arab. Handwritten notations by Herman Lehmann designate amino acid variation from normal hemoglobin. Figure from Dr. Alain Marengo-Rowe.

symmetry. Each heme lies in a separate pocket at the surface of the molecule (4).

Alain J. Marengo-Rowe, MD, director of transfusion services at Baylor University Medical Center, knew Dr. Perutz personally. From 1965 to 1967, Marengo-Rowe was a fellow under Herman Lehmann, professor and chairman of clinical chemistry at Addenbrookes Hospital in Cambridge and a good friend of Perutz. Lehmann was also at the Medical Research Council, in the abnormal hemoglobin unit. Dr. Marengo-Rowe described Perutz as "benevolent, unassuming, and humble." Dr. Marengo-Rowe added, with a chuckle, "Herman Lehmann was exactly the opposite!"

Dr. Marengo-Rowe shared stories from development of the hemoglobin model. "We [the young physician-scientists] would stand outside Max's office and listen to Max and Herman argue about the structure of hemoglobin." The large working hemoglobin model hung from the ceiling in Max's office. Using an actual bucket of water, they would walk around the model arguing over where the water belonged in relation to the structure hanging from the ceiling. Mimicking the heavy German accent, Dr. Marengo-Rowe laughed as he quoted the scientists, "Max, that's not where the water goes! It belongs here! Ah, look what you've done! You've made me spill the water!" "Herman, I will get you another bucket of water!" Max would answer back, and the argument would continue. The eavesdropping, young physician-scientists would laugh uncontrollably outside the office door. According to Dr. Marengo-Rowe, this exchange happened again and again.

Dr. Marengo-Rowe assisted Dr. Lehmann in screening blood for examples of abnormal hemoglobins. This research activity involved obtaining blood samples from random populations, as well as specific individuals. One circumstance was uniquely challenging. Stories existed about a "blue" prostitute who could be found only at night in Hyde Park. The scientists postulated that her skin color was due to a hemoglobinopathy, or disorder caused by or associated with the presence of abnormal hemoglobins in the blood *(Figure 3)*.

Dr. Marengo-Rowe was assigned to find the lady and to obtain her permission to draw her blood. Dr. Marengo-Rowe was able to learn where and when the "blue lady" could be found. He described the awkward conversation as he offered to pay her money in exchange for the opportunity to draw her blood. She agreed and was identified to have a hemoglobinopathy that was given the nomenclature Hemoglobin M Hyde Park. The M denotes methemoglobin, which was responsible for the woman's blue skin tone. Hemoglobin M Hyde Park demonstrates a 92 His → Tyr amino acid substitution on the hemoglobin β-chain (5). America also had a "blue family," known as "The Blue People of Troublesome Creek" (6).

Dr. Marengo-Rowe developed a method to perform haemoglobin electrophoresis on cellulose acetate strips. This method, now known as the "Marengo-Rowe method," was superior to both starch block and starch gel and is commonly used today (7) *(Figure 4)*.

Max Perutz's personal memoirs include a story from his late teens that reveals something about his circumstances, dreams, and goals. During his last year of school, he had an English girlfriend who returned to England in the summer. They had become good friends and continued to correspond. She kept all of his letters and returned them to him during the last years of his life. In August 1932, he wrote to her, "I'm turning over and over in my mind how I could get out of becoming a textile manufacturer in a Czech village and having to give up chemistry. Surely mankind would suffer an incalculable loss if I failed to win the Nobel Prize." Commenting in his memoirs, "We wrote to each other tongue-in-cheek then. It seriously never occurred to me that this might come true. But I was very amused to find myself writing this at age nineteen" (2).

Dr. Marengo-Rowe remembers that in a year that Max's laboratory did not have a Nobel Prize winner, Max attached a note to one of Dr. Marengo-Rowe's papers that said, "Tell Alain Marengo-Rowe to report to Sweden at once. He has won the

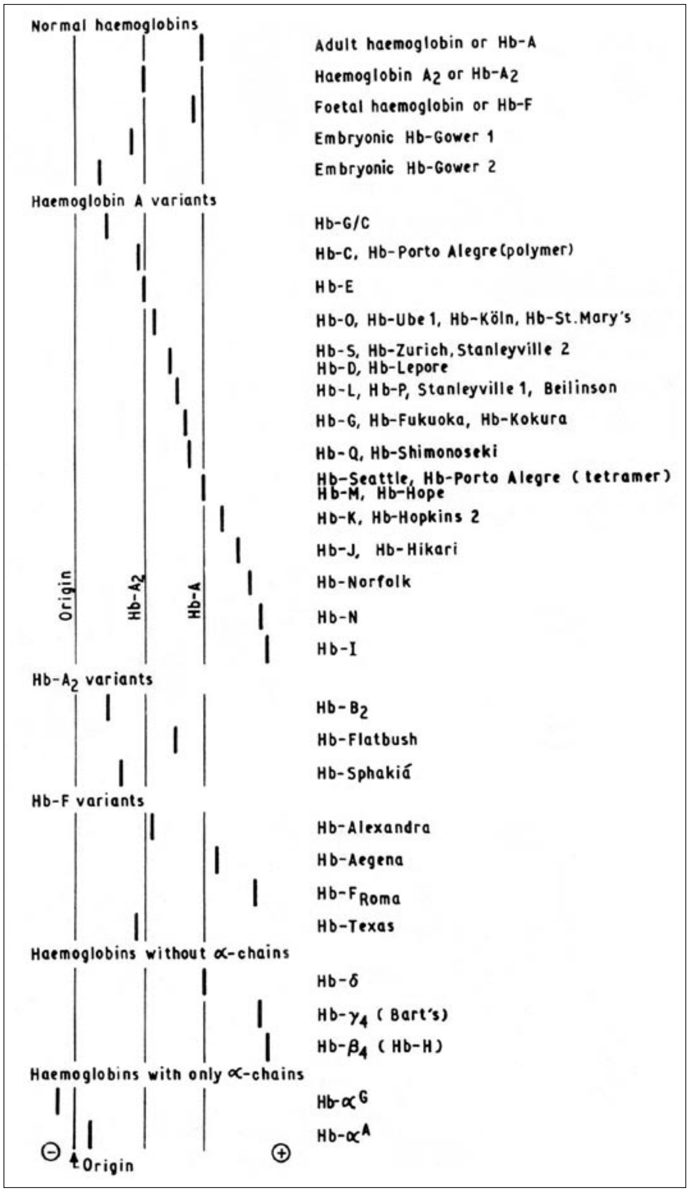

Figure 4. Electrophoretic mobilities of various hemoglobins on starch gel. Figure from Dr. Alain Marengo-Rowe.

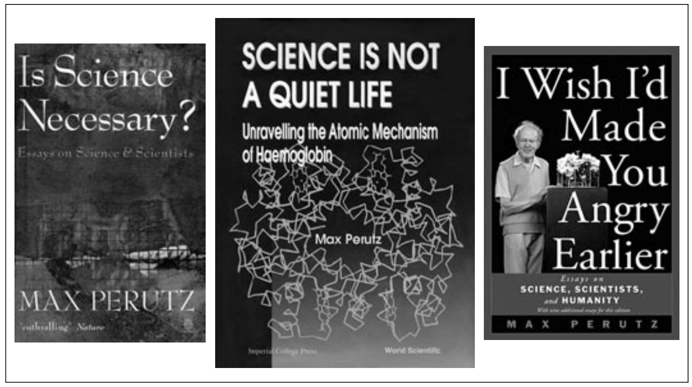

Figure 5. Some of Perutz's popular books on science.

Nobel Prize!" One can almost hear the group enjoying the humor behind the message, as Max sought to encourage, compliment, and inspire his young colleague.

Max Perutz's motto was "In science, truth always wins." He said that unlike in philosophy and economics, where debates continue for generations, in science nature always tells us what is right, and that answer is final (2). Perutz was a great communicator—in the arts as well as the sciences. Some of the popular science books he wrote include *Is Science Necessary?: Essays on Science and Scientists*, *Science Is Not a Quiet Life: Unraveling the Atomic Mechanism of Hemoglobin*, and *I Wish I Made You Angry Earlier: Essays on Science, Scientists, and Humanity* (Figure 5). Many honors were bestowed on this deeply cultured and captivating man.

Research at the Perutz Laboratory of Molecular Biology has resulted in nine Nobel Prizes. Perutz had a knack for recognizing extraordinary talent and creating a work environment where talented people could pursue their ideas. He insisted that young scientists be given full responsibility and credit for their work. No hierarchy existed in the laboratory; everyone was on a first-name basis. Groups were small, and senior scientists—including Perutz—worked at the bench (3).

Perutz knew how great science came about:

> Creativity in science, as in art, cannot be organized. It arises spontaneously from individual talent. Well-run laboratories can foster it, but hierarchical organizations, inflexible bureaucratic rules, and mountains of futile paperwork can kill it. Discoveries cannot be planned, they pop up, like Puck, in unexpected corners (3).

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