

## The man behind the molecular lung

Vivienne Baillie Gerritsen

**M**ax Perutz (1914-2002) solved the molecular structure of haemoglobin in 1960. It had taken him the best part of 25 years. He arrived at the Cavendish laboratory in Cambridge in 1936 eager to start a PhD. In those days, there was marked excitement about the possibility that X-ray photography of protein crystals could deliver the atomic arrangement of proteins. Two crystals were presented to Perutz: one of chymotrypsin and another of haemoglobin. The chymotrypsin crystals grew in such a manner that they were too complex to decipher so Perutz turned to the haemoglobin crystals which he felt would be easier to solve. Haemoglobin was also a choice candidate: it has an important physiological role, supplies are never scarce and it forms crystals easily. And little did Perutz know that this macromolecule would keep him busy for the rest of his life.

Perutz was born in Austria and started his university career in Vienna University where he claimed to have 'wasted five semesters in an exacting course of inorganic analysis.' Biochemistry, however, absorbed all his attention and he chose to explore the boundaries of this novel field in Cambridge. His choice was no doubt not only based on the scientific renown of the laboratory but also on the situation of Europe towards the end of the 1930s. Perutz may well have taken the opportunity to leave a country where he and so many others like him were becoming less and less welcome. And so in 1938, he moved to England with his family with a refugee status. Ironically, he was interned on the Isle of Man in 1939 because British law had decreed that German and Austrian expatriates were to be treated as enemy aliens. And from the Isle of Man, Perutz was sent to Canada... By 1941 however, he was established to be a true refugee and was sent back to Britain where he resumed his scientific activities.

When Perutz undertook to study the structure of haemoglobin, all that was known about the molecule could have been written on the back of a postage stamp. X-ray diffraction patterns of proteins were all the rage, however no one knew how to interpret them yet. In fact, many contemporary scientists thought that solving protein structure by X-ray diffraction was mad. Perutz stuck to it though. And for years he tried to understand how the diffraction pattern could be used efficiently. The answer came in 1953, 15 years after he had decided to crack haemoglobin's atomic structure! The intensities of the reflections in the diffraction patterns he had obtained were too weak to make anything out of. So he decided to label the haemoglobin crystal with a heavy atom such as mercury. If heavy atoms were

docked at specific sites on each protein molecule within the crystal, the reflections at these sites would be more intense. And Perutz assumed it would be easier to make something out of the mass of information he would obtain.



'Heart of steel' (Hemoglobin), 2005

Courtesy of the artist: Julian Voss-Andreae

Though it took a further 7 years to make sense of the novel diffraction patterns, Perutz won his bet. In 1960 he published an article on the structure of haemoglobin in *Nature*. According to today's standards, the information he

obtained was poor, yet he had demonstrated the power of X-ray analysis in deciphering protein structure. He had managed to squeeze the image of a macromolecule out of the X-ray diffraction patterns. The image sported four iron-containing haems each of which was smothered in an electronic cloud – and he assumed the ‘clouds’ were protein chains. His findings were based on what he had managed to make out of the diffraction patterns but also on work that was being carried out on myoglobin – in effect a simpler version of haemoglobin – in the same laboratory. Three years later he announced that haemoglobin was a tetramer of two copies of two identical chains, and each chain had a cleft into which was lodged one haem.

But that was not all. A host of consequences sprouted from what he had discovered. Perutz showed that proteins bore no symmetry, as had been suggested. What is more, he had studied both oxy- and deoxyhaemoglobin and found that their structures were not similar. Did this mean that proteins underwent conformational changes? The idea was not new. The Czech biochemist Felix Haurowitz (1896-1987) had already made such a postulation when he noticed a change of colour in haemoglobin crystals when subjected to oxygen. The change, he assumed, was due to a change of conformation in the protein’s structure.

Perutz had also worked on horse and human haemoglobin and discovered that both were extremely alike. Did this mean that different species could share the same protein? If so, then there must

be an underlying universal code. And what gives haemoglobin its shape? In Perutz’ own words, ‘what mechanism makes these diverse chains fold up in exactly the same way? Does a template force them to take up this configuration, like a mould that forces a car body into shape?’ Perutz himself did not subscribe to this but believed that a protein assumed a structure which was physically and chemically stable. And it was not long before it was discovered that a protein’s tertiary structure was dictated by its primary structure.

Haemoglobin has come a long way. It is known inside out and has paved the way for a host of biological applications and sophisticated physical methods. It was the first protein to be crystallised in 1849 by the embryologist Karl Reichert (1811-1883) and the first to be associated with a specific physiological function. It was one of the first proteins to have its molecular weight determined correctly, the first eukaryotic protein to be synthesized in a cell-free system *in vitro* and the first eukaryotic messenger to be isolated and subsequently sequenced. Haemoglobin – or the molecular lung as Perutz coined it – drove molecular biology well into the second half of the 20<sup>th</sup> century and won Perutz a Nobel prize in Chemistry in 1962. Something he had teasingly predicted in a letter written at the age of 19 to a girlfriend when he was still a chemistry student in Vienna...

### Cross-references to Swiss-Prot

Hemoglobin alpha chain, *Equus caballus* (Horse) : P01958  
Hemoglobin beta chain, *Equus caballus* (Horse) : P02062  
Hemoglobin alpha chain, *Homo sapiens* (Human) : P01922  
Hemoglobin beta chain, *Homo sapiens* (Human) : P02023

A special mention to G.Braunitzer without whom Swiss-Prot would be quite bereft of haemoglobin sequences. Braunitzer participated in the sequencing of 304 haemoglobins! He is also co-author with Perutz of a publication in *Nature* 291:682-684(1981) on the ‘Allosteric regulation of crocodilian haemoglobin’.

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