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Two New Pathological Haemoglobins: Olmsted β141 (H19) Leu → Arg and Malmö β97 (FG4) His → Gln

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We have examined two abnormal human haemoglobins that are representative of two groups of pathological haemoglobins (Perutz & Lehmann, 1968). One of these comprises unstable haemoglobins that are associated with inclusion-body anaemia (Lehmann & Carrell, 1969). These haemoglobins have mutations that result in the haem being less strongly bound and they are more susceptible to oxidation than normal. Many of the unstable haemoglobins have mutations in the lining of the haem 'pocket' (Perutz *et al.* 1968*a*; Perutz, Muirhead, Cox & Goaman, 1968*b*) involving the substitution of a non-polar residue by another of different size or by a polar residue. We have examined haemoglobin Olmsted described by Fairbanks, Opfell & Burgert (1969), which appears to have a Leu → Arg mutation at position 141 (H19) of the β-chain. This is in a position homologous with that of the α-chain-unstable haemoglobin Bibba α136 (H19) Leu → Pro (Kleihauer *et al.* 1968).

Another group of pathological haemoglobins associated with erythraemia (polycythaemia) is characterized by an increased oxygen affinity and decreased haem–haem interaction. Here the mutations are found mainly in the regions of the $\alpha_1\beta_2$ contacts of the tetramer. We have identified a new haemoglobin of this type, Malmö β97 (FG4) His → Gln, discovered in a study of the inheritance of polycythaemia in four generations of a Swedish family.

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Haemoglobin Synthesis in Thalassaemia

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The thalassaemias are a series of genetically determined disorders of haemoglobin synthesis, which all result from a defective rate of production of either the α- or β-peptide chains of haemoglobin. Haemoglobin synthesis *in vitro* has been studied in reticulocytes obtained from thalassaemic patients and compared with that in non-thalassaemic reticulocytes. The parameters measured include the overall rate of α- and β-chain production, the magnitude and properties of any excess of globin chains that are produced, the rate of globin chain assembly and, more recently, the rate of chain initiation.

The results of these investigations indicate that in each form of thalassaemia there is either a partial or total decrease in the rate of synthesis of one of the globin chains. No fragments of chains have been isolated from the cells of these patients. The assembly time of the globin chains has been measured and appears to be normal despite the marked decrease in the rate of chain synthesis. An attempt has been made to examine the distribution of nascent α- and β-chains on polyribosomes of different sizes with the object of studying the process of initiation in thalassaemic cells. Preliminary studies indicate that α- and β-chains from non-thalassaemic individuals are synthesized on different-sized polyribosomes.

The results obtained to date are compatible with a decreased rate of mRNA production of a defect in chain initiation as the underlying genetic defect in some forms of thalassaemia.