

This Week's Citation Classic²

Weatherall D J. *The thalassaemia syndromes*. Oxford, England: Blackwell Scientific, 1965. 272 p.; and Weatherall D J & Clegg J B. *The thalassaemia syndromes*. Oxford, England: Blackwell Scientific, (1972) 1981. 875 p.
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The thalassaemias, a heterogeneous group of genetic disorders of haemoglobin synthesis, are the commonest genetic diseases and affect millions of individuals throughout the tropics. The elucidation of their molecular basis may well have provided a fairly complete picture of the repertoire of mutations that underlie monogenic disease. Because it has been possible to relate the remarkable clinical diversity of these disorders to over 100 different molecular lesions, they constitute the best-characterised model for understanding how abnormal gene action is manifested in the clinic. [The *SCI*[®] indicates that all editions of this book have been cited in over 1,375 publications.]

The Thalassaemia Saga

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My interest in thalassaemia dates back to a typical posting decision by the British Army. In 1958, two years after qualifying in medicine from Liverpool University, I was drafted for compulsory national service. Terrified of flying, I volunteered to serve in the UK, and so it was that a few weeks later I found myself in charge of the children's ward in the military hospital in Singapore. There I encountered a Nepalese Gurkha child with severe anaemia who, surprisingly, turned out to have thalassaemia, a genetic anaemia thought to be restricted mainly to the Mediterranean region.¹ I spent the rest of my spare time in the Orient searching for further cases and, on discharge from the army, obtained a research fellowship at Johns Hopkins Hospital, where I tried to sort out the different forms of thalassaemia in Baltimore's black population. I returned to Liverpool in 1962 and presented this work as my doctoral thesis. Though accepted, one examiner said that the subject was trivial and advised me to pursue a career in psychiatry.

While writing my thesis, I tried to interpret the extraordinary clinical diversity of thalassaemia in the light of haemoglobin genetics. The result was too long (and woolly) to publish in a journal and, fully expecting a rejection slip, I posted it to Per Saugman of Blackwell Scientific Publications, Oxford. For no very good reason he decided to publish it as a monograph; the first edition of *The Thalassaemia Syndromes* appeared in 1965.

In 1963 I returned to Johns Hopkins. By then it was clear that defective α or β globin chain production must be involved in its pathogenesis. About this time I was fortunate enough to meet John B. Clegg, my close friend and collaborator ever since. Together we developed a way to quantify the rates of globin chain production and used it to characterise many different forms of thalassaemia.² On returning to Liverpool in 1965 we embarked on a study of the patterns and rates of assembly of the globin chains in thalassaemia and concluded that some thalassaemias result from a quantitative defect in globin mRNA synthesis.³ By now it was obvious that the thalassaemias, possibly because of heterozygote resistance to malaria, are the commonest single gene disorders and, by analysing family data from different parts of the world, it was possible to start to make some sense of their pathophysiology. In 1972, with John as coauthor, the second edition was published.

In the next decade, the globin genes were cloned and the molecular basis for several types of thalassaemia was determined.⁴ At the same time, our globin chain synthesis techniques were applied successfully to the prenatal diagnosis of the important thalassaemias, leading to a dramatic decrease of new cases in many countries. The number of disorders recognised to result from different thalassaemia interactions continued to grow; over 60 in Thailand alone! In 1981 these advances were incorporated into a third edition. Work carried out since then has left us with a comprehensive picture of the diverse molecular lesions that underlie thalassaemia and, incidentally, may well have provided a fairly complete repertoire of the mutations that cause single gene disorders.⁵

It is gratifying that this book seems to have been useful over the last 25 years, even if by accident rather than design. The thalassaemias are still the only common genetic diseases for which the molecular pathology is so well understood that it can be related directly to an extremely diverse series of clinical phenotypes.

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2. Weatherall D J, Clegg J B & Naughton M A. Globin synthesis in thalassaemia: an *in vitro* study. *Nature* 208:1061-5, 1965. (Cited 175 times.)
3. Clegg J B, Weatherall D J, Na-Nakorn S & Wasi P. Haemoglobin synthesis in β -thalassaemia. *Nature* 220:664-8, 1968. (Cited 65 times.)
4. Maniatis T, Fritsch E F, Lauer J & Lawn R M. The molecular genetics of human haemoglobins. *Annu. Rev. Genet.* 14:145-78, 1980. (Cited 200 times.)
5. Thein S L & Weatherall D J. The thalassaemias. *Recent Advan. Haematol.* 5:43-74, 1988.

10-17