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# This Week's Citation Classic®

Fessas P. Inclusions of hemoglobin in erythroblasts and erythrocytes of thalassemia. *Blood* 21:21-32, 1963.
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This work demonstrated the spontaneous formation of precipitated hemoglobin-like material within the immature and/or mature erythroid cells of patients with severe or intermediate β-thalassemia. These inclusion bodies were attributed to an excess of α-hemoglobin chains and were considered instrumental in the pathophysiology of this hereditary anemia. [The *SCI*® indicates that this paper has been cited in over 135 publications.]

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Thalassemia, in its various forms, is probably the commonest inherited disease worldwide and very frequent in Greece.[1] For some years I investigated various aspects of thalassemia such as prevalence, heterogeneity, and genetic interactions. The research was carried out at the Alexandra Hospital in Athens and had the support of the Hellenic Research Foundation and of the US National Institutes of Health. In fact, this particular work cost almost nothing, but the support allowed me to spend time and effort on research.

It all started in 1961 with the hemolysate of a patient with β-thalassemia, which, on electrophoresis, presented a band of methemoglobin. This latter was known to be associated with certain industrial poisonings and with the presence of poorly characterized formations within erythrocytes, the so-called Heinz bodies. The methemoglobin aspect was abandoned—to be taken up again recently[2]—and I began the search for visible abnormalities within the thalassemic erythroid cells. This led to the initial paper and later to the final identification of the inclusion bodies.

For months, I anxiously wondered whether someone else would publish similar data—all that was needed was to think about it—but I was lucky. The paper was readily accepted, and I am sorry for only two things: (1) *Blood* could not print my colored photomicrographs, of which I was proud, unless I paid US$800 for one colored page (never again did I ask for the price of color printing); and (2) what I considered a very valuable, if not the best, part of the discussion appeared in smaller type!

I believe this work has been cited because it answered fundamental questions of the pathophysiology of this anemia by designating the "primum movens" in a cascade of events deleterious for the erythroid cell and, ultimately, for the organism as a whole. The model also proved useful for understanding the unstable hemoglobin syndromes and the mechanisms regulating hemoglobin synthesis. Interestingly, 23 years later and after fantastic progress in the molecular genetics of these conditions,[3] the mechanism by which the α-globin precipitates damage the erythroid cells is still a subject of research.[4] Perhaps the paper was cited also because it was done with simple methods and was correct in observation, interpretation, and predictions; in 1962, knowledge had advanced to a point that permitted such accuracy.

1. Weatherall D J & Clegg J B. *The thalassemia syndromes*. Oxford: Blackwell Scientific, 1981. 875 p.
2. Tassiopoulos T, Fessas P, Rombos J & Loukopoulos D. Observations on oxygen delivery, methemoglobinemia, and arterial oxygenation in patients with β-thalassemia. *Ann. NY Acad. Sci.* 445:135-47, 1985.
3. Nienhuis A W, Anagnou N P & Ley T J. Advances in thalassemia research. *Blood* 63:738-58, 1984.
4. Rachmilewitz E A, Shinar E, Shalev O, Galili U & Schrier S L. Erythrocyte membrane alterations in β-thalassaemia. *Clin. Haematol.* 14:163-82, 1985.

 

1-18