

This Week's Citation Classic

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Cohen A S. Amyloidosis. *N. Engl. J. Med.* 277:522-30; 574-83; 628-38, 1967.
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The delineation of the basic pathobiologic, immunologic, and biochemical factors involved in the genesis of amyloidosis as well as the clinical behavior of the disease has led to a clearer understanding of its manifestations. The description of the various clinical types including an analysis of the increasing numbers of hereditary amyloidoses has led to a greater awareness of their presence and greater interest in its diagnosis. [The SC¹⁶ indicates that these papers have been cited over 855 times in 423 publications since 1967.]

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"The study of amyloidosis has been of interest to me for over 25 years, starting with my fellowship in rheumatology at Massachusetts General Hospital in 1956. After our startling observations made in 1957-1958¹ that amyloid has a precise fibrous ultrastructure, we embarked on long-term basic and clinical studies that grew in scope when I moved to Boston University School of Medicine in 1960-1961. It became apparent that this substance, which previously had been regarded as a collection of debris, had a unique fine structure (and subsequently it was shown to have an interesting cross beta conformation on X-ray diffraction) and was a highly ordered molecule or molecules. These studies led to a series of observations by my laboratory and others on the isolation, biochemistry, and immunologic properties of amyloid. It is now known that while the fibrous structure is common to all amyloids, several major biochemical subclasses exist (i.e., AL, that related to immunoglobulin light chain; AA, that related to a new protein SAA also found in the serum; A prealb, that related to circulating prealbumin; and others).

"My review, however, followed a detailed analysis of the pathogenesis of amyloidosis² and was meant to bring together in one article the heterogeneous collection of information about types of amyloid, its classification, course, and organ involvement. As I warmed to the subject, the outgoing editor of the *New England Journal of Medicine* viewed with alarm the space requirements of the growing bibliography and tried to persuade me to pare it down to a few general references. When I pointed out that the complete bibliography was more likely to have long-lasting usefulness than the article itself, the editor agreed and the 329 references (about five printed pages) were allowed. The editor, however, did divide the article for publication in three consecutive issues.

"It became apparent to me in the course of writing this article how little opportunity any one clinical investigator had to study more than a handful of patients with any one form of the disease and that an analysis of the natural history of amyloid and its effect on a variety of organ systems was needed. As the opportunity developed for us to embark on such studies, we did so in the course of our basic investigations, and in recent years, a series of discrete clinical studies has appeared.

"I suspect that the article has become a *Citation Classic* since it put together in one place the enormous and confusing literature on etiology and pathogenesis, and suggested the ubiquity of the disease. The multisystem nature of the disorder and its importance to internists, ophthalmologists, dermatologists, hematologists, urologists, etc., led to a fuller understanding of its prevalence and to a broader range of basic investigations. The development led to an expansion from the one or two laboratories studying amyloidosis in the 1950s to the many investigations taking place in the US and abroad at the present time. Indeed, since that time, major international meetings on amyloid have taken place in Holland, Finland, and Spain."³⁻⁵

1. Cohen A S & Calkins E. Electron microscopic observations on a fibrous component in amyloid of diverse origins. *Nature* 183:1202-3, 1959.
2. Cohen A S. Constitution and genesis of amyloid. *Int. Rev. Exp. Pathol.* 4:159-244, 1965.
3. Mandema E, Rutten L, Scholten J H & Cohen A S, eds. *Amyloidosis: proceedings of the Symposium on Amyloidosis, University of Groningen, the Netherlands, 24-28 September 1967*. Amsterdam: Excerpta Medica, 1968. 465 p.
4. Wegelius O & Pasternack A, eds. *Amyloidosis: proceedings of the Fifth Sigrid Juselius Foundation Symposium*. London: Academic Press, 1976. 605 p.
5. Gleener G G, Costa P P & Freitas F, eds. *Amyloid and amyloidosis: proceedings of the Third International Symposium on Amyloidosis, Povoá de Varzim, Portugal, 23-28 September 1979*. Amsterdam: Excerpta Medica, 1980. 629 p.