

Franklin E C, Lowenstein J, Bigelow B & Meltzer M. Heavy chain disease—a new disorder of serum α -globulins: report of the first case. *Amer. J. Med.* 37:332-50, 1964.
[Depts. Med. and Pathol. and Rheumatic Diseases Study Group, New York Univ. Sch. Med., New York, NY]

This paper described a patient with a heavy chain disease, the first example of a plasma cell neoplasm associated with the production of an abnormal, internally deleted heavy chain. It was predicted that similar disorders involving the other immunoglobulin polypeptide chains would be found. [The SCI® indicates that this paper has been cited over 260 times since 1964.]

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"This report clearly illustrates how sudden and often unexpected discoveries made in a clinical setting can contribute to our understanding of biologic problems. A major reason for its frequent citation is the impact it has had on clinical medicine as well as on basic molecular science.

"Patient CRA had been studied for about a year for an unexplained disease, possibly a lymphoma. As is often the case with diagnostic problems of this type, repeated laboratory examinations are ordered by the house staff, in this case Lowenstein and Guggenheim, in the hope of uncovering a clue. One of these tests, the electrophoretic analysis of serum and urine, done on December 24, 1962, showed unexpectedly an enormous α globulin spike which had the same configuration in both fluids. Since this had not been present two months previously and was unlike anything we had seen before, we set out to characterize the proteins. Within three days we had identified proteins which resembled the Fc fragment of the heavy chain of IgG and shortly demonstrated them to be synthetic products. With the deadline for the submission of abstracts to the FASEB meeting almost upon us, we decided to submit our

findings on December 30, 1962, despite some fear that we might be wrong. Fortunately, our conclusion held up and led to the description of the heavy chain diseases (HCD), a term coined by Elliot Osserman who, after seeing our patient, identified four additional examples of α HCD by analysis of stored samples.¹ Since then, the entity has expanded to include α HCD which is the most frequent, a few patients with γ HCD, and only one reported instance of β HCD. δ HCD has not yet been identified.

"The report aroused the interest of clinicians because it delineated a new clinically recognizable variant of the plasmacytic-lymphocytic neoplasms, associated with a new type of biochemical abnormality characterized by the synthesis of abnormal molecules (immunoglobulin variants) rather than intact immunoglobulins and immunoglobulin light chains. For immunologists and molecular biologists, these proteins have provided profound insights into the genetic control of Igs. Based on the nonrandom and by now rather predictable nature of the internal deletions characteristic of these proteins, we were able to predict that multiple genes might code for the heavy chain² several years before the demonstration of discontinuous genes by DNA cloning. The suggestion that the domains and the hinge of the heavy chain are each under the control of a separate genetic element was based on the finding that the internal deletions in these and related variants usually begin or end at the interdomain regions which are now known to correspond to the sites of excision of intervening sequences and the joining of exons.³ Many questions remain. These deal with the reason for the almost invariably associated failure of light chain synthesis and the query whether the defect lies in the DNA, transcription, or processing. Answers to these questions should be forthcoming shortly as they are likely to emerge from DNA cloning and sequencing techniques applied to cells from such individuals."

1. Osserman E F & Takatsuki K. Clinical and immunochemical studies of four cases of H α ² chain disease. *Amer. J. Med.* 37:351-73, 1964.
2. Franklin E C. Structural studies of human 7S α -Globulin (G Immunoglobulin). *J. Exp. Med.* 120:691-709, 1964.
3. Franglone B & Franklin E C. Correlation between fragmented immunoglobulin genes and heavy chain deletion mutants. *Nature* 281:600-2, 1979.