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Citation Classics

Fredrickson D S, Levy R I & Lees R S. Fat transport in lipoproteins; an integrated approach to mechanisms and disorders.
N. Engl. J. Med. **276**:34-44, 94-103, 148-56, 215-25, 273-81; 1967.

The authors review the structure and function of the plasma lipoproteins, with particular reference to abnormal lipoprotein metabolism associated with certain clinical disorders, and discuss two methods for separating lipoproteins–paper electrophoresis and lipoprotein quantification. By identifying the specific lipoprotein pattern, hyperlipidemia may be translated to hyperlipoproteinemia. [The *SCI*® indicates that the five parts of this paper were cited a total of 3973 times in the period 1967-1976.]

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"Perhaps one of the intrinsic reasons for the volume of citation received by our articles is that they drew attention to an important group of diseases that are common and often potentially fatal. Up to the time the articles were published, specialists in the field who attempted to treat patients with hyperlipidemia had to grapple with complicated classifications that often proved contradictory and misleading in clinical practice. The system of classifying blood lipid disorders that we introduced was based on a combination of three things: the rich clinical material we collected at the NIH Clinical Center, a great deal of experience (much then unpublished) and relatively simple methodology.

"We focused principally on two methods of separating lipoproteins–paper electrophoresis and lipoprotein quantification. Although the former has been de-emphasized with the passage of time, its merit at that stage was in highlighting the lipoproteins, rather than lipids, as a basis for classifying and treating hyperlipidemia. The second method–quantification of lipoproteins–allowed for the separation of several disorders with similar plasma lipid levels. Used within the clinical context, it called for a degree of precision which was often absent in the previous management of such patients. A drawback of this method–then and now–is that it is based on systems which are unavailable to many clinicians, although they are accessible to many researchers.

"Our studies at NIH dealt primarily with the genetic or familial forms of hyperlipoproteinemia. But our work was also relevant to the general problem of lipids, lipoproteins and coronary heart disease, introducing concepts that applied to subjects within the so-called 'normal' range of lipid and lipoprotein distribution.

"The typing system for hyperlipoproteinemia that we introduced was a simpler, more convenient code than the existing classifications, but it contains a number of limitations which we recognized from the outset. The major deficiency is that it is not based on the specific metabolic defects which underlie each form of HLP. The precise abnormality associated with a minority of these disorders is only now beginning to be comprehended. There has also been some misapplication of the system, particularly in the steps that have to be taken between recognizing the presence of a hyperlipoproteinemia and in deciding whether it is primary or secondary, familial or non-familial, and in determining the appropriate therapy. Later findings, especially with respect to familal combined hyperlipidemia, highlight some of the present gaps in our knowledge of the lipid transport disorders including their genetic characteristics.

"Despite the deficiencies of our classification (of which, with hindsight, there are many), it did provide, and continues to do so, a useful and practicable system for the classification, investigation and treatment of hyperlipoproteinemic patients. Our objective was to break down some of the conventional cliches and approaches to the management of these patients by providing a more rational and workable alternative. Perhaps the frequency with which our work is cited is proof that in some measure we succeeded."