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This Week's Citation Classic®

Levy R I, Fredrickson D S, Shulman R, Bilheimer D W, Breslow J L, Stone N J, Lux S E, Sloan H R, Krauss R M & Herbert P N. Dietary and drug treatment of primary hyperlipoproteinemia. *Ann. Intern. Med.* 77:267-94, 1972.
[Natl. Heart and Lung Inst., Natl. Insts. Health, Bethesda, MD]

This report describes the first seven years' experience of the National Heart Institute's Lipid Research Clinic. It is based on the evaluation of over 1,000 patients from about 500 kindreds with primary hyperlipoproteinemia. It describes in detail the differential diagnosis and management of the primary hyperlipoproteinemias. The rational and clinical efficacy of specific dietary and drug prescriptions is described for each type of hyperlipoproteinemia. [The *SCI*® indicates that this paper has been cited in over 200 publications since 1972.]

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This report extended and made clinically relevant a previous *Citation Classic* paper that was published in 1967.[1] The earlier report had described with extensive data the biochemical and clinical necessity for translating primary hyperlipidemia into hyperlipoproteinemia. This report convincingly confirmed the enormous value of moving beyond the measurement of cholesterol and triglyceride in evaluating patients. It demonstrated with a mass of clinical data that the different types of hyperlipoproteinemia (differentiated by specific lipoprotein excesses) responded differently to specific dietary and drug prescriptions. Heretofore, the literature on the drug and dietary treatment of patients with high cholesterol/high triglyceride or both was confusing and conflicting. When patients were differentiated by type, a predictable responsiveness could be shown to specific perturbations. The treatment prescriptions described in the report have stood the test of time and are still relevant today. Emphasis is put on accurate chemical diagnosis, ruling out secondary disorders, family screening, and establishing an adequate baseline. The unique responsiveness of the different types of hyperlipoproteinemia to dietary perturbations and to the lipid-lowering agents cholestyramine, clofibrate, nicotinic acid, and D-thyroxine (alone and in combination) are described and extensively documented.

I had not realized that this report had been so extensively quoted. In retrospect, it is understandable why it was. It represents the first comprehensive report on the treatment of primary hyperlipoproteinemia. The multiple authors of the report all participated in the NIH Lipid Research Clinic, following patients on specific clinical protocols for two or more years. Except for a separate annals report on a double-blind evaluation of patients with Type II hyperlipoproteinemia,[2] the raw data presented in this report do not appear elsewhere.

The report has great personal significance for me. It marks the culmination of a most exciting period in our Lipid Research Laboratory at NIH as we revealed the enormous power of looking at the units of lipid transport. Essentially all the coauthors of this report have gone on to make extensive contributions to our knowledge of lipoproteins and lipid transport in health and disease.

The observations described in this report were the basis for the establishment of a network of NIH-sponsored Lipid Research Clinics that were designed to extend the NIH clinic's technology into practice. As such, it moved me away from the research laboratory toward clinical epidemiology and research administration. Of more importance, it set the stage for the Lipid Research Clinics Coronary Primary Prevention Trial, a multiyear, multicenter trial whose results were reported just last year, establishing the clinical efficacy of cholesterol reduction in hypercholesterolemic patients.[3,4] In so doing, it fulfilled the promise of this annals paper and removes the caveat mentioned in the annals report that "the use of drugs is often based on a still unproved presumption (that if lipids are lowered so is the risk of coronary artery disease)." Circumspection is still, however, appropriate today when drugs are used to lower blood lipids, for they are all associated with real or potential side effects. But now that the evidence is in that lowering cholesterol lowers coronary risk, we have entered a new era. No longer is there a question as to whether lowering cholesterol is beneficial, the questions now are more practical ones—when and where and how to treat.

1. **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.
[See also: **Levy R I.** Citation Classic. *Current Contents* (3):11, 16 January 1978.]
2. **Levy R I, Fredrickson D S, Stone N J, Bilheimer D W, Brown W V, Glueck C J, Gotto A M, Herbert P N, Kwiterovich P O, Langer T, LaRosa J, Lux S E, Rider A K, Shulman R S & Sloan H R.** Cholestyramine in type II hyperlipoproteinemia: a double-blind trial. *Ann. Intern. Med.* 79:51-9, 1973. (Cited 75 times.)
3. **Lipid Research Clinics Program.** The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA—J. Am. Med. Assn.* 251:251-364, 1984.
4. ----------. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA—J. Am. Med. Assn.* 251:365-74, 1984.

