CC/NUMBER 38
SEPTEMBER 20, 1993

This Week's Citation Classic ®

Frick M H, Elo O, Haapa K, Heinonen O P, Heinsalmi P, Helo P, Huttunen J K, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M. Sjöblom T & Nikkilä E A.
Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N. Engl. J. Med.* 317:1237-45, 1987.
[First and Third Depts. Medicine. Univ. Helsinki; National Public Health Inst.: Finnish Railways. Posts and Telecommunications: Enso-Gutzeit: Veitsiluto. Helsinki: Dept. Medicine. Univ. Tampere; A. Ahlstrom. Karhula; Kaukas (Kymmene), Lappeenranta: and Neste. Paardeweide, Finland]

This multicenter, prospective lipid-modulating study showed for the first time that increasing the level of high-density lipoprotein cholesterol reduced the incidence of coronary heart disease in dyslipidemic but otherwise healthy middle-aged men. [The *SCI*® indicates that this paper has ■ been cited in more than 900 publications.]

Cholesterol and Coronaries

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The thesis that the level of high-density lipoprotein (HDL) cholesterol is inversely related to the occurrence of coronary heart disease (CHD) was presented some 40 years ago.[1,2] This discovery did not gain the full acceptance of the lipid researchers of those years, notably Ancel Keys, and its further exploration was put to hibernation. The chapter was reopened by Norman Miller in 1975[3] leading to a proliferation of HDL research. Since cross-sectional and observational studies could not fulfill Koch's postulates, a prospective, lipid-modulating study, the Helsinki Heart Study (HHS), was initiated. The HHS used gemfibrozil to increase HDL cholesterol in dyslipidemic individuals. Detailed analyses of the relationships between lipid changes and a 34 percent reduction in CHD incidence revealed that both an increase in HDL cholesterol and a decrease in low-density lipoprotein (LDL) cholesterol contributed to the outcome." The series included a very high risk subgroup characterized by elevated triglycerides, low HDL cholesterol, and high LDL/HDL ratio.[5] In this subgroup the therapy decreased the CHD incidence by some 70 percent.

Compliance to medication was rigorously checked by three methods and found excellent. Not a single person was lost to follow-up. This is because people in Finland do not frequently change address and because the nursing staff in "front line service" was very efficient. One rewarding experience was to keep this staff of more than 100 persons motivated over five years. (One way to do it is to charter an airplane and organize a meeting at the Royal College of Nursing in London.)

We knew from previous studies that blood should be sampled abundantly. As the years pass by, new factors associated with CHD emerge. Blood samples from a large, prospective study render new analyses possible, and have done so in conjunction with the HHS. However, when you are dealing with blood samples from some 19,000 individuals you must remember to include the rent of a warehouse into your budget calculations.

Our group was originally chaired by E.A. Nikkila, a pioneer in HDL research. After his demise in a traffic accident I had the privilege to take over. As a clinical cardiologist, although one involved in lipid research for over 20 years, I believe that the HHS has been a great experience shared by all members of the team, which consists of experts in biostatistics, public health, internal medicine, cardiology, and occupational medicine. We have not received any awards or specific honors, but we have had the opportunity to furnish new substrate to the discussion about lipids and CHD.

Concerning the role of HDL cholesterol in CHD, researchers can be divided into believers and nonbelievers. Our article, selected as a *Citation Classic'*, has evidently been cited more by the former category. We have also been able to survive both random sniping and frontal assaults by the latter category.

1. Barr D P. Russ E M & Eder H A. Protein-lipid relationships in human plasma II. In atherosclerosis and refilled conditions.
Ainer. J. Med 11:480-93. 1951. (Cited 495 times.) 2. **Nikkilä E.** Studies on the itpid-prolein relationships in normal and pathological sera and the effect of heparin on serum
hpoproleins. *Scand. J. Clin. Lab. Invest 5(*Supp .8): 1-101. 1953. (Cited 145 times.) 3. **Miller G J & Miller N E.** Plasma-high-density -lipoprotein concentration and development of ischaemic heaat-disease.
Lancet 1:16-9. 1975. (Cited 2,010 times.) [See also: **Miller G J.** Citation Classic (Barren .J T. ed.) *Contemporary classics in*
the life sciences. Volume, 2: the molecules life: Philadelphia: ISI Press. 1986. p. 41.] 4. **Manninen V. Elo O. Frick M H. Haapa K. Heinonen O P, Heinsalmi P. Helo P. Hutlunen J K. Kaitaniemi P. Koskinen P, Maenpaa H. Malkonen M. Manttari M, Norola S. Pasternak A. Pikkarainen J, Komu M. Sjoblom T & Nikkila E A.**
Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study.
JAMA-J Am. Med Assn. 260:641-51. 1988. (Cited 250 times.) 5. **Manninen V, Tenkanen L. Koskinen P. Huttunen J K. Manttari M. Heinonen O P & Frick M H.** Joint effects of serum
trigyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study

Circulation **85**:37-45, 1992 Received July 22. 1993.