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This Week's Citation Classic

Miller G J & Miller N E. Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. *Lancet* **1**:16-19, 1975.
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A low plasma high-density lipoprotein (HDL) cholesterol concentration in subjects at increased risk for coronary-heart disease, and the discovery of an inverse relation between HDL concentration and body cholesterol-pool size, suggested that this lipoprotein is important for the removal of cholesterol from tissues and the retardation of atherosclerosis. [The *SCI*® indicates that this paper has been cited over 510 times since 1975.]

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"This paper has its origins among the hill-farmers of rural Jamaica. Hypertension, diabetes mellitus, and high cholesterol concentrations are not uncommon in these people, yet few develop coronary-heart disease (CHD). This puzzle eventually prompted me to review the literature in search for ideas.

"The vast bibliography on the subject was highly repetitive and seemingly obsessed with the belief that hyperlipidaemia was responsible for coronary atherosclerosis. The relative tolerance of a high cholesterol concentration among men in rural Jamaica, and among women in general, suggested that the problem was not that simple.

"One observation, confirmed many times, appeared not to have aroused interest. Subjects at relatively high risk for CHD have a low plasma high-density lipoprotein (HDL) concentration, no matter how risk is identified (e.g., obesity, hypertriglyceridaemia, masculinity). Curious, I searched for more information about HDL, and John Glomset's[1] studies on lecithin-cholesterol acyltransferase appeared highly relevant. Suddenly the penny dropped! Perhaps HDL is required for the transport of cholesterol from the arterial wall to the liver for catabolism. If so, then a low HDL concentration might indicate inadequate clearance of cholesterol and potentiation of the atherosclerotic process. Was hypercholesterolaemia in rural Jamaica benign because of an association with a high HDL concentration?

"The hypothesis predicted an inverse association between the amount of cholesterol in the body and plasma HDL concentration, but I could find no reference to this topic. I sent my ideas to my brother Norman, then involved in lipid metabolism, and by a remarkable coincidence he possessed data with which to explore this possibility. These formed baseline observations for published studies of drug effects undertaken with Paul Nestel and colleagues.[2] Norman's discovery of the relation was exciting, and I hurried to join him in Edinburgh. He strengthened the argument considerably and we completed the manuscript over a weekend.

"Several weeks later I sat at my desk facing the rejected manuscript – returned with apologies. Somewhat bewildered, I was urged by colleagues to seek the editor's advice. To my delight, he recalled the paper, re-considered his decision, and accepted in little more than 24 hours!

"The article owes its success partly to the promise of new pastures for CHD research, and partly to the support quickly forthcoming from epidemiologists, notably in Framingham and Tromso. A recent review is available,[3] and the Jamaican hill-farmer does indeed have a high HDL cholesterol concentration!"[4]

1. **Glomset J A.** Physiological role of lecithin-cholesterol acyltransferase. *Amer. J. Clin. Nutr.* **23**:1129-36, 1970.
2. **Miller N E, Clifton-BIigh P & Nestel P J.** Effects of colestipol. a new bile-acid-sequestering resin, on cholesterol metabolism in man. *J. Lab Clin Med.* **82**:876-90, 1973.
3. **Miller G J.** High density lipoproteins and atherosclerosis. *Annu Rev Med.* **31**:97-108, 1980.
4. **Miller G J, Miller N E & Ashcroft M T.** Inverse relationship in Jamaica between plasma high-density lipoprotein cholesterol concentration and coronary-disease risk as predicted by multiple risk-factor status. *Clin. Sci.Mai. Med* **51**:475-82, 1976.