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Letter to the Editors

HDL Cholesterol, LDL Receptor Activity and Response to Dietary Cholesterol

A Reply to the Letter of Cortese, Miller, Marenah and Lewis [2]

Dear Editors,

Variation in the concentration of cholesterol in blood plasma is partly accounted for by differences in diet, age, sex and genetic constitution. No correlation between plasma low density lipoprotein (LDL) cholesterol concentration and the activity of the LDL receptor in white blood cells could be found [1,2]. However, an *inverse* correlation between plasma high density lipoprotein (HDL) cholesterol concentration and LDL receptor activity was reported in a recent letter to this Journal [2]. Although we cannot explain this finding, we would like to point out that a high plasma HDL cholesterol level and a low LDL receptor activity are associated with high susceptibility to diet-induced hypercholesterolaemia.

The serum cholesterol concentration responds more strongly to dietary cholesterol in some individuals (hyper-responders) than it does in others (hypo-responders) [3–6]. Mistry et al. [5] have shown that there is an inverse relation between a subject's LDL receptor activity, measured before the dietary challenge in de-repressed mononuclear cells in vitro, and the response of the subject's plasma cholesterol concentration to dietary cholesterol. The inverse relation of LDL receptor activity and serum HDL cholesterol concentration [2] leads to the prediction that hyper-responders should have higher serum HDL cholesterol levels than hyporesponders. Indeed, we have found this in 2 independent groups of subjects.

The first group consisted of subjects who were accustomed to eat at least 1 egg per day. At our request they stopped eating eggs for 3 weeks in 1976 [7] and 17 men and 17 women did this again in 1982. On both occasions a significant fall in plasma cholesterol occurred. The extent of the fall per individual in the second experiment was correlated with the fall in the first experiment, showing that certain subjects were consistently hyper- or hypo-responsive to elimination of egg cholesterol from the diet [6]. There was a significant positive correlation between the size of the serum cholesterol response to the removal of eggs from the diet, averaged per person over the 2 trials, and the individual serum HDL cholesterol concentration in 1982. This was true for the HDL cholesterol concentration measured on the habitual diet ($r = 0.42$, $n = 33$, $P < 0.05$) and for the HDL level while subjects were on the

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low-cholesterol egg-free diet ($r = 0.37$, n = 34, $P < 0.05$).

A second group consisted of 21 men and 11 women, all of whom participated in 3 controlled dietary trials. Each trial consisted of a low-cholesterol period during which the diet contained 11 mg cholesterol/megajoule (on average about 120 mg/day) followed by a high-cholesterol period, cholesterol in the diet being the only variable. The first 2 experiments lasted 4 weeks and the high-cholesterol diet provided 57 mg cholesterol/MJ (on average about 650 mg/day). The third experiment lasted 8 weeks, and 84 mg cholesterol/MJ (about 1 000 mg/day) was provided during the 4 high-cholesterol weeks. The cholesterolaemic response in each volunteer was partly reproducible from one study to another [6].

There was a significant positive correlation between the mean response of serum cholesterol to dietary cholesterol, and the concentration of cholesterol in the serum HDL_2 fraction isolated by density gradient ultracentrifugation during the low-cholesterol period of the second experiment ($r = 0.41$, $P < 0.05$).

Thus we found positive correlations between serum HDL or HDL_2 cholesterol concentrations and the response of serum cholesterol to dietary cholesterol in 2 independent groups of subjects.

The correlations observed between HDL cholesterol level and responsiveness to dietary cholesterol, although significant, are weak, and so is the relation reported by Cortese et al. [2] between HDL cholesterol and LDL receptor activity. It could be that HDL cholesterol is acting as a surrogate variable for another, more powerful determinant. Therefore further analysis should show whether these correlations are real or spurious. Still, the clustering of high HDL cholesterol levels, high susceptibility to dietary cholesterol-induced hypercholesterolaemia, and low LDL-receptor activity might provide clues to the causes of differences in plasma cholesterol levels between apparently healthy subjects.

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