Ischaemic heart disease and cholesterol

There's more to heart disease than cholesterol

EDITOR,—We are impressed by the "cholesterol papers."[1-3] M R Law and colleagues prove that it is highly probable that lowering the serum cholesterol concentration in the population will reduce the risk of ischaemic heart disease without increasing the risk of other disease. The jump from epidemiological evidence to conclusions regarding public health is not, however, as evident as they suggest.

Law and colleagues state that lowering serum cholesterol concentration is critical in reducing ischaemic heart disease. It certainly was not so in the past; why should it be in the future? Several Western populations have seen a steeply decreasing mortality from ischaemic heart disease in association with constant or even increasing cholesterol concentrations.[4] If we compare the cohort of the British United Provident Association (BUPA), which was recruited in 1975-82, with the Whitehall cohort, which was recruited one decade earlier, we observe higher serum cholesterol concentrations in all the fifths of the BUPA population (fig 1[2]). Despite this, the incidence of ischaemic heart disease was at least three times lower in the BUPA cohort. As far as we can see—the y axis varies tremendously—the incidence of ischaemic heart disease in the patients with the lowest fifth of serum cholesterol concentration in the Whitehall study was still higher than that in the patients with the highest fifth of cholesterol concentration in the BUPA cohort. In the Whitehall study serum cholesterol concentrations were lower in the lower classes, but the risk of ischaemic heart disease was four times higher than that in the highest.[5] Differences in cholesterol concentrations may explain the international variation in mortality from ischaemic heart disease but do not explain the variation in middle aged employed men in London.

Before it is concluded that cholesterol concentrations must be reduced we suggest that the costs and benefits of any health programme must be weighed carefully. There is more to ischaemic heart disease than just cholesterol. To reach the target of a 10% reduction in serum cholesterol concentration, drastic changes in the diet of a whole nation are needed. The material and immaterial costs may be far from negligible: people value their food habits highly. A subsequent decline in mortality from ischaemic heart disease of 27% seems high, but, expressed in terms of individual life expectancy gained, this represents only 2·5 to 5·0 months (depending on the assumptions of the decline in mortality in the older age groups). People do not prefer "health at all costs"; few do not know that a meal of a hamburger and chips is unhealthy, but, still, fast food chains fare better than restaurants providing more wholesome Japanese food. Health programmes addressing smoking, hypertension, or a reduction in the tremendous socioeconomic differences may be far more efficient means of reaching the same goals.

LUC BONNEUX
JAN J BARENDREGT

Department of Public Health,
Erasmus University Rotterdam,
PO Box 1738,
3000 DR-Rotterdam,
Netherlands

1 Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ* 1994;308:363-6. (5 February.)
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5 Rose G, Marmot MG. Social class and coronary heart disease. *BMJ* 1981;45:13-9.

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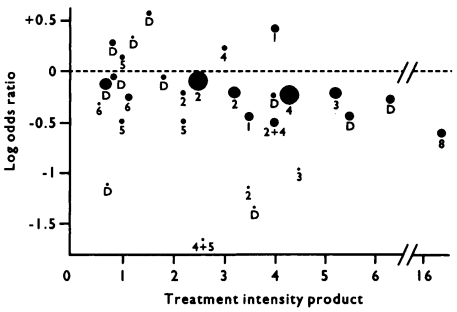
Optimism about drug treatment is unjustified

EDITOR,—M R Law and colleagues' optimistic view on cholesterol lowering is not supported by their evidence.[1,2] Firstly, they belittled the significantly increased mortality from non-coronary causes in the drug trials with the argument that no specific cause of death except haemorrhagic stroke was increased significantly. But death may have been induced by the drugs directly and not by a low cholesterol concentration; and, as eight different drugs with various side effects were used, the time needed for any specific cause of death to appear significantly may simply have been too short.

The excess of deaths from haemorrhagic stroke was said to be balanced by a deficit of deaths from coronary causes. Stroke is a rare disease in the age groups studied in the trials but certainly not in older people. An increased death rate from stroke may therefore outweigh any benefit of lowering cholesterol because in old people high cholesterol is a weak risk factor for death from coronary causes, if it is a factor at all.

Law and colleagues claimed that the effect of cholesterol lowering increased with time.[1] Using the data from their table IV I have calculated the mean differences in fatal and non-fatal infarcts between treatment and control groups in trials where the outcome was known for three time intervals. The mean (SE) decrease of coronary heart disease per 0·6 mmol/ml cholesterol in the intervals was 0·51 (0·26)%, 1·6 (0·60)%, and 0·75 (0·25)% and thus highest in the second period, in disagreement with Law and colleagues' allegation. To reach their conclusion they included results from many trials that contributed data in one or two periods only. Because of the heterogeneity of trials a fair comparison of risk reductions in separate periods is possible only if the outcome is known for all three periods of the trials that are included in this calculation. Law and colleagues also excluded two large, unsupportive trial branches for women,[3,4] which seems irrational because three of the trials they accepted included women.



Odds ratio for fatal and non-fatal coronary heart disease against treatment intensity product (net cholesterol lowering (mmol/l) ×years of treatment) in cholesterol lowering trials. The diameter of the symbols is given by $\sqrt{n/v}$ where n is the number of events in the trial. One trial with only one event is not shown. Intervention: 1=gemfibrozil; 2=clofibrate; 3=cholestyramine; 4=niacin; 5=colestipol; 6=lovastatin; 7=probucol; 8=ileal bypass; d=diet.

Law and colleagues did not explain how they calculated the dose-response relation. No correlation is present between odds ratio for coronary disease and the treatment intensity product for each trial (figure). The treatment intensity product is the mean net decrease of cholesterol multiplied by the number of years in treatment. In weighting with a factor that reflects the strength of each trial—for instance, the reciprocal of the variance of the log odds ratio—a weak, negative correlation may appear owing to the large number of observations in some of the trials. This is misuse of statistics, however, because it demands a dose-response relation for the individual observations in each study to be present, and there was none; individual outcome and degree of cholesterol lowering was sought in 14 trials and found to be unsystematically related in four and unrelated in the rest.[5]

The lack of dose-response relation is crucial because it indicates that the diet-heart idea is fundamentally wrong.

UFFE RAVNSKOV
Specialist in internal medicine

S-233 61 Lund,
Sweden

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Effective diets are unpalatable

EDITOR,—M R Law and colleagues report that reduction of serum cholesterol by 10% will reduce coronary events by 25-30%, and that reduction of cholesterol by change in diet does not increase non-coronary mortality.[1-3] We are in broad agreement with these conclusions, but the recommendations