for action proposed by these authors and by Michael Marmot[4] give us concern. Beyond good intentions and strong rhetoric lies the unforgiving world of therapeutics. The assertion of Law and colleagues that reduction in total dietary fat from 42% to 35% of total energy intake will reduce total cholesterol by 10%.[2] is completely unfounded. Marmot should know better than to cite an analysis based largely on short term experimental data to support his assertion that a reduction of 10% in saturated fatty acids will lower cholesterol by 0·5 mmol/l.[4] He should also recognise the difference between scepticism about diet, which he attributes to us, and realism. All we did was draw together the findings of all long term controlled trials of dietary fat reduction to lower cholesterol.[5] Recent evidence leaves little doubt that our conclusions were correct.

The step 1 diet recommended by the national cholesterol education programme in the United States involves reducing total dietary fat to 30% of total energy intake (lower than the 35% Law and colleagues mention) and an increase in the ratio of polyunsaturated to saturated fat to 1·0. In all controlled trials of individual intervention this diet has lowered total cholesterol by only 2%, and in population interventions the cholesterol response has been even smaller.[5] Recently the OXCHECK and the family heart group studies have reported falls in cholesterol of only 2%.[8] The step 2 diet[6] also aims for total dietary fat of 30% but with a further increase in polyunsaturated:saturated ratio to 1·4. This has been tested in only one short term controlled trial in highly motivated subjects (reference 66[2]). Total cholesterol was reduced by 5%, but a 5% fall in low density lipoprotein cholesterol was paralleled by a similar reduction in high density lipoprotein cholesterol, so that the low density cholesterol:high density lipoprotein ratio was unaltered. What effect this will have on coronary risk is a matter of speculation, but epidemiological data predict no change. A 10% reduction in total cholesterol can be achieved, but only by much more rigorous (which might be considered "step 3") diets with total dietary fat below 30%.[5] In trials of these diets total fat has been reduced to between 20% (Oslo study; reference 58[2]) and 27% (St Thomas's atherosclerosis regression study; reference 43[2]), and serum cholesterol has fallen by an average of 13%.[5] Law and colleagues say correctly that we should not repeat research that has already been performed, but should disseminate the results.[3] It has been shown repeatedly that step 3 diets are unpalatable, and they require intensive supervision and even (as in the St Thomas's study) provision of special foodstuffs. The diets used in the trials cited as successful have generally been abandoned and do not appear in any of the current guidelines.

These studies have included many thousands of subjects in several countries and were conducted by investigators who aimed to show that changes in diet were successful. We agree entirely that reduction in population cholesterol concentrations is highly desirable and likely to reduce substantially the incidence of ischaemic heart disease. However, the authors should apply the same rigour to assessing the effectiveness of interventions as they have to their analyses of the epidemiological and clinical trial data. They do no one a service by overstating the efficacy of the step 1 diet, which has been shown repeatedly not to work, or by pretending that step 3 diets, which do work, are feasible or palatable.

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Drug trial deaths cannot be dismissed

EDITOR,—M R Law and colleagues' report of their meta-analyses of cholesterol lowering trials[1] is misleading as it underplays two important results which agree with results of our work[2]: the increase in mortality from causes other than coronary heart disease in people given drug treatment and the importance of the level of the risk of coronary heart disease in the effect of treatment on overall mortality.

According to table V in their paper, mortality from causes other than coronary heart disease is significantly increased in the drug trials (odds ratio 1·20 (95% confidence interval 1·02 to 1·40)); this finding is unlikely to be due to chance. But the authors attempt to dismiss this finding by selective discussion and dismissal of a few individual trials. For example, they assert that the only significant cause of the increased mortality from causes other than coronary heart disease is the six deaths due to clofibrate. When they report the longer term follow up of some trials (table I), however, they choose to ignore, for example, the widely known results of the longer term (8·5 year) follow up of the Helsinki primary prevention study, which showed a nearly significant 20% increase in total mortality in those receiving gemfibrozil.[3] As with the beneficial effects on mortality from coronary heart disease, any effects on mortality from causes other than coronary heart disease are likely to become more pronounced with longer follow up and therefore be underestimated in the existing trials. Table I shows this trial as having 10 deaths in the treatment group compared with 21 in the control group whereas Frick *et al* reported 19 deaths in the treatment group and only 12 in the control group.[4]

The results also confirm our finding that the benefit of cholesterol lowering treatment is greater for those at higher risk of death from coronary heart disease. This result can also be observed in trials that include subjects with and without evidence of coronary heart disease. In the Upjohn colestipol trial, for example, those with pre-existing disease (mortality from coronary heart disease in the control group 50/1000 person years) showed a clear benefit in terms of reduced total mortality (odds ratio 0·30 (0·1 to 0·8)), whereas those with coronary heart disease at baseline, who had one fifth of the risk of mortality from coronary heart disease, showed no benefit (odds ratio 1·14 (0·5 to 2·9)). Adverse effects of drugs on mortality from causes other than coronary heart disease have to be considered in this context. For example, though the authors point to the well established adverse effects of clofibrate, they fail to point out that in several trials in which clofibrate alone was given to people at high risk of death from coronary heart disease an overall reduction in total mortality was observed.[5-7] Thus the fact that a drug has adverse effects does not necessarily imply that it should not be used; rather, care has to be taken to identify those patients who are at sufficiently high risk of coronary heart disease to benefit from the treatment. Unfortunately, the manner in which the analysis is conducted and interpreted does not contribute to this important aim of all good clinical and public health decision making.

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Hidden bias in observational study

EDITOR,—M R Law and colleagues argue that regression dilution bias and the surrogate dilution effect underestimate the association of serum cholesterol concentration and ischaemic heart disease in observational studies.[1] Their method of correcting for this may, however, introduce bias of another kind.

Many of their 21 515 subjects attending for medicals were likely to have been told that their cholesterol concentration was too high and to modify their diet accordingly. If the repeat measurements of total cholesterol concentration differed solely by random variation then the mean would not be expected to change. In fact, the mean total cholesterol concentration is 0·15 mmol/l lower in the 5696 subjects who underwent repeat measurement—and this reduction is likely to be greater in those subjects with higher initial concentrations. This could have introduced a skew into their correction, and therefore their conclusion—that a reduction in total or low density lipoprotein cholesterol concentration of 0·6 mmol/l corresponds to a reduction in the risk of ischaemic heart disease of 25-30%—must be interpreted with caution.

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"Cholesterol papers" add to the confusion...

EDITOR,—We believe that the adjustment for the so called "surrogate dilution effect" in M R Law and colleagues' re-estimation of the magnitude of the association between serum cholesterol concentration and mortality from ischaemic heart disease is not justified.[1] Stopping smoking reduces the risk of ischaemic heart disease, but not to the level of someone who has never smoked. Law and colleagues confuse the risks associated with various serum cholesterol concentrations in observational studies with alterations in risk consequent on

changes in the concentration as a result of dietary or drug treatment in interventional studies.

The authors' conclusions rest on the assumption that reducing a person's cholesterol concentration by some therapeutic intervention is equivalent to that person shifting from one cohort subgroup into another to acquire the risk that would be associated with his or her new cholesterol concentration in observational studies. This is clearly not necessarily the case (as illustrated by the smoking example) and renders the authors' conclusion untenable.

As a result of this oversight the "cholesterol papers" have added more confusion and shed little extra light on the issue of the association between cholesterol concentration and ischaemic heart disease.

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. . . and mislead on adverse effects

EDITOR,—The paper by M R Law and colleagues[1] contains references to the WHO Cooperative Trial in the primary prevention of ischaemic heart disease using clofibrate.[2-4] Referring to causes of death other than ischaemic heart disease in the WHO trial and in three other trials, Law and colleagues state that "apart from the six deaths from gall stone disease in the WHO trial that were attributable to the drug clofibrate, the higher mortality in treated men in these four trials was spurious: it was concentrated among men who did not take the treatment, was associated with disease present on entry, was not significant in any trial, and there was no significant cause specific excess." The first three of these four statements are not true for the WHO trial, which was larger than the other three trials put together.

These errors are not trivial and so must be corrected. The WHO trial provided no information on compliance other than the cholesterol response; the statement relating to disease present on entry presumably refers to cancer, but cancer showed no greater excess mortality in the WHO trial in the treated group than other non-ischaemic causes of death; the higher mortality in the treated group was significant ($P < 0.01$).

It is a pity that the authors of these timely papers convey the impression that the excess mortality shown in a number of drug trials is false. Adverse effects are an inescapable risk in the use of drugs, and examination of table V in the paper[1] indicates that drugs used to lower serum cholesterol in men without pre-existing coronary heart disease cannot yet be exonerated from carrying a mortality risk. We disagree with Law and colleagues' statement that "total mortality is not an informative arbiter."

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Absolute risk more informative than relative risk

EDITOR,—Most doctors answer in the affirmative when asked whether they would take a daily pill to reduce their chances of dying from a heart attack by 50%. When asked if they would do so for 10 to 20 years if the risk was reduced from 2/1000 to 1/1000, a reduction of 50%, there is much less enthusiasm.

M R Law and colleagues conclude, in part, "that a long term reduction in serum cholesterol concentration of 0·6 mmol/l (10%), which can be achieved by moderate dietary change, lowers the risk of ischaemic heart disease by 50% at age 40."[1] The absolute risk for men of age 40 is not, however, provided, and a clinician could not determine the absolute magnitude of the benefit from the data presented.

The authors drew this conclusion from the 10 largest cohort studies of serum cholesterol concentration and ischaemic heart disease. These included a total of 18 811 events among 494 804 men followed up for seven to 23 years. If all the deaths had occurred among the 40 year old men who had a raised cholesterol concentration, the excess risk of death could have been no more than 2·4%. The use of 50% by the authors, even if technically correct, badly exaggerates the apparent clinical importance of the data as perceived by practising physicians reading a general medical journal.

In the multiple risk factor intervention trial,[2] which yielded 73% of the cohort cases collected by the authors, the risk of death from coronary heart disease is only 21·2/10 000 person years for 40 year old men with a serum cholesterol concentration in the highest fifth of the range. According to Law and colleagues, dietary restriction reducing serum cholesterol by 10% should reduce this risk to 10·6/10 000 person years or about 0·01 event per person decade. While reductions such as this may represent substantial epidemiological benefit, they are of trival clinical importance.

Small benefits were also shown in six randomised trials of treatment of men without ischaemic heart disease included in this and another paper by Law and colleagues.[3] When the ischaemic heart disease events are combined with mortality from other causes the net benefit after two to 12 years of treatment approaches zero (0·6%). In other words, the chance of being alive and free of a myocardial infarction was 91·5% with cholesterol lowering treatment compared with 90·9% without. This observation does not challenge the cholesterol hypothesis, only the appropriateness of treating large numbers of asymptomatic patients without first discussing the small magnitude of potential benefit.

Relative and attributable reductions in risk are valuable measurements for epidemiologists, insurance companies, and government policymakers. They are little help for a doctor informing a middle aged patient of the benefits of changes in lifestyle or the purchase of expensive medicines. When the discrepancy between relative and absolute differences in risk reaches the magnitude found in this study, publication in a general medical journal should include a candid discussion of this fact.

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Cholesterol reduction effective in established disease . . .

EDITOR,—There is a wide gulf between the authors of the *BMJ*'s editorials and the findings of the two particularly important meta-analyses of cholesterol lowering trials that the journal has published. One of these meta-analyses showed for the first time that lowering cholesterol concentrations by even a small amount in patients at high risk of death from ischaemic heart disease significantly decreased all cause mortality.[1] This finding provided a rational basis for the treatment of hypercholesterolaemia in people at high risk of ischaemic heart disease and provided the answer to a question that had troubled many cardiologists—namely, whether such intervention reduced total mortality. Yet the accompanying editorial had the subheading "No light at the end of this tunnel?"[2]

The second paper showed that reducing cholesterol concentration produced a highly significant ($P < 0.008$) decrease in all cause mortality in patients with established ischaemic heart disease.[3] This stemmed from a 20% decrease in new ischaemic heart disease events over five years. Cholesterol lowering treatment had no adverse effect on mortality from causes other than ischaemic heart disease. The accompanying editorial this time was confined to the implications for dietary change in the population.[4] The conclusions drawn were valid as long as it is realised that the medical and nursing profession cannot bring about this change,[5] which probably depends on a change in government policy. Surely, however, it would have been more beneficial to readers and their patients to highlight the fact that even a relatively trivial (0·6 mmol/l) decrease in cholesterol concentration in trials in patients with established ischaemic heart disease, whose cholesterol concentrations at randomisation were only about average for the British population,[6] had at least the same order of effectiveness in preventing reinfarction as interventions such as treatment with aspirin, β adrenoceptor blockers, or angiotensin converting enzyme inhibitors. These latter interventions are widely practised, while treatment for hypercholesterolaemia is largely neglected even after coronary artery bypass surgery.[7]

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