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.

C L M SUDLOW
Senior house officer in general medicine

M R MACLEOD
Senior house officer in cardiology

Western General Hospital,
Edinburgh EH4 2XU

1 Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease: data from the BUPA study. *BMJ* 1994;308:363-6. (5 February.)

. . . 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."

J A HEADY
Reader (retired)

Royal Free Hospital,
London NW1

J N MORRIS
Professor emeritus

London School of Hygiene and Tropical Medicine,
London WC1

M F OLIVER
Professor emeritus

National Heart and Lung Institute,
London SW3 6LY

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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.

DONALD L VINE
Associate professor of medicine

GLEN B HASTINGS
Associate professor of medicine

University of Kansas Medical Center,
1010 North Kansas,
Wichita, Kansas 67214-3199, USA

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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]

PAUL N DURRINGTON
Reader in medicine

Department of Medicine,
University of Manchester,
Manchester Royal Infirmary,
Manchester M13 9WL

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