disease, an effect which is even more pronounced when absolute risk rather than relative risk is examined.[24] The table shows the number of patients who would need to be treated with drugs for a year to prevent one death, estimated from the data from trials that have been done or from a best case assumption of a 20% reduction in risk of death from ischaemic heart disease and no counterbalancing effect on death from other causes.

The real data show an adverse effect for patients who are not at high risk of death from ischaemic heart disease. However, even in the best case large numbers of patients with a risk of death from ischaemic heart disease of 1-5/1000 person years would need to be treated to prevent one death. This range of risk includes many groups of patients whom current guidelines identify as candidates for drug treatment. Clearly the costs—in terms of patient time, the psychological effects of taking treatment to prevent a serious disease, the side effects of drug treatment, and direct expenses for medical care and the drugs—will be great compared with the potential benefits.

Conclusions

Does the current evidence regarding cholesterol, cholesterol lowering, and mortality suggest that we should change direction[1] or carry on with current practice?[2] There is no good evidence that naturally having a low blood cholesterol concentration is harmful. Nor does reducing cholesterol concentration without using drugs seem to be harmful. Reduction of cholesterol concentration will have a small benefit for most individuals, but in whole populations many deaths could be delayed. People and communities should be given this information and the means to adapt to it as they see fit.

On the other hand, strategies to identify individuals with high cholesterol concentrations will be associated with the usual material and psychological costs of screening. Many will fail to respond adequately to dietary intervention and become candidates for lifelong drug treatment. This will be accompanied by high medical costs and the usual array of minor side effects. Except for patients at greatly increased risk of ischaemic heart disease, current evidence suggests such drug treatment will be associated with, at best, little benefit, if not an adverse overall effect on mortality. Here we need a change of direction—to turn away from the identification and drug treatment of asymptomatic people with isolated mildly or moderately raised cholesterol concentrations.

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Disagreements are not substantial

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George Davey Smith and Matthias Egger agree with the conclusions and recommendations in our cholesterol papers[1-3] and also with our recommendation against mass cholesterol testing.[4] They disagree with us on two aspects but these are both minor. One relates to the methods and the other to interpretation. Neither affects the importance of serum cholesterol concentration in the aetiology and prevention of ischaemic heart disease, but both raise issues of general epidemiological application.

Correction for underestimation in observational studies

It is well recognised that cohort studies underestimate the dose-response relation between an imprecisely measured risk factor (here serum cholesterol) and its effect (here mortality from ischaemic heart disease).[5] The statistical procedure to adjust for this regression dilution bias is simple, accurate, and corroborated by direct measurement.

Davey Smith and Egger do not give the correct reason for taking account of the second source of underestimation, the surrogate dilution effect. It is not that low density lipoprotein cholesterol measures an effect closer to the target site than total cholesterol. It is because it permits the quantitative reconciliation of data from observational studies with data from randomised trials. In the trials the reduction in total serum cholesterol concentration is almost entirely due

to reduction in low density lipoprotein cholesterol because the interventions are relatively specific for this cholesterol subfraction. In the observational studies the variation in total serum cholesterol concentration is not due to low density lipoprotein cholesterol alone. This difference needs to be adjusted for if the two types of studies are to be quantitatively compared.

The adjustment is small, changing the estimated decrease in mortality from 24% to 27% for a 0·6 mmol/l decrease in cholesterol concentration.[1] Davey Smith and Egger acknowledge that the association with ischaemic heart disease must be greater for low density lipoprotein cholesterol than total cholesterol so the issue has little practical importance. The conclusions would not alter if the adjusted decrease in risk were in fact 25% or 26%. Our estimate agrees well with direct measurements using apolipoprotein B, the specific protein component of low density lipoprotein cholesterol.[4] The cohort studies that directly measured low density lipoprotein cholesterol concentration were small, had low statistical power, and did not publish data to allow for regression dilution bias.

Safety of cholesterol lowering drugs

We agree with Davey Smith and Egger that cholesterol lowering drugs should not be used in response to mass cholesterol testing but that they may be used in patients with ischaemic heart disease. But we disagree in our interpretation of the data on mortality from causes other than ischaemic heart disease in the trials of cholesterol lowering drugs. In all the 18 drug trials combined, mortality from all causes other than ischaemic heart disease was 20% higher in treated subjects than in control subjects. The 18 trials tested seven drugs in five pharmacological classes, and the 20% difference could have arisen by chance one in 50 times. Davey Smith and Egger hold the view that the cholesterol lowering drugs probably caused this increased mortality. We believe that chance is the most likely explanation.

The non-specificity of both the exposure (the different treatments) and the outcome (all causes of death except one) make a cause and effect relation unlikely. It is inappropriate to make a categorical judgment with respect to all serum cholesterol lowering drugs. The five pharmacological classes of drug have little in common other than their effect on serum lipids so they are unlikely to share the same potential hazards. The evidence on each drug needs to be considered on its own merits.

In the same way it is inappropriate to assess possible hazard by examining all causes of death combined (or all causes except one) as a single outcome measure. No agent is likely to lead to death from every cause or nearly every cause. If there is a hazard, mortality from all causes is too insensitive to identify one disease caused by one drug. Not only could the 20% overall difference be due to chance, but identical death rates from non-coronary causes in treated and control subjects would not provide strong evidence against a hazard. A 100-fold excess risk of a rare disease such as aplastic anaemia could easily be concealed, and the excess mortality from such a cause would need to be 1000-fold to produce an overall difference in death rates of around 20%.

The deaths need to be examined by underlying cause. This identifies only one cause of death in which excess mortality is attributable to a drug—that of deaths related to gall stones in trials of clofibrate. A cause and effect relation can be established not only because of the difference itself (six *v* none), but also because it has a sound pharmacological basis (clofibrate increases biliary cholesterol concentration) and supporting morbidity data. Around 30 different causes of death contributed to the overall 20% mortality difference, and, apart from clofibrate and gall stones, there was no other association of excess mortality from specific causes with use of specific drugs. Furthermore, in all the drug trials as a group, all the trials of drugs in any one class as a group, or any trial considered individually there was no significant excess mortality from any other specific cause, or from all accidents and suicide, or all cancers, the two categories of death which have caused concern.

TRIAL DATA ON ACCIDENTS AND SUICIDES

Davey Smith and Egger believe that we misinterpret the evidence on possible hazard by abandoning the intention to treat analysis. The intention to treat basis of our analysis, however, was its key feature. But after identifying all deaths by allocated treatment and examining the results, it is appropriate to assess possible excess mortality according to whether subjects actually took their allocated tablets. This issue applies to the deaths from accidents or suicide in two of the trials.[3] If the results of the trials were combined (and there is no reason to combine them other than that their results seemed similar) there were 20 deaths in men allocated to the treatment group and nine in men allocated to the control group.[3] This is not particularly surprising. But since nearly all the difference was among men who took no drugs (eight *v* two) or fewer than half their drugs (three *v* none), not among those taking more than half (nine *v* seven), there can be no basis for concluding that the drugs caused death from accidents or suicide.

Analyses based on level of risk

In assessing the contribution of the three largest trials to the results on hazards of cholesterol lowering drugs, Davey Smith and Egger refer to the analysis in which the difference in total mortality between treated and control groups was plotted against the mortality from ischaemic heart disease in the controls, giving a significant association.[6] The two must be associated, whether or not there is a hazard, because the reduction in mortality from all causes when mortality from ischaemic heart disease alone is reduced will be greater in people at a higher initial risk of death from ischaemic heart disease. The analysis does not specifically provide information on harm; it shows only that those who have most to gain from an intervention will gain the most. Had a specific hazard of a particular drug been identified, an analysis of this type could have been used to identify those patients in whom the likely benefit might outweigh the harm. But an alternative cholesterol lowering drug could be used that did not have the hazard.

Use of cholesterol lowering drugs

We see no medical contraindication to prescribing selected cholesterol lowering drugs to people at average risk of ischaemic heart disease. The average risk of death from ischaemic heart disease over the next five years in a 60 year old man in Britain is 3·3%, and it is most improbable that a modern cholesterol lowering drug would kill 1·5% of men—the approximate proportion in whom death from ischaemic heart disease would be prevented. But on grounds of cost and convenience, and because much of the benefit could be achieved nationally by collective dietary change, the universal use of cholesterol lowering drugs is not justified. We therefore agree with the conclusion of Davey Smith and Egger that cholesterol lowering drugs should not be used in low risk individuals,[4] although our reasons differ.

Where we stand

We believe that there is no substantive controversy. Davey Smith and Egger agree with us that lowering serum cholesterol in Western populations is beneficial and safe, and we agree on the clinical and public health strategies needed to reduce mortality from ischaemic heart disease.

Patients with existing cardiovascular disease are candidates for cholesterol lowering drugs, and people in the general population should adopt healthier diets that would lower their serum cholesterol concentrations.

We also largely agree over the quantitative estimates of the association between serum cholesterol concentration and ischaemic heart disease and of the benefits that will accrue from lowering cholesterol concentration. These issues should no longer be regarded as controversial.

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Hands across the equator: the Hereford-Muheza link eight years on

John B Wood, Elizabeth Hills, Filemon J K Keto

Short elective sabbatical visits have been arranged between Herefordshire Health Authority in England and Muheza Health District in Tanzania over the past eight years. Any employee can apply, and the 64 who have participated include midwives, physiotherapists, engineers, and nurse tutors. The possibility of being chosen adds to the attractiveness of working in both districts, and costs have been small. The visits are believed to have led to new ideas and a willingness and confidence to consider change.

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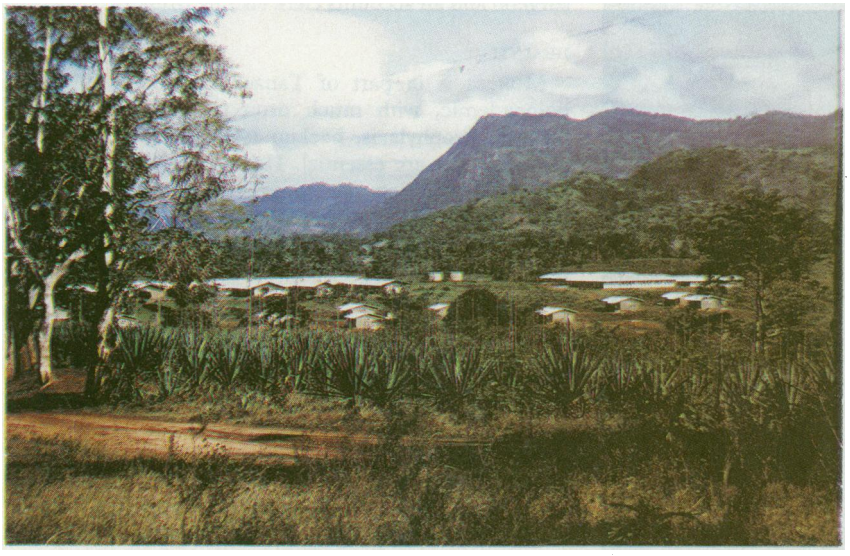
After 64 visits between Hereford in England and Muheza in Tanzania by a wide variety of health workers, contacts and friendships have extended into both communities to form new school, college, church, and local authority links. The beginnings, eight years ago, of this relationship between the Herefordshire Health Authority and Muheza Health District have been described[1]; we now evaluate the link, its effects, and the changes which have occurred.

The two communities

Muheza district is in northeastern Tanzania, just south of the Kenyan border, 50 km from the Indian Ocean; it is fertile and usually well watered. Drought has not affected it as seriously as much of sub-Saharan Africa. Recent rains have been satisfactory, and there has been a gradual improvement in living standards despite very severe inflation. Almost everyone cultivates a garden (shamba) to supplement wages. Malaria remains by far the most serious medical problem, but infection with HIV is increasing. Hospitali Teule serves about 250 000 people. It is a joint government-mission organisation. There are 260 beds and often many more inpatients than beds.



Hospital Teule has 260 beds, an annual budget of £100 000, and serves 250 000 people

Herefordshire in the west of England is also fertile, beautiful, and well watered, but it is much less dependent on a rural economy. The population of about 170 000 is increasing and growing older, and many people retire to the county. Diseases of prosperity, degeneration, and old age are common. The main acute hospitals in the district have about 420 beds.

Nature of the link

This link has concentrated on educational visits in the hope that staff visiting different cultures with different diseases and facilities will take home new ideas and perspectives which may lead to better techniques, better practices, and even better economy. Administration in Hereford is by the Link Society, many of whose members have been to Muheza.

Selection

In Hereford we try to select staff who will be able to cope with a hot climate, difficult travel, and simple living conditions. They must mix well, make good ambassadors, and be able to study and perhaps teach. We prefer candidates with planned projects, and a committee containing previous visitors makes the selection. Interpreters are available in Muheza so the ability to speak Swahili is not essential.

Selection in Muheza is by a panel comprising the medical superintendent, members of the management committee, and a senior church member. Criteria for selection include duration of service, the relevance for the hospital of the proposed programme, whether a previous visit has had a similar programme, the candidate's basic education and ability to communicate, and the expected duration of service after return to