Cholesterol and total mortality: need for larger trials

EDITOR,—It has been suggested that the current trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors can be expected to provide reliable evidence on the effects of lowering blood cholesterol concentration on total mortality.¹ Those trials are, however, designed primarily to assess the effects of lowering cholesterol concentration only on coronary heart disease. Consequently, they have limited ability to detect the sort of effects on total mortality that it is realistic to hope for, except perhaps in the special circumstance of patients who have already suffered a myocardial infarction, among whom nearly all deaths are due to coronary heart disease. But this special circumstance of “secondary” prevention includes only a fraction of the wide range of people who have a moderately raised risk of coronary heart disease and for whom reliable evidence is needed about the efficacy, safety, and overall effects of reducing cholesterol concentration. Moreover, if reducing cholesterol concentration has any real effects on mortality from causes other than coronary heart disease these need to be recognised, as they could be of substantial relevance not only to patients but also to the general population.

In considering total mortality, suppose that in the current trials cholesterol lowering has no material effect on deaths from causes other than coronary heart disease and, as is suggested by previous trials,^{2,3} that there is a roughly one to one relation between the percentage reduction in cholesterol concentration and the percentage reduction in deaths from coronary heart disease during a trial lasting five or six years (so that a 20% reduction in cholesterol would lower mortality from coronary heart disease in a five year trial by about 20%). The table shows the numbers of deaths from all causes that would then be expected and the statistical power of the current trials to detect such reductions in total mortality.

Taken separately from each other, even the studies of secondary prevention among patients after myocardial infarction may well fail to show the sort of effects on total mortality that might realistically be expected (table). Combining all their results in a systematic overview (or meta-analysis⁴) should allow such an effect on total mortality to be detected, but there is still a material chance that it might fail to be. And, even if

the overall results were significant, there would almost certainly be some major subgroup (for example, men or women, young or old, moderately or extremely raised cholesterol concentration) in which ambiguous results would lead to prolonged dispute—especially since an overview of several results may not be as convincing to some clinicians as a single trial of adequate size.^{5,6}

The situation is much worse in the primary prevention of myocardial infarction among people at high risk of coronary heart disease, among whom a larger proportion of deaths are from causes other than coronary heart disease. For even an overview of the studies of primary prevention currently under way may fail to show the expected reductions in fatal coronary heart disease, let alone any effects on total mortality (table). Moreover, for primary as for secondary prevention, the power calculations for the current trials relate only to the overall results: if any subgroups (for example, men or women, middle aged or old) are to be analysed separately to help determine which patients need treatment then the power of the individual trials (and of any overview) is further reduced.

It might have been hoped that the current trials would at least be able to address reliably the suggestion that lowering cholesterol concentration results in an increase in deaths from causes other than coronary heart disease, but this too is uncertain. In assessing any potential hazards of lowering cholesterol concentration the power of the trials depends on the numbers of deaths from causes other than coronary heart disease. Overall in the current trials only about 600 such deaths are expected, of which one third might be from cancer and one sixth from external causes such as accidents, violence, and suicide. Even a meta-analysis of all these studies would have less than a one in three chance of detecting (or excluding) the sort of increases in deaths from all causes other than coronary heart disease (of about 20%), from cancer (of about 30%), and from external causes (of about 50%) suggested by some reviewers of the previous cholesterol lowering trials.^{1,7}

There is therefore a substantial risk of false negative results for total mortality from these trials and of equivocal evidence about any effects of lowering cholesterol concentrations on causes of death other than coronary heart disease (such as cancer). This underlines the need for further large studies which, taken together with the results from the current trials, could answer these questions more reliably. Such evidence would not just be

relevant to drug treatment for a wide range of people at increased risk of coronary heart disease but also help, indirectly, to resolve the long running controversy about the public health importance of lowering cholesterol concentrations by dietary means.

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Diets that protect against coronary heart disease

EDITOR,—Many tests of the effect of diet in preventing coronary disease are flawed by the assumption that a raised blood cholesterol concentration is in itself a cause of the disease. This has led to the use of cholesterol lowering drugs as well as diet to reduce cholesterol concentrations. This approach is a typical result of the common assumption that association denotes cause. But Ram B Singh and colleagues, who assessed the effect of diet specifically on coronary mortality, avoided this error.¹ Nor did they use cholesterol lowering drugs, which have been suspected of

Expected numbers of deaths and power to detect effects on total mortality in current trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors designed to enrol more than 1000 patients

Study	No to be randomised	HMG CoA reductase inhibitor	Estimated 5-6 year average reduction in cholesterol (%)	Estimated No of deaths		Expected No of deaths from all causes*		Power for total mortality (%)*
				From CHD	From non-CHD	Statin group	Control group	
Patients after myocardial infarction								
SSSS	4 500	Simvastatin	23	360	80	197	243	38
LIPID	8 000	Pravastatin	18	700	180	405	475	46
CARE	4 200	Pravastatin	18	260	80	157	183	13
Primary prevention of myocardial infarction								
Post-CABG	1 500	Lovastatin	18	150	25	80	95	7
AFCAPS	8 000	Lovastatin	18	100	150	120	130	2
WOSCOPS	6 500	Pravastatin	18	100	80	85	95	3
Overview of trial results								
All patients after myocardial infarction	16 700	Various	19	1320	340	759	901	85
All primary prevention	16 000	Various	18	350	255	285	320	12

SSSS=Scandinavian simvastatin survival study. LIPID=Long term intervention with pravastatin in ischaemic disease. CARE=Cholesterol and recurrent events study. Post-CABG=Post-coronary artery bypass graft study. AFCAPS=Air force coronary atherosclerosis prevention study. WOSCOPS=West of Scotland coronary prevention study. CHD=Coronary heart disease.
*Expected numbers of deaths are calculated by assuming no effect on deaths from causes other than coronary heart disease and a 1:1 relation between estimated 5-6 year average reduction in cholesterol concentration and percentage reduction in deaths from coronary heart disease; power to detect a difference in total mortality is calculated as probability of achieving 2p<0.01.

producing an increase in violent deaths, so that despite a small reduction in coronary deaths the total mortality in people taking such drugs was no lower than that in a control group.²

Singh and colleagues carried out their trial in 406 patients with suspected acute myocardial infarction. All of the patients were advised to follow a fat reduced diet; one half was also advised to eat more fruit, vegetables, nuts, and grain products. Detailed records of their diets were made before entry into the trial and at the end of the one year. During the year the group taking the stricter diet experienced about 40% fewer cardiac events and 40% fewer cardiac deaths.

The table shows how the trial diet differed from the habitual diet. Differences occurred not only in the quantity and type of the fats but also in the energy and dietary components. The greatest changes were in the intakes of some of the micronutrients: three increased by more than 200% and three by 50% or more. The chief changes in the main nutritional components were in animal protein, vegetable protein, refined carbohydrate (presumably sucrose), saturated fatty acids, and monounsaturated fatty acids. The non-nutritional item caffeine was considerably reduced.

Differences in composition of trial diet compared with habitual diet (values indicate percentage change)

Energy	-14	Caffeine	-73
Carbohydrate:		Vitamin C	+15
Total	-8	Vitamin A	+70
Complex	+10	Carotene	+214
Refined	-54	Magnesium	+216
Protein:		Copper	+220
Total	-26	Selenium	+42
Vegetable	+38	Chromium	+50
Animal	-66	Potassium	+70
Fatty acids:			
Total	-21		
Saturated	-35		
Monounsaturated	-27		
Polyunsaturated	+6		

Which of these changes was responsible for the reduction in coronary mortality? Those for which there is strong evidence, or at least some reasonable evidence, are the changes in fat and energy intakes. Substantial evidence also indicates that reduction in sucrose intake could have a role.³ There is still a long way to go before we can be certain of the best diet (and other lifestyles) that will reduce the incidence of, and mortality from, not only coronary disease but other diseases of affluence.

I thank Patricia Yudkin, of the department of obstetrics and gynaecology, John Radcliffe Hospital, Oxford, for advice on calculating and presenting these results.

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- 1 Singh RB, Rastogi SS, Verma R, Laxmi B, Singh R, Ghosh S, *et al.* Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. *BMJ* 1992;304:1015-9. (18 April.)
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Doctors and control of major releases of chemicals

EDITOR,—Paul R Hunter and Philip T Mannion put forward a good case for public health physicians to be involved in planning for, and responding to, major chemical disasters as incident medical officers.¹ They would have responsibility for assessing the health care needs of victims and communicating this to the relevant local health authority and for providing medical advice to the incident control team.

Although public health physicians have con-

siderable experience in communicating with health authorities, hospitals, and general practitioners, few have equivalent experience or training in toxicology. Increasingly they rely on poisons information centres such as this unit to provide them with toxicological advice in a chemical disaster or smaller but more frequent chemical incidents.

The activities undertaken by this unit follow recommendations made in the international programme on chemical safety's guidelines for poisons control² and were also prompted by a symposium on medical aspects of managing major chemical disasters.³ Thus the unit has developed a research programme which has broadened the scope of its response to chemical incidents by developing a cascade of support services, starting with an immediate response to requests for information by medical professionals, including advice on decontamination and treatment, assessing hazards and risks, case registration, and follow up. Although most incidents can be managed locally, the unit has provided a consultant medical toxicologist to help with the local investigation when this has been requested by public health physicians. Currently the results of this programme are being assessed in order to prepare the case for long term funding.

In my experience, one of the most difficult decisions to be made by those managing a chemical incident is whether the population at risk should shelter at home or be evacuated. I agree with Hunter and Mannion that this requires a strong medical input.¹ Usually, however, these decisions are made by local senior professionals, such as the police or the local authority, who do not have medical training. The unit therefore supports the proposal that greater emphasis should be put on the medical aspects of training in the management of, and planning for, chemical disasters, not only for public health physicians but also for other professionals who have responsibilities related to chemical incidents.

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- 1 Hunter PR, Mannion PT. Doctors and control of major releases of chemicals. *BMJ* 1992;304:1116-7. (25 April.)
- 2 International Programme on Chemical Safety of the World Health Organisation, International Labour Organisation, and United Nations Environment Programme. *Guidelines for poisons control*. Geneva: WHO (in press).
- 3 Murray VSG, ed. *Major chemical disasters: medical aspects of management*. London: Royal Society of Medicine, 1990.

EDITOR,—Paul R Hunter and Philip T Mannion make a plea for consultants in communicable disease control to "participate in planning for, and controlling, major releases of chemicals" because such doctors "often act as advisers on environmental health and toxicological issues to local authorities."¹ We do not believe, however, that individual consultants in communicable disease controls are likely to have sufficient overall skill to deal alone with the immediate and longer term consequences of a major chemical accident.

The need for regional and district health authorities to have detailed plans for dealing with chemical incidents has been emphasised by the Department of Health.² To respond comprehensively to this need in the west midlands a regional advisory committee on chemical incidents has been established to coordinate the considerable body of skill already available within the region. The committee comprises representatives from the emergency services and water authorities, two public health physicians (the regional director of public health and the regional consultant in communicable disease control), a professor of environmental health, two clinical toxicologists, an academic occupational physician, a senior member of the Employment Medical Advisory Service, the regional environmental health adviser, and a senior

manager from the public health directorate. In the event of an emergency a task force is established, with appropriate cooptions as necessary, to review all available clinical, toxicological, chemical, and environmental data.

These arrangements ensure, firstly, that a co-ordinated response can be given in an emergency and, secondly, that accurate information and appropriate advice can be disseminated to the public. We support the plea for adequate arrangements to be made for major chemical incidents at regional and district level but contend that this can be done only if all available skill is coordinated effectively. We recommend that a similar pattern to that in the west midlands should be adopted elsewhere.

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- 2 Department of Health. Health service arrangements for dealing with chemical incidents. London: DoH, 1990. (HC (90) 25.)

EDITOR,—Of course public health doctors must be closely involved in planning for an managing disasters in which there is a major release of chemicals,¹ but Paul R Hunter and Philip T Mannion should not ignore the existing and already trained medical resource—the occupational physician.

Most chemical companies have emergency plans for major disasters, and many employ doctors with considerable knowledge of the toxicological effects of their products and materials. Generally they have close links with poisons centres, where clinical toxicological skill is based. All this skill must be brought together in planning emergency preparedness for disasters, rather than an attempt made to train one person to know all the answers to what will be complex problems.

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Progression of borderline abnormalities on cervical smear testing

EDITOR,—We recently concluded a retrospective study similar to that of Lynn Hirschowitz and colleagues¹ and came up with more or less similar results regarding the likelihood of progression of borderline nuclear abnormalities seen in cervical smears.² Our study, however, differs from the authors' in that we found that the rate of progression to severe dyskaryosis was 7.1% over 12-72 months, which is lower than the authors' figure. Although this could be partly due to the longer follow up in their study, we think that most of this variation is due to observer variation regarding what constitutes a borderline nuclear abnormality. We also think that this is an important cause of the variation between previous studies, in which 19-41% of patients with borderline nuclear abnormality had an underlying cervical intraepithelial neoplasia.^{3,5}

We have used the word progression reservedly because we think that in many cases the more severe changes seen in subsequent smears are not really the result of progression but have been present from the start and missed because of