consequently, the real entity of medical needs. The limitations of the epidemiological data currently available on dilated cardiomyopathy have been pointed out by Rakar *et al.*[1] who, in their paper, carry out a critical analysis of the literature. Their comments are also valid for heart failure in general. The problem must be tackled at national and international levels with the help of the medico-scientific Societies. I am thinking, in particular, of the European Society of Cardiology. The contribution given by the Trieste group is useful from this point of view, both for the results reported and for focusing attention on the problem.

By the way, in the Trieste population, out of 4629 autopsied residents ≤ 90 years old, 2804 (61%) had coronary artery disease. This is the real father of the problems!

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European Heart Journal (1997) **18**, 6–9

Low blood cholesterol and non-atherosclerotic disease mortality: where do we stand?

See page 52 for the article to which this Editorial refers

Twenty years ago Rose and colleagues reported that low blood cholesterol levels were associated with an elevated risk of colon cancer mortality[1]. This paper, appearing shortly after reports that non-cancer mortality appeared to be increased in trial participants assigned to cholesterol-lowering interventions[2], initiated a long-running controversy regarding the safety of policies aimed at reducing population blood cholesterol levels. In the current issue, Behar and colleagues[3] investigate the association between low blood cholesterol levels and future mortality among individuals who have experienced a myocardial infarction. This, the first sustained observational analysis of possible detrimental effects of low blood cholesterol among myocardial infarction survivors, does suggest that the group of patients with low cholesterol levels have increased non-cardiac mortality. This is based on only 27 non-cardiac deaths among the study participants with low circulating cholesterol, however, and it is impossible to analyse causes of death with any confidence, although the excess appears to be due to higher mortality from liver disease and cancer.

If there is a causal relationship between low (or lowered) blood cholesterol levels and non-atherosclerotic mortality then the wisdom of policies aimed at lowering the blood cholesterol levels within whole populations is brought into doubt[4]. Indeed, some authors have suggested that policies aimed at reducing cholesterol levels across populations will change the profile of the causes of death, rather than reduce overall mortality rates[5].

The apparent agreement between the observational studies demonstrating higher non-atherosclerotic mortality in individuals with low cholesterol levels and overviews of clinical trials of cholesterol lowering, which suggest that increased non-atherosclerotic mortality is produced in the groups assigned to active intervention[6], has certainly increased concern in this area. Reviews often link these two sets of findings[7,8], which may obscure the fact that these processes are operating at different ends of the cholesterol spectrum. Trial entrants generally have high cholesterol levels — most cholesterol-lowering trials have been targeted at such individuals — while the participants in observational studies who experience elevated non-atherosclerotic mortality are at the low end of the cholesterol spectrum. This makes it likely that different mechanisms are operating and that explanations in terms of direct detrimental effects of cholesterol depletion are inadequate[9].

Blood cholesterol and non-atherosclerotic mortality in observational studies

A large number of observational studies, some with very large sample sizes and some with long follow-up, have been performed. Meta-analyses of these studies have been carried out[10] or are ongoing[11]. A J- or U-shaped association between cholesterol level and total mortality is seen in many studies. Coronary heart disease mortality rates are positively associated with blood cholesterol concentration, but the risk of death from a variety of non-atherosclerotic causes (in particular lung cancer, digestive disease, respiratory disease, and trauma) tends to be elevated at the lower end of the blood cholesterol distribution.

Various possible explanations exit for this finding. First, low cholesterol levels could be causally associated with a higher risk of developing or dying from several diseases. Second, the prodromal phase of non-atherosclerotic illnesses could lead to reductions in cholesterol levels, with a non-causal association between low blood cholesterol level and future risk of mortality being produced. Third, there could be confounding factors, associated with low blood cholesterol, which themselves increase mortality risk. It is, of course, possible that there is no single explanation for the associations which are seen, and the mechanisms act to a variable degree with respect to different causes of death.

The suggestion that cholesterol levels are reduced by the early stages of illness has generally been examined by analysing the association between cholesterol level and mortality at different stages of follow-up, with the expectation being that as the time interval between the measurement of cholesterol level and death increases the inverse association would decrease in magnitude, as those individuals who were sick at the time of cholesterol measurement died and were removed from the risk set. Thus in the Honolulu Heart Programme a significant interaction between length of follow-up and cholesterol-related mortality was found, with the elevation of non-atherosclerotic mortality amongst subjects with low cholesterol levels decreasing as follow-up time lengthened[22].

In several large prospective studies, however, the negative relationship between blood cholesterol level and mortality remains (although generally in attenuated form) after the exclusion of deaths occurring in the first 5–10 years[4,12,13]. Inverse associations which are robust to the exclusion of the early component of follow-up are taken to illustrate that serious illness — leading to reduced cholesterol levels at the time of cholesterol measurement — cannot be the cause of negative associations, because such seriously ill people would be expected to die relatively soon after cholesterol measurement and would not, therefore, influence the long-term associations. Several disease processes which start many years before death could lower cholesterol levels, however. An example here relates to liver cancer. Several studies have demonstrated an elevated risk of liver cancer among participants with low blood cholesterol concentrations[12–16]. Acute hepatitis leads to reduced blood cholesterol concentrations[17] and long-term infection with hepatitis B virus is related both to low blood cholesterol concentrations[18] and to increased risk of liver cancer mortality. It is thus possible that low blood cholesterol is a marker of hepatitis B virus infection, which increases the risk of liver cancer, but that low blood cholesterol levels in themselves do not produce this increased risk.

The 'pre-clinical disease effect' has been advocated most strongly with respect to cancer. Thus it can be shown that leukaemia has a direct cholesterol-lowering effect, which can be reversed by successful treatment[19,20]. Such direct mechanisms have not been demonstrated with respect to other cancer sites, however, and some studies suggest that low cholesterol levels due to cancer are only seen in the few years before death[21] and that the inverse associations robust to the exclusion of the first few years of follow-up are thus not explicably simply in these terms[10].

Few studies have investigated the possibility of confounding in detail. In the Whitehall study of London civil servants various factors — low socio-economic status, not being married, low body mass index and poor lung function — were associated with low cholesterol levels[13]. These factors themselves will be expected to be related to increased mortality risk from a variety of causes. In the Honolulu Heart Programme[22] high levels of alcohol consumption, smoking and low body mass index and a history of gastrointestinal surgery were associated with low cholesterol concentration. Again these factors will be associated with elevated mortality from several causes. In both the Whitehall and Honolulu Heart Programme studies, adjustment for potential confounders and for markers of disease at baseline, which could have produced low cholesterol levels, greatly attenuated the associations between low cholesterol and mortality[13,22].

In the study by Behar *et al.*[3] data on pre-existing illness and potential confounders is relatively limited. It is possible that the elevated risk of liver disease mortality among post-myocardial infarction patients with low cholesterol levels is due to heavier alcohol consumption among this group. Cancer rates could also be increased by a variety of confounding

factors and the short (less than 5 years) follow-up period does not allow the possible influence of pre-existing cancer in lowering cholesterol levels to be examined. Longer follow-up of the cohort, together with the presentation of more data on potential confounding factors, would be helpful in this instance.

Non-atherosclerotic disease mortality in trials of cholesterol lowering

Single trials of cholesterol lowering have been too small to establish the effect of treatment on non-atherosclerotic mortality. Several meta-analyses have been performed which have suggested that such mortality is increased in the treated groups[6,7]. In an analysis of primary and secondary prevention trials we[23] demonstrated that elevation of non-atherosclerotic disease mortality was restricted to trials using drug therapy to reduce cholesterol levels and was not seen in dietary trials. The degree to which cholesterol was reduced in the different trials was not related to non-coronary mortality, while such an association would be expected if reducing cholesterol levels itself had detrimental effects. After updating this analysis with three recently reported large statin trials[24–26], together with several smaller atherosclerosis regression studies, the drug trials (excluding hormonal treatment) produce an overall 9% reduction in total mortality (odds ratio 0·91; 95% confidence interval 0·85–0·98) and 17% reduction in coronary heart disease mortality (OR 0·83; 95% CI 0·76–0·90). There was no evidence of any increase in cancer mortality (OR 1·06; CI 0·91–1·25) although non-coronary non-cancer mortality is elevated (OR 1·23; CI 1·03–1·46). The reduction in coronary mortality is related to the degree to which cholesterol is lowered in the trials ($P=0·003$), while there is no association between non-coronary non-cancer mortality and degree of cholesterol lowering. The mortality results were significantly ($P=0·006$) worse in the fibrate trials than in the other drug trials combined, once level of cholesterol reduction and initial risk were taken into account. Thus it appears that the elevated non-atherosclerotic disease mortality, which has been seen in some trials, is due to the treatment modalities used rather than cholesterol reduction itself.

What more do we need to know?

Initial concern regarding low blood cholesterol was raised in relation to colon cancer[1]. This concern has not been substantiated by later studies, individually or when combined[10–13]. Interest was regenerated by the apparent increases in deaths from accidents and violence, including suicide, seen in the treatment groups of early primary prevention trials[6]. An updated meta-analysis of all primary and secondary prevention studies shows no evidence of increased traumatic mortality in the treatment group. Speculations that cholesterol lowering could influence mood and behaviour in such a way as to increase the risk of traumatic death have not been borne out in trials which have explicitly examined this issue[27]. The main outstanding concern relates to haemorrhagic stroke. Overall stroke mortality in the meta-analysis of cholesterol lowering trials shows no elevation, and the recent result from the 4S trial[24] actually demonstrated a reduction of combined stroke events in the treatment group. The relative rarity of haemorrhagic stroke, combined with diagnostic difficulties, means that no conclusion can be drawn about risk of these events from the trials. The association of increased haemorrhagic stroke and low cholesterol in several observational studies[1] could result from confounding with alcohol consumption (and thus hypertension), among other factors, although some laboratory studies have indicated that weakening of arterioles through angionecrosis could be occasioned by low circulating cholesterol levels[28]. Further investigation of this is merited and the ongoing large statin trials, in combination with completed trials, will contribute to elucidation of this possible association.

The general picture regarding blood cholesterol and non-atherosclerotic mortality at present is relatively reassuring. Any residual worries should not obstruct efforts to reduce population blood cholesterol levels through moderate dietary changes. The latest series of cholesterol lowering trials, utilizing the statin agents, have not demonstrated any adverse mortality effects, although the number of non-atherosclerotic deaths is small in these trials and more data are required. For individuals at high risk of coronary death the benefits of statin treatment certainly outweigh any (as yet undemonstrated) risks. For individuals at lower risk it should be remembered that starting drug therapy can be a life-time undertaking, with 40 or more years of treatment being envisaged for young or middle-aged adults now started on therapy. We will never have evidence from randomized controlled trials of any (hypothetical) long-term risks. For individuals at relatively low absolute risk of coronary events the absolute benefits of statin therapy cannot be great and any risks of very long-term therapy could be important. Treatment should be focused on those

with most to gain[29], for whom the cost-benefit rates is certainly favourable.

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European Heart Journal (1997) **18**, 9–11

Measuring fatality rates from myocardial infarction

See page 91 for the article to which this Editorial refers

Coronary heart disease mortality rates have declined remarkably in many industrialised countries over the last 30 years. In contrast, rates have risen in several countries, particularly those in central and eastern Europe. The reasons for the decline, where this has occurred, are not entirely clear, but a combination of significant population changes in major risk factors and improved management of disease is likely. The