was much stricter than that recommended by most national bodies. Another potential benefit from greatly reducing concentrations of cholesterol and triglyceride-rich lipoproteins is the positive results emerging from studies of the regression of atherosclerosis.[15]

As restated by Davey Smith and Pekkanen in their review of primary prevention trials in hypercholesterolaemia,[2] there has been an excess of non-cardiac deaths with cholesterol lowering drugs[5] and no decrease in mortality with diets.[16] But their proposal for a moratorium on cholesterol lowering drugs goes too far as it ignores the impressive reduction in non-fatal infarction consistently reported in people at high risk of cardiovascular disease.[17-21] On the basis of the available evidence the use of cholesterol lowering drugs should, however, be confined to this group.

As multiple interventions against risk factors for coronary heart disease in middle aged men at only moderate risk seem to have failed to reduce both morbidity and mortality such interventions become increasingly difficult to justify. This runs counter to the recommendations of many national and international advisory bodies,[22 23] which must now take the recent findings from Finland into account. Not to do so may be ethically unacceptable. One consequence may be that interventions will have to be conducted with much more vigour than previously in really high risk groups, where the attributable risk for mortality from coronary heart disease is great. But the stricter the diet the worse may be the patient's compliance. There is even doubt about which is the best diet to adopt.[24 25]

We must now face the fact that the evidence from large, well conducted trials gives little support to hopes that altering the lifestyle of the community at large, when started in middle age, will reduce cardiac deaths or total mortality. The case for stopping cigarette smoking is, however, strong. Perhaps the explanation is that beginning prevention in middle age is "too little too late." But should the public accept "more, sooner" before there is evidence that it would work?

As it may be years before the results of the relevant trial are available we will have to live with these unexpected findings from Finland, just as we are now learning to live with the fact that lowering cholesterol concentrations in men at high risk does not reduce total mortality and may actually increase non-cardiac mortality. After many years of study we still do not understand enough about the main cause of death in the developed world, which is why coronary heart disease is not really amenable to control except when very rigorous and specific intervention is targeted at those most at risk.

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Asymptomatic hypertriglyceridaemia

Insufficient evidence to treat

The *American Journal of Cardiology* recently devoted a supplement to the hypertriglyceridaemias,[1] reviving the problem of whether a high serum triglyceride concentration should be treated to prevent coronary heart disease. Though intended "to aid the physician in assessing the significance of triglyceride elevations," the report leaves the clinician in a familiar dilemma.

On the one hand, the introduction notes correctly that "the efficacy of reducing triglycerides to decrease coronary heart disease has not yet been conclusively established" and that "the existing body of scientific evidence concerning triglycerides is still insufficient to support the promulgation of a comprehensive set of guidelines for triglyceride lowering in the general population."[2] On the other hand, the introduction also states that "TG 200 mg/dL (>2·3 mmol/l) deserve attention" and a "stepwise approach" asserts that "Diet is the first-line treatment for hypertriglyceridemia" and "Drug therapy may be considered if diet is ineffective, although this remains controversial." The next (and concluding) paragraph in the introduction ignores the controversy about whether drugs should be prescribed, instead advising physicians on which drug to use—"Fibrates and nicotinic acid are the first-line drugs for hypertriglyceridemia."

These two sets of statements don't fit together. If experts don't know whether reducing the concentration of triglycerides in the 10-15% of adults whose fasting levels exceed 2·3 mmol/l[3] will decrease their risk of coronary heart disease, why would doctors need to know which drug to use?

We believe that there is insufficient evidence that lowering triglyceride concentrations will prevent coronary heart disease.[4 5] Treatment directed at asymptomatic hypertriglyceridaemia is therefore not justified. Preventive interventions directed towards lowering risk factors must pass more stringent tests of efficacy than treatments directed at curing patients who are ill.[6 7] Because prevention deals with people who are still in good health strong evidence is required that treatment produces more benefit than harm.

The *American Journal of Cardiology*'s supplement presents few new findings concerning the effect on coronary heart disease of treating high serum triglyceride concentrations. Eight of the 11 articles review classification schemes, laboratory methods, and approaches to treatment. Only three of the articles discuss substantive evidence on the relation between blood triglyceride concentrations and coronary heart disease. Two of these review metabolic data on the binding of triglyceride-rich particles to cell surface receptors and pathophysiological studies of their atherogenic potential.[8 9] The findings provide background information on the biological plausibility of an effect on coronary heart disease of interventions that lower triglyceride concentration, should such an effect be observed in clinical trials.

The third article is a review of epidemiological studies that have historically been the main evidence for a causal relation between high blood triglyceride concentration and the risk of coronary heart disease. In brief, Austin and colleagues find that most studies show an association between triglyceride concentration and coronary heart disease that is independent of the cholesterol concentrations but that "the TG association does not persist in some analyses controlling for HDL-C [high density lipoprotein cholesterol concentration] while in other studies the association remains significant."[10] We agree: in our review of the observational studies during 1980-9 in which an adequate set of multivariate analyses were performed only one of three that studied women and four of nine that studied men found an independent association between triglyceride concentration and coronary heart disease.[5]

The independence of an association between triglyceride concentration and coronary heart disease, however, is not the key question. Even if an independent association exists it does not necessarily follow that interventions to lower high blood triglyceride concentrations will reduce the incidence of coronary heart disease. Firstly, the association between triglyceride concentrations and coronary heart disease may not be causal (that is, it may be due to unmeasured confounders). Secondly, even if it is causal it may be irreversible and thus not susceptible to intervention. Only a randomised trial of the effects on disease outcomes of lowering the triglyceride concentration can resolve these two fundamental questions and address a third: are there adverse effects of the intervention that offset the possible benefits? This last issue is particularly important, given the alarming clinical trial evidence that lipid lowering interventions, particularly fibrates, increase mortality from causes other than coronary heart disease.[11 12]

Although no randomised trials of treatment directed specifically at lowering blood triglyceride concentration have been performed, there are seven trials in which interventions directed at cholesterol also had effects on triglyceride concentrations.[5 13] Inferences about the effects of changing each lipid concentration can be drawn by analysing the findings within the treated groups with the same multivariate techniques that are used for observational studies. Such analyses have been reported for five of the seven trials; in four[14-17] lower rates of coronary disease were associated with decreases in total cholesterol concentration or low density lipoprotein cholesterol, with increases in high density lipoprotein cholesterol, but not with changes in triglyceride concentration.[5] In the fifth trial an association was found between lower rates of coronary heart disease and a fall in triglyceride concentrations, but the authors did not adjust for high density lipoprotein cholesterol.[13]

The Helsinki heart study is particularly informative.[17] Among participants who had a high triglyceride concentration on entry (Fredrickson types IIB and IV) there were fewer coronary heart disease events in the group randomised to gemfibrozil than in those who received placebo. But the overall multivariate analysis suggested that this was due to the effects of the drug on the cholesterol fractions, not on triglyceride. Even though gemfibrozil led to a 35% reduction in mean serum triglyceride concentrations, the lower coronary heart disease incidence was significantly related only to the fall in low density lipoprotein cholesterol and increase in high density lipoprotein cholesterol concentration and not to the fall in triglyceride concentration.

The failure of triglyceride concentration to persist as significant in most multivariate analyses that include high density lipoprotein cholesterol may be a statistical artefact caused by the low precision of measurements of triglyceride concentrations.[18] Moreover, the interrelations among concentrations of triglyceride, high density lipoprotein cholesterol, and low density lipoprotein cholesterol complicate the multivariate analyses. Thus, for example, interventions directed at raising concentrations of high density lipoprotein cholesterol often reduce triglyceride concentrations. True enough, but these are not positive lines of evidence for directing treatment specifically at the high triglyceride concentrations—the more logical implication is to direct treatment at the low concentrations of high density lipoprotein cholesterol. This is particularly true for interventions that do not produce the usual inverse relation between high density lipoprotein cholesterol and triglyceride concentrations: two such examples are cholestyramine and oestrogens, both of which increase triglyceride concentrations while they increase high density lipoprotein cholesterol concentrations, decrease low density lipoprotein cholesterol concentrations, and are associated with lower rates of coronary heart disease.[14 19 20]

What about selective treatment for hypertriglyceridaemia in specific situations? Some authorities believe that a high triglyceride concentration is a suitable target for intervention when it occurs in patients thought to have the familial combined hyperlipidaemia syndrome.[21] Although treatment directed at triglyceride in this or some other subgroup of the population might be beneficial, little evidence exists to support this notion. An exception would be those rare patients with severe hypertriglyceridaemia who are symptomatic; manifestations such as eruptive xanthomas or pancreatitis should receive appropriate evaluation and treatment.

For doctors, the bottom line from this set of articles on hypertriglyceridaemia—and from another recently published set[22]—is still the same. In the absence of evidence from clinical trials that the beneficial effects of targeting this risk factor for intervention outweigh the harm, we side with the many authorities who do not recommend screening and treatment for asymptomatic hypertriglyceridaemia.[23-26]

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Liver transplantation in children

Earlier referral and better surgical techniques have transformed outlook

The improved outcome after liver transplantation in children, reported by Salt and colleagues in this issue (p 416),[1] results from many advances in management. For instance, better, safer immunosuppression has reduced the incidence of acute rejection, and better preservation solutions now permit extended cold ischaemia without sacrificing organ function. But the most important advances in liver transplantation in children have been in the selection of patients and surgical technique.

A trend towards earlier referral has developed as results with liver replacement have improved. In the past much of the mortality before transplantation was attributable to referrals that were made too late. In the series from Cambridge and King's College Hospital almost one in five children waiting for an organ died before receiving it.[1] Referral for transplantation should be considered if the child has deteriorating hepatic synthetic function (coagulopathy, hyperbilirubinaemia, or hypoalbuminaemia), complications related to portal hypertension (variceal haemorrhage, ascites, or hypersplenism), inborn metabolic defects with risk of irreversible complications (malignancy or neurological or other organ damage), or cholestasis with growth failure despite nutritional treatment.

Biliary atresia continues to be the main indication for liver replacement, the remaining recipients comprising children with cholestatic liver diseases (for example, Alagille's syndrome), inborn errors of metabolism (for example, α_1-antitrypsin deficiency and Wilson's disease), and a heterogeneous group of other liver diseases. For biliary atresia it has been suggested that liver transplantation should replace Kasai's portoenterostomy operation as the best treatment.[2]

Proponents of this approach argue that the Kasai procedure increases the technical difficulty, blood loss, and mortality with subsequent transplantation, but this has not been clearly established. In fact, the transplant group from the University of Nebraska found no increase in operative time, blood loss, morbidity, or mortality among children coming to transplantation after Kasai's operation compared with other recipients.[3] Additionally, many patients having portoenterostomy for biliary atresia will achieve long term survival and avoid lifelong immunosuppression (about half the patients survive five years; one quarter to one third of patients survive to adolescence).[4] Without the Kasai procedure most infants with biliary atresia will not survive beyond the first or second year of life. Donors in this age group are scarce, and survival after liver transplantation in infancy is still lower than in older children.[5] It seems, therefore, that transplantations should not replace Kasai's operation but rather should be complementary.

Liver transplantation in children differs fundamentally from the operation in adults because of problems with biliary reconstruction. In most children the common bile duct of the recipient is unusable for duct to duct anastomosis because it is either congenitally absent (as in biliary atresia) or too small to accept a T tube. Biliary reconstruction by choledochojejunostomy has greatly reduced the incidence of bile leaks and strictures. The series published today confirms this point: "direct anastomosis of the common bile duct to a Roux loop was associated with fewer complications than the three other types of anastomosis (5% compared with 21-32%)."[1]

The most revolutionary technical change in the operation in children has been the widespread use of reduced size donor allografts.[6,7] Using only portions of the liver expands the pool of potential donors for children. Unfortunately, this technique only "borrows" donors from the adult pool, where the shortage of donors is not quite as acute. It does not increase the overall number of organs unless one organ is divided between two recipients. The penalty for using one donor liver for two recipients is increased complications and reduced survival.[8] Conversely, living donors (usually parents) may provide a new source of grafts that does not further strain the network of organ distribution. The results in the first 20 children who received liver transplants from living donors at the University of Chicago are similar to those in children who received cadaveric organs.[9] These new surgical techniques, along with advances in management before and after the operation, promise to improve further the results of liver transplantation in children.

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