BMJ

LONDON, SATURDAY 5 FEBRUARY 1994

The cholesterol papers

Lowering population cholesterol concentrations probably isn't harmful

When Gulliver's travels took him from Lilliput he encountered the big enders and the little enders, who argued furiously, to the point of war, over the best end of the egg for extracting the contents. This comes to mind when one contemplates arguments over cholesterol, not because eggs contain it but because in much of the debate facts seem to be used as missiles to defend entrenched positions rather than elements in a solution to a scientific problem of profound importance clinically and for public health.[1]

Not that there is any shortage of facts. We now have several overviews of the data on plasma cholesterol concentrations and mortality, of which the latest are published in this issue of the *BMJ* (pp 363-79).[2-4] While some people have suggested that trial data support the findings of epidemiological studies,[5] others have suggested that low cholesterol may be associated with an increased risk of non-cardiovascular disease[6] and that lowering cholesterol concentrations may not be effective[7] and may even be harmful[8] in anyone other than men at high risk.[9] The big and little enders fought their battles with conventional instruments of war. We fight ours with meta-analysis, regression dilution bias, surrogate dilution bias, risk stratification, confounding, weighting by size of effect, partition of variance, and log-linear models, in addition to the usual multivariate attacks.

The case for the relation between plasma cholesterol concentration and coronary heart disease is well summarised in the three papers by Law and colleagues.[2-4] They put together data from 10 large cohort studies covering nearly half a million men, three international comparisons, and 25 randomised controlled trials of plasma cholesterol reduction. The strength, consistency, and graded nature of the relation between plasma cholesterol concentration and mortality from coronary heart disease make any explanation of the link other than a causal one extremely unlikely. Plasma cholesterol concentration is not the only reason why rates of coronary heart disease vary between individuals and among groups—other factors are clearly important—but it is a reason. We know from other overviews that the relation applies to men and women, young and old,[10] although the strength of the relation is weaker with increasing age.[2,3] This may not entirely be a function of age at death; the power of plasma cholesterol concentration to predict coronary heart disease may be weaker the later in life it is measured.[11]

If the link between plasma cholesterol and coronary heart disease is causal is it of a size to make a difference and is it safe to have a lower plasma cholesterol concentration?

Taking account of regression dilution bias[12] and surrogate dilution bias—the studies measure total rather than low density lipoprotein cholesterol—Law and colleagues estimate that a difference in plasma cholesterol of 0·6 mmol/l (10%) is associated with a 27% difference in mortality from coronary heart disease in cohort studies and a slightly larger difference in international comparisons. These observational data are crucial because randomised controlled trials do not by themselves prove causal hypotheses. The fact that aspirin is good at removing headaches does not mean that headaches are caused by aspirin deficiency. The fact that an intervention that lowers plasma cholesterol concentration is accompanied by a decreased incidence of coronary heart disease does not in itself settle the case for the causal link. Nevertheless, these latest analyses of trial data are consistent with the link between cholesterol and coronary heart disease being reversible over about five years—a 10% lowering of plasma cholesterol concentration associated with a 25% difference in coronary heart disease. Law *et al* find a stronger effect on the lowering of the risk of coronary heart disease than has been found previously because previous meta-analyses did not take the duration of trials into account, and little beneficial effect is seen in trials in the first couple of years.

These data suggest that strategies to reduce plasma cholesterol concentrations in individuals and populations will have a beneficial effect on coronary heart disease. But what of the possible risks?

Law *et al* confirm that low cholesterol concentrations are associated with an increased risk of death from causes other than coronary heart disease. This affects the 6% of Western populations with the lowest cholesterol concentrations. There are five possible reasons for this association.[13] Chance and bias are unlikely. That leaves three: a low cholesterol concentration causes disease, disease causes a low cholesterol concentration, or something else is associated with low cholesterol concentrations that leads to an increased risk of other diseases.

One of the strongest arguments against a causal link between low cholesterol and disease is that the values at which this association is seen, and the diseases with which low cholesterol is associated, vary among populations. A second is that people with low cholesterol concentrations differ in several ways from the rest of the population.[14] Thirdly, cancer and other diseases can lower cholesterol values. Fourthly, the increased risk of non-circulatory disease is not observed in employed cohorts, who are likely to be healthier than the general population. Hence, except for cerebral haemorrhage,

low cholesterol concentrations are unlikely to be causally associated with deaths from non-coronary causes.

The reasons for the apparent high risk of disease at the bottom end of the distribution of plasma cholesterol concentrations are probably different from those underlying the possible deleterious effects of cholesterol lowering drugs and diet. The postulated adverse effect of interventions has been observed in trials of people with much higher cholesterol concentrations and should be evaluated separately. If the reduction in coronary heart disease that follows a reduction in plasma cholesterol concentrations is balanced by an increase in other causes of death, with no change in all cause mortality, the intervention is of doubtful value. Law *et al* point out that if plasma cholesterol concentration were associated with no disease other than coronary heart disease then a lowering of plasma cholesterol by 0·6 mmol/l, which is associated with an 11% reduction in coronary heart disease, should achieve only a 7% reduction in all cause mortality. In fact, combining all trials, they observed a 4% reduction in total mortality (95% confidence interval −10% to +2%). The trials have not had the power to distinguish between the predicted effect and no effect.

They therefore turn their attention to specific causes of death. A previous analysis suggested that any excess was observed only in trials of drugs, not of diet.[9] If cholesterol lowering itself is not harmful, and diet is safe, as the balance of evidence from the current and the previous meta-analysis[9] shows, then attention must focus on the side effects of particular drugs. Law *et al* dismiss all but a handful of the non-cardiovascular deaths as not causally related to the cholesterol lowering treatment. Their argument is plausible but it cannot apply to newer drugs. We shall have to await the outcome from the current crop of trials of the statins to be sure that they do not carry risk.

Where does that leave us? Drugs will be appropriate for those at higher risk only when the benefits outweigh the hazards. Population rates of coronary heart disease will continue to fall only if there are changes that affect most of the population.[15] Despite scepticism about difficulties in modifying plasma cholesterol concentrations with diet[16] a recent review of 420 dietary observations from 141 groups of subjects showed clearly that a reduction of 10% in the proportion of energy derived from saturated fatty acids would be associated with a plasma cholesterol concentration 0·5 mmol/l lower.[17] This week's papers suggest that this would yield a substantial reduction in death from coronary heart disease without increasing the risk of other disease.

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Arthroscopy

Many of the new procedures should be performed only by experts

In 1976 I made a detailed study of the random incidence and clinical cause of meniscal injuries and wrote an article in the *Lancet* called *Unnecessary Meniscectomy*.[1] At that time awareness was increasing that meniscectomy was not a benign procedure. Before long diagnostic arthroscopy confirmed what orthopaedic surgeons had suspected—that too many cartilages were unnecessarily removed. Within a few years arthroscopic meniscectomy was replacing open meniscectomy as a treatment of choice. Patients came to expect day surgery and far shorter periods off work—though even in 1993 a surprising number of menisci are still removed by open arthrotomy.

Endoscopic techniques can now be used to examine and treat shoulder, elbow, wrist, hip, and smaller joints[2-6] and may even be used to release pressure in the carpal tunnel.[7] What is the busy purchaser to make of all this provision? What is the current status of arthroscopy of the knee and what are the indications for and scope of arthroscopy in other joints? These questions are of real economic concern now that arthroscopy has become the most common orthopaedic procedure in Britain.

For diagnostic arthroscopy has certainly now become the norm. But may the pendulum have swung too far? There are many causes for knee pain, and not all of these are helped by arthroscopic manipulations, even if the patient has private health insurance. The decision to examine the knee arthroscopically has to be made carefully and not just because the clinician cannot think of what to do next. We have recently shown,[8] as have others,[9] that arthroscopy may rarely have complications. The indications for its use need careful assessment. For example, do we really need to submit patients to general anaesthesia and surgical intervention to inspect or even shave the back of the patella? The relation between the syndrome known as chondromalacia patellae and pathological changes of the patella articular surface is surprisingly unreliable.[10] Other investigations may be simpler and safer. For example, examination of intra-articular fluid often gives reliable information about the surgically relevant disorders within the knee.[11]

The Bristol group has shown conclusively that magnetic resonance imaging is a very reliable and reproducible method for identifying lesions such as meniscal and cruciate tears.[12] Perhaps a scan should become the primary investigation, with arthroscopy reserved only for those patients in whom tears are