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REVIEW

CHOLESTEROL AND PSYCHOLOGICAL WELL-BEING

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Abstract—The debate about possible adverse effects associated with low or lowered serum cholesterol has raised important scientific questions concerning the links between lipids and behaviour. One of the most unexpected findings has been an association between cholesterol-lowering treatment and accidental death. A similar association has also emerged among the prospective cohort studies, with higher-than-expected numbers of suicide deaths in the lowest cholesterol groups. These observations have prompted speculation that behavioural or emotional disturbances could be part of the process linking lipids and accidental death. In this paper, the epidemiological literature is reviewed briefly, then the evidence for depression as a mediating condition is discussed. Two conclusions are drawn from this review of the literature. One is that understanding the relationship between the biology of lipids and the psychobiology of mood is demonstrably an important scientific and public health issue. The second is that the introduction of new treatments or preventive programmes should include a careful evaluation of the psychological as well as the physical effects.

By the end of the 1980s, the accumulated evidence for links between dietary fat, serum cholesterol and coronary artery disease had led to agreement that elevated cholesterol levels should be reduced by diets or drug treatment and that western diets should be modified to provide a smaller proportion of energy from fat. In 1989, Steinberg [1] suggested that the only remaining question was why it took so long to reach consensus. However, recent events have reopened the debate about the benefits of cholesterol-lowering and refuelled arguments over the relative merits of population-based vs. targeted interventions to reduce heart disease. The controversy began with Muldoon *et al.*'s [2] meta-analysis of cholesterol-lowering trials, which suggested that lowering cholesterol increased non-illness mortality. This was followed by a number of reports indicating that suicide levels were higher in low-cholesterol groups and that depression was related to low cholesterol. The significance of these observations for psychosomatic research is the implication that the psychobiological relationship between lipids and psychological well-being might be much more complex that had previously been thought. The aim of the present paper is to review the evidence relating lipids to psychological well-being and to consider the implications for psychosomatic medicine.

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CHOLESTEROL-LOWERING INTERVENTION TRIALS

Questions about the possible adverse effect of cholesterol lowering originated from the observation that total mortality was not reduced in treated groups in cholesterol-lowering trials because of an increase in non-cardiovascular mortality. Individual trials of cholesterol-lowering were designed to have adequate statistical power to detect differences in coronary heart disease (CHD) morbidity and mortality, and not total mortality, so greater weight must be given to combined analyses. Muldoon *et al.*'s [2] meta-analysis of six randomized primary prevention trials found that total mortality was unaffected by cholesterol-lowering treatment. This appeared to be because the reduction in CHD deaths was offset by an increase in deaths from other causes in the treated groups. Likewise a meta-analysis of seven secondary prevention trials revealed only a non-significant improvement in total mortality, with a similar counterbalancing of lives saved from CHD death with lives lost from other causes [3]. Ravnskov [4] evaluated 22 controlled, primary and secondary prevention trials and also concluded that total mortality was not reduced by cholesterol lowering treatment, nor were there significant treatment effects in any of the subgroups of trials such as unifactorial trials only, trials on men only, or dietary trials only. In another recent meta-analysis, 35 controlled, single factor trials of cholesterol-lowering in primary and secondary prevention were stratified according to level of coronary risk, which was indexed by the CHD death rates in the control group of each study [5]. Total mortality in the treated groups was significantly lower than in the control groups only in the high coronary-risk subjects. In the medium risk subjects, total mortality was similar in the treated and control groups, and in lower-risk subjects the treated groups had higher mortality. Law *et al.* [6] also failed to find a reduction in all-cause mortality when they combined data from 28 randomized controlled trials although there was a significant, favourable treatment effect in the subgroup of trials on subjects with established CHD.

Despite some variation outcome, the meta-analyses of cholesterol-lowering in primary prevention interventions suggest some unfavourable effects on total mortality. However, it is widely agreed that the use of total mortality as an endpoint is unsatisfactory because it is biologically non-specific. In order to understand the mechanisms of adverse effects of cholesterol-lowering, attention has to focus on the specific causes of death which appear to predominate in treated subjects.

In relation to the debate on lipids and psychological well-being, it is the possibility that increased non-illness (NI) mortality—death from accidents, suicide or homicide—might be associated with cholesterol-lowering treatment that is of particular concern. This was observed in Muldoon *et al.*'s meta-analysis of primary prevention trials [2]. A similar association was also found in secondary prevention trials where there was a significant excess of non-cancer, non-cardiovascular (mainly NI) deaths [3], but a later analysis using an updated data set failed to find any significant excess of non-CVD, non-cancer deaths [7]. In a new meta-analysis concerned specifically with NI mortality, a significant association was observed across eight primary and secondary prevention trials, although the effect was not significant in the two secondary prevention trials alone [8]. The exception to the finding of raised NI mortality has been Law *et al.*'s [6] analysis of primary and secondary prevention trials combined, using unpublished data for the trials which had not included data

on all causes of death in the published reports. This meta-analysis found no significant excess risk of accidents and suicide and the authors attributed any individual significant findings of unfavourable results to chance.

The possibility of adverse side-effects is a major concern when new treatments or preventative programmes are introduced on a wide scale. Particular difficulty in establishing causal effects occurs when the adverse effects are infrequent and not obviously linked to the mechanism of action of the treatment. Nevertheless, they need to be taken seriously, and especially when, as appears to be the case in the cholesterol-lowering intervention trials, the magnitude of the adverse effects offsets the benefits.

The important scientific question in the present debate is whether the observed association between cholesterol-lowering and non-illness deaths found in some analyses represents a causal process or confounding of some kind. The fact that it has emerged in randomized, controlled, and sometimes double-blind, trials means that it must be taken very seriously, but causal processes must be proven. One method of approaching this initially is to examine the particular cases of death. There is some evidence for poorer treatment compliance and a past history of alcohol abuse and emotional problems among the individuals who died from accidental causes in two of the drug trials [9]. Careful analyses of the individual's history, treatment compliance and treatment responses in any cases of accidental death might lead to more understanding of the mechanisms. Future intervention trials will also need to monitor not only NI mortality, but also the associated morbidity, such as psychological disturbance or alcohol abuse.

COHORT STUDIES—LOW CHOLESTEROL AND NON-ILLNESS MORTALITY

There have now been a number of prospective cohort studies evaluating the relationship between cholesterol and mortality. Of course cohort studies have limited ability to estimate causal effects and in any case it is possible that the effects of low cholesterol (investigated in cohort studies) is different from the effects of lowered cholesterol which is the subject of intervention trials. The lowest cholesterol group in cohort studies can also be expected to have substantially lower cholesterol levels than treated patients in intervention trials. Nevertheless, cohort studies have contributed important material to the debate about the effects of low cholesterol and the results will be summarized.

The largest single study is the MRFIT screening study in which over 350,000 middle-aged men who were screened for participation in a primary prevention trial, have been followed up for 12 yr [10]. Analyses were carried out separately for deaths occurring in the first 5 yr, after 5–10 yr, and after 10 yr of follow-up, in order to try to exclude the effects of diseases which were already present at the time of the initial cholesterol measurement. All-cause mortality showed a J-shaped relationship with cholesterol with crude death rates increasing with decreased cholesterol below 3.62 mmol/l (140mg/dl). This effect persisted after adjustments for age, race, smoking, income and blood pressure. Nineteen other cohort studies with a total of over 250,000 men and women were pooled and reviewed by Jacobs *et al.* [11]. The results showed a pattern similar to MRFIT in men, with a U-shaped relationship between cholesterol and total mortality even after excluding deaths occurring within 5 yr of

the cholesterol measurement. In women there was an approximately flat relationship between cholesterol and total mortality.

As with the intervention trials, all-cause mortality is a clumsy instrument for scientific questions and attention has focused specifically on mortality from injuries and suicide in some studies. In the Honolulu Heart Study, higher than expected numbers of deaths from suicide and accidents were observed in the lower cholesterol groups [12]. In the MRFIT study there were 1679 deaths from accidents, suicide and homicide, and the rates were significantly higher for men in the lowest cholesterol group (less than 4.14 mmol/l) than the remainder. When the three causes were considered separately, the effect was significant only for the suicide deaths [10]. In a large study from Sweden, over 50,000 men and women were screened in 1964–1965 and followed up for 20 yr [13] yielding over 500 accidental deaths. There was a significant negative relationship between cholesterol and suicide deaths among men, but no such effect in women. This study has been widely interpreted as providing strong evidence for a link between cholesterol and suicide, although without an a priori justification for analysing men and women separately, and for getting different results in the two sexes, these results must be considered as at least a partial failure to find a cholesterol–suicide connection. In the Finnish cohorts of the Seven Countries Study, accidental death was unrelated to cholesterol in one group and significantly lower in the low-cholesterol group in the other one [14]. In the Whitehall study, there was no evidence that men in the lowest cholesterol quintile had higher levels of violent deaths or suicide [15], while in another Finnish study there was no relationship between cholesterol and death from accidents, suicide and violent causes in two cohorts of over 10,000 men and women who were followed up over 10–15 yr [16]. Law *et al.*'s [6] meta-analysis of these results along with unpublished data from other cohort studies, suggests that the risk of death by accident or suicide was not significantly raised when all cohorts were included, but analysing the six community cohorts separately from the employed men, a raised risk of accidental death was associated with low cholesterol.

The results from the cohort studies cast some doubt on the generality of the protective effect of low serum cholesterol. With total mortality as the endpoint (and that is likely to be the greatest concern for the general public), very low levels of cholesterol show a consistent relationship with higher mortality. The evidence for higher than expected levels of mortality from suicide or accidental death appears to be sporadic, but nevertheless low cholesterol and raised risk of accidental death appear to co-occur more often than is comfortable for wholehearted promotion of low cholesterol as a goal of public health. The lack of consistency in the results is disconcerting, but one explanation may be that there are subgroups in the population with both low cholesterol levels and a high risk of death from unnatural causes, who are differentially represented across the various cohorts. Law *et al.*'s [6] finding that employed men, who can be assumed to be healthier on average than community samples, appear not to exhibit the low cholesterol risk, gives some support for this view. What is uncertain is whether the low cholesterol–mortality association in cohort studies could share causal mechanisms with the adverse effects in intervention trials. The coincidence of the particular cause of death, viz. the risk of suicide, suggests common mechanisms, but there are many differences in relation to the circumstances of the at-risk groups. The treated groups in cholesterol-lowering trials rarely reach

the cholesterol levels of the low cholesterol groups in population studies, cholesterol is actively and acutely lowered in intervention trials but may be constitutionally low in cohort studies, and the populations studied in the two kinds of investigation are likely to be very different in terms of other health risk factors.

CHOLESTEROL AND DEPRESSION

One plausible mechanism linking low cholesterol and suicide is pre-existing illness or a personality disposition which both lowers cholesterol and raises the suicide risk. Depressive illness is known to be associated with suicide, and might, either through disturbances of food intake or some other process, predispose to lower cholesterol. However, studies relating cholesterol and depression suggest that the relationship is not as simple as that.

The idea that emotional factors might be linked to lipids is not new, but up until the 1980s it was assumed that there would be a positive relationship between depression and cholesterol. An early investigation [17] found that elevated cholesterol was associated with low 'self-acceptance' on the California Psychological Inventory (indicating tendencies towards guilt and self-blame) in one sample of men, although this finding was not replicated in a second larger sample. Jenkins *et al.* [17] reviewed a number of studies suggesting that intro-punitiveness (comparable to depression) is associated with elevated lipids, and aggression and extra-punitiveness with low lipid levels. Depression was found to be correlated with cholesterol in young obese men, although not normal-weight men, in another study [18], and nurses ratings of depression were associated with elevated lipids among non-defensive subjects in a study of the effects of unemployment [19]. Another review of the psychosomatic literature also identified a consistent relationship between serum cholesterol and negative mood and concluded that depression was an important correlate of raised cholesterol [20]. Further support for the cholesterol–depression connection has come from the observation that psychiatric disorder is associated with excess cardiovascular disease risk.

In a meta-analysis of psychological predictors of heart disease [21], depression emerged as the single strongest predictor both of all coronary heart disease outcomes and specifically of myocardial infarction. The more recent literature on 'vital exhaustion' also implicates depression-like states in the sequence of events leading up to CHD [22]. If clinical depression were related to heart disease risk through atherogenic mechanisms, then depressed patients might be expected to have higher than average lipid levels. However, the research findings have given little support to this view. Oxenkrug *et al.* [23] attempted to confirm a German report of higher cholesterol levels in depressed patients but found no difference between depressed patients and controls. Fritze *et al.* (1982) successfully identified an excess of hyperlipidaemia in monopolar depressives, but Yates and Wallace [24] found normal cholesterol levels in unipolar depressed patients and lower than expected levels in patients with bipolar affective disorder. Glueck *et al.* [25] reported a similar finding in a comparison between depressed patients, patients who had had a CHD event and self-referred attenders at a public cholesterol screening. The proportion of depressed patients with low total cholesterol levels [less than 200mg/dl (5.17 mmol/l)] was 54%, which was higher than in the CHD event groups (27%, 41%) or the

self-referred screenees (25%). In a second report, Glueck *et al.* [26] again found significantly lower total, LDL and HDL cholesterol, but higher triglycerides, in depressed patients compared with self-referred supermarket screenees. However, it is not clear that the comparison groups would have provided appropriate control values, since they were likely to have included more people who had high cholesterol (the CHD event group), or suspected that they had (screening attenders). Overall, these results paint an inconsistent picture, but fail to provide much support for a positive association between cholesterol and depression.

The more recent literature relating depression to cholesterol, developed in the wake of the concern about adverse effects of cholesterol-lowering, has taken a different approach to analysis identifying high and low cholesterol groups in the population and evaluating the prevalence of depressive symptoms. In the Rancho Bernardo Study, depression (based on Beck Depression Inventory (BDI) scores) was assessed in relation both to present cholesterol levels and changes in cholesterol over previous years, in a sample of 1020 men aged 50–90 [27]. In a multiple regression, low cholesterol (less than 4.1 mmol/l) predicted a higher BDI score. Analyses of depression prevalence (BDI score ≥ 13) suggested that the effect was primarily in the older groups (over 70), but the numbers in each cell were very small with this sample stratification, and no direct comparisons between the different age groups were carried out. However, in a partial replication of this study, which included additional controls for physical function, low cholesterol no longer appeared to be associated with depression [28]. In the Helsinki Ageing Study [29] depression was assessed using the Zung self-rating scale and physicians' ratings of depression in 621 men and women aged over 75 who had had their lipids measured one year previously. Change in depression ratings over the year was used to index the 'depressogenic' effect of low cholesterol but no significant relationship between lipids and depression change emerged. Similarly in the Whitehall II study, high scorers on the General Health Questionnaire (a broad-based assessment of emotional well-being) were not found to have lower cholesterol [30]. In a study of older volunteers (in Nantes, France) who had lipids and depression (CES-D) measured concurrently [31], there was no correlation between depression and cholesterol, but those in the 'low cholesterol' quintile (less than 5.2mmol/l for men; less than 5.7 mmol/l for women) had a higher prevalence of depression (over 21%) than the other groups. No relationship between cholesterol and intropunitiveness (a trait characteristic sharing some features with depression) was found in results from the Edinburgh Artery Study [32].

The assumption of a positive relationship between cholesterol and either depression, depressed mood or related negative affective states, has received little support. In fact, the balance of the evidence suggests that cases of depression or low mood are slightly more likely to predominate among the lower cholesterol groups (whatever the cut-off for low cholesterol in that sample) but there does not appear to be a linear relationship between depression and cholesterol and many studies have failed to support this view. The most parsimonious explanation would be that when depression is accompanied by loss of appetite, there may be a reduction in cholesterol caused by the reduction of fat intake and the loss of weight. It is, therefore, vital to examine the cholesterol–depression relationship in the light of information about weight and appetite.

CHOLESTEROL AND AGGRESSION/HOSTILITY

Cholesterol has also been implicated in the biology of aggression and hostility, particularly in the light of evidence that the Type A behaviour pattern (of which hostility is an important component) is predictive of heart disease. Hostility in turn may be involved in the accidental causes of death which seem to be found at lower levels of cholesterol. Recent data from the Finnish Twin Cohort have confirmed that self-rated hostility is associated with higher rates of accidents, suicidal behaviour and accidental death [33]. As with the depression–cholesterol link, the initial assumption was that hostility would be associated with higher cholesterol and the earlier work seemed to support a positive relationship. Friedman and colleagues had observed higher lipid levels in Type A than Type B men and women [34, 35]. Some of the studies which have concentrated on hostility have also provided evidence of a positive relationship with cholesterol [36, 37], but many others have failed to find such an effect (e.g. refs [15–40]). In the Edinburgh Artery Study [32] hostility was unrelated to total cholesterol although a positive relationship emerged between triglycerides and aggression.

The evidence from clinical groups identified on the basis of their propensity to violence, such as violent offenders and aggressive/impulsive criminals, has typically suggested the reverse effect, with lower than expected lipid levels in these patients [41–43]. In a rare prospective study of cholesterol and aggressive acts, violent offenders with low cholesterol (less than 200 mg/dl) were found to have more violent episodes over a 2 yr hospital admission than those with higher cholesterol (200 mg/dl or higher) [44].

The literature on lipids and aggression looks even more inconsistent than the depression work. In both cases chance may have played a part in the variability of the observations, especially as some earlier studies had comparatively small sample sizes. Differences in dietary fat intake may also account for the differences in lipid levels. In some of the studies on Type A behaviour (e.g. ref. [34]), the cholesterol differences were said to be independent of diet, but in the patient and offender studies dietary differences were not evaluated, and they could account for the observed effects. The relationship between lipids and hostility may also be more complex than can be teased out from simple correlational analyses. Williams [45] has argued that hostility would be better understood as a syndrome in which a basic neurobiological abnormality is associated with higher levels of anger, greater stress-responsiveness and more health-compromising behaviours. Raised lipids in the hostility syndrome would be a consequence of a combination of indirect effects from dietary choices and direct effects of catecholamines on lipolysis. Developments in the understanding of the relationship between psychological factors and lipoprotein metabolism [46] suggest that personality is a potential modulator of the relationship between stress and lipid metabolism, along with gender and genetic characteristics. This suggests that the mediating effects of both stress, cardiovascular reactivity and gender would need to be taken into account to understand how lipids and hostility were related, so it is unsurprising if contradictory results emerge from simple analyses.

LIPID-LOWERING AND PSYCHIATRIC MORBIDITY

There have been a very limited number of studies which have evaluated the

relationship between cholesterol-lowering and mood or psychiatric illness, and so far the results have all been reassuring. The 48 week results from the clinical evaluation of lovastatin study [47] failed to identify any significant difference between lovastatin (an HMG CoA reductase inhibitor) and placebo groups in major psychiatric events (0.6 and 0.4% respectively). In the Air Force Coronary Atherosclerosis Prevention Study [48], 'emotional well-being' was assessed by questionnaire after 1 year of treatment with lovastatin in men and women with mild hypercholesterolemia and the results showed no evidence for any difference between treated and placebo groups. In the Family Heart Study [49], the Hopkins Symptom Checklist depression and aggression scores were compared before and after a family intervention to promote lower fat diets. The results suggested beneficial effects of switching to a lower fat diet, but as the cholesterol reduction was so small (1%), and the two groups (compliers and non-compliers) were essentially self-selected, these results cannot be interpreted as comparable to randomized controlled trials. In the Oxford Cholesterol Pilot Study, scores on the Profile of Mood States were obtained after patients had been on simvastatin or placebo for an average of 33 months. There were no differences between the groups in depression, aggression, confusion or energy, nor were there any differences in new use of psychotropic medication over the study period [50].

Two smaller-scale, non-clinical studies have evaluated the short-term effects of cholesterol-lowering drugs with similarly benign results. Strandberg *et al.* [51] compared lovastatin and pravastatin with placebo in a 4-week double blind crossover study in 24 mildly hypercholesterolemic men. No differential effects of the three treatments on anger expression or hostility were detected. Harrison and Ashton [52] used a similar design to compare simvastatin and pravastatin in 25 healthy normocholesterolemic young men. No significant difference between drug and placebo periods were detected in depression or anxiety scores, or in cognitive performance.

Two studies of lipid-lowering in monkeys have given very different results from the human work, suggesting that cholesterol-lowering could have significant behavioural effects. Kaplan *et al.* [53] compared the social behaviour of monkeys who had been on normal or cholesterol-lowering diets. The monkeys who had been maintained on a low-fat diet showed significantly more aggressive behaviour; albeit only in one out of a total of 14 aggression/submission behaviours which were studied. These results have now been partially replicated in a study of monkeys fed high or low cholesterol diets (though all high fat) [54]. Again, the monkeys on the low cholesterol diet became more aggressive and showed less positive social interaction.

Neurobiological mechanisms

One of the major arguments against the low cholesterol / non-illness mortality hypothesis has been its biological implausibility. However, scientists have now risen to the challenge of identifying possible mediating processes. One argument has been that lowering cholesterol could affect cell membrane composition and structure, which might in turn induce secondary alterations in membrane-bound receptor and enzyme activity, and hence influence neurotransmitters with significant emotional and behavioural effects [8, 55]. Dietary fat intake has been shown to influence brain uptake of fatty acids [56], the phospholipid composition of the neuronal cell membrane [57] and neuronal mitochondrial MAO activity [58]. Crane and Greenwood [58] failed to find evidence for concomitant effects on levels of serotonin or its metabolites,

but Mullen and Martin [59] showed that there were higher levels of serotonin in the Raphé area after consumption of a diet which was high in saturated fat than a comparable diet high in polyunsaturated fat, for as little as 4 days. In combination, these observations indicate that changes in dietary fat can affect both neuronal cell structure and neurochemical processes and hence could provide a mechanism for effects on mood.

The importance of serotonin in a range of emotional behaviours has been well-established. Serotinergic abnormalities were identified in depressed patients as long ago as 1960 [60], and this has led to the widespread use of serotonin re-uptake inhibitors in the management of depression. Low levels of serotonin have also been identified in suicidal patients [61] and aggressive offenders [62, 63]. Disturbances of serotonin function have been proposed as the underlying biological abnormality linking a range of mood-related problems and cutting across diagnostic boundaries [64]. The strong inter-relationships among diverse affective disturbances in which serotonin has been implicated in psychiatric patients support this idea [65]. A deficiency of serotinergic activity has also been proposed as the basis of the 'hostility syndrome' [45], with the particular emotional or behavioural effects depending either on the state of other neurotransmitter systems or even on the serotonin receptor subtypes which are deficient.

The strongest evidence for a link between cholesterol, serotonin and emotional behaviour comes from research on the bio-behavioural effects of cholesterol-lowering. In one study monkeys who had been on a low-fat diet were found to have reduced oxytocin release in response to a fenfluramine challenge—an index of serotonin receptor sensitivity [66]. In another study, monkeys on a low-cholesterol diet had lower levels of the serotonin metabolite 5HIAA [54]. These results suggest that there are specific effects of cholesterol-lowering on the neurotransmitters which are known to modulate emotional behaviour. There are other data on dietary restriction which have also found effects on 5HT activity [67, 68]. Low-calorie diets (25% fat for women and 35% fat for men) were shown to produce increased prolactin release in response to a tryptophan challenge in women and to have no effect in men. Although on the face of it these results appear to suggest an opposite effect, the authors have argued that there could be upregulation of the sensitivity of the 5HT pathways in response to lowered serotonin function. In view of varying characteristics of the diets and the endocrine challenges it is difficult to reach any certain conclusions, but all of these observations contribute to the recognition that brain neurochemistry is responsive to modification of diet and serum cholesterol, so the idea that behaviour could be affected is not entirely far-fetched.

CAUSAL INTERPRETATIONS

The findings linking low or lowered cholesterol with the possibility of adverse health outcomes has prompted widespread speculation over whether the effects are causal, and if so, whether alterations in emotional behaviour could play a part in the effect. Intervention studies have established that there is a case to be answered concerning the safety of cholesterol lowering and they have highlighted the need to know more about the consequences of modifying diet and lipid levels. The few lipid-lowering drug studies which have looked at emotionality have not identified any

sign of adverse effects. However, it is possible that individuals with a history of depression, or with lower than average serotonin levels, are the ones who are vulnerable to cholesterol-lowering and they may be differentially represented in different studies. The Oxford Cholesterol Pilot study, for example, excluded participants who were judged by their physician to be potential poor compliers on the basis of mental illness and these could have been the susceptible individuals [50]. This suggests that baseline measures of mood need to be included in future studies of cholesterol-lowering.

The association between low-cholesterol and mortality from suicide and accidents identified in some of the cohort studies also merits consideration. In terms of identifying causal effects, prospective epidemiological studies are in a different league from controlled trials, but the coincidence of the pattern of results is a cause for concern. One issue which needs to be resolved is the variability of the findings—why are the effects detectable in some cohorts and not detectable in other, equally large, samples? The total number of suicide deaths is small, especially among women, and so individual studies are likely to have inadequate power to detect effects if they exist. In the Whitehall follow-up for example, there were only 36 suicide deaths in a 10 year follow-up of over 17,000 men [69], and only 190 suicide deaths over the 20 year follow-up of over 50,000 men and women in the Varmland study [13]. If cholesterol levels were influencing suicide (or were a marker of an important biological change), larger samples, or, alternatively, samples of very high risk subjects, might be required to observe the effect. Another possibility, as in the intervention trials, is that there are some individuals who are vulnerable to adverse effects and these are included in some, but not others of the population samples which have been analysed. Law *et al.* [6] sub-divided the cohort studies which they reviewed into employed vs. general population samples, arguing that employed groups are likely to have fewer such vulnerable individuals. No significant hazardous effect of low cholesterol emerged in employed cohorts, giving some support to the idea of pre-existing vulnerability.

Where convincing effects have been reported in individual cohort studies, direct causal links would appear to be less plausible than associated factors which cause both low cholesterol and increased mortality. Pre-existing serious illness, particularly cancer, might be expected to lead to loss of weight and appetite and thereby lowered cholesterol, as well as increased mortality. Attempts have been made to address this concern by excluding deaths occurring shortly after (or even in the medium-term after) the cholesterol measurement. The effect of this has generally been to attenuate the adverse effect. In the analyses of the NHANES-I epidemiologic follow-up study for example, when deaths were re-evaluated for each of three separate follow-up periods (<5 yr, 5–10 yr, >10 yr) the hazard associated with low cholesterol disappeared for the longest follow-up group [70]. Excluding deaths occurring within the first 14 yr of follow-up removed the excess suicide risk in the Varmland follow up, but the total number of suicide deaths was small [13]. This effect has been widely interpreted as showing that the apparent risk of low cholesterol is related to pre-existing illness and unlikely to be a consequence of the low cholesterol [71]. The problem with excluding deaths occurring within 10 yr of what was often a single cholesterol measurement, is that it will dilute any effects—causal or otherwise, since cholesterol levels may have changed considerably in the intervening years. The force

of this argument is strengthened by the reduction in excess CVD risk in the high lipid groups after a longer follow-up [70].

Depression has been a major contender for the third variable in relation to accidental death, being well-known to be associated with suicide and assumed to be associated with low cholesterol, but the inconsistency of the results makes it difficult to draw any certain conclusions. On the basis of the evidence presented in this review, the case for a causal link between low cholesterol and depression looks weak. Both correlational and cohort studies have produced inconsistent findings and the few cholesterol-lowering intervention studies which have reported affective outcomes give no evidence for adverse effects on mood, despite substantial cholesterol-lowering.

Neurochemical studies probably offer the most interesting perspective on the effects of modification of cholesterol levels. The neurobiology of aggression and depression, and perhaps of other negative affective states, points to an important role for serotonin. Modifications of the internal milieu, including serum cholesterol levels, could affect serotonin availability or receptor responsivity, and there is enough evidence for dietary constituents affecting neurotransmitters, mood or behaviour to suggest that dietary cholesterol-lowering could affect brain neurotransmitter systems more directly.

IMPLICATIONS FOR BEHAVIOURAL SCIENCE

The controversy over the effects of low or lowered cholesterol has brought into sharp focus the necessity for a thorough examination of the psychological effects of new treatments or preventive regimens before they are introduced on a wide scale. The apparently straightforward findings that low or lowered cholesterol was protective against heart disease and that low fat diets had a cholesterol-lowering effect, was widely assumed to lead to simple recommendations concerning both management of high risk cases and public health advice. Likewise, the apparently biologically benign nature of a lower-fat diet (it is, after all, more 'natural') has been used as an argument against the need to assess the effects of the intervention on any end-point except the level of the related pathology (i.e. CVD). However, the modern western diet is so far removed from the diet for which human beings evolved, that it may not be correct to assume that a lower-fat western diet is, in all respects 'better' than a higher-fat western diet [72].

Results from the laboratory, epidemiological and clinical studies reviewed in this paper, have clearly identified a problem. Unfortunately, none of the studies quoted here were designed to address issues of the neurochemical, emotional or behavioural effects of low cholesterol. Consequently, appropriate background information is usually unavailable and many of the indicators of mood or behaviour are unsatisfactory. Studies which set out to answer the outstanding questions concerning the acute and chronic effects of cholesterol lowering are now required.

What has been highlighted in this debate is that a major change in dietary habits has been recommended in western countries in the absence of any scrutiny of the psychological, neurological or behavioural effects. At this late date, the community has been alerted to the possibility that nutrition might influence behaviour and that there are important scientific questions waiting to be answered.

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