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Cholesterol, violent death, and mental disorder

The association deserves further, specific study

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Although primary prevention studies have shown that reducing serum cholesterol concentration leads to a clear reduction in cardiac morbidity and mortality, total mortality is unaffected. The increase in deaths from accidents, violence, and suicide in the treated groups has not yet been adequately explained,[1] though an association between low cholesterol concentration and psychiatric illness has been suggested as a possible cause.[2] The finding has also been elaborated in neurobiological terms, implicating a relation between membrane cholesterol, serotonin, and impulsivity.[3]

How seriously should this association be taken? Is the apparent relation of suicidal, accidental, and violent death with low serum cholesterol concentrations a true finding or simply due to chance? The association was initially regarded as an anomalous occurrence, but it has been too consistent to be dismissed.[4] It has appeared in studies irrespective of whether drugs or diet were used to lower cholesterol concentrations. A study to examine the relation between cholesterol concentration and short term mortality from injury confirmed an inverse association in men.[5] A more recent study, published in this issue (p 445),[6] failed to replicate this finding in relation to death due to accidents and violence, but it used a relatively high cut off for a "low" cholesterol value. In a population with naturally low cholesterol concentrations (Shanghai, China) a low cholesterol concentration was significantly associated with a higher death rate from non-medical causes.[7] The findings are therefore unlikely to be due simply to chance. Furthermore, these studies support an association with low serum cholesterol concentration itself, in addition to a treatment effect.

Possible causes

Why should there be this association? A recent review of cholesterol values and mortality showed a pronounced difference between studies of employed men, presumed to be healthy at recruitment, and community studies[2]: the employed cohorts showed no excess mortality. In the community cohorts the excess mortality was explained by disease, or factors that cause disease, lowering cholesterol concentrations in a proportion of the cohorts. Depression is the main psychiatric illness that predisposes to suicide and could itself cause low cholesterol concentrations through poor diet and weight loss. This explanation would, however, require that there was a chance assignment of a higher proportion of subjects with psychiatric disorder to the intervention groups than to the control groups in all the studies, which seems unlikely. It seems equally feasible that the lowering of cholesterol concentrations caused an increase in deaths only in a population more vulnerable to psychiatric disorder and that employed cohorts are protected from this effect. There is certainly evidence that unemployment predisposes to parasuicide and psychiatric morbidity.[8]

Need to include mood ratings

Our current understanding of the relation between cholesterol metabolism and psychiatric illness is poor. Studies have examined the relation between low serum cholesterol values and psychiatric disorder. Virrkunen found an inverse association between cholesterol concentrations and antisocial personality,[9] but others have found no link with aggressive personality traits[10] or minor psychiatric disorder as defined by the general health questionnaire.[11] Studies of cholesterol concentrations among older men with depressive symptoms showed an inverse relation,[12,13] although in one study significance was lost after correction for weight loss. This supports an association between low serum cholesterol values and depressive illness but does not establish the direction of causality.

More detailed investigation will be required to elucidate the relation between cholesterol, mortality, and psychiatric illness. So far no studies have examined the effect of lowering cholesterol concentrations on mental state. Any further primary prevention studies to assess psychiatric morbidity due to low or lowered cholesterol concentrations should therefore include ratings of mood. The contribution of low cholesterol concentrations to suicide should also be addressed in more severe psychiatric illness, since as many as 10-15% of patients with schizophrenia or manic depression die by suicide.[14] Predicting the risk of suicide in psychiatrically ill patients is notoriously difficult. The possibility that a low or falling cholesterol concentration is a marker of risk merits further study. It may also contribute to an increased understanding of the underlying biochem-

istry and neuropharmacology of psychiatric disorder and suicide.

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Innovation in the pharmaceutical industry

Partnerships with outside organisations will become imperative

The pharmaceutical industry today is operating in an environment whose main feature is an unprecedented pace of change. In most markets the rising costs of health care are of increasing concern, and the medicines bill is being targeted for savings. New constraints are limiting the medicines that can be used and paid for in the system. In the United States health maintenance organisations use formularies, while European governments are resorting to various measures to control the pricing and prescribing of medicines and are increasing the range of medicines available over the counter. Medical practice is also changing for demographic reasons, and the health problems of elderly people are attracting increasing attention.

Drug regulation is both costly and time consuming, particularly in the clinical phases. Now, in addition to the stringent demands for safety and efficacy, the need to show the economic benefits of a new medicine is increasingly emphasised. Although these changes may well sink some pharmaceutical companies, they should be seen as challenges to be met to ensure the future of both the industry and the communities who benefit from its activities. Undoubtedly, the pharmaceutical industry's future success will depend on innovative medicines that meet unmet clinical needs and provide genuine therapeutic advance.

Fortunately, other rapid changes may work in the industry's favour. Advances in biotechnology and the biomedical sciences in particular are providing opportunities to discover medicines that can be targeted at disease processes with a degree of precision rarely possible before. This holds out the prospect of medicines that cure rather than palliate diseases. To make best use of these opportunities, however, the industry must change its approach to discovering drugs.

The "traditional" approach has undoubtedly been successful and provided such important classes of medicines as ß blockers, H_2 antagonists, non-steroidal anti-inflammatory drugs, and antibiotics. Essentially, this approach is based on a knowledge of physiological processes, such as the effects of adrenaline on blood vessels, and of biochemical pathways for molecules suspected of having a role in disease processes, such as the prostanoids. The discovery of medicines has primarily depended on chemical modification of natural mediators or substrates and evaluation of the modified molecule to establish its action at the receptor or enzyme. In terms of the resources needed for discovering drugs the industry was largely self sufficient and not reliant to any great extent on research done outside the companies.

During the past two decades the explosion in biological knowledge, fuelled by the rapid development of molecular and cellular biology, has opened new approaches to the discovery of medicines. These approaches are biological rather than chemical. They put us in a better position to unravel the molecular and cellular processes underlying important chronic diseases and to identify key molecules in pathways and cascades, providing targets for rational, and more precise, design and discovery of drugs. Although chronic diseases such as rheumatoid arthritis have so far defied attempts to find safe, curative medicines, these conditions may now be amenable to study with the tools provided by recombinant DNA technology, genome analysis, and non-invasive imaging techniques.

The advances being made in the understanding of cystic fibrosis are a good example of the power of these technologies to provide novel approaches to the treatment of disease. Biotechnology has shown us the molecular basis for the cellular defect in this condition and allowed the identification of the single mutant "culprit" gene and its defective gene product.[1] This opens the way, theoretically, for the normal gene to be introduced into affected human lung cells to correct the deficiency, opening up the possibility of gene therapy.[2] Clinical trials of gene therapy have started recently,[3] with at least 50 protocols for genetic diseases, including cystic fibrosis; these should define the effectiveness and value of this approach.[4]

We must be careful, however, to recognise the limitations of gene therapy: although of likely value in monogenic diseases, it may be inappropriate in diseases with a polygenic basis—which includes many chronic diseases. New technologies are also, however, providing insights into the molecular processes underlying gene regulation, which may provide routes to the treatment or prevention of diseases in which several gene products may be interacting. Use of antisense molecules, for example, may provide "gene regulating" medicines for the future.[5,6] The key to opening the door to these exciting possibilities lies in the sequencing of the human genome. The international activities in this field are expected to aid the