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Is Atherosclerosis Reversible?

The question whether atherosclerosis is reversible is important because the answer concerns the management of the patient who has angina or has had myocardial infarction. Any study of the progress of atherosclerosis in human arteries is the more difficult because biopsy of the affected vessels is impossible. For this reason the evidence for the reversibility of atherosclerosis in man is somewhat limited.

Pathologists who conducted necropsies on the inmates of concentration camps at the end of the last war observed that atherosclerosis was very mild in these grossly malnourished subjects. In a survey of prisoners in Danish concentration camps[1] not a single attack of angina pectoris was reported, though possibly this reflected both a diminution in thrombosis as well as in the severity of atherosclerosis. Studying the necropsy findings in a fairly large group of subjects, S. L. Wilens[2,3] concluded that in malnourished patients atheroma lipids can be reabsorbed but that calcification and hyalinization (sclerosis) are irreversible. Recent isotope studies in man indicate that cholesterol in the atherosclerotic artery can exchange with that in the blood.[4–6] The rate of equilibration with the blood was slower in arteries than in all other tissues examined, except brain, and the presence of atherosclerosis and masses of free lipid seemed to slow the rate of exchange still further. Nevertheless, this study shows that the cholesterol of arteries can slowly *exchange* with that in blood, though it does not necessarily imply that there is a *net transfer* of lipid from artery to blood. Taken together these observations do strongly suggest that lipids can be reabsorbed from the atherosclerotic artery. However, fibrosis or sclerosis of the intima would be expected to be irreversible because collagen is metabolically inert.[7] Fibrin on the endothelium of arteries or included within thrombus can be digested by fibrinolysin in the plasma[8] and mast cells in the adventitia of the vessel,[9,10] but no proteolytic mechanism that would remove collagenous scars is known to exist in the arterial intima.

The aim of removing lipids from atherosclerotic plaques is to reduce the size of the lesion, enlarge the lumen of the artery, and remove an important cause of further sclerosis—namely, the deposition of cholesterol.[11–13] The question that now arises is how to remove atheroma lipids. The observations on malnourished subjects indicate that severe dietary restriction would result in a satisfactory reabsorption of them. But these measures would be exceedingly unpleasant, would prove impracticable with most patients, and could possibly be dangerous. Hypocholesterolaemic agents do not improve the prognosis after myocardial infarction[14]—though the effect in this respect of the hypocholesterolaemic drugs Atromid S (clofibrate) and Atromid (androsterone and ethyl-α-*p*-chlorophenoxyisobutyrate)[15,16] is not known. One reason for this failure of hypocholesterolaemic agents may be that moderate reduction in the levels of cholesterol and triglycerides in the serum is not sufficiently drastic for proper mobilization of these lipids from arteries that are already

severely atherosclerotic and thrombosed. It is of interest that Atromid given to rabbits with induced atheroma lowers the level of cholesterol in the serum, but has no effect on either fibrous or fatty aortic lesions.[17]

Studies of the effect of the non-ionic detergents (Tweens and Tritons) on atheroma induced in animals with cholesterol show that these compounds increase the capacity of the plasma to bind lipid and prevent the formation of atheroma.[18–20] However, these same compounds may cause lipid to be deposited in the renal tubule[19] and reticulo-endothelial system.[19 21] They also provoke spontaneous atherosclerosis in the dog.[21] Hence they are probably both unsuitable and too dangerous for use in man.

The detergent or surface-active properties of phospholipids[23] disperse cholesterol and other hydrophobic lipids in the cell[24] and appear to displace cholesterol and triglycerides from the tissue into the plasma.[25] Thus, phospholipid mobilizes cholesterol,[13] stabilizes the suspension of cholesterol in the blood,[26] and reduces the amount of lipid deposited in the aortas of rabbits with atheroma produced by a diet rich in cholesterol.[27] Furthermore, the macrophages[28] and other cells in the arterial wall[29] respond to infiltration with cholesterol by synthesizing phospholipid—presumably in an attempt to disperse it. It is tempting to speculate whether infusion of phospholipid may eventually prove to be of some value in human atherosclerosis, but at present too little is known about its effects on arteries and other tissues.

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Leprosy To-day

Leprosy has been known almost throughout the history of man. The human leprosy bacillus (*Mycobacterium leprae*) was the first bacterium to be identified under the microscope as the cause of disease in man, by Hansen in 1874. Leprosy has always been one of the most feared diseases affecting man and has been associated with age-old stigmata. Nevertheless, the successful treatment of this hitherto incurable disease became possible in 1943[1] with the introduction of the sulphones and in particular 4-4'diaminodiphenyl sulphone (Dapsone). Subsequently it has been shown that Dapsone can cure all types of leprosy, and in fact none of the newer anti-leprosy drugs is obviously superior. Though no longer an important disease in Northern or Southern temperate zones, leprosy is still a major health problem in the tropical and sub-tropical countries, particularly in Africa, South Asia including India, Malaya, and Burma, and South America. Recent estimates suggest that there are at least 12 to 15 million cases and the world figures are still rising. About a quarter of the patients are to be found in countries of the British Commonwealth, and one-quarter of all cases are in children.

Though not a killing disease, leprosy causes considerable suffering in patients with established infection from lesions of nerves, which produce severe deformities, particularly of the feet and hands.[2] The World Health Organization[3] estimates that at least one-quarter of leprosy patients have some degree of deformity, and probably not more than a fifth of the world's patients are receiving adequate treatment.[2] And where Government- or voluntary-supported organizations have set up schemes to control leprosy the services have often been poorly balanced and inadequate because of the failure to carry out detailed surveys of the problem. Why has there been so little progress towards the eradication of leprosy when a reasonably active—and, incidentally, very cheap—drug has been available for the last 20 years ? There are three main reasons. First, in many parts of the world horror of the disease is still so strongly ingrained that patients prefer to hide it than to come forward spontaneously for treatment. Secondly, this same attitude seems also to have influenced many medical and public health authorities, since they have often failed to apply to leprosy the general principles used to combat other infectious diseases, and nearly everywhere too much emphasis has been laid on isolating patients in settlements or leprosaria. Though patients in leprosaria receive adequate treatment with Dapsone and respond well, they fear being isolated in them. Thirdly, while the more liberal, so-called mass-treatment schemes based on ambulatory treatment given by the general dispensaries or by special leprosy-treatment centres have been more successful in curing a larger proportion of the patients, the centres are usually so scattered that the patients have to walk very long distances to obtain their treatment. This leads to appallingly high rates of default after the first rush of enthusiasm or the initial improvement. Like all chronic infections leprosy presents the special difficulty of how to ensure that the patient continues to take his drug regularly and in the correct dosage over a long period.

Until recently little fundamental or applied research on leprosy has been carried out in the laboratory. Thus, though *Myco. leprae* was identified 80 years ago, it has still not yet been grown *in vitro*, and until recently no infection had been transmitted to animals. Fortunately this frustrating situation has been successfully challenged, and in the last five years direct and indirect approaches have led to important advances. First, a Medical Research Council group at the National Institute for Medical Research in London showed, using the rat leprosy bacillus,[4] that in the electron microscope it is possible to distinguish living from dead