Platelets, Aspirin and Cardiovascular Disease

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One of the main contributions epidemiologists have made to research on cardiovascular disease is the development of the concept of 'risk factors'; that is, factors such as blood pressure, serum cholesterol, smoking habit, etc., which show a statistical association with manifestations of the disease. At present, more than 25 such factors have been identified but probably too much effort has gone into their identification and too little into testing the nature of their associations by intervention trials. At the same time, it must be conceded that while the detection of risk factors is difficult enough, requiring the surveillance of perhaps thousands of subjects, intervention trials are vastly more difficult to conduct.

The concept of risk factors has been valuable but limitations are becoming more and more obvious (Grundy, 1973). What is needed now is not the identification of yet more, there is already a confusing enough array, but a knowledge of mechanisms in cardiovascular disease so that sense can be made of the known risk factors. A better understanding of the pathological processes involved would enable factors that are causal, or potentiating, to be identified and the effect of their modification evaluated with reference to a relevant mechanism.

One of the more fundamental limitations in the epidemiological approach of linking risk factors to manifestations of cardiovascular disease is that it involves the confounding of several different pathological processes. Almost certainly the mechanisms that lead to angina are distinct from those involved in myocardial fibrillation, or intravascular thrombosis, and each mechanism will have its own causal and potentiating factors. Yet, in surveillance studies of population groups it is impossible to separate the different end results of cardiovascular disease with any certainty. Thus, sudden death may result from ventricular fibrillation or from myocardial infarction, which, in turn, may or may not follow coronary thrombosis. Angina, on the other hand, may follow an infarct or may simply arise as a consequence of atherosclerosis. At present, therefore, it is only possible to consider risk factors as a general group statistically associated with a heterogeneous group of manifestations of cardiovascular disease.

At present there is little understanding of any of the pathological processes involved in cardiovascular disease other than some of the mechanisms involved in intravascular thrombosis. Great interest is focused on platelets, as these appear to play a key role, and indeed the whole process of thrombosis may be initiated by the aggregation of platelets; hence, the interest of epidemiologists in platelet
function. If platelet aggregation were identified with certainty as a mechanism in cardiovascular disease, tests of platelet function could be used as 'tools' in epidemiological studies and certain risk factors could be identified and evaluated with much greater ease than is possible at present.

Evidence that platelet aggregation is a key factor in thrombosis is certainly not conclusive, but it is highly suggestive and is growing rapidly. Case-control studies of patients who have had a myocardial infarct have demonstrated enhanced aggregation (Dreyfuss and Zahavi, 1973). In post-infarction patients, the greater the enhancement of aggregation the greater the risk of mortality during the next six months (Elwood and Rees, unpublished).

Several drugs are known to affect platelet aggregation, and the one on which most attention is at present focused is aspirin. After a single small dose of aspirin marked changes in platelet aggregation occur. In particular, the response to collagen is abolished (Davies et al., 1968) and in some subjects the response to ADP is modified. It is not unreasonable therefore to predict that a drug such as aspirin will, by modifying platelet function, reduce a subject's risk of a thrombo-embolic episode. Several studies have, in fact, been conducted to test this prediction.

The Boston Collaborative Drug Surveillance Group are conducting a large trial in which patients in 24 hospitals are questioned about drugs they took during the week prior to admission. This information is linked with the eventual diagnoses, and significant positive, or negative, associations identified. This approach has disclosed a marked negative association between aspirin-taking and a diagnosis of myocardial infarction (Boston Collaborative Drug Surveillance Group, 1974). On the other hand, a prospective study of possible aetiological factors in breast cancer, based on over one million women, gave no evidence of any reduced incidence of myocardial infarction in subjects who, at the time of the initial survey, stated that they were taking aspirin regularly (Hammond and Garfinkel, 1975).

Both these studies can be criticised on methodological grounds. However, the authors do consider certain limitations in their approach and recognise that there is no adequate substitute for randomised controlled trials. It is essential that in this kind of situation adequate trials are conducted at an early stage before a new treatment passes into widespread use, otherwise work which will generate valid evidence, and which will of necessity require the withholding of the treatment from some patients, will be unacceptable.

Numerous experimental studies have yielded suggestive results but these have been based on animals, or have been small scale laboratory or clinical studies. Much of this evidence has been reviewed by Hirsh et al. (1975). In the main, these studies have been based on drugs that inhibit platelet aggregation, such as aspirin, dipyridamole and sulphinpyrazone. A reduced incidence of thrombosis by all these three drugs has been demonstrated in extra-corporeal shunts in animals.
Patients with prosthetic heart valves, or prosthetic arterial grafts show a decreased platelet survival time, presumably due to consumption of platelets in interactions with the prosthetic surface, which can be restored to normal by dipyridamole. The incidence of thrombocytopenia in patients undergoing haemodialysis is reduced by aspirin. Finally, there is suggestive evidence of benefit from platelet active drugs in patients with transient cerebral ischaemic attacks and in patients with amaurosis fugax, in both of which conditions platelet emboli probably play a causal role.

However, the field of potential use of anti-platelet drugs of greatest interest is coronary thrombosis. While it is argued that thrombosis does not always precede infarction, it is reasonable to predict that an anti-platelet drug would be of value in the prevention of myocardial infarction. Furthermore, evidence has been presented (Haerem, 1974) indicating that platelet aggregates in the micro-circulation may be of relevance in cases of sudden death without infarction.

As yet no adequate trial of an anti-platelet drug in myocardial infarction has been reported. However, there is suggestive evidence from randomised controlled trials. Blakeley and Gent (1975) have reported a trial conducted in 291 institutionalised elderly males given sulphinpyrazone or a placebo over four years. There was no evidence of any reduction in total mortality but re-examination of the results suggested that there may have been a reduction in deaths from vascular causes in men who had previously had a myocardial infarct or a cerebrovascular accident. As this further evidence arose from repeated examination of the data it cannot be accepted as conclusive, whatever the level of statistical significance.

A large randomised controlled trial, set up to test the reduction by aspirin of mortality in myocardial infarction has been reported (Elwood et al., 1974). Over 1,000 patients, discharged from hospitals in South Wales and other selected areas after a myocardial infarct, were kept on specially prepared capsules (acetyl salicylic acid 300 mg once a day, or a matching placebo) for up to two years. The results were consistent with an overall protective effect of aspirin equivalent to a reduction of about 25 per cent in total mortality. Approximately 8 per cent of those on aspirin died during the year as opposed to about 11 per cent in the control group. However, this difference is not statistically significant at \( P < 0.05 \) using a two-tailed test of significance, and furthermore, there were certain inconsistencies in the data that prevented the drawing of firm conclusions.

It is important that further work is done, and trials of aspirin and other platelet active drugs are in progress in Cardiff, in the U.S.A. and in Germany. A fairly conclusive answer should therefore become available within the next few years as to whether or not these drugs do reduce mortality in patients who have had a myocardial infarct.

The answer from these trials will strictly relate only to patients who have already had a myocardial infarct. Prevention of a first infarct may not necessarily follow a simple alteration in platelet function by aspirin and it will be a vast task
to evaluate primary prevention. Similarly, the role of platelets, and hence the place of anti-platelet drugs in cerebral thrombosis, is as yet unknown but a small trial by Heikinheimo and Jarvinen (1971) has given no encouragement.

A most exciting situation will develop if anti-platelet drugs are shown to be prophylactic in thrombo-embolic conditions. Some of this excitement will arise because of the further indirect evidence that platelet function is a key factor in intravascular thrombosis. Further cardiovascular research, not least epidemiological, will then focus on the platelet. Risk factors will then be identified with relative ease, and preliminary evaluation of their alteration, in relation to a defined mechanism, will be a fairly simple matter.

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SOFTLY, SOFTLY
Theodore de Mayerne was a sort of royal medical version of the vicar of Bray. Appointed physician to James I in 1611, he was invited to become a Fellow of the College in 1616. His art lay in keeping governments happy by maintaining a low personal profile. To be granted exemption from taxes by James and Charles I and to have the exemption renewed by Cromwell was a feat achieved by 'keeping the mouth shut and ears long and wide'. Mayerne was game for anything. In a letter to Lord Conway detailing treatment for his Lordship's gravel, he managed to include advice on treating a sick horse and a recipe for red ink. He was a big fat man with a fine sense of business. He petitioned Charles I for a patent to lay his own oyster beds, on the grounds that foreigners were buying up the best and leaving the worst. The petition failed on the advice of the Lords of the Admiralty who opined that 'if the beds are open freely to fishermen, it is a good charity, but if there be property in them the grant would wrong either the lords and owners of the creeks or the fishermen'. Obesity did not trouble Mayerne as he wrote to a friend, 'I have seen the prescription you sent me for curing fat people; it is not bad and can be taken without danger... but I shall never use it, having long recognised that a wicked soul never or rarely dwells in a fat body'.