Editorial

Thrombosis and ischaemic heart disease

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Indexes of the abstracts for cardiology meetings usually show considerable preoccupation with the ischaemic myocardium and its electrical difficulties, some concern over atheroma, and very little interest in thrombosis. In terms of pathogenesis and in many respects from the therapeutic standpoint as well, may this not be a case of putting the cart before the horse?

Thrombosis in myocardial infarction and sudden death

The overwhelming dominance of the lipid hypothesis for atheroma has obscured the compelling evidence—some of it of many years standing¹ but some that is more recent^{2,3}—that both platelets and the coagulation system also contribute to the lesion. There is much epidemiological evidence^{4,5} of some other process besides atherogenesis to account for the clinical manifestations of coronary artery disease. Surprisingly late in the day, and despite the use for many years of the term coronary thrombosis, it became generally accepted that recent thrombus is usually to be found in fatal myocardial infarction and that the first is the precipitating cause of the second. "Recent" should include what may have happened within the preceding days⁶ as well as the preceding hours or minutes. Sudden death, though, is not a thrombotic event—or so we have been led to believe for this assertion has been the Seattle study, in which only 16% of those resuscitated after sudden death showed classical signs of myocardial infarction subsequently.⁷ Nevertheless, two other studies, much less often cited, gave figures of 39%⁸ and 44%.⁹ It is hardly surprising that those who have "died suddenly" once should be at high risk of doing so again, an observation which probably tells us more about the consequences than the causes of the initial event. It is,

of course, quite possible that the processes involved in a first major episode of ischaemic heart disease may differ from those responsible for recurrences once conducting pathways or myocardium have been compromised. Antithrombotic drugs will be of limited value (which does not mean they will be of no value) in these circumstances compared with those where an initial thrombosis or rethrombosis is the major hazard. Assertions that coronary thrombi are not found in sudden death are also the result of a rather oversimplified citation of published reports. Thus a study quite often said (not by its authors) to have shown no thrombi in sudden death actually established that they were present in about 30% of cases.¹⁰ In any case, an inability readily to detect a thrombus in sudden coronary death does not necessarily mean that thrombosis did not occur. The intense fibrinolytic activity of blood in sudden death (from a variety of causes) has been appreciated for many years so that recent thrombi leading to sudden death may not subsequently be easily identifiable at necropsy.¹¹ Be that as it may, perhaps the most careful of the necropsy studies has shown intraluminal thrombi in 74% of those in whom sudden cardiac ischaemic death occurred compared with none of those dying suddenly from other causes.¹² Corresponding figures for intraintimal thrombus were 21% and 10.2%. It may be a question of whether it is the blood supply to conducting tissue or to the myocardium that is mainly affected by the evolving thrombus that determines whether sudden death or myocardial infarction occurs. The theoretical desirability of forestalling plaque rupture or haemorrhage as frequent causes of thrombosis is not yet matched by practical methods for doing so. Attention at this stage of pathogenesis therefore inevitably has to focus on modifying the thrombotic process itself.

Modifying the thrombotic process

If, then, there is a major thrombotic element in both myocardial infarction and sudden coronary death, how can it best be prevented? The Dutch Sixty-Plus

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trial assessed the effects of discontinuing rather than initiating treatment with anticoagulants.¹³ None the less, with its striking results in favour of continuation this trial makes a re-evaluation of anticoagulants essential and reopens the question as to which part of the thrombotic process—platelet activity or coagulation—is mainly involved. So far as the secondary prevention of infarction is concerned, anticoagulants may be more effective than aspirin not only in reducing the risk of death^{14 15} but, in particular, in forestalling thromboembolic events, including reinfarction, where benefits of 50% or over have been found.^{13 16 17} A possible explanation lies in the effects of anticoagulants on the production of thrombin, which is a potent platelet aggregating agent as well as being responsible for the production of fibrin. We do not yet have information about antithrombotic agents in primary prevention where, if both infarction and sudden death are indeed substantially thrombotic, their potential may be very considerable. If so, it is at least arguable—and only the appropriate trials will settle the point—that modifying the capacity for producing thrombin may be more effective in primary prevention than the use of aspirin, which will inhibit neither thrombin induced platelet aggregation nor the production of fibrin. What, on the other hand, should we make of the striking benefit apparently conferred by conventional dose aspirin on those with unstable angina?¹⁸ May it be that the pathogenesis of infarction in unstable angina differs from that after a previous infarction, with platelet activity contributing predominantly in the former case and less in the latter? There is some evidence that may support this view.¹⁹ How, also, does the low dose aspirin hypothesis now stand in the light of the findings of the unstable angina trial?

The haemostatic system

To many, thrombosis seems a purely structural event—mere plumbing, perhaps, compared with what are seen as its more intriguing functional consequences for the conducting system and myocardium. This is to undervalue not only the clinical importance of thrombosis but also the scientific interest provided by the study of the haemostatic system. The processes that lead to the production and removal of fibrin under both physiological and pathological circumstances are among the most complex in the body. In his early account of the coagulation cascade Macfarlane proposed that its intricate and self-amplifying nature is the result of the natural selection of increasingly efficient biological mechanisms for the sudden conversion of fibrinogen to fibrin.²⁰ The question is whether some stimuli (smoking or obesity, for example) may increase the risk of “haemostasis in the

wrong place,” to use Macfarlane’s shorthand description of thrombosis.²¹ Some argue that since clotting factors are mostly present in considerable excess anyway, high concentrations are unlikely to be involved in thrombogenesis. This argument is, however, surely only logical in terms of their physiological function—the control of bleeding. A minimum level of blood pressure is required to ensure an adequate circulation, but there is no dispute that raised levels have undesirable consequences. Why, in principle, should the same not be true of some of the clotting factors? Three examples are worth considering in this light.

Factor VII occupies a key position in the extrinsic system, and, on the cascade model, quite small increases in activity might be expected to have substantial effects on the potential for thrombin production, particularly as the extrinsic system is, at best, poorly counterbalanced by antithrombin activity. It now seems increasingly likely that factor VII activity is an index of coagulability if not also a contributor to the degree of this coagulability.²² The general epidemiology of factor VII activity is consistent with the hypothesis that high concentrations are of pathogenetic significance—for example, high concentrations are found in oral contraceptive usage, after the menopause, in obesity, in diabetes, and with increasing age. Prospectively, high concentrations are associated with an increased risk of death from ischaemic heart disease.²³ Nor does there have to be any continued polarisation between the lipid and thrombotic hypotheses for ischaemic heart disease so far as factor VII may be involved, since it is also likely that lipids are one of the determinants of factor VII activity.²²

A second component, already referred to, is thrombin. The presence of fibrin in arterial wall lesions³ establishes that intravascular thrombin production occurs. The ability to detect and measure thrombin production is limited since its half life is so momentary. Practicable if indirect methods are, however, now available, including the radioimmunoassay of fibrinopeptide A, the initial cleavage product of the thrombin proteolysis of fibrinogen. The use of this assay is beginning to confirm and characterise the crucial role that thrombin may play in the pathogenesis of ischaemic heart disease. Thus, *in vitro*, an increase in factor VII activity is remarkably closely paralleled by an increase in fibrinopeptide A.²⁴

A third component of the coagulation system whose importance is now increasingly recognised is fibrinogen, which has effects other than its obvious involvement in the production of fibrin. It is a cofactor in platelet aggregation^{25 26} and increases blood viscosity both in cellular and plasma terms and thus, very probably, the risk of coronary artery disease.²⁷ At p 483 in this issue Yarnell and his colleagues

describe the cross sectional associations between fibrinogen and other indices of ischaemic heart disease risk in their South Wales population. They point out that their results are compatible with the concept of a "hypercoagulable state" whose definition may be improved by the heparin-thrombin clotting time. In due course, prospective data will also be available from the South Wales group. In the three incidence studies that have so far been reported, high concentrations of fibrinogen have been associated with increased risks of ischaemic heart disease, strongly in two from the United Kingdom^{23 28} and convincingly though not as strongly as for cerebrovascular disease in a Swedish study.²⁹ Just how striking this association may be is indicated by the distinct possibility that the fibrinogen concentration has the edge over age²⁸ in multivariate analyses of the risk of ischaemic heart disease. In view of the several effects that high fibrinogen concentrations may exert, it remains a question of perhaps secondary importance as to whether these concentrations are simply a marker of underlying vessel wall damage or the result of genetic and environmental influences. The development and evaluation of acceptable agents for lowering plasma fibrinogen concentrations are now of considerable importance. Stanazolol is an example, though since it is an anabolic steroid its widespread use is unlikely.

Perhaps because of its particular complexity, the haemostatic system has tempted many to try to work out its contribution to ischaemic heart disease by theory rather than fact. Nowhere has this recently been more apparent than in the low dose aspirin hypothesis for differentially modifying thromboxane and prostacyclin production. The studies that have been undertaken have in general only extended the hypothesis—they have not convincingly confirmed or refuted it. Not only is the "right" dose still undefined but the relevance of thromboxane and prostacyclin to the vessel wall under other than exceptional circumstances is being questioned. But no one knows for certain. The thrombogenic effects of changes in fatty acid intake and metabolism currently run the risk of being decided more on theoretical than experimental grounds, though it is not too late to forestall this. The crucial evidence, usually, will be what happens in man under conditions that are not grossly artificial. As often as not, this means randomised controlled trials. The fact that these may be long and often difficult is a poor argument against doing them.

Conclusions

If there were no atheroma there would be virtually no ischaemic heart disease. To the extent that the prevention of clinical ischaemic heart disease in developed, and developing, communities can realisti-

cally be attempted through the prevention or regression of atheroma, further work in this field may be justified. The effects of coronary occlusion on electrical and myocardial function vary from patient to patient, so for this and many other reasons the study of the functional consequences of thrombosis in both pathophysiological and clinical terms must continue. Clearly, appreciating and understanding thrombogenesis is not the whole story. At the same time, there is now a robust hypothesis that thrombogenesis does play a central part in ischaemic heart disease not only as one of the acute or subacute complications of atheroma but also, much more chronically, in the initial development of the atheromatous lesion. It is quite conceivable that the significance of thrombosis as an initiating or aggravating process differs between first and recurrent episodes and that the relative contributions of platelets and fibrin formation vary from one set of circumstances to another. These possibilities and the hints that suggest them are surely additional reasons for not side stepping an issue which, controversial and complex though it may be, needs to be clarified in the interests of both the prevention and management of ischaemic heart disease.

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