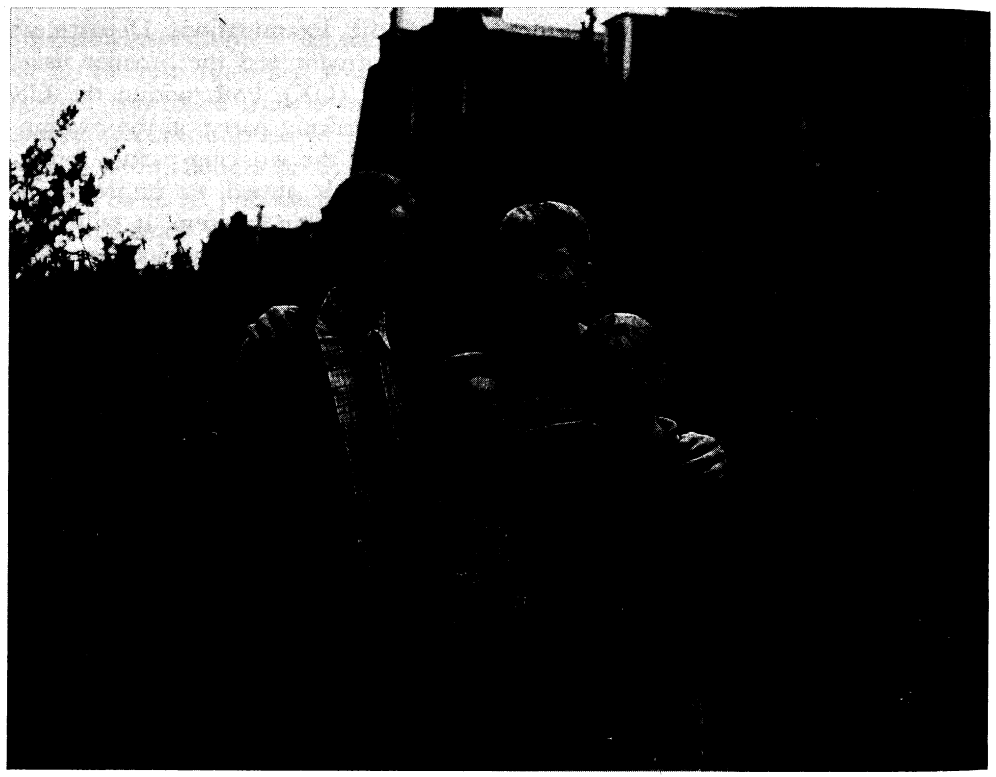
When Gordon was an honours student in physiology, one of the staff, David Bell, took him, myself and my undergraduate son to play on the old course at St Andrews and afterwards entertained us in the Royal and Ancient club house. This was a memorable day. The day before he left for Paphos, Gordon told me that he had arranged another match against my son and I, this time at his beloved Luffness with Tony Toft as his partner.

Hector Chawla writes: Gordon's friendship was special to me. It began with a tarsal cyst, blossomed at Luffness and survived partnership in the winter foursomes. I remember him for a gauntness that defied the consumption of more butter than seemed politically correct, for the reek of bogie roll and paraffin when he set fire to his pipe, for a majestic triumph over adversity and for his unique blend of trenchant wit, perception and compassion. A man of quality.



With all his professional achievement Gordon remained devoted to his local church, of which he was an elder, and was deeply attached to his family. His many friends are shattered by our personal loss, as well as by the loss to medicine and society. We feel very deeply for his wife, a GP, who has given him such wonderful support over the years, and for his three children to whom he was so close. They can indeed by proud of a man who has given so much, and in so many ways, over his all too short life.

JOHN CROFTON

ANTITHROMBOTIC STRATEGIES IN THE MANAGEMENT OF ACUTE MYOCARDIAL ISCHAEMIA AND THE PREVENTION OF ITS RECURRENCE*

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Coronary atherosclerosis an insidious disease of unknown cause is highly culture and race related. It is a slowly progressive disorder which is silent for many years and can only be diagnosed non-invasively by electrocardiography or scintiography at rest or during exercise. Coronary collaterals can be recruited by asymptomatic ischaemia, severe coronary arterial stenosis may be asymptomatic due to extensive collateral circulation. Also myocardial infarction can be silent or accompanied by non-specific symptoms. Therefore the first manifestations of ischaemic heart disease can be misdiagnosed, and the ultimate manifestation, sudden death, may be the first and also the last symptom.

First symptoms of ischaemic heart disease

Ischaemic heart disease becomes symptomatic, when the impediment to coronary blood flow results in a dysbalance between oxygen demand and oxygen delivery in the myocardium. The symptoms so induced include chest pain, arrhythmia and heart failure. This condition can be complicated by superimposed acute occlusion of an already narrowed coronary artery resulting in persisting myocardial ischaemia and eventually in infarction, the size of which depends on the presence or absence of the collateral circulation. Otherwise, coronary atherosclerosis is a relatively benign disorder whose symptoms can be easily managed.

In general, the first manifestations of ischaemic heart disease are angina, stable or unstable, and acute myocardial infarction. In many patients the first signs and symptoms are insidious and a clinical picture of stable angina pectoris evolves. However, in a considerable number of patients the initial signs are sudden, rapidly progressive angina pectoris, acute myocardial infarction or sudden death. The pathogenic mechanisms differ between the two groups. With slowly progressive signs the progress of atherosclerosis is the basis for the symptoms, whereas with unstable or acute ischaemic syndromes, thrombosis on an atherosclerotic plaque is the final pathway to symptomatic ischaemia. These considerations are important in the selection of appropriate measures for the primary and secondary prevention of ischaemic heart disease.

The slow phase of ischaemic heart disease

The process of atherosclerosis has been extensively described, although causative mechanisms are almost unknown. The first event is ulceration of the endothelium, which exposes subintimal collagen-like material to the bloodstream. The stimuli that lead to endothelial ulceration are unknown; arterial bifurcations are prone to endothelial loss, especially in the presence of elevated blood pressure.

*A Sydney Watson Smith Lecture delivered at the Symposium on *Cardiology* held in the College on 30 November/1 December 1995.

Platelet aggregates cover up the defect and platelet derived growth factor, dissipated from the aggregated platelets, induces proliferation of subintimal smooth muscle cells. During this process the defect is often covered again with endothelium which, however, does not function efficiently for some time. This endothelial injury/repair theory is widely accepted as the initial mechanism. For unknown reasons the thickened intima is invaded by macrophages which become loaded with low density lipoprotein (LDL) cholesterol particles and are called 'foam cells' because of their histological appearance. The foam cells eventually perish and in old atherosclerotic plaques cholesterol crystals and dystrophic calcification are the remains of this very slowly progressive process.

The rapid phase of ischaemic heart disease

In and around atherosclerotic plaques thrombosis can occur. Plaque rupture exposes subintimal material to the haemostatic constituents of the blood; platelet aggregation occurs and initiates intra-arterial thrombosis.[2] However hypercoagulability of the blood, especially seen in smokers and users of oral contraceptives,[3] might also be responsible for the acute thrombotic events in a narrowed coronary vessel. Inhibition of the natural plasminogen activation induces this hypercoagulability and may cause massive myocardial infarction even in angiographically normal coronary arteries.[4] Plasminogen activation follows a circadian rhythm with a dip in the early morning hours, the time when the incidence of acute myocardial infarction, sudden death and stroke is highest.

Acute coronary thrombosis constitutes the rapid phase of ischaemic heart disease and is considered 'malignant'. If the thrombus is not occlusive a clinical picture such as unstable angina develops but when the thrombus is completely occlusive, a myocardial infarction occurs, especially in the absence of an efficient coronary collateral circulation which is likely if the existing coronary stenosis was not severe. When the thrombotic coronary occlusion is proximal, a large infarction can occur with disastrous consequences: sudden death, aneurysm formation and impending pump failure. There is probably a third form of coronary thrombosis when an ulcerated coronary artery plaque releases micro-emboli, which clog peripheral arterioles causing islands of myocardial ischaemia. This form of patch myocardial ischaemia may cause malignant ventricular arrhythmia and, in patients who died suddenly and unexpectedly, these emboli have been found in the absence of significant stenotic coronary artery disease.[5]

Treatment of the rapid phase of ischaemic heart disease

Thrombolysis. Acute myocardial infarction follows a thrombotic occlusion of a major epicardial coronary artery,[6] with the downstream myocardium becoming ischaemic and eventually necrotic. Any restoration of coronary flows salvages myocardial cells whose viability is better the shorter the duration of ischaemia. Thrombolytic therapy produces coronary reperfusion which improves residual left ventricular function with a direct impact on hospital and follow-up mortality.[7,8] The earlier thrombolysis is instituted, the better is the effect on outcome. The value of early coronary reperfusion is widely accepted, but many questions still remain unanswered about pharmacological and logistic aspects of this therapy.

The aim of thrombolytic therapy is to produce coronary reperfusion as early, as prolonged as possible. Thus the time interval between first symptoms and the reperfusion is critical. This depends on the patient and the thrombolytic agents used and only the latter can be influenced by the attending physician. Recombinant tissue plasminogen activator (r-TPA) has been shown to unblock coronary arteries earlier and in more patients than streptokinase, resulting in a better outcome for the patients treated with r-TPA.[9,10]

The second important aspect of any interventional strategy is to keep the recanalized vessel open. Aspirin started immediately after thrombolytic therapy prevents re-occlusion[11] and an improved clinical outcome.[12] Heparin also improves vessel patency after thrombolysis with r-TPA[13–15] and indeed the best thrombolytic results in terms of survival are achieved with rapid infusion of r-TPA followed by full heparinization.[9] The effectiveness of intravenous compared with subcutaneous heparin after streptokinase was addressed in the GUSTO study and was not shown to be significantly more beneficial in terms of clinical outcome. Finally, the duration of heparin therapy after thrombolysis can be as short as 24 hours.[16] The logical follow-up treatment after heparin therapy is stopped would be the institution of oral anticoagulation, but this has not yet been fully investigated. It is interesting that aspirin was clinically, but not angiographically, superior to coumadin[17] in the prevention of re-occlusion after coronary thrombolysis.

There are newer antithrombotic drugs like hirudin (a highly specific antithrombin agent), the selective thromboxane receptor blockers, and the platelet glycoprotein IIB/IIIA receptor antagonists and these new but expensive agents are being compared with the accepted regimens of aspirin and, possibly, heparin.

Mechanical preservation of the patency of the occluded vessels after successful thrombolysis has not been shown to improve clinical outcome.[18] In some studies percutaneous transluminal coronary angioplasty (PTCA) had an adverse effect on re-occlusion and recurrent myocardial ischaemia and thus routine PTCA after coronary thrombolysis is not advisable. Coronary artery surgery is very invasive and expensive and its use after successful coronary thrombolysis has not been studied and is not advised.

Optimization of therapy should include optimization of safety. Thrombolytic agents used for the treatment of acute myocardial infarction are not safe. It was feared that early coronary reperfusion might produce malignant arrhythmia, haemorrhagic infarction or cardiac rupture but in fact these complications are less frequent in the era of thrombolytic therapy. Bleeding is the major risk of thrombolytic therapy. While gastrointestinal haemorrhage and bleeding at the site of intra-arterial instrumentation[19] are not usually life-threatening and are easily managed, cerebral bleeding which occurs in between 0·5% (streptokinase) and 0·7% (TPA) of all patients treated,[9] is often fatal and remains the main drawback of the therapy. Nevertheless the benefits on outcome are so overwhelming, that they outweigh the risks.

It is still unclear how thrombolytic therapy causes cerebral bleeding. Apparently, useful clots in the cerebral circulation, probably not much different from coronary thrombi, are lysed by the thrombolytic agent. Cerebral bleeding is not due to the systemic fibrinogenolysis, which is much less drastic with the use of r-TPA.[20] Interestingly, the second generation thrombolytic agents were designed to prevent this catastrophic complication, but their use has increased the incidence of haemorrhagic stroke. One of the major aims of improving thrombolytic therapy must be the prevention of cerebral bleeding. However, the mechanisms of this complication must be studied more extensively before a novel therapeutic approach can be advised.

Primary angioplasty. Although thrombolytic therapy for acute myocardial infarction is relatively inexpensive and widely applicable, it is only successful in restoring full patency in about 50% of patients, and is accompanied by a low, but significant risk of very severe side effects. Acute percutaneous transluminal coronary angioplasty (PTCA), as an alternative to thrombolysis, circumvents the cost and risk of thrombolytic therapy, and may restore effective patency in nearly 90% of cases. Recent data from randomised trials comparing acute PTCA versus thrombolytic therapy are highly promising.[21-23] Acute PTCA is however expensive, needs a very costly infrastructure and is therefore not widely applicable or available.

Other anti-thrombotic strategies. Unstable angina pectoris, being the most frequent first acute manifestation of ischaemic heart disease, is best treated with antithrombotic drugs like aspirin and heparin.[24-27] Thrombolysis in these patients is probably ineffective and may even be dangerous (TIMI-IIB). Aspirin treatment is therefore mandatory in all patients presenting with acute myocardial infarction whether or not treated with thrombolysis.[28]

Prevention of recurrence

As stated above, in many patients the first symptoms of ischaemic heart disease are not primarily due to the 'slow phase' of the disease i.e. the coronary atherosclerosis, but to acute thrombotic complications of this phase. The primary treatment of those patients should therefore be directed towards lysis and prevention of further clot formation within the coronary arteries. Antiplatelet therapy, after the acute episode of unstable angina pectoris, reduces the occurrence of myocardial infarction and death by 50% during the first two years. Both antiplatelet and oral anticoagulant drugs reduce mortality during and after myocardial infarction[28-30] mainly in the first 3 months after infarction; this highlights their influence on the rapid phase of ischaemic heart disease. Many complications of myocardial infarction in the acute, subacute and chronic phase are thrombotic in origin and can be effective prevented by antithrombotic therapy. Other treatment modalities against the rapid phase of ischaemic heart disease like coronary angioplasty or coronary bypass surgery as a routine have not improved prognosis.[31]

CONCLUSIONS

Coronary atherosclerosis is insidious and slow and only gives rise to symptoms after several years. Coronary-associated syndromes such as unstable angina pectoris and acute myocardial infarction should be treated aggressively with antithrombotic drugs during the acute phase. The optimal thrombolytic therapy for acute myocardial infarction is early thrombolytic therapy followed by immediate administration of aspirin and possibly, heparin. Search should be aimed at finding other thrombolytic agents that increase the rate and the speed of recanalization, and lower the rate of re-occlusion and the incidence of cerebral bleeding.

After the acute episode these patients should be protected against the acute manifestations of the disease with antithrombotic drugs.

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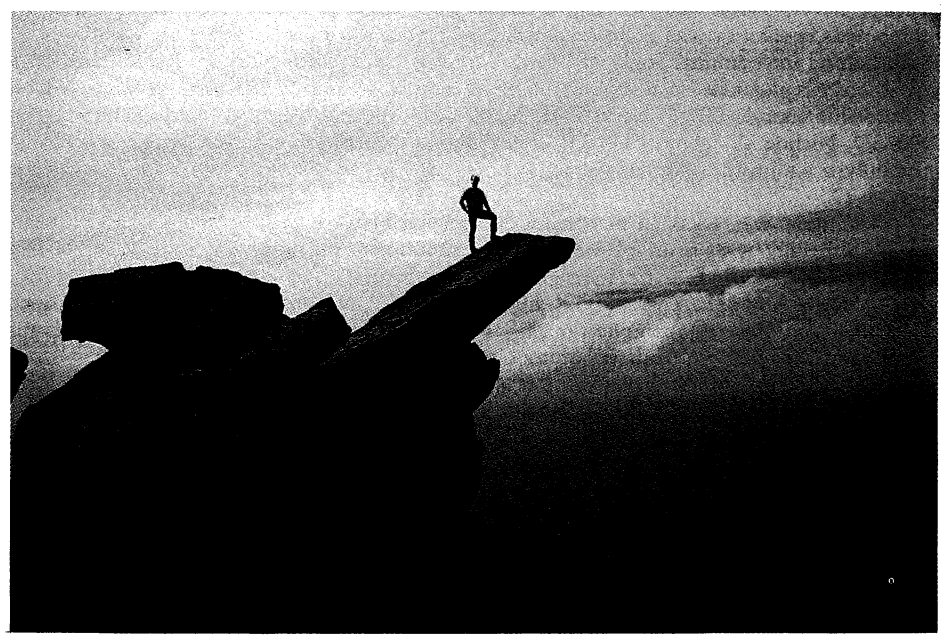

The Lover's Stone, St Kilda. Tradition has it that suitors on the island had to prove their manhood by balancing precariously on one foot on the edge of this 300 foot sheer drop to the sea. The resident population of the island was evacuated in 1930 and it is now owned by the National Trust for Scotland. (Photograph by David H. A. Boyd).

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MOLECULAR APPROACHES TO CARDIOVASCULAR DISEASE: A GLIMPSE OF THE FUTURE*

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The impact of molecular biology on clinical cardiological practice has so far been modest. However, research in laboratories throughout the world is focused on identifying genes responsible for the development or progression of cardiovascular disease with the realistic expectation that their findings will be translated into novel therapeutic strategies in the not too distant future. As in all other branches of medicine, it is the relatively rare single gene defects which have proved most amenable to molecular study, hence the genetic mutations responsible for diseases such as Marfan's syndrome, familial hypercholesterolaemia, hereditary haemorrhagic telangiectasia and hypertrophic cardiomyopathy have been identified. However, whilst knowledge of the genetic defects which result in these rare conditions has provided important insights into the pathogenesis of these and commoner related diseases and has significantly improved diagnostic accuracy, it has not yet led to effective therapeutic advances. Ultimately, cure of these conditions requires replacement of the defective gene by some form of gene therapy, an area of clinical science only in its infancy and likely to be confined for the forseeable future to a few specialist centres.

Of more interest to most practising cardiologists are the genes which cause common cardiovascular disorders such as coronary artery disease, which almost certainly results from the interaction between a number of 'normal' gene products and environmental factors such as diet and smoking. The future management of coronary disease therefore lies in the identification of genes whose products contribute to the progression or stabilisation of atherosclerosis with the aim of manipulating their expression to modify disease progression. Ultimately, this is likely to require the use of novel therapeutic agents which target enhancer or suppresser sequences in the non-coding region of candidate genes; an approach which could be termed 'pharmacological gene therapy'. Although this may seem somewhat far fetched, it is important to recognise that many drugs in current use achieve some of their therapeutic effect indirectly through this mechanism. For example, in addition to reducing cholesterol synthesis, HMG CoA reductase inhibitors also up-regulate expression of LDL receptors, thereby targeting the fundamental genetic defect in some forms of hypercholesterolaemia. Elucidation of the mechanism by which this is achieved may lead to drugs which directly modify expression of the LDL receptor.

It is likely that over the next decade new therapeutic approaches to the management of coronary heart disease will evolve from today's laboratory research. The aim of this article is: firstly, to outline some of the molecular approaches being used to identify potential candidate genes and to determine their contribution to vascular disease; secondly, to introduce molecular strategies

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