18. The management of occult atherosclerosis in arteries of the lower limbs

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Most apparently normal adults have occult atherosclerotic disease in arteries to the lower limbs. Many older subjects have objective evidence of disease without being aware of disability. Even if disease is causing symptoms, the obvious stenosis or occlusion may be less important than occult disease in arteries above and below the lesion for planning the best treatment. Intervention to correct a stenosis or occlusion on one side may expose symptoms from occult disease on the other.

Most current knowledge about both the cause and natural history of atherosclerosis has come from epidemiological studies, and these have been a triumph for the modern scientific approach to evaluating disease. However, they have generally concentrated on coronary artery disease (CAD) rather than disease in arteries to the lower limbs. The Framingham study [1] has followed more than 5000 subjects now for over 40 years. The Multiple Risk Factor Intervention Trial (MRFIT) [2] screened more then 360,000 men to focus resources on some 12,000 who were in the top 10% for risk. At the other extreme, a Finnish study [3] and the Bogalusa study in the USA [4] are tracking children and adolescents.

The days of such enormous, prolonged, expensive trials must be numbered. Since clinical end-points are few and late in the evolution of disease, the trials need to follow large numbers over many years at enormous expense. They are being replaced or at least supplemented by studies that use objective techniques to detect early arterial disease, and these are well-suited to examine accessible peripheral arteries. They should require much smaller groups followed for a relatively short time at far less expense. Arteriography can detect early disease in arteries to the lower limbs and can measure disease progression with sufficient accuracy to relate progression to aetiological factors [5, 6]. However, it is probably not ethical to follow early arterial disease in asymptomatic subjects by this invasive technique. The thrust now is to study accessible arteries by non-invasive ultrasound techniques [7–14].

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Occult disease in arteries to the lower limbs in apparently normal subjects

The pathology of occult arterial disease

Rational treatment can be developed only if it is known how disease starts and progresses. These have been extensively reviewed by Ross [15] and by Schwartz *et al.* [16]. Atherosclerosis is considered to result from arterial injury on a background of inherited or acquired susceptibility. Changes start with fibrofatty thickening followed by accumulation of mononuclear inflammatory cells in the intima. These changes progress to smooth muscle proliferation and migration then thinning, fibrosis and necrosis in the media. In the later stages, there is extension of the inflammatory process into the adventitia. Thus, there are lipid-laden atheromas and associated fibrous sclerosis, and different methods of diagnosis and treatment may be required for each depending on the stage of evolution [17]. Presumably, the more advanced the changes through the wall, the more difficult it is to reverse the process, but it is not known whether it is ever too late to try.

Recent evidence suggests that active inflammatory processes may play an important role in development of plaques. In particular, recent studies by members of our unit examine the role that macrophages play as mediators of injury [18]. It appears that both macrophages and endothelial cells modify low density lipoprotein so that it can be taken up by scavenger receptors to form foam cells, macrophages may be activated to produce tissue factors which induce local thrombus formation, and modified low density lipoprotein may be an important stimulus for activating macrophages within the plaques.

Endothelial cells, smooth muscle cells (SMCs), macrophages derived from circulating monocytes, and cytotoxic T-lymphocytes all interact in the wall. SMCs replicate, migrate from the media to the intima, and change from functioning 'contractile' to lipid-containing 'synthetic' cells, but most lipid-rich foam cells at the edge of atheromas are macrophages, and SMCs may be more concerned with laying down the connective tissue matrix which develops in established lesions. Platelets adhere to the intima but probably contribute only to late phases of lesion progression. More needs to be known about cellular interaction to allow specific therapy to retard the changes.

The cells release attractant, suppresant, mitogenic and cytotoxic chemicals. Platelet chemo-attractants, notably platelet derived growth factor (PDGF), bring SMCs and monocytes to the region. Monocytes produce cytokinins which attract other cells, stimulate connective tissue matrix formation, carry in and oxidise LDL to release circulating tissue peroxides and produce free oxygen radicals which damage tissue. Endothelium produces growth factors and prostacyclins. Movement of SMCs from the media to intima may result from loss of normal inhibitory mechanisms. There is great untapped potential to develop drugs which influence these effects.

Risk factors for occult disease

Epidemiological studies have largely defined the factors responsible for atherosclerosis. Genetic predisposition has been shown by pedigree, twin and ethnic studies. The Framingham study showed innate susceptibility by a two-fold increased likelihood of coronary artery disease (CAD) if siblings had clinical CAD [1], and a 30% increased rate if parents died from CAD [19]. The added risk factors have been defined by cross-sectional, case-control and cohort studies. The Framingham study showed the personal characteristics and living habits which promote atherosclerosis, both endogenous (blood lipids, blood pressure, blood sugar, and fibrinogen) and exogenous (diet containing excess calories, fat and salt, sedentary habits, unrestrained weight gain and cigarette smoking, and perhaps 'Type A' behaviour and marital status) [1]. However, a WHO study to define the prevalence of risk factors in adults from 40 centres world-wide [20] showed wide disparity for prevalence and mortality rates and a poor correlation between the two in some centres, raising the possibility of other influences. Wahlqvist *et al.* [21] have reviewed the risk factors for lower limb arterial disease in diabetics. In general, risk factors become less active with advancing age and in females, there is debate as to whether they cause risk across their entire distribution or only above threshold levels, and it is not certain whether their effect is linear.

The diagnosis of occult disease in apparently normal subjects

Arteriographic studies

The difficulty has been to develop highly reproducible techniques. Brooks, Blankenhorn and colleagues [22] pioneered computer-controlled femoral arteriography to measure minor changes in wall thickness, and derived an index which they termed 'computer estimate of atherosclerosis' (CEA). In a preliminary study of 54 men, correlation between CEA and risk factors was significant at the first examination only for smoking and the diastolic blood pressure, and multivariate stepwise regression analysis for change between arteriograms showed that there was a significant correlation only with lipoprotein-a and maximum systolic blood pressure during exercise. The variance for CEA was low enough to predict that it should be possible to detect a 5% change in CEA over a 1-year trial with only about 130 subjects.

Ultrasound studies

Current interest is with techniques that show changes in the wall by ultrasound B-scans of carotid arteries and arteries to the lower limbs. Pignoli and colleagues [9, 10] performed *in vitro* studies of carotid arteries and the aorta and found two echo layers that correspond to the lumen/

intima and media-adventitia interfaces, the media appearing anechoic, and best definition of the inner surface was obtained from the far wall. They were able to measure thickness of the inner layer with an error less than 20%. Future *in vivo* studies are likely to confirm that the combined intima and media thickness relates to the degree of early fatty deposition, and when normal values have been defined, it should be possible to identify occult disease. If stereotactic techniques are then used to relocate the site of examination, it should be possible to track the progress of disease. We are using B-scans to measure common femoral arterial wall thickness and to relate the measurements to risk factors, and an example of a scan is shown in Figure 18.1.

Picano and colleagues [11, 12] used ultrasound backscattering to characterise arterial plaques in the aorta and found that peak amplitude and fast Fourier transform analysis of the reflected signal, particularly from the intima/media interface, were altered by collagen, cholesterol crystals and calcium, and this defined whether the segment was normal, fibrofatty or calcified. In the future, it may be possible to use this approach to relate the efficacy of treatment to the type of plaque.

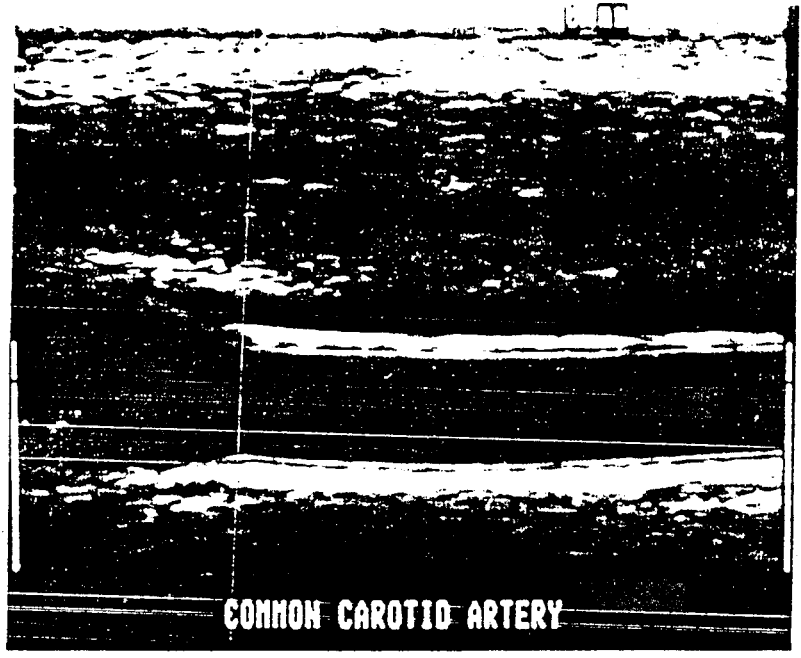

Figure 18.1. A high resolution ultrasound image of the artery in longitudinal section. The echogenic intima and echolucent media can be readily identified.

Arterial wall rigidity relates to atherosclerosis and can be studied by further ultrasound techniques, although other changes such as glycosylation and calcification in the wall may cause confusion in the interpretation of findings. We studied subjects with no apparent clinical arterial disease by pulse wave transit times from the subclavian to common femoral arteries to calculate arterial wall compliance, and the Laplace Damping Factor (LDF) to measure pulsatility in the common femoral and posterior tibial arteries. Derivation of these measurements are described elsewhere [23]. There was a significant relation between compliance and advancing age, raised blood pressure, increased serum cholesterol and triglyceride levels, and reduced serum HDL levels. We found significant correlations between compliance and total cholesterol and HDL cholesterol even after partial correlation analyis to eliminate the effect of age and blood pressure [7]. In addition, there was significant decreased compliance and increased LDF in non-insulin dependant diabetic (NIDDM) men with no clinical evidence of arterial disease compared to normal controls [8]. Further, when the NIDDM subjects and normal controls were combined to provide as wide a range of blood glucose levels as possible, then after allowing for age, there were significant negative correlations between compliance and free fatty acid and insulin levels which were almost completely accounted for by differences in blood glucose levels, so that it was concluded that arterial compliance in the aortoiliac segment was best predicted in this part of the study by age and the area under the blood glucose curve [24, 25].

Current interest centres on the ability of ultrasound to measure arterial wall movement with each pulse, which should also be reduced as the wall becomes more rigid. This approach is used in the Bogalusa Heart Study of adolescents [4] to calculate the carotid pressure-strain elastic modulus (pulse pressure/fractional diameter increase during the pulse cycle): this was highly reproducible (r=0.84) and significantly higher in those with a high risk factor profile, particularly those with a positive parental history. Van Merode and colleagues [26] used the technique to show that carotid arteries are stiffer in hypertensives. Currently, we are measuring arterial wall movement by M-mode ultrasound techniques to calculate the arterial elastic modulus and to relate this to risk factors to confirm the earlier studies of arterial wall compliance. An example of the tracing used to obtain results is shown in Figure 18.2.

The natural history of occult disease in apparently normal subjects

The Atherosclerosis Risk in Communities (ARIC) Study [13] will use B-scan ultrasound measurement of wall thickness of the carotid and popliteal arteries on two occasions three years apart in some 16,000 subjects aged 45–64 years from four centres in the USA. Ultrasound findings will be

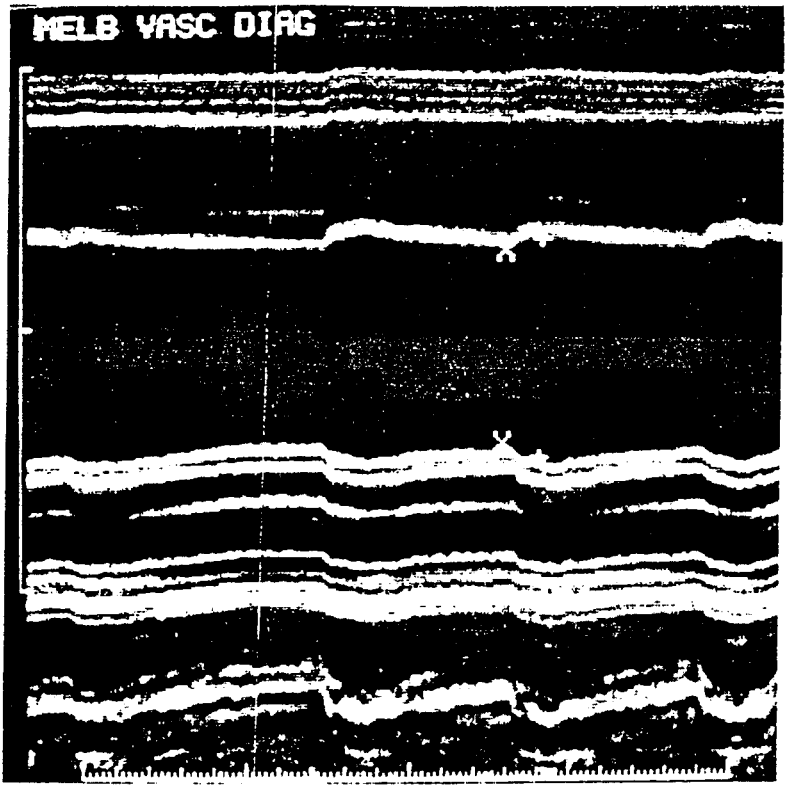

Figure 18.2. M-mode ultrasound imaging of the arterial wall showing the degree of wall movement through the pulse which allows calculation of the elastic modulus

related to personal characteristics, blood analyses, and clinical events for CAD, stroke and intermittent claudication. Preliminary studies show that it should be possible to measure wall thickness to within 0.2 mm and to demonstrate a change in thickness of more than 0.3 mm. The aim is to investigate the aetiology, clinical sequelae, and variation in risk factors for atherosclerosis; it may be the first time that peripheral arteries will be examined in order to make indirect postulates about CAD, rather than the reverse. The same techniques will be used in the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) [27] to assess drugs intended to retard atherosclerosis in hypertensive patients. Expertise gained by the groups will then allow the techniques to be adapted to a wide range of studies.

Ultrasound measurements of arterial compliance and LDF can be used to study the course of pre-clinical disease. Campbell *et al.* [28] used LDF at the

posterior tibial artery to follow 90 middle-aged men over 3 years, and found that 11 of 49 (22%) who had high values developed signs of lower limb arterial disease whereas only 2 of 41 (5%) with normal values developed signs of disease, but they were unable to accurately follow individual subjects with this technique.

Our longitudinal studies of the femoral and carotid arteries by measuring compliance, arterial wall thickness and arterial wall movement are designed to determine whether rates of progression vary in relation to risk factors and as part of randomised trials of drugs to lower lipid levels.

Treatment of occult disease in apparently normal subjects

Experiments in primates show that conservative treatment can inhibit progression of occult arterial disease or even cause regression [29–31] but it is not certain whether regression can occur in humans [32, 33]. However, since most subjects in 'western communities' have atherosclerosis, even from childhood, it is difficult to know how best to attempt to arrest the process. Rose [34, 35] distinguishes between 'sick individuals and sick populations' and compares the merits of the 'high-risk' and 'population' approaches for intervention to modify risk factors: at present, there is a combined approach of intensive treatment for those identified (usually by accident) as being at high risk and attempts at a community education programme. Since genetic predisposition may profoundly influence results in individuals but is generally lost in a heterogeneous population, it is far more difficult to predict the outcome in an individual subject than for a community.

There might seem to be benefit from concentrating on 'high risk' subjects but these could turn out to be the most difficult to motivate and the most refractory to treatment, while the 'high risk' approach is far more expensive [36]. The 'population' strategy to modify behaviour in the entire community is now preferred. The Australian-National Heart Foundation Risk Factor Prevalence Surveys of 1980 and 1983 [37] provide typical evidence for the effects of educational programs. Changes between the two assessments were all in the appropriate direction and most achieved statistical significance, but the degree was encouraging rather than striking. Rose [34, 35] points out that 'a large number of people exposed to a low risk is likely to produce more cases than a small number of people exposed to a high risk' and suggests that 'hypertension clinics, lipid clinics, diabetic clinics . . . offer only a limited answer to the community problem', but he also points out that this means that many at low risk will be involved without benefit while those at high risk will be less well defined, eventually leading to the risk of both the community and doctors losing motivation. This may be the reason why recent critical reviews question the benefit from changing eating habits to attempt to reduce blood lipid levels, perhaps due to frustration at perceived

regimentation, and a cynical attitude to commercial opportunities to promote costly aids to treatment.

Specific measures to modify risk factors

Since there is a direct relation between atherosclerosis and serum cholesterol, triglyceride, low density lipoprotein (LDL) and apoprotein-B levels, and an inverse relation with high density lipoprotein (HDL) and apoprotein-A levels, it seems reasonable to at least measure serum cholesterol, particularly if there is premature arterial disease or a strong family history of arterial disease or hyperlipidaemia [38]. The Australian National Heart Foundation recommend dietary treatment if the serum cholesterol is >5.5 mmol/l, the aim being to reduce saturated fatty acid and cholesterol intake by a low fat diet, to substitute oils and foods containing the omega-6 linoleic-acid, omega-3 polyunsaturated fatty acids and the monounsaturated oleic acid, and to avoid excess calories. However, even the best-motivated patients are unlikely to reduce their fat intake by more than 10% of energy intake. The Foundation also advise drug treatment if the serum cholesterol level is >6.5 mmol/l, and various drugs can reduce LDL to normal levels while most also increase HDL levels; it is not yet certain whether treatment to change the lipid status acts by causing a fall in LDL-cholesterol or an increase in HDL-cholesterol, and it is difficult to separate the effects of changing lipid levels from other biochemical changes.

A normal feedback mechanism to cell receptors stops continued LDL uptake when the cell is replete, but LDL altered by oxidation is taken up by alternate 'scavanger receptors' with no feedback inhibition. The largest cell mass is the hepatocyte population and if their lipid content rises due to increased ingestion of saturated fat, available LDL receptor numbers fall and plasma LDL levels rise. Thus, serum cholesterol may be reduced by not allowing it to get to hepatocytes, by diet or by drugs which bind bile-acids in the gut (bile-acid sequestrants). Alternatively, serum LDL may be reduced by agents which affect enzymes involved in uptake and synthesis in the cell, such as drugs which increase lipoprotein lipase activity (fibric-acid derivatives), or which compete with a rate-limiting coenzyme, 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG CoA reductase inhibitors). Other drugs block LDL oxidation so as to reduce its uninhibited uptake. At present, the choice of the best drug is empirical and combinations such as a resin and nicotinic acid or a HMG CoA reductase inhibitor may be desirable. The overall reduction in disease progression must be weighed against side-effects for treatment over many years, so that it is not known at what age to start treatment, and whether less vigorous treatment should be chosen in the elderly.

Diet and exercise cause a fall in serum triglyceride and increase in HDL-cholesterol levels [39], but it is not known whether exercise and weight

reduction result in benefit for pre-clinical lower limb arterial disease. Fish oil fatty acids (omega-3 acids) can have a beneficial effect [40], by acting through appropriate changes in lipids as well as reduced platelet aggregation and adhesion [41], but the precise role of these agents has yet to be defined.

The relation between diet and arterial disease is subtle but powerful and there is much yet to be learned. We showed that lower limb arterial wall indices of compliance and LDF in 31 apparently normal and 22 NIDDM patients without clinical evidence of arterial disease were significantly more likely to be within the normal range if the subjects had a wide variety of total food and plant food intakes, and it was calculated that up to 20% of the variance in arterial wall indices was explained by food variety [42]. In addition, the same group were analysed to determine whether compliance and LDF were related to fish consumption, and it was found that compliance was significantly lower for 'non-fish eaters' in the healthy and NIDDM groups, and that LDF was significantly higher for 'non-fish eaters' for the healthy subjects and for both groups combined [43].

Stopping smoking should reduce lower limb arterial disease progression. Antihypertensive drugs have varying effects on serum lipid levels [44]. Rosenstock and colleagues [45] measured lipid levels at 6-month intervals in insulin-dependant diabetics and showed that they were significantly improved by 'intensive treatment' but not by 'conventional treatment' so that they postulated that intensive treatment should reduce the risk of future atherosclerosis. It is not certain whether benefit from treating these conditions is due simply to controlling associated risk factors or whether there is a direct effect [46]. Whether good control of hypertension or diabetes slows lower limb arterial disease progression is a further area for assessment by non-invasive ultrasound studies.

Clinical studies of risk factor modification

It is generally agreed that primary and secondary clinical intervention trials show that intensive modification of exogenous and endogenous risk factors result in a moderate reduction of cardiac events. It remains to be seen whether the same can be shown for disease in arteries to the lower limbs. Treatment to manipulate the biochemical environment can be achieved by removing exogenous influences, by diet, stopping smoking, and perhaps by avoiding stress, or by adding treatment, at a simple level by manipulating the diet or by exercise, or by drug treatment to reduce lipid levels, to reduce blood pressure, or to better control diabetes. The former is 'natural' and is unlikely to harm the subject, whereas the latter can lead to dangers.

The results of clinical trials relating to intervention have been extensively reviewed [47, 48]. Large primary prevention trials which reduced exogenous influences by diet, stopping smoking, etc. have shown a lower incidence of cardiac events, both in selected high risk groups (such as MRFIT and the

Oslo Trial) and in general community groups (such as the European Collaborative Trial and the North Karelia Study). The reduction in cardiac risk from drug treatment for high risk men has been shown in other large primary intervention trials (such as the WHO Cooperative Trial, Lipid Research Clinics Coronary Primary Prevention Trial, and Helsinki Heart Study) and secondary prevention trials after myocardial infarction (such as the Coronary Drug Project). It is not known whether early intervention in childhood would increase the benefit, whether it is ever too late to bother in older patients, and whether the results also apply to women and to subgroups such as diabetic or hypertensive patients. Unfortunately, results are often presented in such a way as to dramatise an effect which though significant may not be very striking [49]. The effect of such intervention on lower limb arterial disease has not yet been assessed by clinical trials.

Arteriographic studies of risk factor modification

Arteriography provides evidence that intervention can retard or perhaps even reverse occult arterial disease in humans. A review of small numbers of patients studied by coronary angiography to assess the effect of drug treatment [50] (such as the National Heart, Lung and Blood Institute Study, University of Helsinki Study and Cholesterol-Lowering Atherosclerosis Study) showed highly significantly reduced new lesion formation, delayed progression and even variable regression, associated with marked fall in serum lipids. Blankenhorn and colleagues [6] studied femoral arteries in 25 patients without clinical disease who were treated for hyperlipidaemia and they found that serial arteriograms at an average of 13 months apart showed that significant progression of disease correlated with triglyceride and cholesterol levels. However, Olsson [51] used femoral arteriograms performed 12 months apart to study 63 asymptomatic hyperlipidaemic patients randomised into a control group and a group treated with nicotinic acid to show that there were changes in atheroma size in only 25% and that there was no significant difference in the treated group. Two further separate femoral arteriographic studies from Sweden are in progress, with considerably larger numbers of patients.

Ultrasound studies of risk factor modification

The MIDAS trial [27] will compare isradipine and hydrochlorothiazide for their effectiveness in retarding progression of peripheral atherosclerosis in hypertensives. A number of other studies combining dietary and drug therapy to control cholesterol levels and associated risk factors such as hypertension are under way. In addition to clinical end-points, peripheral arteries will be studied by ultrasound techniques. While the difference in outcome is likely to be small so as to require relatively large numbers of patients followed for several years, with the consequent risk of type II errors, nevertheless we consider that this is the direction for the future.

Early clinical disease in arteries to the lower limbs

Pathology of early clinical disease

Widmer and colleagues [52] studied 6400 factory workers by oscillometry and found that about 5% had occlusive disease and that the distribution of occlusions was: superficial femoral arteries – 49%, crural arteries – 23%, iliac arteries – 14%, upper limb arteries – 12%, and the aorta – 2%. Atherosclerosis occurs particularly at vessel curves, angles and bifurcations, with predilection for disease at areas of low shear stress [53]. The aortic bifurcation angle appears to influence the risk of arterial disease. An autopsy study [54] showed that the normal angle is 35° (SD 11°) with no difference between males and females, although a wide range was quoted from other arteriographic studies. Sharp and colleagues [55] found that the average angle was 38° in the presence of occlusive disease and 52° in normal subjects or patients with aneurysms. The most common site for superficial femoral artery disease is at the adductor hiatus, but the mechanism for early changes at this site have not yet been adequately studied. Nor is there any clear explanation for the relatively high incidence of crural artery disease and low incidence of iliac disease in diabetics.

Risk factors for early clinical disease

Widmer and colleagues [52] found that the prevalence of occlusion in males was less than 1% under the age of 50 years, but that this rose to 5.2% at 55–59, and 7.5% at 60–64 years, with a male:female ratio of 1.6:1. The Framingham study [56] showed that 'women lagged behind men by 10 years', and that the incidence of claudication developing was about one-quarter of that for coronary artery disease. The relative effect of risk factors measured by regression coefficients differed at various sites [57]. For claudication, the association in descending order was with cigarette smoking, serum cholesterol, glucose intolerance and systolic blood pressure in men, and glucose intolerance, smoking, cholesterol and blood pressure in women, and these patterns were different to those for coronary and cerebrovascular disease. However, since claudication tends to present at a later age than CAD, the pattern of risk factors may appear to be different because the group is attenuated by death of patients due to myocardial infarction [58]. The prevalence of risk factors then determines their actual influence. In the Australian National Heart Foundation Risk Factor Prevalence Survey, a population study of 25–64-year-old males and females in 1983, the prevalence for each was: serum cholesterol >6.5 mmol/l – 20.9%; current smoking – 29.6%; hypertension – 29.6%; overweight or obesity – 34.7%. Fowkes [58, 59] reviewed the association between risk factors and lower limb arterial disease and concluded that smoking 'seems especially import-

ant' although clinical disease is more likely to be associated with smoking than early disease, perhaps because haemodynamic changes from smoking could bring more severe disease to attention, that hypertension is a risk factor, but that there is conflicting evidence for an association between glucose intolerance and disease in non-diabetics, and inconsistent results for an association with lipid abnormalities. Criqui and associates [60] used ultrasound techniques to relate disease to risk factors in 565 subjects aged 38–82 and found that 69 had lower limb arterial disease, that large vessel disease was related to age, smoking, systolic blood pressure, fasting plasma glucose and obesity in men, and age and systolic blood pressure in women, but that there was no significant relation between disease and any measured lipids in either sex. It may be that the distribution of obesity is of considerable importance.

There are at least 4 other confusing reports relating lower limb arterial disease to lipid abnormalities. A Dutch study of 37 young patients [61] showed a high incidence of abnormal cholesterol, triglyceride, LDL and HDL levels. A Danish study of 76 patients and 21 controls [62] showed significantly higher LDL and lower HDL in patients but no difference for cholesterol or triglycerides. A Norwegian study of 110 patients with lower limb arterial disease compared to 548 controls [63] showed that both cholesterol and triglyceride levels were significantly higher in the patients. A British study of 32 patients with peripheral arterial disease and 38 controls [64] showed that triglyceride levels were higher amongst male patients but that total cholesterol and HDL-cholesterol were not significantly different, although the ratio of HDL-chelesterol to total less HDL cholesterol was significantly reduced in both sexes, perhaps due to an association with smoking.

From Finland, Laakso and colleagues [65] studied over 2000 diabetics and controls aged 45–64 years and found that claudication was at least 4 times more likely in diabetics, and Siitonen and associates [66] showed that ankle pressure indices were reduced in 7.3% of NIDDM males compared to 2.3% of male controls, although there was no difference in females. Beach and colleagues [67] studied 258 NIDDM patients and 158 controls by ankle pressure indices at rest and after exercise and by Doppler waveform analyses of the femoral and tibial arteries, and found that the prevalence of lower limb arterial disease was 22% in NIDDM patients and 3% in controls, and that there was a 14% incidence of new disease and 87% likelihood of disease progression with NIDDM within 2-years; their patients had a higher incidence of elevated triglyceride, low HDL, hypertension and smoking, but diabetes was an independant risk factor.

Diagnosis of early clinical disease

Fowkes [68] has criticised the use of claudication as a marker for epidemiological studies, pointing out the difficulty in defining when an atheroma becomes a stenosis, what constitutes unequivical claudication, the inter-observer variability for assessing pulses and arteriograms, and the need for objective tests. Various non-invasive objective tests have been used to detect patients with stenosis or occlusion causing minimal or no disability. Widmer and colleagues [52] used oscillometry and Ulrich and associates [69–72] used plethysmography, but these are now outdated. Criqui and colleagues [73, 74] used strain gauges on the toes to measure segmental pressures down the legs and post-occlusion pulse reappearance half-time, and Doppler ultrasound to measure flow velocity and post-occlusion reactive hyperaemia patterns in the common femoral and posterior tibial arteries. Marinelli and colleagues [75] and Beach and associates [67] relied on Doppler ankle pressure indices at rest and after exercise and continuous-wave Doppler wave-forms from the common femoral and tibial arteries.

While early stenotic or occlusive disease is relatively common in arteries to the lower limbs, many subjects are asymptomatic or do not appreciate the significance of mild claudication. In Widmer's study [52] at least one-third of patients with occlusions were asymptomatic. Criqui and colleagues [73, 74] found that only about one-fifth of patients with abnormal ultrasound tests had claudication. In a study of 458 diabetic patients, Marinelli and colleagues [75] reported that 19% of diabetic patients who were thought to have a normal history and examination had abnormal non-invasive tests, and that 44% of those thought to have an abnormal history or examination had normal tests.

The natural history of early clinical disease

Dormandy and colleagues [76] reviewed the extensive evidence that the larger proportion of patients with claudication do not worsen, but that in part this is because many do not live for very long. Ulrich and associates [69–72] used plethysmography to follow 306 patients with intermittent claudication for an average of more than 3 years. There was a pattern characteristic of iliac occlusion in 49 legs, which remained unchanged in about 60% or converted to a pattern of femoro-popliteal disease in the other 40%, and about 40% showed gradually improving flow while none worsened. There was a pattern characteristic of femoro-popliteal disease in 271 legs, which remained unchanged in about 80% or converted to a pattern of iliac

occlusive disease in some 10%, and most legs showed gradually worsening flow due to progression of distal disease while only about 10% improved. There were 153 contralateral limbs with a pattern of non-occlusive disease and follow-up showed that 12% improved to apparently become normal, about one-half remained unchanged, one-third worsened to develop a pattern of femoro-popliteal occlusion, and 2% worsened to develop a pattern of iliac occlusion; of those who apparently developed occlusions, only about one-third noted that symptoms became worse. Control legs in apparently normal subjects showed no change over a comparable period.

Treatment of early clinical disease

In general, conservative treatment to correct risk factors is all that is required, since there is no strong evidence to show that rapid disease progression is common and no means of predicting which patients are likely to be at future risk.

Duffield and colleagues [77] reported femoral arteriogram findings in 48 claudicants randomised to 'drug treatment' or 'usual care', and found that serum lipid levels became much lower in the drug-treated group and that lesion progression occurred in 10 of 144 segments in 'drug-treated' and 27 of 156 segments in 'usual care' patients, a 60% reduction in the rate of progression ($p<0.01$).

Objective studies measuring ankle pressures and walking distance have shown that stopping smoking significantly improves claudication [78]. However, a Norwegian study of 225 patients with claudication compared to a reference group of some 25,000 subjects in the community [79] showed the difficulties in persuading patients to stop smoking. The patients were evaluated by self-declaration and by serum thiocyanate measurements. Almost all males and 70% of females in the patient group stated that they were smokers or ex-smokers, but only 38% of smoking male patients compared to 77% of reference male smokers admitted smoking more than 10 per day, in spite of having higher thiocyanate levels. About 15% of patients who claimed to have stopped had raised thiocyanate levels.

Exercise has been shown to significantly improve walking distance [80]. The benefits claimed for more esoteric measures such as transcutaneous nerve stimulation, electrotherapy, external carbon dioxide, ultrasound, ultraviolet radiation, massage and external compression have yet to be evaluated [81].

Drug treatment may improve perfusion. Pentoxifilline reduces blood viscosity and improves walking distance in some claudicants [82]. Ketanserin, which inhibits platelet aggregation induced by serotonin, improves blood filtration and has an anti-hypertensive effect, has been studied in a randomised, placebo-controlled, double-blind trial of 3899 claudicants [83]; there

were 17 major amputations in the treated group compared to 32 in the placebo group, but an adverse interaction between ketanserin and potassium-losing diuretics made it difficult to assess any real benefit from the drug.

Occult disease in patients with severe clinical disease in arteries to the lower limbs

Clinical peripheral arterial disease is usually focal so that treatment is possible by an operation to restore a circuit in the affected area. However, atherosclerosis is generalised so that further occult disease is likely to be present above and below the most affected segment on the affected side and on the other side. The severity and distribution of further disease may determine whether an operation relieves symptoms, how likely it is to succeed for a long time, and whether further symptoms will develop at another site. Thus, occult disease should be assessed before proceeding to any form of intervention, so as to allow a more accurate long-term prognosis.

Diagnosis of occult disease in patients with severe clinical disease

Clinical assessment

A careful history may disclose early claudication in the ipsilateral thigh or the contralateral calf at about the time that severe calf claudication stops the patient on the more affected side, but absence of symptoms does not exclude appreciable disease. Careful examination may raise the probability of pulse deficits, but we found that the ability of any of the members of our unit to agree as to whether femoral or popliteal pulses were normal or reduced in amplitude was little better than chance [84] so that it would be unwise to make a confident assessment of disease in proximal or contralateral arteries on the basis of palpating pulses.

Arteriography

If arteriography is required, it is our practice to show the full length of the arterial system on both sides from the renal arteries to the feet, in two planes if necessary. However, Slot and colleagues [85] found that arteriography is not very reliable: disease was classified into 4 grades by 11 observers and their agreement was not much better than expected from chance, particularly for the aorta, iliac and profunda femoris arteries. Even with biplanar arteriography, Theile and Strandness [86] could detect aorto-iliac disease with only 70% sensitivity and less than 80% specificity as judged by intra-arterial pressure measurements. Arteriographic scoring of runoff crural arteries can be calculated and has been compared to measured

resistance distal to femoral artery occlusions [87], with reasonably good correlation (r=0.64).

Invasive pressure measurements

Several authors have described the use of invasive common femoral artery pressures for diagnosis of occult aorto-iliac disease [88, 89] and others have described a combination of non-invasive tests with invasive pressure measurements in selected patients [90]. These can be performed well before intervention, seperately or at the time of arteriography, or in the operating theatre immediately before commencing surgery.

Non-invasive ultrasound techniques

In practice, we find that one of the most valuable investigations from the vascular laboratory is the measurement of pressure indices in each leg when the patient is first seen, for although these do not relate well to the severity of symptoms, they do show whether there is disease in the limb, and whether there is occult contralateral disease [91]. Laing and Greenhalgh [92] studied 100 asymptomatic contralateral legs in patients with claudication, and found that more than one-half had reduced ankle pressures but that less than one-third of these had abnormal physical signs.

Analysis of the common femoral artery Doppler ultrasound pulse wave can help to determine whether there is occult aorto-iliac disease. Several methods have been used including pulse rise time, pulsatility index (PI), the Laplace Damping Factor (LDF), and principal component analysis (PCA). Their derivation and relative merits have been reviewed elsewhere [23, 91] and there have been further recent reports. Bagi and colleagues [93] found an excellent correlation between common femoral pulse rise time and arteriographic assessment of disease, a pulse rise time >120 ms relating to stenosis >50% with a sensitivity and specificity of 95% and 97% respectively for aorto-iliac disease and 79% and 93% respectively for femoro-popliteal disease. However, Kitslaar and colleagues [94] compared pulse rise time and PI with arteriography and intra-arterial pressures to grade aorto-iliac disease and found that the correlation was poor, though it was best for the pulse rise time. Baker and associates [95] up-dated their experience with common femoral LDF compared to aorto-iliac arteriography in 98 legs and showed that LDF detected stenosis >50% with a sensitivity of 92% and specificity of 93%, independant of whether the superficial femoral artery was patent or occluded. Goss and colleagues [96] showed that a computer-generated diagnosis including PCA more accurately predicted the clinical outcome than did clinical judgment alone.

Various ultrasound tests have been used to assess stenosis in the femoro-popliteal segment. Baker and colleagues [97] studied transit times, pulse damping and an index of peripheral resistance derived by Laplace trans-

form, but none showed good correlation with arteriographic measurement of stenosis.

There is now considerable interest in whether the duplex ultrasound scan can supplement or even replace arteriography for diagnosing the presence and severity of stenotic disease in arteries to the lower limbs [98]. Because the examination is extensive, it is really only feasible for regular practice using colour-Doppler scanning. Undoubtedly there is scope to more accurately define criteria for grading disease. At present, we follow criteria described by Cossman and colleagues [99] who rely on peak systolic velocity ratios and absolute velocities to define diameter stenoses as:

	Velocity Ratio	*Peak Velocity*
Minimal or no stenosis	—	<150 cm/sec:
30–49% stenosis	1.5–2:1	150–200 cm/sec:
50–75% stenosis	2–4:1	200–400 cm/sec:
More than 75% stenosis	>4:1	>400 cm/sec

Cossman and colleagues [99] used these criteria to study arteries distal to the common femorals, with arteriography as the standard of reference, and found that they could grade >30% stenosis with a sensitivity of 83% and specificity of 96%, the highest accuracy being for the distal superficial femoral and popliteal arteries. Legemate and associates [100] found that >150% increase in peak systolic velocity predicted >50% stenosis on arteriography with sensitivity and specificity of 92% and 98% respectively for aorto-iliac disease and 88% and 98% respectively for femoro-popliteal disease, although the accuracy was less when compared to intra-arterial pressures, and they also found that an end-diastolic velocity >40 cm/sec accurately predicted that the diameter stenosis was >75%. Langsfeld and colleagues [101] calculated pressure gradients by the modified Bernoulli equation (pressure gradient = 4 × maximum velocity^2) to define significant aorto-iliac stenoses with a sensitivity of 82% and specificity of 93% as compared with arteriography, and showed an excellent correlation with pull-through intra-arterial pressures (r=0.9). The degree of turbulence shown by spectral analysis expressed as a power-frequency analysis should relate to the degree of stenosis [102]. Disagreement between duplex scans and arteriography appears to be more likely with minimal disease.

Treatment of occult disease in patients with severe clinical disease

Patients with severe ischaemia are likely to have disease at multiple levels, each contributing in different degree to restricted perfusion of the limb. One

segment may stand out as being obviously affected but this does not mean that it is the only site that needs to be treated. Even although relief of rest pain or healing of necrotic sites is the prime goal, the traumas from intervention will be doubly rewarded if a procedure also leaves the patient with no claudication.

Occult disease above a symptomatic occlusion

It is probable that long-term patency after any form of intervention is less likely if there is low velocity and volume of blood flow through the segment. Flow could be restricted by occult disease in 'inflow arteries' above the operation, for example unrecognised iliac artery disease above a femoro-distal bypass [103].

A common problem is how to predict whether treating proximal stenotic disease by aorto-femoral bypass in a patient with a superficial femoral artery occlusion will improve symptoms. Faris and colleagues [104] measured intra-arterial common femoral and arm pressures to determine an aorto-femoral pressure gradient index and multiplied the pre-operative ankle or toe pressures by this index to predict the post-operative pressures. If the predicted post-operative ankle pressure index was >0.60, then claudication was relieved and if it was <0.56 it was not: if the predicted toe pressure was >40 mm Hg, it was likely that a conservative amputation for gangrene would heal.

Occult disease below a symptomatic occlusion

Again, it would seem likely that patency rates for bypass grafts and endovascular procedures might be adversely affected by disease in 'outflow arteries' below the operation site, but the evidence is inconclusive.

For aorto-femoral bypass, Harris and colleagues [105] found that late patency rates were significantly lower if there was associated superficial femoral artery occlusion than if the femoral outflow was patent, to the point where they advocate combined aortic and femoral artery bypass, but we found no difference between the two groups, perhaps because of a high proportion of distal anastomoses to the profunda femoris artery [106].

The influence of tibial artery and pedal arch disease have been studied after femoro-distal bypass. Early occlusion seems to be more likely if there is a high outflow resistance measured at operation [107] or if arteriography shows occlusion of the pedal arch [108]. However, late patency does not appear to be influenced by arteriographic grading of tibial artery outflow [109] or the state of the pedal arch [110], although Ascer and colleagues [111, 112] found that outflow resistance measurements predicted late patency rates for femoro-crural but not for femoro-popliteal grafts, and that foot-salvage rates in patients with critical ischaemia were well predicted by outflow resistance for all grafts.

There are varying opinions as to where to best place the distal anastomosis for a femoro-distal bypass. At one extreme, there is some enthusiasm for using the above-knee popliteal artery if possible, to keep the bypass short and to allow selection of a synthetic graft if preferred so as to spare the long saphenous vein for later use if needed [113], for the results of above-knee synthetic grafts may be little worse than those for vein [114], and best results from this approach may rely on being able to treat occult disease in the popliteal artery by endovascular procedures. There may be a place for taking a vein bypass to an 'isolated popliteal segment' below the knee, relying on collateral outflow to relieve symptoms and ensure long-term patency, and there is evidence that this may give as good results as more distal bypass [115]. However, there is now more enthusiasm for avoiding adverse effects from occult distal disease by taking autogenous vein down to a crural or pedal artery if the popliteal artery is not satisfactory, and there is no evidence that this gives worse long-term patency rates than for femoro-popliteal bypass. Andros and colleagues have shown that improved results can be obtained by taking bypass grafts down to below outflow occlusions by making the distal anastomosis to a tarsal artery [116]. There is also a push to perform multiple distal anastomoses if there is more than one patent crural artery, the proposition being that it is not possible to tell which has the best outflow and which is likely to give the best long-term results, so that there may be 'safety in numbers' [117], but there is no evidence yet to show that this is associated with improved results. There is not yet enough information to show whether these considerations also hold for endovascular procedures.

Occult contralateral disease

Frequently, arterial disease is bilateral but assymetrical. Claudication in the worst affected leg is likely to stop the patient from walking far enough for pain to develop in the contralateral leg. If claudication is relieved by operation in the worse-leg, symptoms may then become manifest in the second leg. Predicting this may influence management, for a patient might wish to have one operation but not two operations to gain relief. A patient with critical ischaemia is not likely to complain of lesser contralateral symptoms, and critical ischaemia demands treatment to the worst affected leg, but residual claudication in the second leg after treatment is likely to lead to fear of future deterioration that may not be warranted. At least the patient should be warned if there is a possibility of staged bilateral surgery.

Management of occult contralateral disease is not always rational. It has long been conventional practice to treat serious aorto-iliac disease by aorto-bifemoral bypass, irrespective of whether disease is predominantly unilateral or bilateral. In a review of 57 aorto-bifemoral grafts [88], we found that the bypass on the 'second side' did not increase ankle pressure indices measured 4 weeks after operation in about three-quarters of the legs and indeed many

had normal ankle pressure indices (>0.9) before operation. Because of this, it became our practice to treat apparently unilateral iliac disease by an extraperitoneal unilateral ilio-femoral/profunda synthetic bypass rather than by transperitoneal aorto-bifemoral bypass, and in 110 consecutive operations, we found that only 4 patients later required proximal surgery for contralateral iliac artery disease [118].

There is an increasing tendency to treat iliac disease by endovascular balloon dilatation, atherectomy or laser angioplasty, alone or in combination with femoral artery surgery. This allows a more selective approach to each side independently. The possible combinations of treatment are now considerable, with staged or simultaneous treatment of bilateral disease by endovascular surgery, or by balloon dilatation for the less affected side at the same time or separate from a unilateral ilio-femoral or femoro-femoral cross-over bypass. In our unit, aorto-bifemoral bypass is reserved now for patients with extensive aortic and bilateral iliac disease.

Conclusion

Detection and treatment of occult disease is becoming the prime focus for clinical research and practical management. Many people in the community are likely to develop lower limb ischaemia. Identifying subjects at risk when disease is still occult should allow appropriate modification of risk factors, hopefully to reduce and delay disease progression and defer or avoid expensive, traumatic surgical intervention. Surveillance will identify rapid progression and the need for early conservative treatment. Although a new era of proliferating non-invasive investigations should facilitate the process, how best to seek out subjects at risk with the greatest cost-benefit to the community has still to be determined. In the past, major arterial reconstruction tended to be reserved for foot-salvage in patients with advanced disease. However, claudication is a very disabling symptom and does not always follow a benign course. The next few years are likely to see greatly expanded indications for more early intervention by better bypass techniques and by endovascular surgery, as well as improved pharmacological management. Sophisticated non-invasive diagnostic techniques will be used to diagnose disease at an increasingly early stage, and more accurate mapping of disease will allow the most rational techniques for intervention.

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