REVIEW

Atherosclerosis: inhibition or regression as therapeutic possibilities

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Therapeutic modulation of the atherosclerotic process in human coronary arteries is now being attempted. A major aim of such attempts has been regression—that is, a diminution in the volume of atherosclerotic tissue. Many patients would, however, settle for stabilisation of their disease without further progression, and with a reduced risk of acute ischaemic events in the future. These may be more achievable aims.

Mechanisms of plaque growth

Atherosclerotic plaques grow by the accumulation of lipid and the production of connective tissue matrix proteins, such as collagen, by smooth muscle cells. Lipid accumulation within the intima is a complex process. Plasma low density lipoproteins (LDL) freely enter and leave the intima across the endothelial surface. The first morphological change in the initiation of atherosclerosis in humans and in all animal models^{1,2} is the migration of monocytes through an intact endothelial surface into the intima; these monocytes subsequently take up LDL and become lipid filled macrophage foam cells within the intima. Monocytes do not, however, have a receptor which enables them to take up native LDL within the intima. This paradox was resolved when it was realised that modification of the LDL by acetylation or oxidation leads to avid uptake by macrophages via the alternative scavenger receptor.³ Oxidation of LDL occurs within or adjacent to endothelial cells and after binding of LDL to proteoglycans, within the intima. Oxidised LDL acts as a chemoattractant for monocytes, which it immobilises in the intima. It also acts as an activating factor and is cytotoxic as well as being ingested to form cholesterol filled foam cells. Oxidised lipid has been shown within the intima both in experimental and human atherosclerosis.⁴ The progression of plaques⁵ is also associated with the accumulation of cholesteryl ester and cholesterol outside cells; this may be due either to release from dying foam cells or to direct extracellular conversion of LDL bound to the connective tissue matrix in the intima.⁶ Smooth muscle cells will also take up low density lipoproteins but it is now apparent that most cells within the intima in which the cytoplasm is completely distended by lipid to form the classic foam cell are monocyte derived.⁷

Removal of cholesterol from the intima is

mediated by high density lipoproteins (HDL), which also freely enter the arterial wall across the endothelium.⁸ They are less avidly bound by the connective tissue matrix and, being smaller than LDL particles, can move freely within the intima. HDL has an affinity to bind unesterified cholesterol; subsequently, within the HDL/cholesterol complex the enzyme lecithin cholesterol acyl transferase (LCAT) re-esterifies the cholesterol and the whole complex passes back into the plasma. Cholesterol ester is now transferred, via the activity of cholesteryl ester transfer protein, to LDL and very low density lipoprotein (VLDL) particles which can be taken up by the liver cells. The initial step of creating unesterified cholesterol that is available for binding to HDL is complex and crucial to an understanding of how lipid can be removed from established plaques. Direct binding of unesterified cholesterol to HDL within the extracellular lipid component of the intima may occur but most current knowledge concerns the release of cholesterol from within macrophage foam cells. The reaction is mediated by the specific interaction of HDL with a macrophage surface receptor, the whole complex being internalised and then resecreted, having been enriched with cholesterol within the cell. There is a second pathway, in which conglomerates of cholesterol and phospholipid formed within lysosomes are extruded from the cell surface to be available for binding with HDL.^{9,10} The rate and mechanisms by which crystalline cholesterol could be removed from the lipid core of human lesions are less certain.¹¹

Smooth muscle proliferation and collagen synthesis are the other integral parts of plaque growth. This is, however, not always directly coupled to lipid accumulation; some plaques seem to be predominantly collagenous without a significant cholesterol component.

Within an individual coronary artery there can be plaques ranging from those with a negligible lipid content to those with over 50% of their volume occupied by lipid. It is not known whether these different forms of plaque evolve from each other or are initiated in different ways. Smooth muscle proliferation is driven by growth factors,² one potential source of which is the macrophage activated by lipid ingestion. Other sources include platelets, endothelial cells, smooth muscle cells, and the degradation products of fibrinogen.

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The processes of smooth muscle proliferation and lipid accumulation might be expected to be linear with time. But angiographic studies show that the progression of coronary artery disease in humans is neither linear nor predictable.^{12,13} New high grade lesions often appear in segments of artery that were normal at previous angiographic examination¹⁴; and it is impossible to foresee the site of a subsequent occlusion causing infarction. This unpredictable and episodic progress can be explained by the occurrence of thrombosis, as a complication of the basic atherosclerotic process, leading to intermittent plaque growth.^{15,16}

It is important to appreciate that thrombosis occurring in an atheromatous plaque, often as a result of deep intimal tearing or fissuring, is very frequently clinically silent. Episodes of intraplaque thrombosis are an important mechanism of plaque growth¹⁵ and it is only when significant intraluminal thrombosis occurs that there is a risk of acute myocardial ischaemia or infarction.

Methods of quantifying atherosclerosis

A major difficulty in any trial of antiatherogenic drugs in humans is quantification of the arterial lesions. The angiogram delineates the lumen which is at best an indirect guide to the state of the arterial wall. There are several reasons for this inexactitude. Plaques cause atrophy of the adjacent media, and when situated eccentrically the plaque shifts outward rather than bulging inward.¹⁷ A consequence of this outward shift of the plaque, which comes to lie outside the original line of the artery, is that large plaques may not be associated with any stenosis, and can go totally undetected by angiography. In the early stages, diffuse atherosclerosis is also associated with a compensatory dilatation of the artery to preserve lumen size. This capacity to preserve the lumen size is not overcome until the area of the plaque exceeds 40% of the original cross sectional area of the artery.¹⁸

In the context of angiography "new" is not a relevant term because the threshold for detection of a plaque is high and not reached until it occupies 40% of the area of the cross section of the vessel. The appearance of a new lesion on angiography indicates a rapid growth phase and not the actual initiation of the plaque.

The conventional method of interpreting angiograms in clinical practice is to compare a test segment with an adjacent reference segment that is judged to be normal. But the reference segment may itself be diffusely narrowed (leading to an underestimate of the significance of the stenosis) or dilated (leading to an overestimate of the stenosis).¹⁹

Because the lumen is not necessarily circular different examinations can be compared only if the views of the arterial segment are in identical planes.²⁰ The crescentic and slit shaped lumens that often appear in pathology papers are artefacts of examining unperfused vessels, but even in vessels distended at high pressure D shaped lumens with flattening over a plaque do occur.¹⁹

Absolute lumen dimensions are less likely to be affected by these errors and are probably the ideal method in comparing angiograms.^{21,22} This implies use of automated methods of quantification with an edge detection algorithm and computer assisted prediction of the outline of the normal vessel, exemplified by the Cardiovascular Angiographic Analysis System (CAAS) developed by Reiber *et al.*²³ The reproducibility of repeated measurements is better than that of visual assessments over a wide range of severity of stenosis.^{24,25} The variability of absolute changes in vessel diameter is less than the calculated values of percentage diameter stenosis based on comparison with an adjacent reference segment of artery judged to be "normal".²⁶

For all angiographic methods of measuring atherosclerosis it is essential that the vascular tone is identical during the two angiograms on which comparisons are being made. This proviso applies to both diffuse and focal disease. Atherosclerotic vessels have an abnormality of endothelial mediated vasodilatation²⁷ and any treatment that improves endothelial function or acts as a direct vasodilator can increase lumen size and give the spurious impression that this was caused by reduction in the mass of atherosclerotic tissue. Hyperlipidaemia can have a direct effect on endothelial function that is manifested far more widely than just within segments of coronary artery affected by atherosclerosis²⁸ and studies in rabbits showed that this was reversed by lowering plasma lipids.²⁹

Clinical end points such as fatal and non-fatal myocardial infarction, unstable angina, or death from a cardiac cause are another way of assessing the response to treatment. They test the likelihood of episodes of major thrombosis, and thus the frequency of a plaque becoming unstable. As such they are measuring a different variable from the angiogram; it is to be hoped that antiatherogenic drugs will not only reduce inherent plaque growth but also reduce the risk of plaque instability—but this is not known for certain. Drugs with no action on the basic process of atherosclerosis itself but which reduce the thrombotic response to unstable plaques will also reduce fatal and non-fatal acute events in patients with coronary atherosclerosis.³⁰ There is, however, some evidence that aspirin not only reduces acute events but also the number of new coronary lesions that appear,³¹ emphasising once again the important role of thrombosis in plaque growth.

In animal models of atherosclerosis more exact and direct methods of quantifying the extent of arterial disease can be used. The standard method is to measure the percentage of the intimal surface of the aorta that is occupied by lipid containing lesions after staining with lipid soluble dyes such as oil red O. The mean percentage intimal involvement can be compared in groups of animals that have been treated differently. Such models allow drugs to be evaluated either for inhibition of development or for the regression of atherosclerosis; but they give no indication of the risk of thrombosis because most experiments are short term.

Regression and inhibition in animal models of atherosclerosis

Atherosclerosis in animals is induced by hyperlipidaemia, either produced by high fat diets or by metabolic defects in lipid metabolism. The Watanabe rabbit³² is deficient in the LDL receptor, and thus is analogous to human familial hypercholesterolaemia. The models can be criticised³³ for testing cholesterol accumulation in the aorta rather than the development of atherosclerosis per se, with grossly unphysiological levels of consumption of dietary fat compared with human consumption, and for being very short term. The morphology of the lesions is often dominated by the presence of intracellular lipid rather than the extracellular lipid cores characteristic of human advanced plaques. Monkey¹ and pig models³⁴ which produce a disease in the long term more analogous to human atherosclerosis, particularly if associated with hypertension,³⁵ are prohibitively expensive.

In animal models several drugs have been successful in retarding the development (drug given simultaneously with high lipid diet) or in causing regression (drug given after high lipid diet) of aortic lesions. They can be divided into those in which there is a significant lowering of plasma lipids and those which must have other mechanisms.

The models in which there was plasma lipid lowering include rabbits, pigs, dogs, chickens, pigeons, and monkeys.³⁶ Most of the studies compare the findings at necropsy in groups of animals treated differently, but in one the aorta was inspected at successive surgical explorations.³⁷ All these models showed that it is possible to reduce cholesterol content, lesion size, and the total number of lesions. Cholesterol is removed from the plaques far faster than collagen. In some models the amount of collagen within plaques actually increases, and heavily cross-linked collagen resistant to collagenolysis is deposited in the regression phase.^{38,39} In many animal models, unlike in humans, a high proportion of the cholesterol is contained within foam cells and is thus easily mobilised; in rhesus monkeys intra-arterial lipid was reduced within 4 weeks of the plasma lipid concentration returning to normal.⁴⁰ The mechanism by which lowering plasma lipids causes inhibition or regression of atherosclerosis is by reducing the amount of LDL entering the intima, which allows the natural clearance pathway via HDL to predominate.

With probucol inhibition of atherosclerosis was much greater than expected for the observed reduction in plasma lipid concentration.^{41,42} Carew and his colleagues showed that when plasma cholesterol decreased from a mean (SEM) of 761 (29) mg/dl to 618 (21) mg/dl with lovastatin the percentage area of the aorta occupied by plaques was reduced from 40.6 (5.1)% to 27.5 (4.6)%.⁴¹ Probucol lowered plasma cholesterol (to 671 (20.7) mg/dl) less than lovastatin but reduced intimal involvement with atherosclerosis more (to 14.3 (2.1)%). The current view is that probucol prevents oxidation of LDL and therefore lipid uptake by macrophages within the intima to

form foam cells.⁴³ Prevention of lipid oxidation may also reduce monocyte recruitment into the intima.

Calcium antagonists can also influence atherosclerosis. Most studies indicate inhibition of lesion development with a range of calcium antagonists including verapamil, diltiazem, amlodipine, and nifedipine.⁴⁴ A dose dependent inhibition occurs both in the amount of cholesterol deposited and in the number of plaques in nifedipine treated NZ rabbits on a high lipid diet.^{45,46} Results with nifedipine in the Watanabe rabbit, however, were more equivocal,⁴⁷ and at least in one high fat diet model showed no effect of nifedipine.⁴⁸ In another study calcium antagonists in general were shown to alter atherogenesis in the aorta but not in the coronary arteries.⁴⁹

The mechanism by which calcium antagonists might inhibit the atherosclerotic process is far from certain but there is an embarrassing choice of possibilities. The role of calcium in atherogenesis may have been underestimated; Fleckenstein *et al* pointed out that by weight calcium is a major constituent of many plaques.⁵⁰ But Fleckenstein's original demonstration of the prophylactic value of calcium antagonists against toxic doses of vitamin D was in a model resembling Monckeberg's sclerosis rather than human coronary atherosclerosis.⁵¹ While this beneficial effect in the vessel wall may be related to calcium channel inhibition, there must be an alternative mechanism for the ability of verapamil to inhibit cataract formation in the eyes of alloxan-diabetic rats.⁵² This ability raises the possibility that some of the effects of calcium antagonists in inhibiting the formation of new atheromatous plaques could be the result of actions remote from an influence on the slow inward (calcium) channel of vascular smooth muscle cells.

There is increasing recognition that atherosclerotic plaques are the sites of intense inflammatory activity involving an interplay between T lymphocytes, monocytes, and smooth muscle cells signalled by the expression of a range of cytokines and growth factors.^{53,54} Calcium antagonists might influence the transmission of these signals between cells. In vitro models of cell activation by platelet derived growth factor or interleukin 2 show that control of this step is mediated by synergistic interaction between triggering of the protein kinase C pathway and an increase in cytoplasmic free calcium.⁵⁵⁻⁵⁷ If the concentration of intrinsic intracellular calcium is low one arm of the activation process becomes dependent upon exogenous calcium, which will no longer be available in the presence of a calcium channel blocking agent. In these circumstances the calcium antagonist is an inhibitor of cell activation.

Smooth muscle cells express voltage dependent (L type) calcium channels and in vivo experiments suggest that the calcium antagonists do inhibit smooth muscle proliferation and migration^{45,58-60} possibly through blocking the action of platelet derived growth factor.⁵⁷ In the Watanabe rabbit, drugs such as cortisone

reduce the rate of plaque formation. This emphasises the "inflammatory" nature of the atherosclerotic process.⁶¹

Accumulation of extracellular lipid derived from dying foam cells⁵⁷ and necrosis, with the formation of an acellular lipid core within the plaque, is an integral part of progression in human atherosclerosis. Various lipid soluble factors can selectively accumulate within foam cells; the best characterised example of such a factor is 1,25-dihydroxycholecalciferol (vitamin D₃) which has a considerable calciotropic effect leading to increased calcium mobilisation into the cell.⁶² This increase may be toxic and lead to cell death that is manifest as plaque necrosis. Calcium antagonists might thus be potential vitamin D₃ antagonists capable of breaking a self perpetuating cytotoxic cycle, and indeed they are known to block the arterial damage after external administration of the vitamin. Vitamin D₃ is, however, also produced within the macrophage⁶³ and this in situ production might continue at a lower level in the face of a calcium antagonist shifting what was a plaque with predominant necrosis to one which calcifies and becomes more stable.

Yet another possible cellular effect of calcium antagonists is that the intracellular enzymatic metabolic pathways may be sensitive to a calcium deficit and hence to a blocking agent. Such enzymes may be responsible for degradation of endogenous and exogenous protein and for intercellular lipid handling.⁶⁴ Hydrolysis of cholesterol ester within cultured smooth muscle cells is increased by calcium antagonists.^{65,66} It is possible that if an atherogenic process continues in the presence of calcium antagonists there may be intrinsic changes in the nature of the intercellular lipids and hence in the behaviour of the foam cell. So far the effect has been studied in the smooth muscle cell whereas most foam cells are macrophages. The net uptake of lipid in vivo by macrophages has also been shown to be inhibited by calcium antagonists.^{67,68}

Calcium antagonists may affect lipids within the intima at a simpler level than that of intracellular metabolism. Two dissimilar calcium antagonists, flunarizine and nimodipine, both reduced the permeability of the endothelium to LDL and thus would reduce lipid accumulation.⁶⁹ In a different context an article in this issue of the *British Heart Journal* reports that verapamil and nifedipine have antioxidant properties, which means that they may have an effect analogous to probucol in atherosclerosis.⁷⁰

At present the mechanisms by which calcium antagonists influence atherogenesis are unknown. There is fragmentary evidence for an effect on cell interaction, on smooth muscle cell proliferation, on prevention of plaque necrosis, on modifying intracellular lipid metabolism, on reducing lipid influx, and that they prevent lipid oxidation.

It seems likely there will be further demonstrations that drugs including antioxidants and anti-inflammatory agents have local effects on cells in the microenvironment of the plaque and these will be shown to be effective in modifying atherosclerosis in simple animal models.

Should this be so, they will be worthy of human studies.

Human studies of inhibition and regression of atherosclerosis

In human coronary arteries high grade stenotic lesions contain large amounts of both collagen and calcium in addition to lipid; the relative proportion of lipid varies considerably from plaque to plaque, and is often very low. If the lessons of the animal models are correct, and lipid is removed rapidly but collagen is removed very slowly, significant regression of lesions causing high grade obstruction in man is unlikely other than over a long time.⁷¹ But the appearance of new lesions might be prevented, and lipid rich lesions might regress.

The propensity of plaques to become unstable and undergo fissuring and thrombosis is, however, related directly to the amount of extracellular lipid contained within the central core.^{15,72,73} A reduction in the amount of lipid with only a modest reduction in overall plaque volume might be accompanied by an increase in plaque stability with a decrease both in episodic plaque growth and a reduction in the risk of acute ischaemic events. For this reason, data both on the angiographic severity and on the clinical event rate are needed to assess any intervention in atherosclerosis.

Despite all the reservations concerning the ability of the angiogram to measure wall disease it remains the only technique available. Computerised image analysis has improved the subjective bias inherent in any visual interpretation of angiograms and must be considered the optimum method. Subset analysis can be made of the progression of lesions of different severity in the initial angiogram.

Given the interplaque variation in the proportions of the volume of tissue made up of collagen, lipid, and calcium it is unlikely that all lesions in any patient could regress at the same rate. The usual method of interpreting quantitative angiographic data is to take the mean change for all the angiographically detected lesions. This has statistical convenience for comparing study groups but the mean changes are often very small in haemodynamic terms and may be biased by a large change in a single lesion. An alternative method is to give a visual score for progression or regression to each patient based on the number of lesions in that individual showing a recognisable change in lumen size and ranging from +3 (change for better) through 0 (no change) to -3 (change for worse).

Since 1969 both angiography and the frequency of acute ischaemic events have been used as end points in trials of various methods to lower plasma lipids.

In 1976 a small study of 42 patients with femoral atherosclerosis showed that reduction in plasma lipids for one year was followed by angiographic improvement in six patients: on the other hand there was further luminal narrowing in 16 patients.⁷⁴ A randomised controlled trial of 24 subjects with hyperlipidaemia and intermittent claudication showed that after

treatment with cholestyramine, nicotinic acid, and clofibrate the number of femoral arterial segments that showed progression of atherosclerosis was reduced from 17.3% in the control group to 6.9% in the treated group.⁷⁵

Similar encouraging, though not startling, results were obtained by lowering plasma lipid concentrations in patients with coronary atherosclerosis. The National Heart Lung and Blood Institute study tested the effect of cholestyramine on coronary atherosclerosis in hyperlipidaemic individuals and reported cholesterol concentrations reduced by 26%.⁷⁶ Repeat angiography at five years in 59 treated patients and in 57 patients in a placebo group showed progression in 35% of those in the placebo group and in 25% in the test group; subclass analysis based on a range of angiographic variables suggested a favourable influence of treatment but clear statistical significance in the primary analysis was not achieved. A major difficulty in the study was that many individual patients showed both progression and regression at different sites within their coronary arteries.

Since these pioneer angiographic studies of regression other studies have been published. But there is no consensus on how to assess angiographic progression or regression in humans and trials of different methods both of deriving and analysing the measurements of stenoses are being reported. Direct comparison of these trials is therefore not easy.

In the Leiden Intervention Trial the plasma lipids were modified by diet alone; there was a modest reduction (mean (SD)) in total cholesterol (16.9 (1.4) mmol/l to 6.2 (1.3)) in 39 patients over two years without a control group.⁷⁷ In 307 lesions found on initial angiography, ranging from minor to high grade, quantification was by a computer assisted analysis using the CAAS system. The mean (SD) percentage stenosis of all 307 lesions increased from 44.1 (31.6)% to 48.6 (30.9)% over the two year period. Thus overall there was a significant progression of disease. Of the 39 patients, 21 showed an increase in the mean percentage stenosis and 18 showed no increase. Comparison of the total cholesterol and total/HDL cholesterol ratio in the two groups showed significant differences. In those with lesions that progressed total cholesterol was 6.5 (1.5) and total cholesterol/HDL ratio 7.1 (1.7) as against 5.8 (0.9) and 5.7 (1.2) respectively in those whose lesions did not progress. The results, while not showing regression, emphasised the role of raised total and LDL cholesterol and diminished HDL in influencing the progression of atherosclerosis.

In another study involving both a change in diet and lifestyle over a year LDL cholesterol was reduced by a mean of 37.4%.⁷⁸ One hundred and five lesions were detected by angiography in the 22 patients in the test group and 95 in the 19 patients of the control group. Quantification of the angiograms showed that there was an overall decrease (40.4 to 37.8%) in the mean degree of stenosis in the test group and an increase (42.7 to 46.1%) in the control group. The changes were similar for lesions

causing more than and less than 50% stenosis. Four of the patients in the test group showed progression and 18 showed regression while in the control group 11 either showed no change or progression and eight showed regression.

In the Cholesterol Lowering Atherosclerosis Study (CLAS) 162 men undergoing coronary artery bypass grafting were randomised to treatment with colestipol and nicotinic acid or to placebo.^{71 79} Angiographic assessment was visual and used both grades of progression and regression (+3 to -3) for lesions present at the initial angiogram and the appearances of new lesions. Repeat angiography at two years showed a reduction in the number of new lesions that appeared in both the native vessels and the grafts. In 80 treated patients 8 (10%) developed new lesions in the native coronary arteries compared with 18 (22%) of the 82 patients in the placebo group. The figures at four years continued the same trend with the difference in the frequency of new lesions being 14.3% *v* 10.4%. According to the overall scoring system, at two years 45% of the drug treated group were static compared with 36.6% of the placebo group; progression had occurred in 38.8% of the treated group and 59.8% of the placebo group. Regression at two years was noted in 16.2% of the treated group compared with 3.6% of the placebo group; by four years the figures were 17.9 and 6.4% respectively. Despite all of the difficulties inherent in an overall scoring system of the state of the coronary artery tree the different patterns of progression in the drug and placebo group seemed well established.

The Programme on the Surgical Control of Hyperlipidaemias (POSCH) study compared 421 patients treated by partial ileal bypass with 417 patients in a randomly allocated control group.⁸⁰ The entry criteria were survival after one infarct and a plasma cholesterol concentration of at least 5.69 mmol/l. A mean reduction in total cholesterol of 23.2%, a reduction of LDL cholesterol of 37.7%, and an increase of 4.3% in HDL were achieved. Mean follow up was 9.7 years with the angiograms being graded visually by two observers according to an eight point scale ranging from +3 to -3 from the CLAS study. Comparison of the angiographic scores showed that 38.9% of patients in the treated group and 11.3% in the placebo group had remained static. In the treated group 54.8% showed progression but only 4.2% of these were graded as -3; in the placebo group 85% showed progression with 26.2% of them graded as -3. Regression was seen in 6.4% of the test and in 3.8% of the placebo group. The five patients with the best regression score (+3) all belonged to the placebo group—this result shows the unpredictability of atherosclerosis. The conclusion overall was that though there had been no regression, the rate of progression of atherosclerosis had been significantly slowed.

In the Familial Atherosclerosis Treatment Study (FATS) 146 individuals with angiographic evidence of coronary atherosclerosis and at least one segment of significant stenosis, a family history of coronary artery disease, and raised lipid concentrations were randomised to

a control group, to lovastatin/colestipol, or to niacin/colestipol treatment.⁸¹ In the two treatment groups LDL concentrations fell significantly and plasma HLD concentrations rose. Angiography was repeated 30 months later. Angiograms were visually assessed and selected lesions manually traced to allow accurate measurement of the stenosis and lumen diameter. Nine standard proximal segments of the three main coronary branches were identified and the worst stenosis in each segment was measured. The average percentage stenosis of the worst lesion in all segments was calculated and regression or progression was expressed as the change in this value between the two sets of angiograms. In a second end point, regression and progression were defined for each patient individually by a change of at least 10% stenosis in at least one of the lesions. In this particular study only five of the 120 patients who completed the study had a mixture of progressing and regressing lesions; the rest could all be clearly classified as no change, regression, or progression. The 52 patients in the placebo group showed a mean increase of stenosis of 2.1% (SD 3.9%) while the niacin/colestipol group ($n = 48$) showed a decrease of -9% (3.0%) and the lovastatin/colestipol group ($n = 46$) a decrease of -7% (5.3%). Forty six per cent of the placebo group progressed, 11% regressed, and 43% showed no change. The corresponding figures for the niacin/colestipol group were 25%, 39%, and 36% and for the lovastatin/colestipol group 21%, 32%, and 47%. One possible drawback in the study is that three of the four examples of striking angiographic regression illustrated could be regarded as acute unstable plaques in the initial study and the "regression" is caused by remodelling after organisation and lysis of thrombus.

Though these four recent angiographic studies of the effect of lipid lowering on the progression of coronary atherosclerosis used different selection criteria and methods to quantify regression and progression, some broad conclusions can be drawn. The studies that used some form of objective quantification of the stenosis and lumen diameter did show some evidence of regression overall but the changes were small in functional terms and achieved statistical significance by virtue of the power and precision of the studies. What is clear is that all the studies whether they use automated quantification or semi-quantified visual grading show evidence for a slowing in progression of the disease. It may be that more aggressive lipid lowering over longer periods will increase angiographic change but the evidence so far does not suggest that diseased vessels will miraculously return to normal or high grade lesions resolve and so avoid the need for angioplasty.

The FATS and POSCH studies were primarily concerned with the angiographic development of the coronary artery disease after lipid lowering but they also examined clinical events. In the large POSCH trial overall mortality caused by coronary heart disease was reduced (deaths overall 62 *v* 49,

$p = 0.16$; coronary deaths 44 *v* 32, $p = 0.11$) but significance was achieved only if death due to coronary disease and non-fatal infarction were combined (125 *v* 82, $p = 0.001$).⁸⁰ In the far smaller FATS trial death caused by coronary disease and acute events such as unstable angina were considered together and were more common in the placebo group (10/52) than in the combined treatment groups (6/94, $p = 0.01$) representing a reduction in the incidence of clinical events of 73% but with wide confidence limits (23–90%).⁸¹

Evidence that calcium antagonists inhibited the development of atherosclerosis in animals prompted studies of their effect in humans in the International Nifedipine Trial on Anti-atherosclerotic Therapy (INTACT).⁸² The aim was to see whether nifedipine could inhibit the progression of angiographically demonstrated disease. The trial was a double blind randomised study of 425 patients, all aged less than 65 with mild disease and an ejection fraction of >0.40 . Three hundred and forty eight patients were restudied at three years; 175 were in the placebo group and 173 had been treated with 80 mg of nifedipine daily. The angiograms were quantified by a computer analysis system (CAAS).

An increase in the degree of stenosis by more than 20% in established lesions was equally common in the two groups (9.4% of lesions on placebo, 11.7% on nifedipine). In the controls 4.1% of lesions regressed compared with 3.0% in the nifedipine group. Thus progression or regression of established lesions was not different. Two hundred and forty seven new lesions (including 19 new occlusions) appeared at sites where the angiogram had previously shown an apparently normal vessel. Of these new lesions, 103 occurred in treated patients and 144 in patients in the control group ($p < 0.034$). In terms of new lesions per patient the average was 0.59 *v* 0.82—a difference of 28%. These results thus suggested that nifedipine can slow the rate at which new atherosclerotic lesions appear on angiography. The study cannot, and never set out to, determine whether this modest reduction in the rate at which new lesions appeared was of any long term benefit to the individual patient. In the study cardiac events and mortality were, however, recorded, and correctly have been reported by the authors. There were eight deaths (three acute myocardial infarction, five sudden cardiac death) in the treated group and two sudden deaths in the controls.

The data from the INTACT study are supported by some other studies. In high risk patients nifedipine reduced the frequency of coronary vein bypass graft atheroma. In one study, one year after surgery 62 of 93 grafts in patients on nifedipine were disease free compared with 71 of 136 in the placebo group (67% *v* 52%, $p < 0.04$).⁸³ In a small study to compare angiographic progression over two years new lesions appeared in 10% of 39 patients on nifedipine, 34% of 36 patients on propranolol, and 29% of 38 patients on isosorbide dinitrate.⁸⁴ In a larger study of nicardipine 383 patients with coronary atherosclerosis that was

demonstrable on angiography were randomised to treatment or placebo.⁸⁵ Quantification used the CAAS system. When all lesions were analysed irrespective of their initial severity an increase of 10% in diameter stenosis was found in 147 (12.7%) of 1153 lesions in the treated and 170 (14.5%) of 1170 lesions in the control group (NS). In 178 lesions of initially less than 20% of the diameter in the treated group 9.0% progressed compared with 16.3% of the 233 lesions in the control group ($p = 0.038$). The results based on absolute changes in vessel diameter were similar. The result thus resembled that found in the INTACT trial. There was a positive relation between the inhibition of progression of mild lesions and the lowering of blood pressure. This suggests that control of hypertension might be the simplest explanation for the beneficial effect on lesion progression. In animal models, however, calcium antagonists do not lower blood pressure. So this simple explanation of the beneficial effect is unlikely to be the only one. The clinical event rate was similar in the two groups.

Larger, more complex, and expensive trials are needed to ascertain the influence of calcium antagonists and lipid lowering drugs on the subsequent risk of cardiac events. Reducing the number of new plaques that appear and preventing further progression should reduce the risk; geographic surveys of atherosclerosis in the human aorta and coronary arteries show that on a population basis the number of plaques, measured as a percentage involvement of the intima, predicts the frequency of acute myocardial infarction and deaths related to atherosclerosis.⁸⁶

For all their technical complexity therapeutic trials using angiographic measurement of the development and progression of atherosclerotic lesions have considerable attraction. Because all the subjects in the trial have a measurable variable, differences between two treatment groups can be identified with relatively small numbers. Any result to which the word regression can be applied, albeit to a minor degree, has considerable emotive appeal. In contrast, trials using clinical events and mortality as end points need to be far larger and to last longer for sufficient adverse events to accumulate for comparison. The effects on events and mortality are, however, what we really need to know. However interesting they are in scientific terms, the angiographic studies are not yet a definite surrogate.

A review of all the randomised trials that have so far considered the effect of cholesterol reduction on total mortality⁸⁷ and coronary heart disease events confirms the original view⁸⁸ that if there is a significant increase in total cholesterol a 1% reduction produces a 2.5% reduction in event rate but a lesser effect on total mortality. There is no difference between primary and secondary trials in this regard and the basic pathology of the disease would not suggest there could be. The trials so far have been concerned with at best modest reductions in plasma lipids: the best recorded in the 19 trials analysed⁸⁷ is a mean of 17%. These

statements are bedevilled by the confusion caused by talking of relative risk reduction when a clearer idea of the magnitude would be given by absolute values. Definitive recommendations for the control of plasma lipid concentrations must await the results of drug trials which produce a more considerable lowering of plasma lipids.

The angiographic studies published do not so far contain any information that should alter, one way or the other, the current therapeutic indications for calcium antagonists, but they are encouraging because they show that the early progression of atherosclerotic plaques can be modified. Where they are likely to have symptomatic benefit by controlling angina or lowering blood pressure they may also have an additional antiatherogenic effect. The current evidence is an inadequate basis for recommending calcium antagonists outside the previously established indications, though they may ultimately turn out to have other properties as a useful by-product. Definitive recommendations on the role of calcium antagonists as antiatherogenic drugs must be based on the results of further trials designed to evaluate their effect on clinical events.

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PLANTS IN CARDIOLOGY

Coffea arabica L. From Bentley R, Trimmen H. *Medicinal plants*. London: J and A Churchill, 1880:144.

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Methyl xanthine diuretics

Caffeine, theobromine, and theophylline were first studied in 1886 and although they are now obsolete they were important before the discovery of the synthetic diuretics in 1951 and especially before organic mercurials were introduced in 1920. They act by depression of renal tubular reabsorption. Caffeine is only a weak diuretic. Theophylline was shown to be better than theobromine by H M Marvin in an excellent early clinical trial (*Journal of the American Medical Association* 1926;87: 2043-6). It was effective in two thirds of patients who were still oedematous after treatment with digitalis. Theophylline also has a direct stimulant effect on the myocardium which was demonstrated at cardiac catheterisation by McMichael and colleagues at Hammersmith Hospital (*Clinical Science* 1946-48;6:125-35) and shown by them to be greater than that of digoxin in hypertensive right heart failure.

Theophylline is found in the tea plant *Camellia sinensis* (Theaceae) a native of China and India but the amount, 0.1%, is small for clinical use so it has to be synthesised. Theobromine is present in the cocoa tree *Theobroma cacao* (Sterculiaceae) which comes

from the tropical forests of South America. Caffeine is present in both tea and cocoa and in other traditional beverages. In Africa these are coffee *Coffea arabica* (Rubiaceae) and the cola nut *Sterculia acuminata* (Sterculiaceae). In South America the ancient drink maté is made from a species of holly *Ilex paraguariensis* (Aquifoliaceae) while yoco comes from a species of *Paullinia* (Sapindaceae). Thus the methyl xanthines come from six plant families in the Old and New World that have no obvious botanical similarities. As has so often happened with medicinal plants, their therapeutic value was discovered by chance.

Purgatives were often used to treat heart failure before the xanthine diuretics were introduced and several of them were plants—elaterium, senna, aloes, cascara, croton, rhubarb, and podophyllum. Presumably they produced their effect because of the coincidental sodium loss that accompanied diarrhoea.

Theophylline seems to be making an exciting therapeutic comeback. It is now used to control erythrocytosis in patients with renal transplants. It reduces erythropoietin production by adenosine antagonism (*New England Journal of Medicine* 1990;323:86-90.

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