Pathogenesis of Myocardial and Cerebral Infarction: Nodular Arteriosclerosis*

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[WITH SPECIAL PLATE]

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One of my greatest bits of good fortune was to spend nine years as an assistant to Thomas Lewis and during that time to have the privilege of his friendship. Some of you here knew Lewis, but to others he is merely a name—you know him as one of the founding fathers of electrocardiography, you know him for his study of the blood-vessels in the human skin, you know him for his textbook on heart disease, you know him for his work on pain, and you know him as the father of clinical science. To Lewis, more than to any other man, is due the revolution that has brought the scientific method back to the study of disease in man. Such achievements betoken a remarkable man, and Lewis was a remarkable man in his passion, his singleness of purpose, and the efficiency of his work. Artists have told me that there is only one recipe for success as an artist—namely, hard work. Lewis used to say to me: “You get nothing worth while in this life except by the sweat of your brow.” When I knew him he wrote easily and well, but T. R. Elliott told me that as a young man writing came hardly to him. I remember explaining to him that I had not written something because I was not in the mood and thought therefore that the writing would not be very good. He said to me: “There is only one way to write and that is to sit down and write. You may have to throw away everything that you have written in the first hour, but after that you will find it will go, and then the thing to do is to go on writing until it is finished.” That, I think, was the essence of Lewis.

It is most appropriate that Lewis's memory should have been kept green by the endowment of a lectureship by his friends and colleagues. It is a great privilege to be asked to commemorate him in this way the first time. I was tempted to talk about him and his work, but I think that he would rather have a different precedent set. His greatest passion was the advancement of knowledge in the field of human disease. I rather think he would like his lecture to be used to this end.

Lewis had his first myocardial infarction at the age of 48. He had his second some seven years later; his third happened a year before he died of a fourth attack at the age of 63. Why was he so prone? Not because he had an elevated arterial pressure—it was taken many times in the course of experiments in the laboratory and was never, to my knowledge, over 130 systolic. Not because he was physically inactive—even after his second infarction he excavated some tons of gravel from his garden to build a swimming-pool. I do not know whether he had an abnormal blood lipid pattern, but I never observed him eating a conspicuously high-fat diet. He smoked cigarettes heavily until his first infarction; after that not at all until the last year of his life. He did, however, have a strong family

history: his father and his grandfather both died suddenly in their sixties.

One of the first pieces of work that I did with Lewis was on the mechanism of pain in intermittent claudication (Lewis, Pickering, and Rothschild, 1931). Our experiments on ourselves suggested strongly that the pain was due to a substance, which we called “P factor,” liberated within the muscle fibre during contraction and diffusing out to stimulate the pain nerves in the spaces between the fibres. This seemed to be the basis also of cardiac pain. Lewis was very anxious to have angina pectoris worked out, and this was done by Wayne, working successively with Laplace and Graybiel (Wayne and Laplace, 1933; Wayne and Graybiel, 1934). Their observations suggested that the mechanism of pain was similar to that of intermittent claudication. One thing puzzled me greatly—namely, the abrupt onset of claudication and angina pectoris in many patients. I remember, for example, a Cook's courier who got up to walk home after having had dinner in the Champs-Élysées; he was stopped by pain in the calf, which went off after a few minutes' rest but quickly stopped him again so that he had to have a taxi home. Blumgart and Schlesinger's demonstration that in patients with angina pectoris it was common to find at least one coronary occlusion suggested that in a similar way this man probably thrombosed his femoral artery while he was having dinner. This sort of incident impressed on my mind the importance of the thrombotic episode. I have no doubt at all that it has influenced my thinking about this disease.

Widespread Disorder

The problem I want to discuss in this lecture is the disease of large arteries in which intimal nodules or plaques narrow the lumen; finally a thrombus occludes it and manifestations of ischaemia develop in the territory supplied. This disorder of the arteries tends to be widespread and to affect the aorta and the larger arteries such as the carotids, vertebrals and circle of Willis, the coronaries, the renals and iliacs, femorals and popliteals. While the patient commonly presents with symptoms arising from occlusion of one of these arteries, he is quite likely subsequently to develop symptoms from another. Thus it is known that the repair of arteries occluded by this disease in a lower extremity tends to be rather unsatisfactory because this does not prevent a subsequent myocardial or cerebral infarction.

This disease is essentially an intimal one. The plaques or nodules consist mainly of fibrous tissue with variable amounts of fatty infiltration; collections of cholesterol crystals in thin characteristic clefts in more or less acellular amorphous tissue

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are variable in extent and tend to be deeply situated (Fig. A). Since you will rightly suspect a clinician of heresy in morbid anatomy, let me quote two pathologists of unblemished objectivity. Turnbull (1915) defined atheroma as follows:

"Atheroma is a degeneration which affects, and is almost confined to, the intima. It is found in both the elastic and the muscular arteries but is commoner in the large elastic. The degeneration is characterized by the accumulation of debris, which is at first fatty and is later frequently impregnated by calcium. Intimal fibrosis is merely a modification of atheroma."

FIG. A.—Rindfleisch's (1872) diagram of an intimal nodule which he, as a pupil of Virchow, termed "chronic endoarteritis." His legend reads: "Section through an indurated elevation of the inner coat which is undergoing fatty degeneration in its interior. *b*: Junction of inner and middle coats; *a*: inner coat; at *c* this is hyperplastic and thickened, while at *d* it has become converted into an atheromatous abscess."

Muir (1925), in his textbook, wrote:

"Atheroma or, as it used to be called, endarteritis deformans, is a condition characterized by the formation of patches of thickening of the intima attended by degenerative change. It occurs in arteries of all sizes, but is especially common in the aorta and in various smaller vessels which are poorly supported, for example the cerebral arteries, coronary arteries of the heart, splenic, etc."

"The superficial part of the patch is composed of thin laminae of connective tissue with proliferated cells between them. Underneath these, the laminae become swollen and degenerated and merge into the accumulation of degenerated material in the deeper part. This material comprises globules of ordinary neutral fat, myelin and albuminoid granules; crystals of cholesterol and fatty acids are common, and lime salts may be deposited in varying degree. It is noteworthy that a patch of such a nature may be markedly developed, whilst the subjacent part of the media may show little or no change. Fatty change or even fibrosis may affect the superficial part of the media, when the lesion is advanced, but there appears to be no doubt that such change is secondary, and that, unlike what we find in the case of syphilitic lesions, the disease is, in the first place, essentially an intimal one."

Lipid Hypothesis

By far the most popular hypothesis of the pathogenesis of this disease, and the hypothesis to which some 90% of the research is devoted, is that it represents a consequence of a disturbance in lipid metabolism. The Virchow-Aschoff imbibition theory, as it is often called, assumes that lipids from the plasma are absorbed directly through the endothelium into the intima and, when conditions are suitable, some of these, cholesterol esters in particular, are deposited. Virchow thought the preliminary stage to this deposition was loosening of the connective tissue ground substance caused by mechanical strain. Aschoff stressed the importance of cholesterol esters and overlooked the possible significance of the other lipids. He postulated that increased concentrations of lipids, especially cholesterol esters, *must* be present before atheromatosis appears, a view that analyses of the blood have not supported.

Leary (1936, 1941) proposed a modification and suggested that lipid-containing macrophages ("foam cells") collected in the subendothelial layers of the intima and later disintegrated, leaving their charge of fat and lipids intracellularly. This agreed with Klotz's (1905) earlier observations.

Irvine Page (1959) summarizes these views in his usual lucid manner:

"I suppose the commonest notions with regard to the lipids in this country are two: (a) That lipid enters the blood vessels by filtration or phagocytosis, some of it becoming sequestered, thus setting up a focus of irritation. Fibroblastic and endothelial proliferation provide the scarring. (b) The other suggests that lipids are synthesized within the vessel wall itself and atherogenesis is the result of a local disturbance of lipid metabolism."

The alternative view began with Carl von Rokitansky (1852). He saw the intimal thickening as arising from an excessive deposit on the inner membrane of the vessels accompanied by hypertrophy of this membrane and terminating in two forms of metamorphosis—atheroma and ossification.

Rokitansky's hypothesis has been revived by Duguid (1946), who wrote (1959):

"I was demonstrating the principles of organization to a class of students, using a thrombosed and canalized coronary artery. Each member of the class had his own section and in the course of the demonstration I noticed that some were in difficulties because, instead of a canalized artery, they had an artery with a thickened intima. It was obviously the same vessel, but in cutting the sections the technician had gone beyond the occluded part. This fortunate accident drew our attention to an aspect of arterial thrombosis which held the key to the problem. When the sections were recalled and examined in serial order the fibrous mass which represented the occluding thrombus was found to be continuous with that which formed the intimal thickening. In other words, the thrombus did not end with the occlusion, but extended further along the artery as a fibrous thickening. Here was evidence that thrombosis could be a source of arterial thickening and, in fact, the solution to the problem of narrowing. A thrombus occupying the lumen of an artery was bound to narrow it, and the only difficulty now was to understand how thrombosis could fit into the picture of atherosclerosis."

Duguid's views, as expressed in 1955 were:

"As I have explained, the formation of a covering layer of endothelium and a subjacent layer of connective tissue has the effect of burying mural thrombi in the intima, but this effect is carried further when fresh surface deposits are superadded. As may be seen from some of the illustrations, mural thrombosis is a recurring condition, and successive layers of fibrin tend to be deposited one on top of another and in turn organized, so that cumulative thickenings of the intima are produced. This, in medium or small vessels such as the coronaries, results in progressive narrowing of the lumina, and constitutes the danger in atherosclerosis, but it must be realized that the narrowing of arteries by thrombosis can be a temporary affair. Mural thrombi under the influence of the blood-pressure become compressed and reduced in size, so that a mass which may at first almost occlude the lumen becomes flattened out and, if completely organized, forms a relatively thin layer of fibrous tissue. In fact we frequently find that arteries which have obviously been thrombosed are actually dilated, the fibrous thickenings of their walls having interfered with their elasticity and rendered them liable to permanent stretching. The narrowing of arteries by mural thrombosis has therefore to be looked on as both a regressive and progressive process, regressive in that each individual thrombus, given time, shrinks; but progressive in that thrombosis tends to recur, so that it is in rapidly recurring thrombosis that the danger lies."

"It is not suggested that all atherosclerosis is thrombotic in origin—for there are fatty changes to be found in the young aorta which are undoubtedly the outcome of other processes—but it can be shown that most of the features we regard as characteristic of the advanced atherosclerosis, including fibrous thickening, hyaline and fatty degeneration, atheromatous softening and vascularization of the intima, can be the products of mural thrombi. In fact it is difficult to explain them in any other way; and the further we inquire into the histology of atherosclerosis the more frequent an occurrence does arterial thrombosis seem to be."

Duguid and Robertson (1957) suggested that the atheromatous deposits might be the products of intramural haemorrhage occurring through shearing of tissue at the junction of two semi-rigid tubes, an inner and an outer, subjected to the pulsation of the arterial pressure. Crawford and Levene (1952),

made an alternative suggestion—namely, that the atheroma occurred through ischaemic degeneration of a central area of thrombus remote from its centres of organization, the media and the luminal surface.

While credit for resuscitating this hypothesis is justly given to Duguid, he did in fact have predecessors whose work has been overlooked. Clark, Graef, and Chasis (1936) noted:

"Homogeneous masses which exhibited the tinctorial properties of fibrin were frequently encountered on the surface and within the superficial fibrous regions of intimal aortic plaques of atherosclerosis and syphilitic aortitis. . . . As a result of repeated deposition of blood clots on the surface of the plaques and progressive organization of such hyalinized elements, the plaques of syphilitic aortitis and atherosclerosis may undergo a progressive increase in size. A thrombus of formed configuration may frequently supervene on such laminated hyalinized and partially organized surface deposits."

The popularity of the lipid hypothesis may be ascribed to three factors. First, fatty deposits in the intima of the large arteries can be produced experimentally by feeding rabbits with cholesterol; however, the doses are large, the arterial deposits are part of a generalized cholesterosis, and thrombosis does not occur. Second, there is a tendency to elevated blood lipids in subjects who have had a myocardial infarction, and an increased probability that those with elevated blood lipids—for example, cholesterol—will develop an infarction (Dawber *et al.*, 1962). Third, there seems to be a correlation between the fraction of calories provided by fat, and particularly animal fat, and frequency of myocardial infarction; many other factors are, however, more highly correlated—as, for example, the issue of licences for radio and television sets (Yudkin, 1957). Perhaps the strongest argument for the hypothesis has been the magic name of Virchow, conjured up by Aschoff (1933). Virchow's later views were, in fact, quite different, as may be seen from an abstract of his classical article of 1856, which I give as the Appendix to this paper. Virchow was struck by three features of the intimal plaque—the presence of abnormal substances between the cells, the presence of actively dividing cells as in a tumour or in the irritated cornea, and fatty metamorphosis. He thought the abnormal constituents of the ground substance came from the blood, and, since the intima was intact, came by imbibition; he thought the fatty changes were secondary; and he thought the lesion essentially inflammatory, so he gave it the name *endarteriitis deformans sive nodosa*.

The great weakness of the lipid hypothesis is that it does not account for the thrombus. It thus supposes the early and the late manifestations represent different processes. Increasing knowledge shows us that, in general, ischaemic symptoms in brain, heart, and limbs are due to thrombosis on top of a nodule. According to the lipid hypothesis, this thrombus represents an event of a totally different kind from the process conceived to underlie nodule formation. The hypothesis sees this major event as almost an irrelevant accident happening because alterations in lipid metabolism also predispose to thrombosis; or by supposing that the thrombus is a by-product, as it were, of the nodule which sets up eddies and so leads to thrombosis. Neither is very satisfying to a clinician, since it assigns a minor role—in fact almost an afterthought—to the event that determines life or death.

In this paper is presented evidence that the disease is essentially a thrombotic one. The hypothesis closely resembles that of Rokitsansky, of Clark, Graef, and Chasis, and of Duguid, but differs in suggesting that these thrombi are not, in the first instance, simple fibrin thrombi but are platelet-leucocyte-fibrin thrombi. They are, in fact, exactly similar in composition to the thrombi that eventually close the artery.

The evidence comes from three sites—the coronary arteries, the internal carotid artery, and the aortic bifurcation. Illumination also comes from the subclavian artery in cervical rib and from mural thrombosis of the endocardium. Before proceeding to the evidence a brief diversion must be made to the Augean stable of "atherosclerosis."

Atherosclerosis

Atherosclerosis is a term introduced by Marchand in 1904 as an alternative to arteriosclerosis, to emphasize the fatty component of some of the lesions in the latter. Aschoff sold it to a world made receptive through the demonstration that a fatty intimal thickening of the aorta and large arteries could be produced by feeding animals with astronomical doses of fatty foods and cholesterol (Anitschkow, 1933). One of the advantages which Aschoff adduced for atherosclerosis is that the term emphasized the essential unity of the medial disease described by Mönckeberg and the intimal lesions.

Arteriosclerosis means hardening of the arteries, but Lobstein (1829) when he introduced it left no doubt that the hardening he was describing was associated with a mammillary thickening of the inner coat. The weakness of the term is that, because there was no other name, it became used for all diseases of all the coats of all different types and sizes of arteries that were not plainly of an inflammatory type.

Atherosclerosis means a "porridge-like hardness." Even my memories of breakfast at school, and they are horrible enough, fail to convince me that this is what I, or indeed anyone else, sees or feels in any type of diseased arteries. Indeed I can see no reason for the prevailing passion for this word other than an ignorance of the Greek language, and an urge to conform to the latest style. It is, in fact, an interesting example in medicine of what psychologists call mass hysteria, "of keeping up with the Joneses."

Be that as it may, the fact is that this meaningless word is now in current usage, supposedly to describe a specific disorder, but in fact to describe every deviation from the norm in every coat of every artery from the aorta to the tiny arteries about 100 μ in diameter that course over the retina. For it is now fashionable to talk of retinal atherosclerosis. Can technological jargon sink to greater depths of absurdity than to talk about a porridge-like hardness of the retina when it is dealing with a variety of changes in the arterial wall?

It is not surprising that in this field everyone is able to ride his own particular hobby-horse and to find people who will back his horse. I have no doubt that fat droplets do accumulate under the intima of the aorta as the so-called fatty streaks. I have no doubt that in certain people, possessing what seems to be a single gene defect leading to familial xanthomatosis, there is an increased liability to arterial obstruction. I have no reason to doubt that disturbances do occur in the mucopolysaccharides of the aortic wall. It seems inherently probable that the enzyme pattern changes with advancing age and that it changes more in some people than others. And it would seem to me a perfectly harmless pursuit to suppose that these lipoid, polysaccharide, and enzyme changes are the cause of porridge-like hardness (atherosclerosis) so long as no one is misled into thinking that this is a specific arterial disease.

You will no doubt think I have been about as damning as I could possibly be about the term atherosclerosis. This is quite deliberate, though I do hope I have not given needless offence to respected colleagues and friends. The use of this all-embracing term as synonymous with what has many of the characteristics of a specific disease is I think the most disastrous obstacle to scientific advance in this field.

Myocardial Infarction

The problem of assigning an anatomical cause to angina pectoris and myocardial infarction has suffered much from inadequate methods. What we want to know is the state of the coronary arteries from their origin to their final branchings as they were just before death. The greatest single advance was the introduction by Gross (1921) of injection methods and subsequent radiological display of the whole coronary tree. This method was elaborated by Blumgart, Schlesinger, and Zoll

(1941), who found in 355 consecutive cases examined at necropsy that every patient suffering primarily from angina pectoris without valvular disease or hypertension showed old complete occlusion of at least one coronary artery. Thirty-eight patients without symptoms or signs of heart disease had old occlusion of a main coronary artery. Twelve of 45 hearts with acute myocardial infarction had neither acute coronary thrombosis nor acute coronary occlusion. They concluded that coronary ischaemia depended on balance of demand and supply and that duration determined symptoms, the greatest duration of ischaemia manifesting itself as actual infarction of the heart. Subsequent workers have not always agreed with these findings—for example, Branwood and Montgomery (1956). The matter is of great importance because of the vast amount of man-hours of research now being devoted throughout the world to the problem of myocardial infarction. I know of no more useless occupation than trying to find an answer to the wrong question. Accordingly Drs. Mitchell and Schwartz tackled the problem afresh.

Mitchell and Schwartz investigated two series of patients who came to necropsy. The first consisted of every tenth and latterly every fifth patient aged 35 years and over on whom a necropsy was performed at the Radcliffe Infirmary, Oxford. This "unselected group" consisted of 75 men and 62 women. The second was a selected group of 57 men and 22 women who had evidence of previous myocardial infarction. In each case in the two series they examined aorta, carotid, and iliac arteries. In each heart they cannulated the right and left coronary ostia, washed the vessels through with warm saline, and injected at a pressure of 80 mm. Hg a barium sulphate gelatin mass simultaneously into the two coronary circulations; that injected into the right coronary artery was coloured blue. After five minutes the heart was immersed in 10% formalin at 4° C. After fixation the hearts were x-rayed stereoscopically and sectioned by a bacon-slicer. The sections were also x-rayed and then cleared in methyl salicylate. Selected pieces were examined histologically.

At the outset they were faced with the usual problems of classification and nomenclature; that is to say, with the problem of grouping like with like and separating them from unlike and giving these lesions a name that all may understand.

They classified the cardiac lesions in which muscles fibres had been replaced by scar tissue as small, area 1 sq. cm. or less, or large, area 4 sq. cm. or more.

In the aorta and larger arteries they concluded that there were two quite different kinds of lesions (Schwartz and Mitchell, 1962a).

1. *Fatty Streaks*.—These essentially unraised lesions vary from small spots to large areas covering many square centimetres and stain intensely with fat stains (Sudan IV). The intima shows a variable but slight thickening consisting of fat-laden macrophages in a fine meshwork of fibrous and elastic tissue. There are no changes in the other arterial coats.

2. *Raised Plaques*.—These raised areas of intimal thickening are associated with medial atrophy and adventitial vascularization and cellular infiltration. Histologically the intima shows varying combinations of fibrosis, elastosis, calcification, granulomata, and fatty deposits, particularly the pultaceous material fissured by numerous acicular clefts containing cholesterol crystals.

They concluded that these two lesions were essentially dissimilar for the following reasons. They are dissimilar histologically. Their frequency differs in different racial groups. Their distribution in the aorta differs; fatty streaking is usually absent from the mouths of the intercostal arteries and most conspicuous around the midline of the aorta posteriorly, sparing the lateral and anterior walls; raised plaques are most conspicuous around the mouths of the intercostal arteries and on the lateral and anterior walls of the thoracic aorta. They commented: "We endorse the views of Ophüls (1933), who in

discussing the significance of fatty streaking in the development of 'atheroma' remarked, 'The microscopic appearance of the fatty streaks suggests a semi-physiological deposition of lipid material in the intima . . . while the atheromatous lesions from the beginning are distinctly pathological in being accompanied by the development of new fibrous tissue and areas of necrosis.'"

Of the two kinds of arterial lesion only the raised plaques encroach on the lumen and therefore contribute to stenosis. They graded arterial disease according to the area and thickness of these plaques. In the case of the coronary arteries they assigned a score to each heart according to the degree of stenosis (W.H.O. classification) of the named branches.

In the unselected series (Schwartz and Mitchell, 1962c) they found that the prevalence of small lesions increased with age but was otherwise not related to the severity of coronary artery disease. By contrast, large lesions were more frequent in those with the more severe grades of coronary artery disease. It therefore seemed that the large lesions were a consequence of coronary artery disease and thus the relics of myocardial infarction. Small lesions originated differently, perhaps from focal myocarditis.

The degree of coronary artery disease was related to the extent to which the surface of the aorta was affected by raised plaques and to the extent to which the neck and iliac arteries were similarly affected. They found that certain sites were preferred by these lesions, such as the left anterior descending branch of the coronary arteries, the common and internal iliacs, and the carotid sinus. They considered that the preference of the disease for these sites might be due to turbulence, which had permitted blood particles to adhere and had thus encouraged thrombus formation.

The selected group (Mitchell and Schwartz, 1963) consisted of every patient coming to necropsy during the period of study who showed any of the following features:

1. *A clinical history of* (a) severe retrosternal chest pain lasting for more than an hour; (b) a fall in blood-pressure, the onset of cardiac failure, or the development of an arrhythmia for which no adequate clinical explanation could be found; (c) sudden death in patients in whom examination of the organs other than the heart at necropsy had provided no explanation for their death.
2. *Electrocardiographic abnormalities*: (a) Pathological Q waves; (b) changing ST and T patterns on serial records.
3. *Necropsy findings*: (a) Ventricular discoloration and softening; (b) ventricular thinning.

Of the 70 hearts selected on the above criteria 64 were found to have large lesions; 15 patients with large lesions were added from the unselected group to give a total of 79.

The same relationship was found between the severity of coronary disease and the presence of these lesions as in the unselected group (Figs. B and C).

Tables I and II show the relationship between coronary artery occlusion and the histological age of the infarct as estimated by the criteria of Mallory, White, and Salcedo-Salgar (1939). Fig. 1 (Special Plate) shows occlusion by a thrombus, Fig. 2 occlusion by "atheroma." The tables make it clear that the frequency with which large lesions are associated with occlusion or near-occlusion is related to the age of the lesion. The older it is the less frequent is occlusion or near-occlusion and the less frequent is thrombus and the more frequent is a recanalizing thrombus or atheroma. I would like to quote some of Mitchell and Schwartz's (1963) conclusions.

"From the random survey we concluded that large lesions were commoner in men than women, that they occurred at an older age in the women, and that they were associated with severe coronary narrowing and coronary occlusions. This selected group confirms these findings, and in particular emphasizes the strong correlation with coronary occlusion. This is most clearly seen in the group of patients with a single lesion, which shows that recent large lesions are related to coronary thrombosis, and can therefore be accurately described as myocardial infarcts. As the lesion ages, the frequency of occlusion falls and thrombus is replaced by recanalizing thrombus

or 'atheroma' as the main type of occluding mass. This is of considerable importance when one realizes that nearly half our total group of patients with large lesions showed more than one lesion, and that their arteries would carry a legacy of their previous episode. One cannot assess then, from the whole group, what the state of the coronary arteries was before each patient's first lesion. The patients who provide most information on this important point are those with single recent lesions, and it is significant that their coronary scores differ less from the random population than do those of the whole large lesion group. The factor that marks out these patients, therefore, is not the severity of coronary stenosis alone but the presence of coronary thrombosis. It is often suggested that wall disease must be present for a thrombus to form, but the main evidence for this concept is the rarity with which thrombosis occurs in a normal vessel. However, if one postulates that stenosis and thrombosis are not related, but are both age-dependent phenomena, thrombosis would thus be rare in normal arteries, for patients at risk from thrombosis would be unlikely to have normal arteries. There is considerable evidence however that thrombus and atheroma are not unrelated, but that organizing and recanalizing thrombus can produce arterial plaques (Duguid, 1946). We consider that our findings in lesions of different ages strongly support Duguid's views: the severe degree of stenosis seen in our complete group

may in part relate to the presence in the group of patients with several lesions and with old lesions, whose arteries carry the residue of old occlusions."

I would like to make two additional and important points from this very beautiful work.

Nature of the Thrombus

As Poole and French (1961) have explained in their admirable review of thrombosis, thrombi formed in circulating blood have a characteristic structure. Masses of platelets appear closely packed together surrounded by leucocytes, in a meshwork of fibrin strands which may or may not contain masses of trapped red cells. This is the classical platelet-leucocyte-fibrin thrombus. Experimental work which is also reviewed in their article has shown the crucial importance of platelets in thrombosis; probably platelet clumping on the vessel wall is the initiating event.

The fresh thrombi found by Mitchell and Schwartz in occluded coronary arteries are of this classical type. Fig. 3 (Special Plate) shows a typical example. As these thrombi age, the nuclei disappear from the leucocytes; the platelets coalesce, the red cells become decolorized. What remains is a more or less structureless mass sometimes called amorphous thrombus which gives some of the staining reactions for fibrin. This becomes organized by invasion of histiocytes from the underlying wall and from the luminal surface if there is one. As Dible (1958) has pointed out, there is a difference between the organization of a mural thrombus and an occlusive one, the latter showing a much more conspicuous development of new blood channels.

Endocardial Thrombus

Of great interest to our present theme is the mural thrombus which develops on the endocardial aspect of a myocardial

TABLE I.—Occlusion Status and Nature of Occlusion in Men and Women With Single Massive Lesions of Various Histological Ages (Mitchell and Schwartz, 1963)

Histological Age of Lesion	No. of Patients				Nature of Occlusion or Probable Occlusion—as No. of Arteries		
	Total	With Occlusions	Probably Occluded	Stenosis Only	Thrombus	Recanalizing Thrombus	Plaque
Less than 2 days	10	7	3	0	15	0	1
2-13 days	11	7	3	1	15	1	1
2-4 weeks	2	2	0	0	1	3	0
1-4 months	2	2	0	0	0	1	3
Over 4 months	21	10	4	7	0	24	6
All ages	46	28	10	8	31	29	11

TABLE II.—Occlusion Status and Nature of Occlusion in Men and Women with More than One Massive Lesion, According to Histological Age of Youngest Massive Lesion (Mitchell and Schwartz, 1963)

Histological Age of Youngest Lesion	No. of Patients				Nature of Occlusion or Near Occlusion—as No. of Arteries		
	Total	With Occlusions	Probably Occluded	Stenosis Only	Thrombus	Recanalizing Thrombus	Plaque
Less than 48 hours	6	5	1	0	9	5	5
2-13 days	13	13	0	0	21	8	6
2-4 weeks	5	4	1	0	3	6	3
1-4 months	9	7	2	0	1	15	5
Over 4 months	0	0	0	0	0	0	0
All ages	33	29	4	0	34	34	19

FIG. B.—Coronary scores of men with large lesions compared with men from the random necropsy sample without large lesions (Mitchell and Schwartz, 1963). O=Random: no large lesions. Δ=Random: large lesions. ▲=Selected: large lesions.

FIG. C.—Coronary scores of women with large lesions compared with women from random necropsy sample without large lesions (Mitchell and Schwartz, 1963). Indications as Fig. A.

infarction. Fig. 4 (Special Plate) shows that this has the characteristic structure of a platelet-leucocyte-fibrin thrombus. Fig. 5 shows a later stage in which the thrombus has become amorphous and is being organized. Fig. 6 shows the final stage of complete organization into scar tissue and the development of elastosis, the new tissue being separated from the surviving muscle by a dense layer of elastic tissue forming an internal elastic lamina.

Cerebrovascular Accidents

Cerebrovascular accidents, or strokes, are not all of one kind. The classical division is into haemorrhage, thrombosis, and embolism; to which some would add cerebral artery spasm. Without special investigations such as angiography, differentiation is difficult and uncertain. Even when there is manifest infarction of the brain its cause may not be apparent; Hutchinson and Yates (1957), investigating 100 such cases, thought stenosis of carotid or vertebral arteries was the most probable cause, but Schwartz and Mitchell (1961) found the frequency of stenosis of these arteries not dissimilar in a random series of routine hospital necropsies of similar age and sex.

The cerebral arteries are much more difficult to dissect out or to study by injection methods than are the coronaries. Only recently, and using an injection technique similar to that of Mitchell and Schwartz, has Ross Russell (1963) confirmed Charcot's original observation that cerebral haemorrhage is often associated with aneurysms of the smaller cerebral arteries, and has shown that such aneurysms are more frequent in subjects with raised arterial pressures. Much less is therefore understood of the pathology of the cerebral than of other arteries and of the intimate mechanism of cerebral infarction and other varieties of stroke. That strokes affect an older age-group, show less predominance of males, have not increased in prevalence in Western countries since the war to the same extent as has myocardial infarction (Ustvedt, 1959), and are common in countries such as Japan, where myocardial infarction is rare, no doubt reflects a different pathology. Perhaps the special factor operating here is the causal relationship between cerebral microaneurysms and a long-continued rise of arterial pressure.

Carotid Artery Disease

In this lecture I want to restrict my attention to the syndrome resulting from nodular arteriosclerosis of the internal carotid artery and the related internal carotid thrombosis. The syndrome of thrombosis of the internal carotid was first described by Egaz Moniz, Lima, and de l'Acerda (1937), who recognized it through the medium of cerebral angiography which Moniz had recently introduced. Many papers amplifying the original account have subsequently been published—for example, Denny Brown (1951), Fisher (1954), and Edwards, Gordon, and Rob (1960). Characteristically, a hemiparesis, complete or partial, or aphasia develops in phases and may be preceded by transient attacks of a similar kind with or without attacks of blindness in the opposite eye.

I became interested in this syndrome because I disbelieved the commonly accepted explanation of these transient attacks—namely, cerebral artery spasm. In one patient, described in 1954 with Eastcott and Rob, the transient attacks seemed to be due to fall of arterial pressure in the presence of a stenosed carotid artery, since the attacks were preceded by tachycardia and sternal discomfort and since excising the stenosis ended a series of attacks of blindness and contralateral hemiparesis that had numbered 33, though the attacks of tachycardia and sternal discomfort continued. I had previously seen two other patients (Pickering, 1951) with repeated transient attacks that might have been of similar origin. Since then, however, I have seen no patient in whom a similar mechanism seemed a probable explanation.

A decisive experience (Pickering, 1959) was of a woman aged 36 (T.S.) who had a hemiparesis followed by a series of transient attacks of blindness in the opposite eye, the last attack leaving her permanently blind with all the signs of central retinal artery obstruction. She also proved to have a plaque projecting into her carotid sinus, excised by Professor Charles Rob, but not examined histologically. Subsequently she developed ischaemia of the fourth and fifth toes on both feet, with a central abdominal murmur, but has not yet allowed an aortogram.

The only reasonable explanation of the ocular and cerebral symptoms in this patient was of emboli arising from the arterial plaque. But I was then only familiar with emboli that were stable; I saw them rather like lead shot that travelled to

LEGENDS TO SPECIAL PLATE

FIG. 1.—Coronary artery occluded by laminated thrombus (P.T.A.H.). The stripes are mainly fibrin: the pale area in the centre of inferior surface consists of agglutinated platelets with leucocytes and fibrin. Note the intimal thickening is mainly fibrous tissue, but there is an extensive poorly staining area that contained cholesterol crystals. There is also a small granulomatous area. (Mitchell and Schwartz, 1963.)

FIG. 2.—Coronary artery occluded by "atheroma." (Trichrome: $\times 15$.) (Mitchell and Schwartz, 1963.)

FIG. 3.—Fresh thrombus in a coronary artery. The fine granular mass centrally represents conglutinated platelets; the strands are fibrin, and the black dots the nuclei of white cells (from Dr. Mitchell).

FIG. 4.—Endocardial aspect of myocardial infarction showing ill-defined zone of surviving muscle overlaid with recent platelet-leucocyte-fibrin thrombus. (Trichrome stain.) (Mitchell and Schwartz, 1963.)

FIG. 5.—Endocardial aspect of myocardial infarction showing fibrin (black) in organizing mural thrombus. (P.T.A.H. $\times 20$.) (Mitchell and Schwartz, 1963.)

FIG. 6.—Fibrous endocardial rind intervening between endothelium and surviving rim of surviving heart muscle in an old myocardial infarct. (Trichrome. $\times 90$.) (Courtesy of Dr. Mitchell.)

FIG. 7.—E.D., aged 54. Endarterectomy specimen removed by Mr. A. J. Gunning from left internal carotid artery soon after the events shown in Fig. D. The platelet-leucocyte-fibrin thrombus is plainly shown, the clear areas being platelet masses. It sits on an older amorphous thrombus, which in turn is on thickened intima.

FIG. 8.—H.S., male aged 59. Endarterectomy specimen from left carotid removed seven weeks after right hemiparesis. A fresh platelet-leucocyte-fibrin thrombus sits on an older amorphous thrombus, which sits on a layer of fibrous tissue overlying grumous material with cholesterol clefts.

FIG. 9.—V.M., male aged 56. Two episodes of right hemiparesis, the first transient, the second permanent. Section through nodule removed from left internal carotid one month after last episode. Deeply is an atheroma (with cholesterol clefts), then a layer of fibrous tissue, then organizing amorphous thrombus, and projecting into the lumen a tag of fresh platelet-leucocyte-fibrin thrombus.

FIG. 10.—High-power of tag of fresh platelet-leucocyte-fibrin thrombus projecting into the lumen of the carotid of V.M. (Fig. 9).

FIG. 11.—M.F., female aged 41. A section through a fresh mural thrombus in the subclavian artery. The leucocyte-platelet-fibrin thrombus is superficial to an older amorphous thrombus undergoing lysis. This in turn lies on fibrous tissue with large numbers of fibroblasts.

FIG. 12.—G.T., a male aged 48, with bilateral intermittent claudication and aortographic narrowing of lower aorta. A section of the specimen removed by endarterectomy from the terminal aorta. The mural thrombus was originally continuous but has been split by the surgeon's knife. One part is largely platelet-leucocyte-fibrin thrombus (Fig. 13). The other half is mainly amorphous and is being organized (Fig. 14).

FIG. 13.—G.T. Enlarged view of the platelet-leucocyte-fibrin part of the aortic mural thrombus.

FIG. 14.—G.T. The amorphous part of the thrombus seen in Fig. 12 being invaded with fibroblasts.

FIG. 15.—Thrombus produced by injury of cortical artery in the rabbit. It is composed of conglutinated platelets and a rim of leucocytes. (Honour and Russell, 1962.)

FIG. 16.—Electron-microscopic section of a thrombus produced by injuring the cortical artery of the rabbit by Honour and Russell (courtesy of Professor Barer).

SIR GEORGE PICKERING: MYOCARDIAL AND CEREBRAL INFARCTION

FIG. 1

FIG. 4

FIG. 2

FIG. 5

FIG. 3

FIG. 6

SIR GEORGE PICKERING: MYOCARDIAL AND CEREBRAL INFARCTION

FIG. 7

FIG. 10

FIG. 8

FIG. 11

FIG. 9

FIG. 12

SIR GEORGE PICKERING: MYOCARDIAL AND CEREBRAL INFARCTION

FIG. 13

FIG. 15

FIG. 14

FIG. 16

arterial bifurcations and stayed there, though sometimes slipping into one of the branches, and were organized *in situ*. I could not imagine a series of emboli being delivered time after time to precisely the same small arterial branch (the ophthalmic) lodging for long enough to produce five minutes' ischaemia and then passing on.

The answer came two days after Christmas 1960, when my registrar, Ross Russell, got me out of bed to see what was happening in the retinal arteries of a patient (E.D.) aged 54 admitted with a stroke and who complained of his left eye, just after Russell had found nothing strikingly abnormal in the fundi. He had been admitted with a right hemiplegia preceded by several previous attacks of blindness in his left eye and of weakness of the right arm and leg. His loss of vision was associated with the emergence of a white plug from the origin of the central retinal artery (Fig. D). This slowly passed through the retinal arteries, breaking up as it went. After the embolus had

scopy that these thrombi were composed of platelet aggregates containing no fibrin and an occasional red cell, and fringed with leucocytes. Recently McBrien, Bradley, and Ashton (1963) sectioned an eye got from a patient in whom similar white bodies had been seen passing through the retinal arteries a few hours before death, and found that the retinal arteries contained plugs composed of conglomerated platelets with a few leucocytes.

The import of this case (E.D.) was clear. The transient attacks were due to platelet emboli detached from the edge of a platelet-leucocyte-fibrin thrombus. It was, moreover, clear that such an event could happen many times and over the course of months or years. There must be, therefore, a succession of such thrombi formed on the vessel wall. Moreover, the repeated episodes of blindness in T.S. and the even more striking case described by Fisher (1954), who saw a similar retinal white body in a patient who had had hundreds of attacks of blindness over the course of one and a half years, made it clear that these

FIG. D.—E. D., aged 54. Passage of white body through arteries of left eye. Soon after the final drawing was made, a thrombus was removed from the left internal carotid. It was of the platelet-leucocyte-fibrin type, and the tail, which was shaped like the ophthalmic artery, was free of red cells. The time at which each drawing was made is shown. ABCD are the successive branchings of the inferior artery. (Russell, 1961.)

passed, the patient was taken to the theatre, and a thrombus was removed from his internal carotid artery, as well as the intimal plaque to which it was attached. The thrombus was of the familiar platelet-leucocyte-fibrin type; it sat on a thrombus, presumably older, from which the nuclei had gone, leaving an amorphous structure (Special Plate, Fig. 7); this in turn sat in a cavity with lining and jaws of fibrous tissue, presumably a ruptured atheromatous abscess. The thrombus had a tail composed of platelets, leucocytes, and fibrin only, corresponding in shape to the ophthalmic artery. Presumably the embolus was a fragment from this tail (Russell, 1961).

This explanation seemed the more plausible when Honour and Russell (1962) showed me that mechanical injury of the cortical arteries in the rabbit would regularly produce white thrombi which broke off as emboli behaving exactly like those seen in the retinal arteries. Barer showed by electron micro-

thrombi must form repeatedly on precisely the same site. The older amorphous thrombus underneath the platelet-leucocyte-fibrin thrombus made it seem likely that some thrombi were not detached as emboli, but remained where they had formed.

To pursue this matter further Gunning, Robb-Smith, Russell, and I (1964) collected all our patients in whom carotid endarterectomy had been performed for cerebral or retinal ischaemia, and in whom the excised tissue was available for histological examination. Including E.D., there were six patients in whom the nodule showed fresh platelet-leucocyte-fibrin thrombus on the luminal surface of the intimal plaque. Fig. 8 (Special Plate) shows a section through the plaque removed from the left carotid of H.S. seven weeks after a right hemiparesis, which followed two months after two attacks of blindness in the left eye. The section shows platelet-leucocyte-fibrin thrombus superimposed on amorphous thrombus, which rests on fibrous tissue which

overlies poorly staining material containing cholesterol clefts. Fig. 9 shows the nodule nearly occluding the lumen of the carotid artery of V.M., a man aged 56. This was removed four weeks after his second attack of right hemiparesis. The nodule shows a tag of fresh platelet-leucocyte-fibrin thrombus (high power in Fig. 10) lying on an organizing thrombus lying on fibrous tissue, surrounding a collection of cholesterol clefts. In six patients no fresh thrombus was found. The nodule had fibrous tissue superficially and a grumous mass with cholesterol clefts more deeply. In the first group the last ischaemic attack had happened a few hours to seven weeks before endarterectomy; in the second group seven weeks or longer.

The chief importance of these observations has been in the insight gained into the structure and growth of the nodule. For here displayed in front of us was the very process Rokitsansky and Duguid had postulated, with the layered structure which Duguid had noticed in coronary nodules. What was new, and surprising only, because it was new, was that the thrombi were not fibrin thrombi, they were platelet-leucocyte-fibrin thrombi of the familiar type. Because some of us were clinicians interested in the living, we had seen nodules soon after the detachment of emboli. We had seen them in their active phase. And we saw not only an amorphous thrombus giving some of the staining reactions for fibrin, but, upon it, its presumed predecessor, the platelet-leucocyte-fibrin thrombus.

The idea that cerebral infarction may result from an embolus detached from a mural thrombus in the internal carotid artery is not new. Chiari (1905) was forced to a similar conclusion by his careful examination of the cardiovascular system in a patient who died of a stroke. His subsequent investigations convinced him that it was not infrequent. Symonds and Mackenzie (1957), discussing bilateral loss of vision from cerebral infarction, believed it more probable that in most, if not all, cases in which there is vertebral or basilar thrombosis the infarction of the occipital lobes results from emboli derived from the clot.

To me these new observations of ours have been of chief interest in two directions. They provide, I believe, the correct explanation for those kinds of transient attacks of blindness and cerebral dysfunction whose cause has hitherto eluded me. Second, the combination of the patient's experiences and the structure of the nodules, provides a clear pointer to the evolution of the latter. The retinal and cerebral circulations have the great merit that arrested blood flow produces the most profound disturbance almost at once. Here we have the most sensitive index of variations in blood flow that is known in man. It has thus been possible to examine the nodules during periods of activity and of inactivity and to get an insight into their behaviour. Again the layered structure of the nodules in the internal carotid artery has previously been noted by Samuel (1956).

To put these observations into perspective I should make it clear that carotid thrombosis and embolism account for only a small fraction of strokes and for an unknown fraction of cases of cerebral infarction. Having said that, we may leave this relatively uncharted morass, cerebrovascular disease.

Cervical Rib

During this time my colleague, Professor Allison, and I had had three patients with cervical rib in whom emboli had entered the limb arteries from mural thrombi formed on the wall of the injured subclavian. The subclavian at the point of injury showed an enormously vascular and cellular adventitia, a media oedematous and infiltrated with inflammatory cells, and an intima whose thickness was augmented by a number of layers. The most superficial was fresh leucocyte platelet thrombus, beneath that amorphous thrombus, sometimes being dissolved by lysis, underneath that organizing thrombus, and under that fibrous tissue often with a lot of histiocytes, suggesting that this resulted from recent organization (Special

Plate, Fig. 11). In one patient the intimal tissue deep to the thrombus appeared necrotic.

Gunning, Robb-Smith, Russell, and I (1964) have described these cases in detail. They are of interest in providing conclusive evidence for the embolic nature of the vascular systems in cervical rib suggested by Symonds (1927) and by Lewis and Pickering (1934). In the present context the chief importance lies in the fact that here the cause of the arterial lesion is known. It is mechanical injury of the artery, at the point where it is nipped between the abnormal rib and the clavicle. Apparently this injury produces a platelet-leucocyte-fibrin thrombus which, as it ages, changes into amorphous thrombus which in its turn is invaded by histiocytes and incorporated as scar tissue into the intima of the artery. Here in fact we have an example of a simple experiment in man and the results of that experiment. What is notable about the intimal thickening in cervical rib is the absence of any collection of cholesterol crystals. I do not know the explanation of this challenging fact.

Leriche Syndrome: Arteritic Thrombosis of Aorta, Insidious Thrombosis of Aorta

The syndrome, in which thrombi develop on the wall of the termination of the abdominal aorta and ultimately obliterate it, was brought to the attention of medical science by René Leriche in 1940 on the basis of five cases in which he had verified thrombotic occlusion of the terminal aorta at operation. He made the diagnosis on five grounds: first, the impossibility of maintaining a stable erection; second, extreme fatigability of both lower limbs; third, diffuse atrophy of both lower limbs; fourth, absence of trophic changes; and fifth, pallor. Since that time the condition has been described many times. Elkin and Cooper (1949) described 10 cases and Burt, Learmonth, and Richards (1952) 11 cases. The condition is almost confined to the male and affects the same age range as myocardial infarction, the 24 patients collected by Goodwin and Petri (1951) being aged 29 to 64. It is also now known that the commonest early symptom is intermittent claudication. Commonly, pain is first experienced in one or both calves after considerable amounts of exercise. Later the exercise tolerance diminishes and pain is experienced in the thighs and buttocks. Sometimes buttock or thigh pains are the first symptoms; sometimes symptoms are bilateral from the onset but at other times one-sided.

There are very few reports on the pathology of the condition. In France it is regarded as essentially a chronic endarteritis with thrombosis. In this country and the United States it is usually ascribed to arteriosclerosis or atherosclerosis with subsequent thrombosis. Leriche suggested that the thrombus began in the iliacs and spread upwards to involve the aorta. This view was supported by Burt *et al.* (1952), who wrote: "It is understandable that blocking of the aorta by thrombus as a rule begins in the common iliac arteries, the calibre of which is smaller than that of the aorta, and extends proximally up to and even higher than the bifurcation." They described the distribution of the thrombus in their cases, but there is no description of its nature or of the nature of the changes taking place in the aortic wall. In Case 8 they had clear evidence that a recent friable thrombus had been deposited on top of an older thrombus during the four weeks before death.

I became acquainted with this condition when I was a colleague of Professor Charles Rob, and I also learned from the history and progress of his patients that the condition was a rapidly advancing one with gradual narrowing and ultimately occlusion of the aorta. As the occlusion extended proximally the danger point was, of course, the renal arteries.

The question posed by the coronary arteries and partially answered by the carotids is so important that it seemed worth while looking at this third site. For I suspected that, if nodules grow by the deposition of mural thrombi and their subsequent organization, we should see this process brilliantly displayed in

the Leriche syndrome. Such has proved to be the case. Gunning, Hackett, Mackenzie, Oliver, Tibbs, and I have now examined the endarterectomy specimens from seven patients with insidious thrombosis of the lower end of the aorta. Six of these seven were male. They ranged in age from 49 to 70. In all cases the chief and early symptom was intermittent claudication as before mentioned. In only one, the man aged 70, was the aorta completely occluded by thrombus. In the remainder the aorta at operation showed an appearance rather like a relief map of a mountainous area, the foothills being often of a yellowish colour, the mountain tops and ranges usually pink. Histological examination showed that in every case there was at least one deposit, and usually many deposits, of fresh platelet-leucocyte-fibrin thrombus. Often these would overlie amorphous thrombus just as was seen in the carotid arteries and in the subclavian in cervical rib. Sometimes the amorphous thrombus would be itself the surface deposit.

Fig. 12 (Special Plate) shows a section through the aortic endarterectomy from G.T. The thrombus has become partly detached and separated into two by the surgeon's incision. One of these is a platelet-leucocyte-fibrin thrombus (Fig. 13), the other an amorphous thrombus with a platelet thrombus on top of it. The large platelet-leucocyte-fibrin thrombus measures 10 by 6 mm. in its two long axes. The older amorphous thrombus (10.5 by 4.5 mm.) is being invaded by histiocytes, and collagen fibres are being laid down in an irregular fashion within it (Fig. 14). The wall underneath the thrombus shows the thick fibrous tissue characteristic of the arterial nodule or raised plaque. There are areas of poorly staining tissue containing cholesterol clefts. There are some areas of granulation tissue. In some places the rim of intimal tissue contains no or few cells and gives the staining reactions for fibrin. Its appearance is consistent with the view that here is an older thrombus undergoing organization and incorporation in the wall, such as Crawford and Levene (1952) have described. In some places clefts remarkably like those housing cholesterol crystals are seen in that part of the intima that gives the fibrin-staining reactions.

It would be quite beyond the purpose of this lecture to describe in detail what seems to happen when these thrombi are organized and incorporated in the wall. Moreover, a good deal of this has been done previously. In 1952 Crawford and Levene examined 50 aortas obtained at routine necropsies on subjects of all age-groups but with a predominance of elderly males. Fibrin deposits were seen, and were identified by their characteristic staining reactions in 30 of the aortas. No mention was made of other types of thrombi. They described how these fibrin thrombi become organized from the surface and from the media. They say:

"These two processes of surface organization and organization from the media prove adequate, between them, for the conversion of many mural thrombi into collagenous intimal thickenings. Not infrequently, however, with the larger thrombi, or when repeated deposition of fibrin occurs at the same site, the superficial and deep processes of organization may fail to link up. When this happens an intermediate zone of unorganized material persists between the two zones of organization. This unorganized material soon loses the characteristic staining reactions of fibrin and remains as an amorphous, acellular layer, staining feebly with collagen stains and prone to regressive changes with conversion to the grumous fatty debris with which we are familiar as constituting the contents of a typical atheromatous plaque. Fat droplets and acicular crystals make their appearance, and a proportion of the fat is anisotropic."

"The interesting modification of the process of organization by the dual mechanisms from the surface and from the media provides the means by which unorganized remnants of thrombus may come to be covered by a layer of collagen fibres and later develop the appearances of atheromatous debris. The process may be modified by recurrent thrombus formation at the same site, and it is probably as a result of this, with the consequent impairment of oxygen supply to the underlying layers, that atheromatous ulceration occurs."

Again we have been fortunate, because of our interest in the living, to see fresh platelet-leucocyte-fibrin thrombi on top of amorphous thrombus, giving the staining reactions for fibrin.

While it is not justifiable to suppose that all fibrin thrombi arise in this way, the question does in fact arise.

Nodular Arteriosclerosis: the Disease

We begin with what has long been common knowledge. One of the most frequent disorders of the larger arteries is that in which fibro-fatty nodules or plaques are found in the intima associated with medial atrophy and adventitial vascularization and cellular infiltration. As a pathological entity this disorder has been termed atheroma, chronic endarteritis deformans sive nodosa, and nodular arteriosclerosis. These intimal plaques or nodules are generally widespread, but have certain preferential locations such as the carotid sinus, the origin of the vertebral, the left anterior descending coronary, the common and internal iliac, and the abdominal aorta. In a random sample, or in patients who have had a myocardial infarction, the severity of the lesions in the coronary arteries is related to that in the aorta, the iliacs, the carotids, and the vertebrals. The severity of the disease increases with age, and for a given decade males are more severely affected than females, coronary artery disease reaching a given severity in females one or two decades later than in males.

Mitchell and Schwartz, who confirmed or established many of the points already enumerated, showed that in patients dying soon after a myocardial infarct it is the rule to find occlusion of a coronary artery by a platelet-leucocyte-fibrin thrombus, the thrombus usually being found where the lumen is narrowed by a plaque. The longer the interval between the infarct and death, the less likely is a fresh thrombus to be found; instead the arteries are narrowed by plaques. Apart from fresh thrombi, the extent and degree of coronary stenosis is greater in patients who have had myocardial infarcts. These facts can be simply explained on the hypothesis that the plaques are the products of the organization of mural thrombi.

A study of the healing of mural thrombi on the endocardium and on the subclavian artery in cervical rib shows that these form raised fibrous plaques that closely resemble the plaques of nodular arteriosclerosis, except that cholesterol clefts are absent.

However, by far the most important evidence concerning the nature of the plaques has come from the internal carotid in patients with recent ischaemic attacks of brain or retina and in particular those presenting transient attacks of blindness. In such patients the carotid nodule is frequently layered, and, as a cliff displays the world's history to a geologist, these layers display the building of the nodule to us. The nodule seems to grow by a series of thrombi which age and are organized into the intima. These thrombi are not fibrin thrombi at first, as previous workers have so generally supposed. They are the usual form of arterial thrombi, composed of platelet clumps fringed by leucocytes and permeated by fibrin strands in which red cells, or ghosts of red cells, may be enmeshed. As they age the nuclei disappear, and the mass becomes more uniform and gives many of the stains for fibrin; it is amorphous thrombus. Later this is invaded by histiocytes from the surface and the depths; collagen is laid down and it becomes fibrous tissue. Deep in these nodules is the grumous mass containing cholesterol crystals.

In the Leriche syndrome of the aortic bifurcation a similar process is seen, but on a grander scale. Again the sequence is platelet-leucocyte-fibrin thrombus, amorphous thrombus, organization and incorporation into the arterial wall. But here, as Crawford and Levene (1952) had first noticed, it seems that segments of the thrombus are not organized into fibrous tissue, but become laden with Sudan-staining material from which cholesterol crystals are deposited in the characteristically acicular clefts. Here also one can see masses of blood vessels growing into the thrombus either from the lumen or the depths and producing a vascular-cellular tissue like a granuloma. Study

of these aortic lesions thus suggests that the fatty and granulomatous parts of the plaque may also arise from organization of thrombus.

I hope, and think, it will be possible to verify this supposed sequence experimentally.

From these scraps of information this concept of the disease emerges. At certain sites, and because of unknown stimuli, platelets conglutinate on the arterial wall, attract leucocytes, and fibrin is formed. Scores, hundreds, or thousands of these, initially platelet, centres of activity occur adjacent to one another, so that a thrombus forms on the wall. It may become detached as an embolism. Such an embolus entering the arteries of brain or retina may cause transient paralysis or blindness; elsewhere it is usually symptomless. Alternatively the thrombus is not detached. It remains *in situ* and is organized into fibrous or fatty or granulomatous tissue. The repetition of this process leads to growth of the nodule, which is accompanied by atrophy of the media and vascularity and cellular infiltration of the adventitia. All this while, except for cerebral and retinal emboli, the disease is symptomless. Eventually, however, there comes a time when the lumen is narrow enough and these foci of platelet activity are numerous enough to close the vessel by thrombosis. The patient abruptly changes from a symptomless apparently healthy man to a dead man, or a man incapacitated by stroke, myocardial infarct, or gangrene, or lesser consequences of sudden ischaemia.

Such is the picture that emerges by synthesis of the fragments of information gained from what archaeologists would term "excavation of several sites." Does it make sense? The first doubt must be whether all intimal plaques or nodules arise in this way. To suppose so as a working hypothesis is to adopt a well-known principle in science enunciated thus by Willard Gibbs: "to find the point of view from which the subject appears in its greatest simplicity." At least the hypothesis may stimulate work to disprove it in whole or in part. The second doubt in my mind is the relatively advanced age at which transient attacks of cerebral and retinal ischaemia first manifest themselves. At that age the arteries and aorta show intensive nodule formation, and even the "geological age" of the carotid nodules is quite substantial. Is it possible that there are indeed two processes going on in nodule formation, and that thrombus is the later of the two? Obviously this is possible. It is, however, equally possible that thrombi become detached as emboli only at a certain stage of nodule formation.

Internal consistency supports a hypothesis. An interesting and unexpected feature is the common predominance of the male. The greater prevalence of myocardial infarction and the earlier age at which it usually occurs in the male is common knowledge. Mitchell and Schwartz's observations show the greater severity of raised plaques in, say, the fifth decade in the male. Of our 13 patients with carotid nodules and cerebral or retinal ischaemia (Gunning *et al.*, 1964b), 12 were male. Of our seven cases of the Leriche syndrome so far collected 6 are male. Thus it would seem that the male is more susceptible, and that this susceptibility is particularly displayed in certain sites such as the aortic bifurcation.

That there is little or no excess of males in cerebrovascular accidents or strokes, as a group, emphasizes the heterogeneity of this category, and the preponderance in it of a totally different disease.

If this is the nature of the disease what of its aetiology? Does the disorder lie in the blood or the wall or both? This remains unanswered. Virchow thought the preferential sites were loci of mechanical strain on the vessel wall. They may also be sites of turbulence (Schwartz and Mitchell, 1962b). Clearly were there a disturbance in the blood itself favouring thrombus formation, the sites of actual thrombosis might be determined by lesser factors. It is to be hoped that if the hypothesis is favourably received a possible disturbance in the blood will be sought energetically.

How does the hypothesis conform to the data currently being accumulated about the influence of "civilized" living, including diet, smoking, and lack of physical exercise? Any of these may clearly be related to blood changes favouring thrombosis.

Disturbances in the Wall Producing Thrombi

In 1875 Zahn, repeating and confirming experiments by Wharton-Jones (1851), injured the arteries of the frog's mesentery by pressure or a crystal of common salt and noticed that cells were deposited on the inner wall and accumulated in layers until the lumen became completely blocked. In 1882 Bizzozero showed that thrombosis begins with the deposition of platelets on the inner surface of a blood-vessel. In 1886 Eberth and Schimmelbusch and in 1887 Welch studied the sequence of events in further detail. Platelets were deposited first. Next, as the blood flow became reduced, polymorphonuclear leucocytes collected on the surface of the platelet mass and fibrillary fibrin appeared on the surfaces of the platelet framework. Finally, a fibrin coagulum filled the interstices of the platelet framework.

Florey (1925) also noticed that mechanical injury of the cortical vessels in the cat and rabbit led to the appearance within them of white bodies largely composed of platelets.

As mentioned earlier, Honour and Russell (1962) showed that pinching with a pair of forceps the cortical arteries or the mesenteric arteries of rabbit or guinea-pig or pigeon would lead to the appearance at the site of injury of a white plug which quickly increased in size until it had occluded the vessel. The plug seemed to be made of platelets fringed with leucocytes (Special Plate, Fig. 15), and this was substantiated by their containing nuclei in the pigeon and by the electron-microscopic study of Barer (Fig. 16). In the rabbit these platelet thrombi can be watched from their beginning, gradually increasing in size until they block the lumen and/or are detached as emboli. After detachment they show no further increase in size but disintegrate as they pass through the vascular system. It almost seems as though a disturbance initiated at the point of injury is propagated to the surface of the mass, and that, after detachment from the point of injury, this active process ceases.

If one watches the platelet thrombus grow on the wall of the injured artery it is clear that once platelets in the blood-stream impinge on it they must stick fast to the surface. Red cells and white cells do not, until the platelet mass has ceased to grow. Then leucocytes stick, to form a fringe around the platelet mass. Later, fibrin is presumably deposited from the plasma—but this process we have not witnessed in the rabbit, though we hope to study it in the guinea-pig. Thus in the formation of a thrombus there are three separate and probably successive steps—the conglutination of platelets, the fringe of leucocytes, and the formation of fibrin-strands. Each of these steps probably results from a specific chemical or physico-chemical event. Let us restrict our attention to the first, on which alone we have enough data to justify speculation.

Presumably the cells in circulating blood remain separate because they repel one another. Apparently they all carry a negative electrostatic charge. The acquisition of an opposite electrostatic charge by the surface of the platelet mass would not alone account for the platelet conglutination, since other blood cells would also be attracted by this electrostatic force and they are not. Clearly something which is quite specific to platelets is concerned.

The nature of the process became apparent as the result of a chance experiment. Hellem (1960) had shown that an extract of rabbit's red cells would increase the adhesiveness of platelets *in vitro*. He called the unknown active principle of his extracts "factor R," and the work of Gaarder, Jonsen, Laland, Hellem, and Owren (1961) showed that these extracts contained adenosine diphosphate (A.D.P.), which was capable of producing platelet clumping *in vitro* in very low concentrations. Mitchell

and Sharp (1964) confirmed this finding and went on to show that A.T.P., 5-hydroxytryptamine, adrenaline, and noradrenaline were also capable of producing platelet-clumping, the pattern of activity differing in man and the rabbit, which were the two species studied. In particular, 5-hydroxytryptamine was active, while adrenaline and noradrenaline were inactive, in the rabbit. Mitchell and Sharp went on to show that enzyme inhibitors such as azide, fluoroacetate, and iodoacetate, in concentrations capable of blocking enzymic processes in cells such as muscles, had no effect on platelet agglutination *in vitro*.

By applying red-cell extracts or A.T.P. or A.D.P. to the uninjured rabbit cortex, Honour and Mitchell (1963) failed to produce white bodies until one day thrombi began to form in a vessel which was being abraded by a spicule of bone. Deliberate experiment showed that an injury, not severe enough of itself to produce the platelet thrombi and emboli already described, could be made to do so by a local application of rabbit red-cell extract and by equivalent amounts of two of its constituents, A.T.P. and A.D.P., as well as by 5-hydroxytryptamine; noradrenaline was inactive. Locally applied 5-hydroxytryptamine antagonists blocked the effect of 5-hydroxytryptamine but left the other actions unaltered. Cyanide was without effect. However, enzyme inhibitors such as sodium azide, sodium fluoroacetate, and sodium iodoacetate stopped the formation of thrombi from a more severely injured artery which was forming platelet masses spontaneously. When A.D.P. or A.T.P. or 5-hydroxytryptamine was applied to an injury site thus inactivated, white bodies were produced so long as application was continued. It would seem, therefore, that the specific enzyme inhibitors are interrupting chemical processes necessary for the conglutination of platelets on the injury site. Presumably A.D.P., A.T.P., and 5-hydroxytryptamine activate the specific mechanism responsible at a more distal site.

These experiments are of great interest in themselves. They have, however, an even greater import since they have some resemblances to the processes concerned in muscular contraction and the clot-retraction produced by platelets.

The contractile mechanism in muscle is now known to depend on the presence of two specific proteins—actin and myosin. Each of these is a long molecule. The long fibrilli, which gather together in bundles to form the contractile structure of muscles, consist of alternate actin and myosin molecules. During contraction the molecules slip over one another. In relaxation they return to their original positions. The contraction of muscle requires energy, which comes from the conversion of A.T.P. to A.D.P. The close arterial injection of A.T.P. will make a muscle contract. The addition of A.T.P. to actomyosin *in vitro* will cause it to contract. Rephosphorylation of A.D.P. to A.T.P. is carried out by creatine phosphate (phosphagen), and the energy for rephosphorylation of creatine is eventually provided by the breakdown of glycogen to lactic acid, which is stopped by sodium iodoacetate. Sodium fluoroacetate and sodium azide, which each act on specific enzymes, depress the tricarboxylic acid cycle.

The researches of Lüscher and his colleagues (Troup and Lüscher, 1962), of the University of Berne, have shown that a somewhat similar set of circumstances operate in the cell fragments which constitute platelets. Thus glucose was demonstrated to be necessary for the clot-retracting activity of platelets, and lactic acid is produced during the process. A.T.P. content also diminishes during clotting. Bettex-Galland and Lüscher (1959) have extracted an actomyosin-like protein from human platelets. This superprecipitates at low ionic strength in the presence of A.T.P. and magnesium ions. The actomyosin-like protein (which they call "thrombosthenin") is an A.T.P.-ase splitting a phosphate group from A.T.P.

It is tempting to suppose that the process that can be observed to follow the injury of a cortical artery in the rabbit is due to the activation of some such mechanism. Suppose that platelets contain actin and myosin molecules, or their analogues, on

the surface, is it not possible that the process by which they stick firmly together is due to the activation of these protein molecules? The electron microscope shows that the platelets are closely packed, with nothing intervening between their cell membranes. Some process such as this would account for the fact that in the first phase only platelets stick and that the surface of the platelet mass itself is active, for contractility is the result of a propagated disturbance. In the experimental model a metabolic process inhibited by the enzyme poisons initiates the process in the arterial wall. A.T.P. and 5-hydroxytryptamine are among the agents which activate the platelet surface. Presumably the next phases—namely, of leucocyte attraction and of fibrin formation—depend on a different mechanism.

I recognize that this is no more than speculation, and that the ultimate explanation will probably turn out to be something different. Nevertheless, it is fun to allow the fancy to wander, and hypothesis is the mother of experiment.

Conclusion

This lecture will have served its purpose if it has interested you in the nature of a common and obscure disease. I hinted earlier that I thought the reason why it remained obscure and failed to excite interest was because it had become buried in that rubbish-heap with the nonsensical label of atherosclerosis. May I remind you that the first steps in scientific method are the collection and classification of facts. It is utterly futile to suppose that every alteration in the aorta and large arteries between birth and death is the same as or a necessary antecedent to the disease here considered. Hence the great importance of abandoning this name once and for all and accepting the name which refers to the particular disease in question. This I believe Councilman's (1891) name adopted by Osler of nodular arteriosclerosis satisfactorily does. It is a disease with a unique pathology, and, that pathology being understood, is capable of being explored both in the sick man and in the experimental animal. To have pointed this out is, I hope, to have done what Lewis would have liked his lecturer to do.

ADDENDUM.—Finding platelet-leucocyte-fibrin thrombi on the surface of carotid nodules as long as seven weeks after a clinical episode of retinal or cerebral ischaemia had led me to suppose that these deposits may last in this form for some considerable time. Animal experiments recently carried out, however, suggest that the cells rapidly lose their identity and disintegrate. One begins to wonder whether some of these mural thrombi may also disintegrate without actually becoming emboli. In fact, we still have a great deal to learn from them.

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Appendix

VIRCHOW, R. *Gesammelte Abhandlungen zur wissenschaftlichen Medizin*, "Phlogose und Thrombose im Gefässsystem," p. 500. Max Hirsch, Berlin. 1862. (Translated by Dr. H. Hauffe.)

My own microscopical investigations led, as we shall see, to the confirmation of Risse's general view concerning the course of the process, and also includes the beginning of this process (neglected by Risse) as well as acceptance of an exudative process and complete exclusion of a process of layer aggregation. Only this do I believe needs emphasis from the start, namely that combined with the change of the intima, a layering process involving the blood can indeed occur and that therefore not the vascular endothelium, but blood clots aggregate, and that finally these thrombotic aggregates are only quite accidentally accompaniments of the process of thickening. We are, therefore, returning substantially to the view of Lobstein, who compares the wart-like thickening of the arterial walls with the process of osteosclerosis.

In all conditions the process probably begins with a certain degree of loosening of the connective-tissue ground-substance, the main constituents of the arterial endothelium. This loosening does not inevitably lead to the complete jelly-like stage, but only in those cases where the rather thicker cartilaginous patches are being formed does one often see only a light, transparent, but still dense tissue that differentiates itself from its surrounding by its somewhat more succulent nature. This swelling of the ground-substance, from which I feel I must conclude, as stated, that it has its origin to a large extent in an increased imbibition of the fluid constituents of the blood flowing over it, can also be recognized microscopically by the greater width and homogeneity of the connective-tissue lamellae. In quite marked jelly-like metamorphosis, these fluid constituents increase even more and the ground-substance becomes more and more like a piece of glass or brawn, whereas the harder forms show more the indistinct fibrillary horny-ground-substance appearance. At no time, however, is the continuity between changed ground-substance and the girders and lamellated disposition of the inner coat lost completely. On the contrary, one can entirely convince oneself by looking at vertical sections through the thickened and neighbouring layer of the inner coat that the features of the latter blend into the ground-substance of the thickened patch, and only its direction changes so that the inner surface is no longer disposed in a parallel and horizontal fashion, but rather that it becomes elevated in an at first small and soon larger acute angle, forming a shallow curve or passing over completely into the homogenous ground-substance. The verification of this continuity, especially as regards the most recent as well as the oldest patches,

is no less important; indeed, perhaps more important than the continuity of the epithelium over the surface of the patch as demonstrated by Risse. For, although I also repeatedly found this phenomenon, no particular importance can be attached to the absence of the epithelium, since this is not infrequently destroyed from the start.

With this thickening and transformation of the ground-substance the cells (connective-tissue particles) of the endothelium simultaneously undergo a change. They enlarge in all diameters and usually at first present as lenticular cavities, from which it is possible to follow up threadlike and reticular processes, as Risse observed. With sections, particularly those cut parallel to the surface, one easily finds such reticulated appearance which Rokitansky regarded as the essential part of the whole structure, while he overlooked the cellular elements that were enmeshed within it. For these apparent cavities or gaps are either mere cross-sections of connective-tissue girders or they are occupied by cellular elements in which one usually sees early enlargement and diversion of the nuclei, later a true division of the cells, and thereafter a focal proliferation, which I have seen in a whole series of neoplasms. No structure offers such a close correspondence of circumstances as the irritated cornea.

Circumstances are evidently different for the jelly-like structures. In these cases cavities or gaps, areolar or reticular tissues are rarely in evidence since the soft ground-substance possesses a homogenous structure. For this reason one sometimes sees the cells more clearly even when these, because of their delicacy and pallor, are difficult to recognize, but one sees the nuclei all the more clearly. These enlarge, become more granulated, eventually divide and one sees intermediary forms from simple initially oval or lenticular, to more round multiple types that consist of two or more going side by side, and sometimes also form a small focus. Not infrequently the process remains at this stage, in which early fat-metamorphosis occurs; sometimes, however, a further division of the cells occurs here, so that similar smaller and younger round forms emerge and these can present a puriform structure.

In this way the process assumes a truly active character, as in an inflammatory process in general. This is not a re-forming as described in the simple fat-metamorphosis, but a formation of new tissue elements, an actual neoplasia apart from the hypertrophy of the ground-substance. The ground-substance both takes up more material in its cells and incorporates this into its mixture of analogous material, so that the process is not merely one of hyperplasia but one in which, although not exhibiting a very great tendency to heteroplasia, the ground-substance resembles more the

mucus- or chondrin-containing tissues, and in which the cells can progress to puriform structure. To this is added the fact that blood-vessels incorporate themselves into the thickened places, that simultaneously with the thickening there is a hyperaemia of the underlying membranes which can consolidate themselves; it thus becomes clear that one cannot overlook either the irritative nature of the process or the nutritional disturbance. The whole series of events that makes up the well-known inflammatory process is therefore present.

Once the thickening of the inner wall has progressed to a certain degree, fatty metamorphosis usually sets in. But even this does not necessarily always lead to formation of atheroma, and the fatty change itself cannot once and for all be described as atheromatous. The true arterial atheroma arises only from the second kind of patch, namely the real sclerotic (half-cartilaginous) type and in a way often described—namely, not at the surface but under the surface—so that an initially closed and fatty mash-filled focus of softening is formed. In contrast to this it is much commoner in the jelly-like patches to have the fatty softening from within the surface itself in an exactly similar way that the degeneration occurring in joint cartilages in *malum senile articularum* leads to superficial destruction. These two processes differ from each other as ulceration differs from abscess formation, except that, instead of pus, a finely granular fatty mass develops and that the process carries with it not a productive but a destructive character. The atheroma, like the abscess, forms enclosed foci which open and likewise show ulcerous surfaces, but these latter retain almost always a greater depth and sharper outline than the primarily superficial festering and fatty suppuration. So little as one calls a superficial ulcer an abscess, so little does the expression atheroma apply to the superficial suppuration of the arteries and for the fatty ulcer.

The atheroma as well as the fatty ulcer begins with a fatty metamorphosis of the connective-tissue particles in the thickened segments of the endothelium—that is, in the same way. Within these particles and in the hard patches apparently in the gaps and cavities of the girder and meshnet, very small fatty particles are deposited, and these gradually accumulate so that eventually one finds thick and large granular cells, often of stellate structure and complete with anastomosing processes. Even here a further difference becomes evident in that in true atheroma the granular cells become larger and more numerous, and eventually, as the ground-substance between them softens, consolidate to one communal form in which the granular spheres quickly change to a granular mash in which larger fat droplets and cholesterol crystals precipitate out. Upon the surface and particularly in the more jelly-like patches in contrast, this formation of the granular cells is often incomplete; the individual cells themselves develop only small amounts of fat and the fat particles therefore lie more scattered within the soft ground-substance. After destruction of the cells the ground-substance is unable to hold them together in an orderly fashion and then begins, as already described for the ordinary fat-metamorphosis of the intima, at its surface a probably very fine, but not exactly molecular, detachment of the softened products which then lands up in the blood stream. In this way the superficial ulcer is formed and one can detect these macroscopically as being somewhat raw, dull and muddy; microscopically long vertical sections no longer reveal a smooth boundary like on the intima, but one sees liberal prominent fragments, soft girder and fibre tracts, matter protuberances and uneven hollows, indeed everything of minor height and depth. One can see these conditions most easily in the pulmonary artery with prolonged dilatation, while the atheroma formation commonly occurs to a most marked extent in the aorta.

Chylous Reflux

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The term “chylous reflux” is used to describe a backflow of chyle from its normal route from the bowel through the cisterna chyli and the thoracic duct to reach the blood-stream. It may show itself clinically in many different ways. Small blisters containing chyle—chylous vesicles—may appear on the skin in the lower parts of the body and discharge milky fluid, forming one type of chylous fistula. Patients with this condition are often seen in dermatological clinics. Occasionally chylo-metrorrhoea causes a vaginal discharge of chyle, presenting a diagnostic problem for the gynaecologist. Chyle may collect in the serous cavities of the body—chylothorax, chylous ascites, and chylocele being examples. These are only a few of the ways in which the disordered flow of chyle may show itself. They have been recognized for centuries. Rusznayk *et al.* (1957) refer to many old case records. The underlying structural and functional defects in the lymphatic system responsible for the clinical effects were largely a matter of conjecture until, in recent years, better methods of studying human lymphatic physiology were developed.

We report here the results of and conclusions from studies of a group of patients with chylous reflux. The lymphatic system has been investigated by lymphangiography, which has given information about the faults causing clinical disturbances. The 19 patients in the group have all been followed long enough after investigation and treatment for conclusions to be drawn about the results and the prognoses. Patients studied more recently have been excluded from review.

These 19 patients with chylous complications were encountered among 650 patients with *primary lymphoedema* about whom we have been consulted at St. Thomas's and at St. Bartholomew's Hospitals during 10 years. This shows an incidence of 1 in 34. No patients with disease of the lymphatic system secondary to usually recognized factors such as neoplasia, trauma, filariasis, or other conditions are included.

The patients, with one exception which is discussed below, fell clearly into two clinical groups of syndromes. In chylous reflux syndrome I there was usually oedema of one lower limb and discharge of chyle from it or from the external genitalia. Lymphangiography showed large incompetent lymphatics, and a patch of capillary angioma was often present on the skin.

In chylous reflux syndrome II the oedema was often congenital and more widespread, affecting several limbs. Lymphangiography revealed few or absent subcutaneous lymph trunks. There was hypoproteinaemia, often with other metabolic disturbance, and the long-term prognosis was poor.

The details of the individual case histories, which are recorded elsewhere (Kinmonth *et al.*, 1964), are not given here, but the main features of the two syndromes are tabulated and analysed. The state of the lymphatic system is discussed in the light of the lymphangiographic findings, and comments are made on treatment and prognosis.

Syndrome I (Megalympatics)

Nine patients were male and five female (Table I). There was no marked tendency for one sex to be affected more than

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