

THE PATHOLOGICAL ANATOMY AND PHYSIOLOGY
OF VASCULAR DISEASE IN THE LOWER LIMBS

by

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INTRODUCTION.

During recent years the literature on peripheral vascular disease has grown enormously. Especially frequent have been articles on the clinical features and the response to treatment, but strangely enough since the publication of Buerger's book (1924) relatively little has been written on the correlation of the morbid anatomical appearances and the physiological readjustment of the circulation. This is all the more surprising in view of the fact that so much attention has been directed to functional derangement of the arterial circulation in the heart and kidney, especially as it is so much simpler to make absolute measurements of the arterial circulation in the limb than in the other organs.

The present study is based on material obtained from a variety of sources. My interest was first aroused in the subject by experience gained in the investigation of material kindly supplied by Prof. J. R. Learmonth from his peripheral vascular diseases unit. Apart from one biopsy performed on a superficial vein this material consisted of lower limbs amputated as a result primarily of ischaemic gangrene. The greater part of this work accordingly consists of an account of observations made in examining this tissue in the Pathology Department of the University of Edinburgh. The study has however been continued in the Medical Unit of St. Mary's Hospital in an attempt to answer some of the questions raised during the course of the investigations made in Edinburgh, and a brief account of some of this later work will accordingly be included.

Although many specimens were available in the departmental collections of the R.I.F. and the University of Edinburgh pathology Department the account has been restricted to include only cases of thromboangiitis obliterans and atherosclerosis personally studied. Thus every case on which this account is based has been investigated by me both in the ward and in the laboratory. This is considered to be a most valuable point, namely that both the anatomical and physiological aspects should be studied by one and the same person.

There are many obscure aspects of the pathology of peripheral vascular disease and in the routine study of the material available many points emerge that are intriguing and might possibly lead to profitable lines of investigation. In order to avoid these tempting bypaths the scope was limited to certain definite aims. In the first place it was essential to acquire familiarity with the anatomical and histological appearances of healthy and diseased arteries. Accordingly in the examination of specimens received during the first part of the study reliance was placed entirely on dissection and histological methods. Information gained in this manner revealed many possible lines for further investigation, but out of these two were chosen for special concentration of effort; namely the part played by disease in the popliteal artery in determining the development of gangrene in the lower limb and the mode of development and the efficiency of the collateral circulation when the main arteries are obstructed. By the supply of material the investigation has been limited to three forms of peripheral vascular disease, thromboangiitis obliterans, senile atherosclerosis and diabetic atherosclerosis.

These diseases are discussed under their separate headings but the methods of investigation, described subsequently, have been directed to answering some specific questions with regard to each disease. Certain general principles however have been discovered which apply to all types of vascular disease, particularly with regard to the development and the efficiency of the collateral circulation. These general points have been described in detail in one of the sections but have not been fully repeated in the descriptions of the findings in each individual disease.

PART I.

Methods of Investigation of the Pathological Anatomy.

As the study included the investigation of the condition of the arteries in both amputated and living ischaemic limbs a considerable variety of methods had to be called into use. The well established techniques will merely be mentioned and reference made to the original accounts where necessary. On the other hand for some purposes new methods had to be evolved; greater attention will be paid to their description, and their limitations and accuracy will be discussed.

With regard to amputated limbs, in the first instance the external appearances were noted and particular attention was paid to recording any naked eye evidence of infection in the gangrenous areas. The condition of the superficial veins was also noted, as were any scars or ulcers attributable to the long standing effects of vascular disease. Following this external inspection various further methods of investigation were utilised. They comprised the following:-

1. Gross dissection of the vascular tree.
2. Histological study of selected portions of arteries and related structures.
3. Injection of the vasa vasorum of selected portions of the arterial tree.
4. Injection of the arterial tree of the whole limb with coloured and radio-opaque substances.

In the earlier cases the investigation was limited to the first two methods in order to gain a basic knowledge of the different types of disease. Later these two fundamental methods were supplemented by the injection

procedures. It was found possible to make good histological preparations after use of the injection techniques. The particles of the injected suspension remained in the sections and it was thus a simple matter to determine the adequacy of filling of the various vascular channels. This was found to be particularly helpful with regard to tracing out the course of the small vessels canalizing occluded arteries.

Gross dissection and histological study were carried out in all the 28 limbs that have been received for examination and in eight limbs an injection of a coloured radio-opaque substance was also performed. The different methods of study and types of disease were distributed as follows:-

1. Dissection and histology.

Atherosclerotic gangrene	12 limbs
Diabetic atherosclerotic gangrene	3 limbs
Thromboangiitis obliterans	5 limbs

2. Radio-opaque injection followed by dissection and histology.

Atherosclerotic gangrene	4 limbs
Diabetic atherosclerotic gangrene	3 limbs
Thromboangiitis obliterans	1 limb

These last eight limbs do not however represent all that were subjected to injection as preliminary trials were made on limbs removed at autopsies on mental patients. These will be described later when the detail and limitations of the injection technique are explained.

In dissecting a limb the femoral artery was located at the point of section and the whole vascular tree was separated distally, care being taken to include the accompanying veins and nerves. It was usually possible to

dissect on the front of the foot to the point where the dorsalis pedis passed down between the two metatarsal bones. On the sole, the proximal parts of the lateral and medial plantar arteries were included in the dissection. By drawing the anterior tibial artery through the interosseous membrane the whole vascular tree was removed intact. Thereafter it was preferable to fix the tissue in 10% formalin solution for at least 24 hours. If a tall cylinder was used as a container the whole tree could be kept straight which was a considerable advantage in the further investigations. Better results were obtained if the fixation were prolonged for four days. The vessels were then examined either by slitting longitudinally or by a series of transverse sections. The former method was better suited for the larger vessels. Suitable blocks were taken for microscopic study; they were designed to include the artery, veins and nerve together with the surrounding connective tissue.

The blocks were post-fixed in Helly's solution in the usual manner. For examination haematoxylin and eosin, Verheoff and Van Gieson and Weigert's elastic stains were used. Serial sections were cut from several of the blocks to elucidate special points, particularly with regard to the connexions of the new channels recanalizing occluded arterial segments. In addition to the blocks taken from the main vascular tree, tissue in selected cases was also taken from extensor digitorum brevis for the study of ischaemic muscular changes, from the edge of ulcerated areas, and from the toes to show the digital arteries. In the last instance the simplest method was to remove the toe, shell out the bone and cut a suitable transverse block.

In studying the femoral-popliteal segment of the arterial tree, injections with india ink were carried out on several occasions, both in material obtained from the amputated limbs and from autopsies. Particular attention was paid to the part of the artery passing through the adductor hiatus and an attempt was made to demonstrate any peculiarities in the vasa vasorum of this segment. The method employed was to dissect out about 10 cm. of the artery centred on the hiatus, the position of which was marked by a small suture. Care was taken to include the small side branches and some tissue around the artery. The proximal end was cannulated and the distal clamped with artery forceps. India ink was then injected under a pressure of 400 mm. of mercury and the leaking points were clamped with artery forceps and tied off. The pressure was maintained for half an hour. The artery was subsequently fixed in 10% formalin solution overnight, a procedure which aided greatly the subsequent dissection of the vessel from the surrounding tissue. The adventitia was then stripped and the artery thus bared was dehydrated and cleared by the Spalteholz method. The technique advocated by Winternitz and his colleagues (1938) was in the main adopted and found satisfactory. The artery was thus passed through 60%, 70%, 80% and 95% alcohol, two changes of absolute alcohol and benzene. Clearing was performed in a mixture of equal parts of benzyl benzoate and methyl salicylate. The material was left for 24 hours in each solution. By this method it was possible to demonstrate small capillary vessels in the media and intima of atherosclerotic femoral-popliteal arterial segments. The results in these and apparently normal vessels will be discussed later. Certain difficulties however may be

mentioned here. With regard to the actual injection it is essential to choose a water miscible India ink as the product has to be diluted eight times with distilled water before use. Winternitz had recommended the use of Higginson's ink, an American product not readily obtainable in this country. Several British brands were tried and the most suitable was found to be Winsor and Newton's drawing ink.

The apparatus used for injection was improvised from material available in the laboratory and a foot-pump was used as a source of pressure. The arrangement is essentially similar to that described by Pettigrew (1934). The leaks from the side branches of the artery during the injection often occasioned considerable difficulty, but usually they could be controlled fairly adequately by forceps. It was always considered advisable to include in the specimen plenty of tissue around the artery so that the clamps might be applied at a short distance from the arterial wall in order to avoid obstructing the vasa at their origin from the side branches. In certain types of case difficulties arose in stripping the adventitia. It was not possible to make a satisfactory preparation of the vasa of an artery affected with thromboangiitis obliterans. The obstructed lumen prevented satisfactory injection and the adventitia was too tightly bound to the media to allow stripping. Similar difficulties arose in grossly atherosclerotic arteries. The method was most suitable for moderately atheromatous vessels, and in these the most satisfactory results were obtained. There are however several unsatisfactory features in the method, the most objectionable being the excessively high pressures required to demonstrate the small intramural channels. It is

difficult to be certain under such conditions that they are not artefacts. One minor disadvantage was the time taken by the Spalteholz method to display the result of the injection. Rapid, though rather less satisfactory, clearing can be obtained by immersion of the stripped artery in pure glycerine. The result of the injection can then be seen in an hour or two.

After a few dissection and histological studies it soon became apparent that in arterial disease it would be a great advantage to obtain a picture of the arterial tree as a whole throughout the limb. In many cases the main vessels were grossly diseased and it was obvious that the major part of the blood supply must be passing through collateral channels. Considerable interest was also entertained in the functional significance of the thrombosed but recanalized arteries. In an attempt to elucidate such problems a series of experiments was carried out to develop a suitable injection technique. There were two possible lines of approach - either to inject a coloured substance and display the arteries by dissection or digestion of the surrounding tissues, or to inject a radio-opaque substance and radiograph the result. Various attempts were made with injections of a suspension of India ink in celloidin (fig.15) and certain information was obtained in this way regarding the significance of side branches and the recanalized main vessels. Little further information could be obtained by this method regarding the circulation to the limb as a whole. The injection of 1% celloidin coloured with alkanin was considered. This method requires the subsequent digestion of the tissues with concentrated hydrochloric acid and leaves only a cast of the injected arteries. It has been used successfully for the arterial

system in foetal limbs. The time required for the digestion of a whole adult lower limb would be excessively long and there is the added disadvantage that as all the tissue is destroyed by the acid no dissection or histological studies are possible. Similar objections apply to the injection of neoprene as used by Trueta and his associates (1947) in the demonstration of the renal vascular system. Accordingly no experiments were carried out along these lines.

The ideal method obviously lay in developing a technique whereby both radiological and dissection with clearing studies might be performed on the same limb. A satisfactory solution was found by modifying the Schlesinger method of coronary arterial injection (Schlesinger 1938). The modified injection mass was prepared as follows:-

Solution A: Lead acetate 60 gms.

Distilled water 172 c.c.

Dissolve by heat, filter and allow to cool.

Solution B: Anhydrous disodium hydrogen phosphate 24 gms.

Distilled water 190 c.c.

Dissolve by heat, filter and allow to cool.

Preparation:-

1. 1.5 gms. agar-agar in 2000 c.c. flask.
2. Add 100 c.c. of solution A and boil till frothing ceases.
3. Add 1 c.c. of 0.06% phenol red as indicator.
4. Add 70 c.c. of solution B.
5. Add by pipette 10% sodium hydroxide till indicator changes pink.
6. Add distilled water till total is 250 c.c.
7. Boil 10 minutes till agar is fully dissolved.
8. Add 2 gm. trypan blue.

9. Heat for 1 minute and stir.
10. Strain while hot through gauze.
11. Preserve at room temperature.

The mass now consists of about 8% precipitated lead phosphate which is sufficient to give a clear outline of the injected vessels on an X-ray film of the leg.

To perform the injection the limb was immersed for one hour in a water bath maintained at 45°C. The popliteal artery was cannulated and the vessels were irrigated with 200 c.c. physiological saline at 40°C. The lead phosphate previously warmed to 40°C. was then injected at 400 mm. pressure, the bottle being agitated during the whole of the procedure to prevent any settling of the precipitate. About 150 c.c. was used for each limb, but as several leaks usually occurred from small arteries at the amputation site it was not possible to ascertain how much actually remained in the limb. The foot was finally cooled in the refrigerator and X-rays were then taken. A lateral view was first photographed and depending on the results and the extent of the injection further films were taken as required.

Such has been the technique used in performing the injection experiments. As the work progressed and further experience was gained several criticisms, improvements and modifications became apparent. Thus the pressure of 400 mm. mercury was probably excessive, but as it was desirable to maintain comparable controlled conditions in studying the circulation in the different diseases it was not changed. The high pressure was used originally on account of difficulty in injecting some of the atherosclerotic arteries. In them the popliteal artery was usually grossly obstructed, while the site of amputation was at the juncture of the middle and lower

thirds of the thigh. Accordingly in many specimens the obstruction was thus only a few centimetres below the tip of the cannula and as the popliteal artery has no large side branches the injection was accordingly extremely difficult, and it was not surprising that in many of the early attempts the filling of the vessels of the leg and foot was inadequate. Before the injection and dissection it is impossible to ascertain how complete the obstruction is in the popliteal segment. If the injection mass does not flow freely through the popliteal artery one cannot get a true picture of the circulation in the leg, as the collateral vessels to circumvent the obstruction in the popliteal artery arise at a level above the site of amputation. It is accordingly not profitable to attempt an injection of a limb amputated at the thigh if there is clinical evidence available that the popliteal artery has been thrombosed. This probably explains why so little has been written on the injection of amputated lower limbs. Horton (1930) who used mercury as the radio-opaque material made no mention of this difficulty, but Pickering (personal communication) encountered similar troubles and abandoned the method. In the present study in those cases in which the popliteal artery was patent throughout its length the injection mass entered freely and spread right down to the tips of the toes (fig.30). Similarly in the case of amputations below the knee the results of injections were only satisfactory when there was a considerable length of patent artery distal to the tip of the cannula. The difficulty about being certain of the levels of obstruction before the injection is begun means that only a proportion of the attempts on amputated limbs are successful. The method would of course be admirable for use in the cadaver

for the study of atherosclerotic lesions in the limbs as the femoral artery which is rarely obstructed could be cannulated at a high level. Owing to the legal position regarding subsequent removal of the limb it was not possible to carry out any such studies.

There are several minor points in the technique which are deserving of short mention. The use of agar in the injection mass had certain disadvantages, especially with regard to the temperature that had to be maintained within the limb. Some substance that solidifies is however essential both for the radiological studies and for the subsequent demonstrations of the vascular channels in cleared portions of the arteries. Gelatin was used in one experiment but did not prove as satisfactory as agar. The selection of a colouring agent was only determined after several trials. It was essential to have a non-diffusible substance especially for the clearing studies. Trypan blue proved reasonably satisfactory. In the cleared specimens, however, it did not always give such a sharp picture as India ink. An attempt was made to introduce a water miscible ink into the injection mass but the chosen brand of Winsor and Newton ink "curdled" and the result was obviously unsuitable. The majority of water miscible India inks can only be diluted with distilled water but one variety of Reeves' ink gave fair results which however were not substantially better than those obtained with trypan blue.

After radiography dissection of the limb was carried out with the films at hand for comparison. In the larger arteries radiological filling defects were checked by naked eye section to avoid drawing conclusions from artefacts due to incomplete injection. Similarly in the smaller vessels blocks from poorly filled areas were taken for histological

section to make sure that the injection mass had penetrated into the arterioles, which should be filled down to a diameter of 40μ (Schlesinger 1938).



Fig. 1. X-ray of a leg after injection of the arterial tree through the posterior tibial artery. This artery and its peroneal branch are clearly shown, but the filling of the anterior tibial artery through collateral channels is incomplete. On dissection there was no gross evidence of arterial disease. The specimen was a traumatic amputation below the knee as a result of an accident in a male of 21 years. In such a subject there are few collaterals between the main arteries.



Fig. 2. A section of an artery and its venae comitantes from a case of thromboangiitis obliterans. The elastic coated recanalizing vessels in the arterial thrombus and the accompanying veins are entirely filled with precipitated lead phosphate. A lumbar sympathectomy had been performed in this case and considerable filling of dilated cutaneous vessels was obtained. The presence of lead phosphate in the veins must be due to passage of the injected material through arterio-venous anastomoses greater than 40 μ in diameter. Stained haematoxylin and eosin X 60.

PART II.

Investigation of the Pathological Physiology.

The problem of accurately assessing the dynamics of the arterial circulation in a limb with some degree of arterial obstruction is considerable and no entirely satisfactory methods have yet been evolved. It is not proposed to discuss in any detail the methods of recording routine clinical observations in such cases. These obviously constitute an essential preliminary to any more detailed investigation and their significance has been discussed by numerous authorities (Pickering (1933), Lewis (1936), Allen et al.(1946)). In the discussion of the cases that follow the clinical observations will only be commented upon when they throw further light upon the pathological physiology of the circulation in the affected limb. In addition to the routine clinical methods of inspection and palpation further experimental methods have been brought into use. These include the saline wheal (Stern 1927) and histamine wheal (Kramer 1940) tests and the reactive hyperaemia test (Pickering 1933). The last has been found particularly useful on numerous occasions and further mention will be made of the information that it can yield.

There are only two reasonably accurate methods of measuring the blood flow through a portion of a limb and these are either by means of a Stewart's calorimeter or a plethysmograph. It will be noted that skin temperature methods are not regarded as sufficiently accurate for the purposes of this investigation; such methods only reflect in a very rough manner the total circulation through a leg or foot (Greenfield 1948). Calorimetry has been used

extensively by the writer in determining the circulation through the limb. If a suitable modification of the original pattern (Stewart 1911) is used such as that of Greenfield (1948) consistent results can be obtained and can be shown to agree with those obtained under similar conditions by plethysmography. The method depends essentially on the transfer of heat from the skin surface to the water within the calorimeter. The result can be expressed as calories per minute. Previous attempts to translate the calories per minute into blood flow per minute have been shown to be unsound (Sheard 1926). In spite of this disadvantage it is a useful method and has been used extensively in the past for the determination of blood flow in the lower limbs (Brown 1926). It is however more suitable for investigations in the hand and accordingly little further reference will be made to its use.

A plethysmograph consists essentially of a chamber into which an organ or extremity may be inserted. The entrance must be sealed to prevent the escape of the air or water surrounding the part and spontaneous or induced volume changes can then be recorded by connecting the system to a Brodie's bellows or a miniature paraffin spirometer. The plethysmograph was first described and named by Mosso (1879) and reference to his original illustration will make the principles clear. (Fig. 3). Mosso used his instrument to record changes chiefly in pulse volume and did not make any direct observations on blood flow. Brodie (1905) demonstrated that by occluding the venous outflow the initial resultant swelling of the enclosed part represented the arterial inflow and used this method for estimating the circulation to the kidney. He also mentioned the possibility of applying the method to the limbs and this suggestion was

taken up by Hewlitt and Van Zwaluwenburg (1909).

Numerous modifications and improvements have subsequently been reported, the most noteworthy being those of Lewis and Grant (1925), Grant (1938), Abramson et al. (1939) and Goetz (1946).

The determinations of blood flow that follow have been made by the use of calf and foot plethysmographs. The foot has been found peculiarly suitable for plethysmographic studies as it contains a relatively large venous bed, and during the first few pulse beats after the occlusion of the veins the inflow tracing even at full vasodilatation can be represented as a straight line. Once the venous bed has become distended the tracing falls off in a curve (fig.5). The plethysmographs used have been personally constructed of celluloid. The difficulty of making a watertight seal at the ankle joint without occluding the veins has been overcome by manufacturing a thin sock of latex rubber sealed at the upper end through a thick rubber diaphragm to the celluloid of the instrument. The construction of the apparatus is best appreciated by a study of the diagrammatic illustration (fig.5). The thin rubber sock is collapsed firmly and completely by the water on to the skin of the foot. The outer surface of the celluloid was covered with a quarter inch thick cork sheeting to act as a heat insulator. It is highly essential that the local temperature surrounding the part is kept constant throughout the observations. The plethysmograph was always filled with water in spite of the fact that Berry (1948) has recommended air as the most suitable medium. It is much simpler to keep water circulating at a constant temperature than air and, as it has been found that even small variations in local temperature markedly affect the blood flow, the former medium is always to be preferred unless an elaborate apparatus is available

for circulating air at a fixed temperature. In the plethysmographs personally constructed water at the desired temperature has entered at the bottom of the instrument and escaped at the top thus ensuring that the limb is maintained at a constant temperature up to the time of the readings. The part was always kept in the plethysmograph for at least half an hour with the subject at rest on a couch to establish basal conditions before any observations were made.

When a new pattern of instrument has been designed, and particularly when it embodies new devices such as the rubber sock, it is first essential to determine the accuracy of the records that it provides. The absolute accuracy of measurements of blood flow in human subjects is of course impossible to assess but as in this study importance is only attached to differences between normal subjects and those with arterial disease a determination of the relative accuracy of the instrument is obviously of the highest importance. There are several difficulties in making such an assessment. Thus it is known that in the hands and feet exposed to a normal room temperature, about 22°C, the vasomotor tone is continually changing. Resting blood flows in the hands or feet recorded at half minute intervals thus show considerable differences and are only capable of comparison if an average is taken of many readings. The fluctuations in the feet are not so great as those in the hands (personal observation), but even so an approximate idea of the circulation through the foot can only be obtained by taking an average of a large series of observations. The fluctuations in vasomotor tone and thus in blood flow to the periphery are determined by the heat elimination required at the moment, which will obviously be increased if, for instance, the subject has recently been exercising or eating. The

extreme importance of establishing basal comparable conditions before each series of readings will thus readily be appreciated. It will also be understood that under resting conditions the functions of the blood circulation to the leg and foot differ considerably. The upper part of the leg, the site chosen for the fitting of the plethysmograph, consists largely of muscle while the skin in this region under normal conditions plays a relatively small part in heat elimination (Grant and Pearson 1938). The circulation here is accordingly adjusted to meet chiefly resting muscle metabolism and large fluctuations in a series of readings are not to be expected. A series of ten consecutive calf blood flow tracings with the local temperature of the water in the plethysmograph maintained at 34°C gave the following figures 2.8, 2.9, 3.0, 3.1, 2.9, 3.2, 3.1, 2.8, 3.0, 3.0, average 3.0 c.c.s./100 c.c.s./minute. In general it has been found that after calculating the standard deviation of several series of resting calf blood flows, the coefficient of variation has not exceeded 10% and in the majority of cases it has been about 5%. In the case of the foot however the circulation performs two main functions, namely nutrition of the tissues and elimination of heat from the skin surface. Under basal resting conditions the former is a constant element while the latter is continually varying. Thus in a series of observations on the foot in a plethysmograph at 34°C, the blood flow readings at half minute intervals fluctuate greatly. This may be illustrated by the following series of ten readings from a foot obtained under such circumstances - 4.8, 4.5, 5.4, 4.3, 6.0, 4.5, 7.0, 4.5, 5.5, 5.3, average 5.2 c.c.s./100 c.c.s./minute. An average of ten such readings is obviously of little statistical significance for comparative purposes. If however a similar series of readings

is made with the water in the plethysmograph at 44°C to ensure full local vasodilatation there is considerably less variation in the individual readings. Thus in the same patient ten consecutive figures for blood flow at 44°C read 20.4, 21.4, 20.7, 21.2, 21.4, 20.0, 20.7, 20.2, 20.5, 20.3, average 20.7 c.cs./100 c.cs./minute. The coefficient of variation under these circumstances was 2.4% and in a large series of observations the coefficient of variation has lain between 2% and 9%. Thus, provided full vasodilatation is ensured and maintained, it is possible to make comparative observations between the blood flow in different feet. In conclusion it will be appreciated that in one series of observations fairly consistent readings can be obtained in measuring the blood flow in the calf at 34°C, and the foot at 44°C, in normal subjects.

The above conclusions only apply to blood flow observations made in rapid succession, usually at half minute intervals. If however the limb is left in the plethysmograph and the observations are continued over a period of about two hours, it is found that small variations occur between the groups of readings. In some cases the readings on the foot at 44°C tend to increase slightly during the first hour and to decrease slowly during the second hour. This trend has not been observed in every case and in many the flow rose to a maximum in 45 minutes and then remained constant. No definite reason has been found for these changes which are not closely associated with fluctuations in blood pressure. The blood flow in the calf measured at 34°C is much more constant and this is generally accepted as the best temperature at which to make these determinations (Barcroft and Edholm 1943). In instances where a difference has occurred between groups of readings made at 44°C, the average of the highest

group of readings has been taken as the maximum circulatory capacity of the part. The variation that occurs in groups of readings may be seen in fig.9.

The next essential is to determine the variability of observations made on different days. It is obviously not to be anticipated that exactly similar readings will be obtained under these circumstances. If care is taken to reproduce the conditions of previous readings as regards time of day, room temperature, and period of rest after insertion of the foot and before readings are made, it has been found that figures always agree to within $\pm 15\%$. Many of the cases have been subjected to repeated blood flow determinations and the figures are usually within $\pm 10\%$. The difference between the blood flow in healthy and diseased limbs is normally considerably greater than this variation. In doubtful cases the standard deviation of all the readings has been calculated and the T test of significance applied (Chambers 1940).

The type of result that may be obtained from observations on successive days is illustrated in the following case:-

J. G. age 49 years. Right popliteal thrombosis. Blood flow determinations were carried out on both feet on successive days. Plethysmographs were maintained at 44°C to ensure full vasodilatation. The readings in c.cs./100 c.cs. foot tissue/minute were:-

9.9.48 R. foot 10.4, 10.7, 11.2, 11.3, 11.9, 11.0, 10.7,
10.4, 10.1, 11.0.

Average 10.9. Foot volume 1,185 c.cs.

L. foot 16.6, 15.8, 16.2, 16.5, 16.6, 16.8, 15.5,
15.8, 16.0, 16.8, 15.3.

Average 16.2. Foot volume 1,200 c.cs.

10.9.48. R. foot 10.7, 10.4, 10.9, 10.2, 10.7, 10.7,
10.8, 11.5, 11.2, 11.5.
Average 10.9. Foot volume 1,195 c.cs.

L. foot 17.9, 16.2, 16.5, 17.2, 18.3, 19.2,
19.0, 17.4, 17.0, 20.4, 18.0.
Average 17.9. Foot volume 1,200 c.cs.

The results of blood flow determinations have been expressed as c.cs. of blood flow per minute per 100 c.cs. of tissue. When a series of observations has to be made it is highly important that an equal amount of the limb is inserted into the plethysmograph on each occasion. Thus in the case of the foot it is not satisfactory to insert for example 1,200 c.cs. on one day and 900 c.cs. on the following day and to compare the results by dividing the total blood flow to the part examined by 12 and 9 respectively. In the former case a greater amount of ankle and lower end of leg has been included. These tissues have a relatively lower blood supply, while the toes and distal part of the foot with its relatively large cutaneous surface and the presence of numerous arteriovenous anastomoses has a large supply. In examining the foot the upper end of the plethysmograph has been fixed at the narrowest portion of the leg immediately above the prominence of the medial malleolus. When a series of observations are to be made the level has been marked with a silver nitrate pencil so that similar fittings of the plethysmograph may be made on each occasion. When the two feet are to be compared corresponding marks are made at the lower ends of the legs after measuring the correct distance above the tip of each medial malleolus. In many of the observations on blood flow measured plethysmographically in the past sufficient attention has not been paid to the importance of tissue volume and it has been incorrectly assumed that in a comparative series of observations

discrepancies in total volume can be adjusted by expressing the result as blood flow per 100c.cs. of tissue. Attempts have been made to record the flow in terms of skin surface, but, though in the case of the hand this may be more satisfactory, it is not regarded as suitable for the foot as this structure contains a small proportion of muscle, and in addition the blood flow to the skin is not evenly distributed, that to the toes being much greater than that to the skin around the ankle. Similarly in investigating the blood flow through a muscular part such as the calf the plethysmograph must be placed high on the leg and the upper and lower levels of the instrument marked if repeated observations are required. If it slips down towards the foot a higher proportion of bone and tendon will be included and invalidate the results.

The above points with regard to plethysmography have been stressed in some detail as they have been apparently overlooked by many authorities in making comparative observations. There are of course many other points which require attention if accurate reproducible results are to be obtained. These have been emphasised on many occasions (Lewis and Grant 1926, Grant 1938, Abramson 1944). In measuring blood flows in limbs with obstructed arteries certain other considerations apply. It is particularly important in these circumstances to ensure that the venous occlusion cuff proximal to the plethysmograph does not occlude small collateral arteries in which the pressure may be unduly low. In normal subjects it can be shown that the blood flow readings are constant with a wide variation of pressures in the venous occlusion cuff, provided that this is kept at or below the diastolic arterial pressure. The only effect of reducing the pressure in the cuff is to

shorten the period of the tracing which is a straight line (fig.17) as the pressure in the veins more rapidly reaches that in the cuff. The values obtained for arterial inflow are usually similar between occluding pressures varying from 40-90 m.m. of mercury, as is demonstrated in the following series of observations:-

Subject J. W. B. P. 110/80. Foot in plethysmograph at 44°C.

<u>Pressure in Collecting Cuff</u> <u>in m.m. of Mercury.</u>	<u>Blood Flow Readings in</u> <u>c.cs./100 c.cs./minute.</u>
90 m.m.	21.9, 25.4, 22.0, 20.4
80 m.m.	24.8, 22.5, 24.7, 25.0, 23.3
70 m.m.	25.8, 23.9, 24.2, 24.6, 25.2
60 m.m.	23.0, 23.4, 22.6, 25.8, 24.6
40 m.m.	23.9, 24.2, 24.6, 22.0, 22.4
20 m.m.	19.0 (unsatisfactory tracing owing to shortness of straight rise).

In the above experiment it will be seen that there is no significant difference in the blood flow determinations over a wide range of collecting cuff pressures. The disadvantage of using the lower range of pressures is the shortness of the measurable period of the tracing which considerably affects the accuracy of the result. At 20 m.m. pressure a distinct rise occurred but in the form of a curve, and no reliable readings could be made by drawing a tangent to the first part of the tracing. At the upper level the readings do not fall off until at least 10 m.m. above the diastolic arterial pressure. In cases of arterial disease it is essential to show that this constancy of values at different pressures is maintained. Obviously if the small collateral arteries are being compressed the values for arterial inflow at the higher venous occlusion pressures will be reduced (Grant 1938). In the cases of arterial disease no such reduction was found and the majority of observations were made with the venous pressure between 50-70m.m.

of mercury (fig.6). As will be shown later there is no doubt that the pressure in arteries distal to an obstruction is considerably reduced in comparison with that recorded in the brachial artery. The reduction however was not sufficiently great to affect the accuracy of the plethysmographic readings. In this connection it is worth emphasising two points, firstly that a pressure in an artery below 30 mm. will not be able to contribute significantly to the nutrition of tissues if the capillary walls and plasma proteins are in a normal state, and secondly that owing to the presence of pain it is not possible to measure the blood flow in cases of incipient gangrene and that the observations have thus necessarily been confined to the relatively mild cases of ischaemia, in which the pressure has not been grossly reduced. It will have been noticed that the above observations on the blood flow in the foot were carried out at 44°C. which is in many ways an inconvenient temperature to maintain in the plethysmograph. This temperature is however essential to determine the maximum circulation in the foot. It has been found by repeated observations of many cases that the resting blood flow at 34°C. is frequently higher in a diseased limb than in an unaffected fellow limb (Sharpey-Schafer 1949). A possible explanation is that in the case of a mild ischaemia an additional blood supply may be required with the limb at rest to bring about healing of the minor lesions. The main feature of arterial disease is however the reduction in the ability of the circulation to develop to its maximum. Thus if the blood flow in a normal foot is measured at a local temperature of 44°C. to ensure full vasodilatation the flow may be found to have increased fivefold above that at 34°C. In the foot with occlusive vascular disease the response will be much more limited and in many instances there is no increase at all. It is accordingly obvious that if comparative measurements of blood flow are to be made in cases of occlusive vascular disease the maximum

circulatory capacity of the limb must be measured. In the case of the foot two methods are available. The circulation may be measured with the temperature of the water in the plethysmograph at 43-44°C. which ensures full vasodilatation of the majority of the arteries though possibly not of those supplying the deepest structures in the foot. This method was employed by Kunkel and Stead (1938). The second method is to measure the reactive hyperaemia that develops after a period of arterial occlusion (Landowne 1942). The arteries of the limb are occluded by a cuff applied around the thigh and blown up to a level above systolic pressure for five minutes and the blood flow into the foot after release of the circulation is recorded at half minute intervals, until the previous resting level is reached. In this way it is possible to record the highest blood flow level reached and also to estimate the period of time during which the circulation is increased and what proportion of the blood flow debt has been repaid. (Abramson 1941).

Similar considerations apply in measuring the blood flow through the upper part of the leg. Even in patients complaining of severe claudication pain on exertion the resting blood flow through the calf measured plethysmographically at 34°C. may be found to be within normal limits. In these cases it is not satisfactory to make the measurements at 44°C. as this will not bring about full vasodilatation in the deeper arteries supplying the muscle tissue. The greatest stimulus to dilatation of these vessels is exercise, and accordingly measurements have been attempted after a standard period of measured exercise consisting in contracting the calf muscles to plantar flex the foot against a known weight once per second. As with other authors the results have been found very variable and it has not been possible

to draw any satisfactory conclusions (Abramson 1944). It had been hoped to make some observations as to the extent to which the circulation was reduced before claudication was appreciated, but this was not possible. It appeared that in many cases the pain resulting from exertion must have arisen as the result of ischaemia of a small portion of muscular tissue. The other method of investigating the reduction in circulatory capacity of the calf muscle arteries is to apply the reactive hyperaemia test as in the foot. This will often show a reduction in the maximum flow attained in comparison with a healthy fellow limb, but here again there may be little significant difference between those with symptoms of vascular deficiency and symptom-free limbs.

It will be appreciated that in all the types of vascular disease open to study by the plethysmographic method it is essential to determine the maximum circulatory capacity of the part. In other words, the first feature of a pathological physiology in vascular disease is a reduction in the circulatory reserve of the limb. As the disease progresses the reserve circulatory capacity is steadily reduced, but the blood flow at rest remains within normal limits. Presumably when pain is present in the limb at rest and gangrene is developing the resting blood flows are reduced but under such circumstances accurate plethysmographic tracings cannot be obtained. If any pain develops in the foot while the records are being made the investigation should be abandoned, as, under such circumstances, a reflex vasoconstriction occurs (Sturup 1935) and the results do not represent the maximum circulatory capacity of the part. The development of pain may be very troublesome while attempting to measure the circulation in feet at 44°C. In the majority

of cases of mild vascular disease this temperature can be tolerated without ill effect for the hour required to make the observations, but in the more severe cases such a temperature cannot be used. In the latter cases the maximum circulatory capacity can be ascertained either by applying the reactive hyperaemia test with the plethysmograph at 34°C. or by raising the temperature gradually in the plethysmograph in a series of steps. Thus the initial observations are made at 34°C. The temperature is then increased to 38°C. and further readings are taken. Thereafter further rises are made to 40°C. and 42°C. In a normal limb under such circumstances a steady increase in blood flow occurs with each rise. In the diseased limb there may be little increase after 38°C. or 40°C. and the flow at this temperature immediately before the development of any discomfort may be taken as the maximum possible. The figures for the blood flow at the highest temperature reached and for the peak of the flow after reactive hyperaemia are usually remarkably similar and may thus be taken to represent the maximum circulatory capacity of the part.

The blood flow through an artery depends chiefly on the calibre of the vessel, the pressure within it and the viscosity of the blood (Poiseuille's law 1843). Other less important factors have also been recognised (Bradley 1948). From the point of view of peripheral vascular disease it is important to remember that a reduction of pressure in an artery will not only lead to a decrease in the rate of blood flow but will also affect the pressure within the arterial ends of the capillary loops and thus if the reduction is sufficiently great it will interfere with the nutrition of the surrounding tissues. As a study had been made of the collateral arterial circulation by the methods described in

the previous section it was particularly desired to measure the blood pressure in arteries distal to occlusions. In man this is obviously extremely difficult to do by any direct method and accordingly an indirect approach had to be developed. Normally the blood flow estimations are made with the foot at heart level. At the same time the blood pressure is measured in the brachial artery with a sphygmomanometer with the arm also at heart level. The idea of reducing the blood pressure in the lower limb by raising the foot of the couch was prompted by the observation of the prompt development of gangrene in a limb after raising the foot of the bed on to ten-inch blocks. In this case of diabetic vascular disease of the lower limbs the bed had been raised in an attempt to reduce the inflammatory oedema around an area of infection. The decrease in arterial inflow consequent on reduction of the local blood pressure by gravity determined the onset of gangrene. A series of experiments was accordingly designed to measure the reduction in blood flow in the foot that could be brought about by postural changes in subjects with normal and occluded arteries in the lower limbs.

It can be shown that by raising the feet to a height of 190 m.m. above the heart level the blood pressure in the arteries of the feet will be reduced by the effects of gravity a known amount provided that the blood pressure at heart level remains constant. Assuming that the specific gravity of blood is 1.06 and that of mercury 13.6 the reduction may be expressed in millimetres of mercury as $190 \times \frac{1.06}{13.6}$, that is 15 m.m. For the purposes of the experiment the end of the couch was raised 20 cms. to an angle of 70° and as the plethysmograph was secured at the extreme end of the couch and the axis of the tilt was at approximately shoulder level the feet were brought about 19 cms. above the heart level.

For practical purposes the fall in blood pressure brought about by gravity in the foot was calculated to be approximately the equivalent of 15 m.m. of mercury. The observations of the blood flow were made with a local temperature of 44°C. in order to ensure constant full vasodilatation. Five readings were obtained with the couch level; the foot was then raised 20 cms. and a further ten tracings were recorded; finally five readings were made with the couch level. The first and second series of five readings served as a check that the blood flow was constant apart from the postural change (fig. 9). A comparison of the average of ten readings in each position was available and the percentage decrease of the blood flow in the elevated position was calculated. The blood pressure in the brachial artery at heart level was estimated in each position. For purposes of calculation the mean effective arterial pressure was regarded as the diastolic pressure plus one third of the pulse pressure and to record the result graphically the percentage decrease in mean effective arterial pressure in the elevated position was assumed to be given by the formula:-

$$\frac{15}{\text{diastolic pressure} + \frac{1}{3} (\text{pulse pressure})} \times 100$$

Many objections can of course be raised against the use of this formula. In the first place it has been shown that when the body is tilted head downwards the fall in blood pressure in the femoral artery measured directly is greater than can be accounted for by the effect of gravity alone. Thus Green and his colleagues (1947) showed that on tilting the body head down to an angle of 45°C. the fall in femoral blood pressure occurred in two stages, the first immediate fall being due to gravity and the second fall to reflexes arising from the aortic and carotid sinuses. The angle obtained in the above experiments was only 7°, so that the

second fall originating from reflexes to protect the brain against excessive pressure is probably very slight. Some controlled observations were made by raising one foot only 20 cms. and leaving the couch level. The fall in blood flow under such conditions was strictly comparable to those obtained by raising the whole of the end of the couch. As however this investigation arose from a study of the effects of raising the foot of the bed on to ten-inch blocks, that is to an angle of 7° the original method of study by raising the whole of the couch 7° was continued. By plotting the percentage reduction in blood flow against the calculated percentage reduction in arterial blood pressure a remarkably consistent curve was obtained in individuals without evidence of occlusive vascular disease (fig.10). It will be appreciated that if the arteries and arterioles behaved as rigid tubes the decrease in blood flow would be exactly proportioned to the decrease in pressure and the points would be on a straight line at 45° passing through the origin. The decrease in blood flow is however proportionately greater than that in pressure, except in the case of individuals with a gross degree of hypertension in whom the percentage decrease in pressure on raising the limb is slight and in whom the arteriolar walls are considerably thickened. The evidence at present available thus suggests that the proportionately greater fall in blood flow is due to a partial collapse of the arterial walls with the decrease in pressure. It will be remembered that a fluid flow through a rigid tube varies as the fourth power of the radius of the lumen (Poiseuille's law), so that even a small degree of collapse of the arterioles on raising the feet would account for a considerable fall in flow. The cause of the disproportion is however being further investigated by raising the limbs to different heights. The effects of elevating

the foot of the couch in those with occlusive vascular disease will be discussed in later sections.

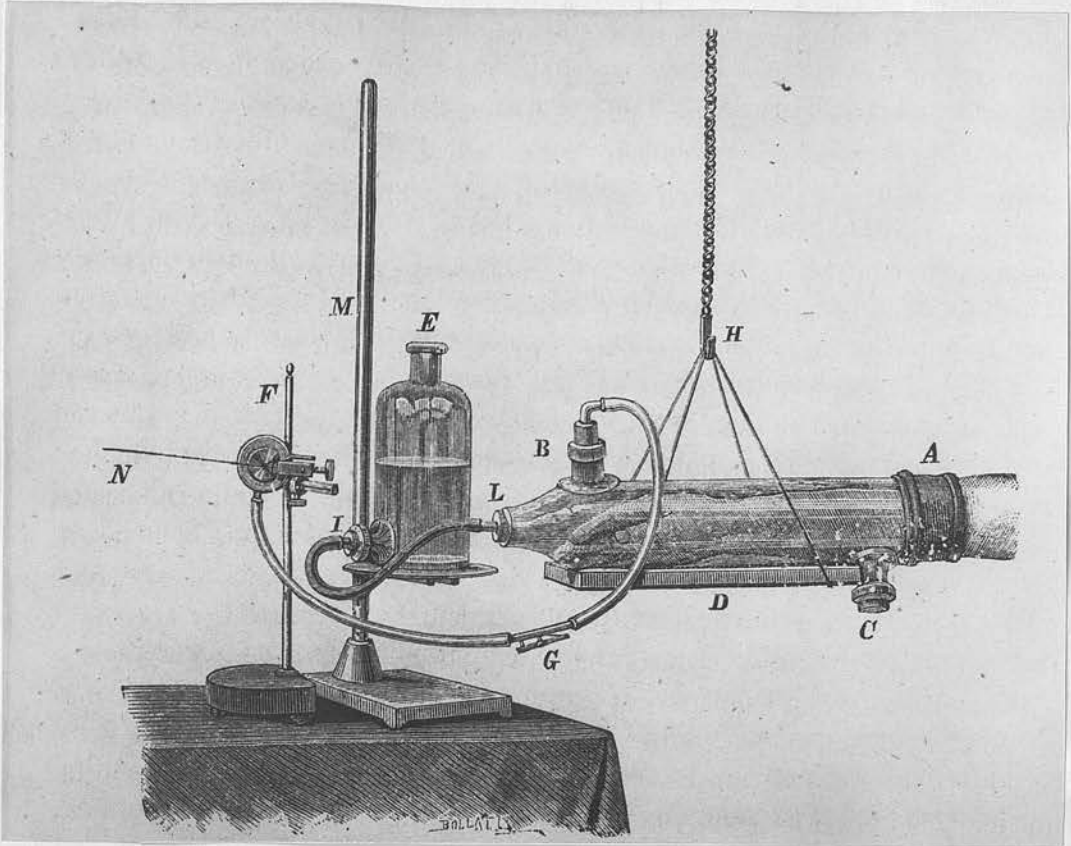


Fig. 3. Mosso's illustration of his original plethysmograph. It was used only to record arterial pulsations. The instrument was sealed to the forearm by the rubber sleeve A. In order to record the arterial inflow the addition of a venous occlusion cuff immediately proximal to A would be required. The chief difficulty with this type of plethysmograph is to maintain a water tight seal at A which at the same time does not occlude the veins.

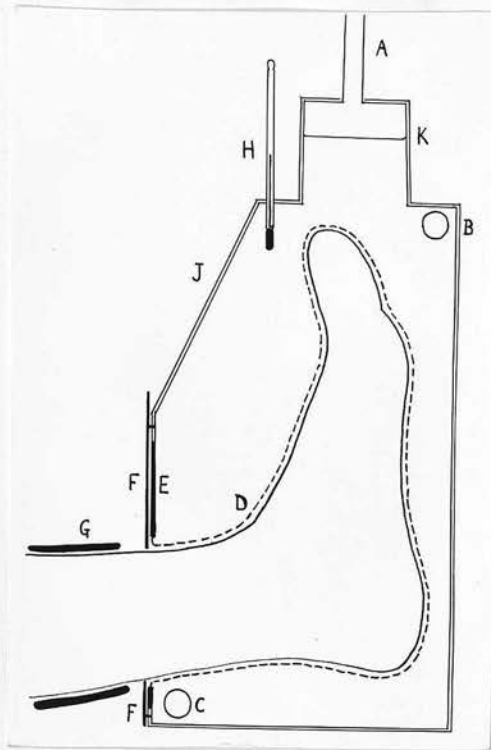


Fig. 4. Diagram of the foot plethysmograph. A connexion leading to volume recorder. B and C outflow and inlet for circulating hot water to maintain constant temperature. D dotted outline of latex rubber sock maintained in apposition to foot by the weight of the water. E thick rubber diaphragm to allow insertion of foot. F sliding baffle plates to prevent bulging of rubber diaphragm. G venous occlusion cuff. H thermometer. J celluloid wall of plethysmograph. K upper level of water. The advantage of this type of instrument is the avoidance of a direct water tight seal between the skin and the rubber diaphragm.

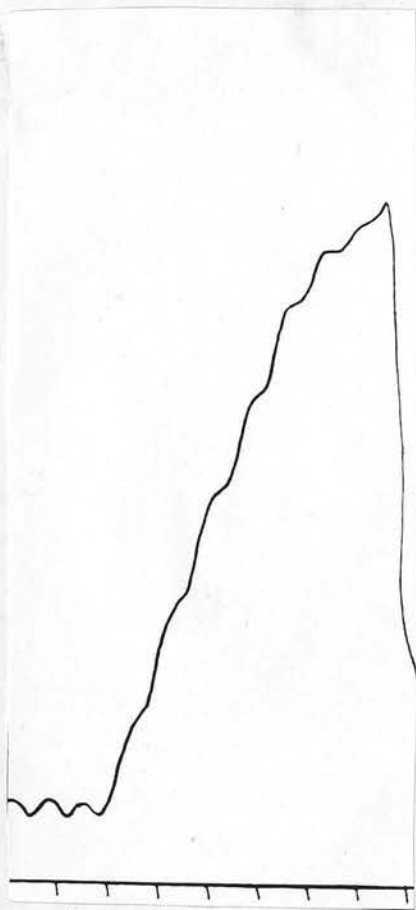


Fig. 5. A normal blood flow tracing as recorded by the venous occlusion plethysmograph at 44°C. The first five pulse beats are in a straight line and represent the arterial inflow up to the point when the venous bed is fully distended. Thereafter the rate of filling falls off in a curve until the point when the pressure in the cuff is released. Time marker 1.5 secs.

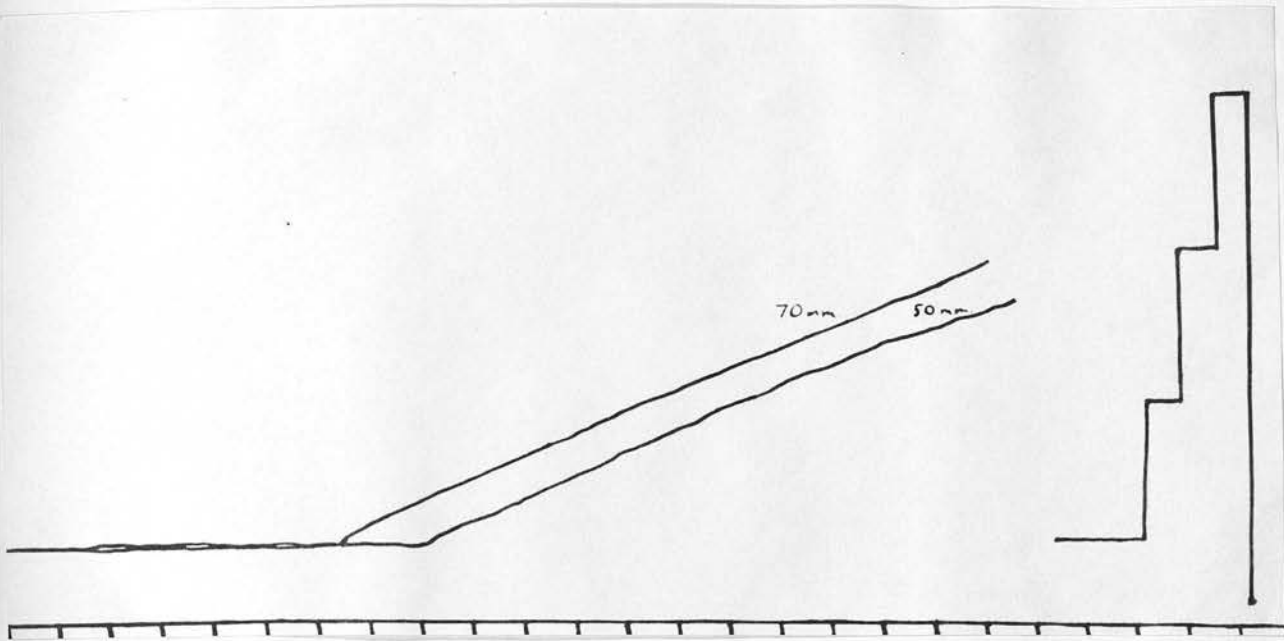


Fig. 6. Blood flow tracings from the foot in a severe case of thromboangiitis obliterans. The first parts of the two tracings with the occlusion cuff at 70 mm. and 50 mm. are parallel, showing that small collateral arteries are not affected by this pressure. With the lower occlusion pressure the uniform rate of swelling is not so long maintained as the pressure in the venous bed more rapidly reaches that in the cuff and return of blood beneath the occluding cuff accordingly takes place. Pulsations are absent in the tracings owing to the obstructions in the main arteries. On the right is shown the method of calibrating the instrument, the steps representing 5 c.c. increments. The rate of arterial blood flow in these tracings is 3.8 c.cs./100 c.cs./min. Time marker 1.5 secs.

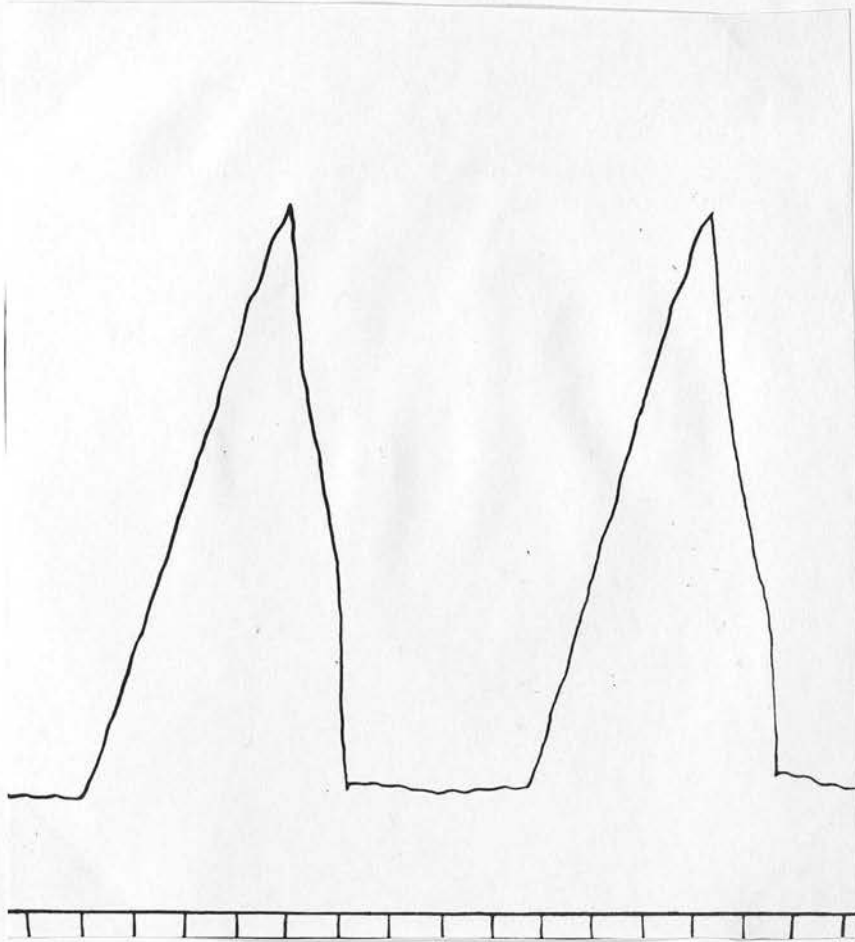


Fig. 7. Blood flow tracings from the foot in a case of coarctation of the aorta. Plethysmograph temperature 44°C . In spite of the full vasodilatation pulsations are almost entirely absent. The extent of arterial pulsations in vascular disease affords no true indication of the blood flow and in this case, in spite of absent pedal pulses, the flow was 26.5 c.cs./100 c.cs./min. Time marker 1.5 secs.

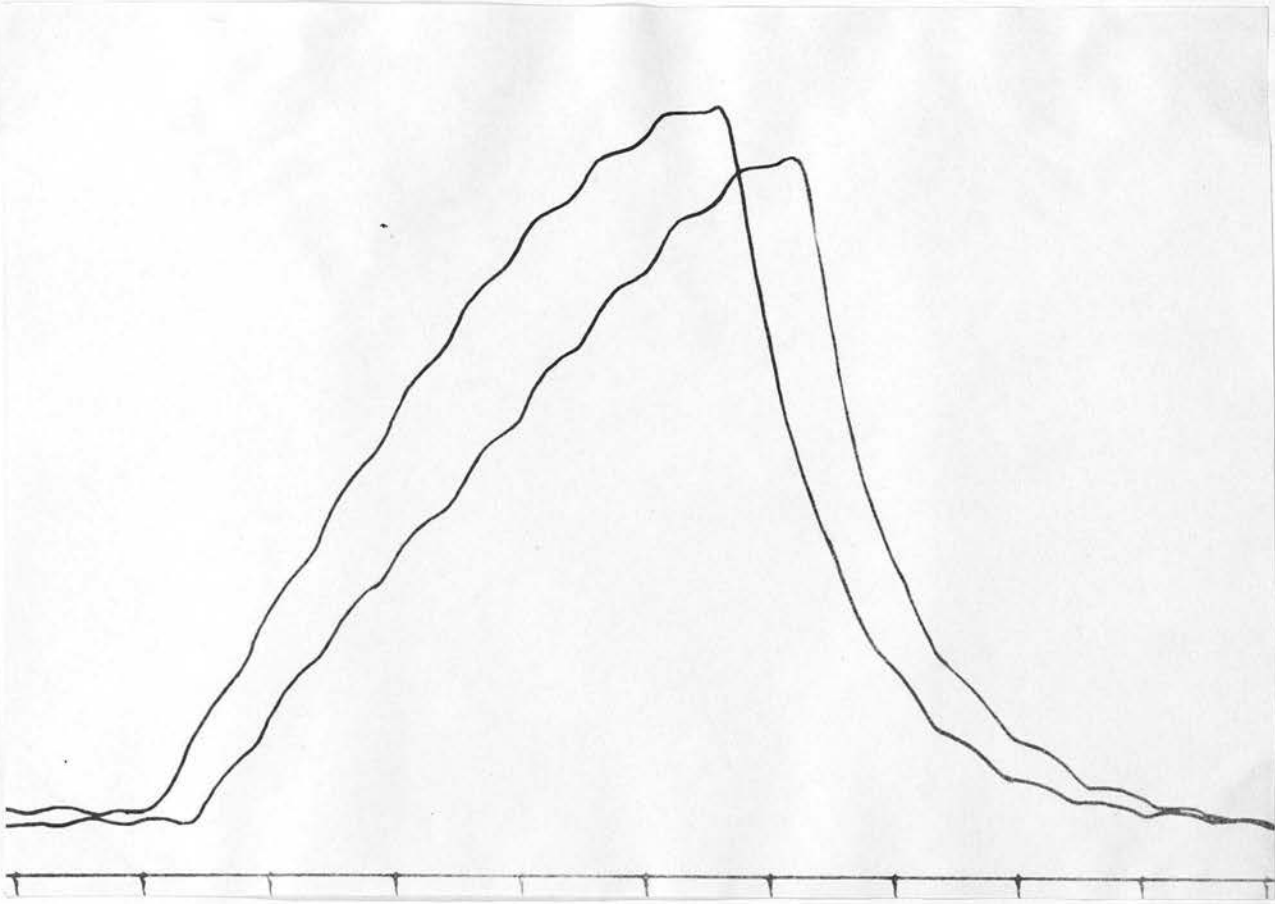


Fig. 8. Blood flow tracings from a normal foot. Plethysmograph temperature 44°C . The left hand tracing is with the limb horizontal at heart level; the right hand with the foot of the couch raised 20 cm. to an angle of 70° . The respective blood flow readings are 16.5 c.cs. and 11.6 c.cs./100 c.cs./min. Time marker 1.5 secs.

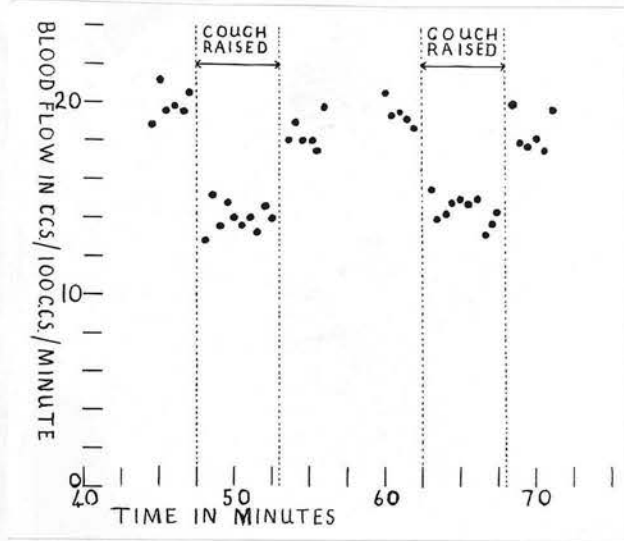


Fig. 9. Blood flow readings from the foot of a normal subject with the couch in the horizontal and raised positions. The estimations were made at half minute intervals and the couch was raised 20 cm. at the foot to an angle of 7° . The degree of variability of individual readings and the reduction in arterial inflow on raising the couch are shown.

PART III.

Thromboangiitis Obliterans.

It is with considerable diffidence that the title of this section has been written for it is no easy matter to establish a clear cut diagnosis of this condition on either clinical or pathological grounds. On studying pathological reports on limbs amputated at the Edinburgh Municipal Hospitals, it was found that over a period of three years in a series of eight cases originally diagnosed on pathological grounds as thromboangiitis obliterans, the diagnosis was subsequently changed to atherosclerosis in six of them after consultation with the clinician. The difficulties in separating these two conditions on histological grounds in males about middle age is so great that some authorities have ceased to make the distinction (Gery et al. 1939). They considered that the pathological lesions of Buerger's disease lacked specificity and did not feel that the disease was worth preserving as a separate entity in the general group of juvenile arteritides with which it is identified. Nevertheless there are certain features on which a separation of this group of cases from atherosclerosis may be attempted, and in general it is probably convenient to try to maintain the distinction between them. Thus in the present series 12 cases have been regarded as thromboangiitis obliterans. The material studied pathologically has included five amputated limbs, two being above the knee and the rest below the knee, and two biopsy specimens from superficial veins. Blood flow determinations have been carried out on eight patients, one of whom subsequently underwent amputation. In the other four amputation cases no blood flow determinations were carried out prior to operation.

With regard to the aetiology of the condition I have nothing new to add. The present position has been fully reviewed by many writers (Allen et al. 1946). From the present study it is however possible to add confirmation to the views expressed by many authorities regarding the deleterious influence of tobacco (Freeman 1947). The five major amputations were all carried out in subjects who had continued smoking. The other seven patients have stopped smoking entirely and have shown no clinical features suggestive of progress of the disease. In several of these cases accessory pulses have appeared around the patella and ankle. In four of them blood flow determinations have been made over a period of a year and maintenance of the previous level or a gradual increase in flow has been observed. In one patient, studied over a period of nine months, who has not ceased smoking, blood flow determinations have shown a slight decrease. The evidence from such small numbers is of course far from conclusive but at least lends a little support to the view that tobacco smoking tends to lead to the progress of the disease whatever its prime aetiology may be. It is also interesting to note that in the present series seven of the patients were Jewish and that three of them were immigrants from Eastern Europe. Little significance however should be attached to these observations for the proportion of Jewish refugees attending St. Mary's hospital for every type of complaint is high. Similarly Buerger's hospital in New York tended to draw largely on an Eastern European Jewish community. It is thus extremely doubtful whether there is any significant racial incidence of the disease.

In the cases of thromboangiitis obliterans the gross characteristics of the vessels varied considerably depending on the age of the lesions at the time of examination. The occluded segments were definitely indurated but not brittle and their distribution was strangely localised, the transition

from apparently normal to obliterated artery being singularly abrupt. In all the cases the earliest lesions were in the more distal parts of the limbs, a point that was confirmed both by the clinical and pathological examinations. The involvement of the proximal portions of the tibial arteries and popliteal artery was a late feature, though an extremely important incident as it frequently induced the onset of massive gangrene of the extremity. The early lesions of thromboangiitis during the period while this disease is possibly confined to only one toe are thus frequently overlooked or misdiagnosed. From the point of view of the distribution of early lesions the following case is of particular interest:- M. M. aged 38 years, a tailor of Polish Jewish parentage, born and educated in England and first seen on 7.6.48, noticed pain in the right calf about ten years previously. The pain developed after walking about half a mile and subsided promptly on resting. The attacks lasted a few months and then subsided. He served throughout the war in Burma and undertook active exertion, including playing football and route marches, without developing any features of intermittent claudication. The pain in the right calf returned slightly $1\frac{1}{2}$ years ago, but again disappeared after a few months. Three months ago the right second toe suddenly became blue and painful and later developed a small septic lesion which only healed gradually over a period of several weeks. There was no significant previous or family history. He smoked about 20 cigarettes a day.

On examination the second right toe was cyanotic and had a small dry scab at the tip. When dependent the right first and second toes were more deeply coloured than their fellows and on elevation showed a mottled pallor. After soaking in water at 45°C . capillary pulsation was demonstrated

in all the toe pulps except in these two toes. The femoral, popliteal and posterior tibial pulses were present on both sides, but both dorsalis pedis pulses were absent. A reactive hyperaemia test showed considerable delay in return of the circulation to the right second toe and to a lesser extent to the right first toe. The return to the other toes of both feet was not delayed. Plethysmographic determinations at 44°C. gave the following figures for maximal circulatory capacity:-

R. foot 20.5 c.cs./100 c.cs./minute average of 22 readings; standard deviation 0.7 c.c. and coefficient of variation 3%.

L. foot 21.7 c.cs./100 c.cs./minute average of 21 readings; standard deviation 0.8 c.c. and coefficient of variation 3%.

The difference between the two circulations was statistically significant and was thus probably chiefly due to the obstruction of the digital arteries in the second right toe. The reduction in the total circulation to the right foot was thus minimal and the disease in the foot was limited to the small digital vessels. Similarly only small vessels in the calf can have been involved as the major vessels were pulsating and the foot circulation as a whole was not grossly impaired.

It will be noticed that attention has been directed to lesions in the small distal arteries. On clinical grounds attempts have been made to distinguish between proximal and distal types of the disease (Kinmonth 1948). This distinction is however difficult to confirm on pathological examination and in all the amputated limbs it has been possible to demonstrate some lesions in the digital arteries, though these may not be extensive. It will be appreciated that symptoms of ischaemia arise when collateral vessels cannot carry sufficient blood distal to the obstruction to meet the functional requirements of the part. Obstruction of the popliteal artery

is extremely difficult to circumvent, as will be demonstrated in a later section, and immediately gives rise to symptoms. In such circumstances minor arterial lesions in the foot may readily be overlooked on clinical examination. The reactive hyperaemia test demonstrates such obstructions in the toes by the delayed return of blood to the affected areas and by this test it has always been possible to demonstrate small peripheral obstructions in cases where the main lesion is situated proximally. It is unfortunate that this test is not more widely used for the demonstration of these small distal lesions which may be important. They are not commonly present in atherosclerosis, which involves chiefly the larger arteries, but frequently constitute the earliest changes in thromboangiitis obliterans. In individuals of middle age where distinction between the two conditions is most difficult, this difference in distribution of the earliest lesions may form a most valuable diagnostic point. Apart from the singularly localised nature and peripheral distribution of the lesions several other features were noted in these cases. In the most recent arterial occlusions the obturating mass was red or brown, while in the longer standing it was yellow and centrally located in contrast to the bulging seen in the atherosclerotic cases. In the amputated limbs involvement of the arteries was considerably commoner than of the veins. Frequently fibrous tissue spreading out from the adventitia of the artery enclosed the venae comitantes in a firm cord; in such circumstances the veins were often patent, even though the artery was blocked by old standing disease. On the other hand the veins might be affected in close relation to a healthy artery. It was also noted that one vena comitans might escape entirely while the other was obliterated with organized thrombus. It was only occasionally that the fibrosis was

found extending out to include an accompanying nerve, and in the amputation cases such firm adhesion of artery, veins and nerve occurred more rarely than in the cases described by Buerger (1924).

The earliest histological changes of thromboangiitis were not seen in the amputated limbs, as naturally the disease had been present for some time in the majority of the arteries. Indeed I was unable, even after cutting numerous serial sections of arteries in which recent thrombosis had apparently occurred, to detect what from Buerger's descriptions might be regarded as the earliest changes. This difficulty has apparently been encountered by numerous other investigators. Gery et al. (1939) did not confirm the acute lesions described by Buerger who regarded the earliest change as an acute polymorphonuclear infiltration of all the coats of the vessel. In the peripheral portions of the clot he described focal collections of leucocytes - the so-called "purulent foci". He did admit, however, that these acute lesions could be more easily demonstrated in superficial veins which were the seat of a typical migrating phlebitis. "They are rarely to be seen in the deep vessels for the reason that patients do not allow amputation until the disease has lasted for months or years." He claimed however to have shown that the histological features in the superficial veins were identical with the acute lesions in the deep vessels. It is nevertheless extremely difficult to understand why, if the lesions are identical, they are not more readily found in the arteries. In amputated limbs the majority of the lesions are admittedly old, but it is usually possible to find a few recently affected arteries; indeed it is frequently a final recent thrombosis that determines the onset of massive gangrene and amputation without undue delay. In all the cases studied pathologically

portions of such arteries were taken for serial section but no "purulent foci" were found. It is noteworthy that in Buerger's book no illustrations of "acute lesions" in arteries appear, even though he has described them. All the "acute" illustrations are confined to veins. No later authorities have been able to detect these lesions in arteries (Allen et al. 1928).

An opportunity of studying the earliest changes in affected veins was afforded by biopsy specimens taken from two patients with migrating phlebitis, complicating thromboangiitis obliterans. Serial sections were cut from different portions of the veins. In a few sections small focal collections of polymorphs were found, but they were not numerous and did not constitute outstanding features. More prominent were the giant cell formations which are often regarded as typical of the condition (fig. 11). These giant cell formations were also more rarely found in some of the sections of arteries in the amputated limb, but they were not so common as in the veins and I can confirm Leriche's observation that many sections have to be cut in order to demonstrate them (Leriche 1940). The resemblance of the giant cell formations to a tuberculous follicle is obvious in the figure, but no tubercle bacilli could be demonstrated in the sections. Giant cells of this type are not peculiar to thromboangiitis obliterans and may occur in all types of arterial disease. They were originally described in cases of "spontaneous gangrene" by German pathologists (von Winiwarter 1879, Haga 1898, Bunge 1901) and have more recently been described as occurring in periarteritis nodosa (Grant 1940, Miller and Daley 1946) temporal arteritis (Cooke et al. 1946) and in other less clear cut types of arterial disease (Gordon and Thurber 1946, Scheinker 1945, Gilmour 1941). The case

described by Barnard (1935) as tuberculous arteritis showed lesions very similar to those in figure 11. No tubercle bacilli or adjacent source of tuberculous infection were found and Barnard's case would now fall into the category of temporal arteritis. It is thus apparent that a diagnosis of thromboangiitis obliterans cannot be founded on the presence of giant cells alone. In the biopsies of the veins the markedly cellular organization of the thrombus, the increased number of fibroblasts in the media and adventitia and the proliferative changes in the intimal coat were the most noticeable features. The mild infiltration of polymorphs and lymphocytes was generally overshadowed by this rich cellular organization.

In the amputated limbs several well developed yet still relatively recent lesions were seen. In them there was a definite proliferation of the endothelial cells of the intimal coat and small focal infiltrations with lymphocytes were also apparent. Giant cells were very rarely seen even in serial sections. The lumen was occluded by thrombus in which extensive organization was taking place with endothelial cells and fibroblasts. In these arteries the internal elastic lamina was characteristically preserved intact. The medial coat contained many dilated capillaries showing considerable endothelial cell proliferation, but the muscle fibres showed no definite changes in the early stages. By contrast in the adventitia there was an extensive fibroblastic proliferation even at a relatively early period in the development of the lesions. Other noticeable features in this coat were prominent vasa vasorum often showing intimal proliferation and swollen lining endothelial cells. A perivascular infiltration of lymphocytes was commonly present. polymorph leucocytes were infrequently present in the thrombus

and arterial coats, and often they were entirely absent, even in the apparently earliest lesions. It was noticeable that when they were present there was frequently considerable tissue necrosis or heavy infection in the distal part of the limb.

In arteries in which the disease had been longer present there was usually canalization of the thrombus by new blood vessels with well developed endothelial linings. Some of these new vessels acquired elastic and muscular tissue within their walls and had a definitely arterial structure. Others, though of similar size, had no distinct consolidation of tissue around them. As the lesions progressed the thrombus became more fibrous and less cellular, but the internal elastic lamina and the media remained intact and well preserved. In some of these older lesions the distinction from atherosclerosis sometimes became particularly difficult as the fibrous tissue was densest around the periphery of the thrombus in close relation to the intima and a picture that in many ways resembled certain types of atherosclerosis was frequently produced. Even in these cases however the striking feature was the relatively large number of endothelial cells and fibroblasts which were outstanding in all cases of thromboangiitis.

The process of organization of the original thrombi was studied in conjunction with Dr. Y. Y. Akrawi. In accordance with previous views it was found that the vascular supply to the organizing thrombi came chiefly by capillaries connecting with the vasa vasorum and penetrating the vessel wall to invade the blood clot (Huecking and Thoma 1887). The blood clots were replaced by vascular granulation tissue which, becoming more fibrous, contracted and allowed for the formation of small and large blood spaces that gave the fully



organized thrombus its characteristic cribriform appearance. In still older lesions some of the spaces became surrounded by elastic coats. Accordingly the following types of blood channels were to be found in old occluded vessel segments:-

1. Small capillaries scattered in the thrombus.
2. Blood spaces or sinuses lined by endothelial cells only.
3. Elastic coated channels running in the long axis of the artery.

In the cases of thromboangiitis obliterans the elastic coated channels in the serial sections were found to take origin from small arterial side branches of the occluded vessel. Some of these elastic coated channels in the thrombus broke down to give rise to capillaries which were traced draining into blood sinuses that were lined only by endothelial cells, varied in diameter between 200-500 microns, and ran transversely through the thrombus towards the periphery. These sinuses subdivided into smaller sinuses, penetrated the internal elastic lamina, transversed the media and ended in the vasa vasorum of the adventitia. Such vasa were finally followed in the sections until they joined a vein. Other elastic coated channels were seen not to divide, but after running for a variable distance in the long axis of the thrombus ended by communicating with one or more side branches. The elastica surrounding these channels was continuous with the internal elastic lamina of the side branches which they joined. The channels were either fully patent or occluded by thrombus and organization tissue of a more recent nature than that occupying the main vessel lumen. The side branches were also either fully patent, partially occluded, or occluded by the same kind of recently organized thrombus that occupied the elastic coated channels. All these side branches were

peripherally connected with fully patent small arteries. In general it was noted that occluded segments of artery distant from and devoid of patent side branches showed little tendency to recanalization by elastic coated channels.

In the injected and radiographed limbs the X-ray photographs showed that stretches of the affected arteries were only intermittently filled with the opaque mass. Numerous well-filled side branches were however seen in relation to the portions of the artery containing the injected substance. After dissection of the affected parts the main arteries of the leg were cleared by the Spalteholz method. It was thus demonstrated that channels originating from the side branches ran through the occluded lumen for some distance. They either ended blindly by breaking down into capillaries not filled by the injection mass or by leading into canalizing channels derived from other patent side branches at different levels. Histological sections showed that canalizing channels filled with injected lead phosphate were invariably surrounded with elastic tissue coats. Often there was no direct connexion between these canalizing channels and the patent portions of the arterial lumen above and below the obstruction. The majority of the side branches attached to the occluded segments were filled with the injected material that had come through tortuous collateral vessels shown in the X-ray photographs (fig.16). Occluded segments distant from the patent side branches usually did not contain any elastic coated canalizing vessels but merely small capillaries and venous sinuses not penetrated by the injection mass. Histological sections taken from portions of the artery seen in the cleared preparations not to contain injection mass were never found to contain elastic coated channels.

The examination of these occluded vessel segments affected by thromboangiitis obliterans showed that when the lumen of a main artery was occluded the side branches were

not primarily involved but generally remained patent to take part in the development of the collateral circulation. Under such conditions complex reversals of blood flow occurred. (Buerger 1924). The side branches thus carried blood under arterial pressure but the flow came to a standstill near the attachment of the branch when the main vessel was blocked by the thrombus. When the thrombus was invaded by organizing tissue the arterial blood stream effected a passage through it. The formation of such a passage might be helped or retarded by many factors, such as the efficiency of the collateral circulation and the number and patency of the side branches. The elastic coated channels ended either by breaking down into capillaries or by leading into other patent side branches at different levels. The functions of these channels thus appeared to be twofold. In the first place they helped to supply the vessel walls and the tissue in the lumen with arterial blood, while the venous return was affected by the sinuses as described above. Secondly, the channels formed shunts between patent functioning side branches and thus appeared to act as anastomotic links between different parts of the collateral circulation. In some instances the elastic coated channels were affected later by the same process that had originally occluded the main arterial lumen. They became thrombosed and organized and some of them again became recanalized by elastic coated channels originating in still patent side branches. When however the side branches themselves became extensively occluded no such recanalization was evident as the source of arterial blood was obstructed.

Elastic tissue appeared around every functioning arterial lumen whose size permitted the blood to flow through it under some pressure. The number of elastic fibres and the thickness of such a coat depend upon this pressure and

the age of the channel. In the case of the elastic coated vessels within the occluded arteries it has been demonstrated that these channels were invariably connected by collateral pathways with the general arterial system. The new elastic fibres developed first around the channels nearest the side branches and then gradually spread along the channel wall as it penetrated further into the occluded lumen. The new elastic fibres appeared to form extracellularly around some of the connective tissue cells that were outside the endothelial lining of the channels. It thus appeared that when these channels began to carry arterial blood under pressure from the side branches the elastic producing cells normally present in the intima of the vessel walls were stimulated to proliferate. These cells, starting from the intima of the side branches, spread along the walls of the canalizing channels outside their endothelial lining. The amount of elastic tissue thus formed was proportional to the importance of the channel, its age, and the calibre of the patent side branches.

The demonstration of these new arterial passages in thrombosed arteries naturally led on to the next part of the investigation which was to determine to what extent thromboangiitis obliterans reduced the circulation in the foot before features suggestive of tissue ischaemia appeared and what degree of increase of blood flow might occur as a result of the development of collateral channels. In order to make these determinations the necessity of measuring the circulation of the foot at its maximal capacity has been emphasised. Two methods have been utilised for this purpose, namely, measuring the blood flow either during the height of reactive hyperaemia after arterial occlusion or at full vasodilatation secured by exposing the foot to a temperature of 44°C. Using the second method Kunkel and Stead (1938) concluded that the circulation in the foot must be reduced at least 50% before features of

vascular disease became manifest. In attempting to confirm this finding many difficulties were encountered. In the first place the disease may be extremely localised and may for example be confined to one toe and yet sufficiently severe in that small region to cause severe symptoms. In such circumstances obviously there will be little difference between the maximal circulatory capacity of the normal and abnormal foot. These points were exemplified in the case M. M. quoted above.

If however the arterial lesions are at a level above the foot it is possible to make some estimate of the extent to which the circulation can be reduced before symptoms appear. In six cases in whom obstructive lesions were present above the foot the highest blood flow obtained in the presence of symptoms of ischaemia in the foot was 12.5 c.cs./100 c.cs./min. The results in these cases may be tabulated as follows:-

<u>Case</u>	<u>Age</u>	<u>Blood Flow at 44°C.</u>	<u>Blood Flow during reactive hyperaemia.</u>
H.E.	39	7.8 c.cs./100 c.cs./min.	7.6 c.cs./100 c.cs./min.
W.W.	38	12.5 c.cs./100 c.cs./min.	
G.H.R.	25	12.0 c.cs./100 c.cs./min.	
J.T.	33	10.2 c.cs./100 c.cs./min.	
A.J.W.	40	9.8 c.cs./100 c.cs./min.	10.0 c.cs./100 c.cs./min.
P.S.	49	6.0 c.cs./100 c.cs./min.	6.6 c.cs./100 c.cs./min.

It can thus be seen that the blood flow must be reduced to about 50% of maximum before symptoms of tissue ischaemia appear. This figure may well be too high as it is probable that the symptoms that develop in the foot are not only due to the occlusions in the arteries above the ankle but also to more localised obstructions in the arteries of the foot itself. The symptoms may thus arise only from a small area of more intense ischaemia superimposed on a generalised reduction in the foot circulation. The uneven spread of the colour changes observed

during reactive hyperaemia certainly suggested that this was so in the cases studied. It is thus apparent that a very great reduction in the circulatory capacity of the part is necessary before ischaemic features appear and the great reserve capacity of normal vascular supply is demonstrated. During the early stages of obliterative vascular disease the process consists essentially in a diminution of this reserve and while this is taking place symptoms are absent. When they do first appear it is often in an extremely localised area, for example in a toe through extension of thrombosis in a digital artery. The localised nature of such a lesion may however be difficult to determine and this renders any assessment of the degree in reduction of the blood flow to a large part such as the foot before symptoms appear of doubtful validity. Even a toe plethysmograph such as that developed by Goetz (1946) cannot be relied upon entirely as in many cases, even in a toe, the ischaemia may be confined to a small area. When the blood flow figures in this series of cases were plotted against control figures for the respective ages it was seen that the decrease in the affected feet was considerable and the great reserve of vascular capacity was clearly demonstrated (fig.17).

Plethysmographic records have been obtained from several of the cases of thromboangiitis obliterans over a period of several months, but during this period there has been relatively little change in the maximal circulatory capacity of the feet, except in some who have ceased smoking. In these cases the figures have tended to increase slightly. The following case may be quoted as an example:-

H. E. aged 39 years, a garage proprietor, first noticed pain on walking in the right great toe in November 1945. The disturbance was transient lasting only a fortnight. During 1946 the right little toe suffered from a similar attack, the skin breaking down and the ulcer healing slowly after a course

of penicillin injections. During May 1947 he developed pain in the right foot after walking about 100 yards. The pain appeared in the sole of the foot and around the first metatarsal and promptly subsided on resting. Further small septic lesions subsequently developed on the right third and fourth toes. In addition small red spots have been noticed appearing along the courses of the veins on the dorsum of the right foot. No trouble has been experienced at any time in the left foot and there is no history of claudication in the calves. He has had no previous illnesses of note and has habitually smoked about ten cigarettes a day.

He was admitted to hospital in January 1948 on account of the persistent septic lesions about the toes. These healed after a course of penicillin and a period of rest in bed. A biopsy of a superficial thrombosed vein presented the typical lesions of thromboangiitis obliterans including giant cell formations. At that time the relevant observations on the circulation in the lower limbs were as follows:-

<u>Pulses</u>	<u>Right</u>	<u>Left</u>
Femoral	+	+
Popliteal	-	-
Dorsalis pedis	-	-
Posterior tibial	+	++

The reactive hyperaemia tests gave the following figures for the time for the flush of the returning arterial inflow to reach various parts of the two limbs.

<u>Site</u>	<u>Right</u>	<u>Left</u>
Calf	5 seconds.	3 seconds.
Heel	15 "	10 "
Base of toes	50 "	19 "
Tips of toes	80 "	25 "

There was thus considerable delay in the right lower limb throughout its whole length but particularly in the foot.

Maximal circulatory capacities of the two feet were determined by plethysmographs at 44°C. on 20. 1. 48.
R. foot 7.8c.cs./100c.cs./min. L. foot 17.0c.cs./100c.cs./min.

During reactive hyperaemia the maximum flow recorded through the right foot was 7.6c.cs./100c.cs./min.

On medical advice he entirely gave up smoking and his exercise tolerance considerably improved. Subsequent maximal circulatory capacities have been as follows:-

10. 2. 48 R. foot 8.0 c.cs./100 c.cs./min.

23. 3. 48 R. foot 8.2 c.cs./100 c.cs./min.

L. foot 16.6c.cs./100 c.cs./min.

19. 5. 48 R. foot 8.3 c.cs./100 c.cs./min.

L. foot 18.6c.cs./100 c.cs./min.

16. 6. 48 R. foot 9.3 c.cs./100 c.cs./min.

2. 2. 49 R. foot 10.5c.cs./100 c.cs./min.

L. foot 17.5c.cs./100 c.cs./min.

It is of interest that in spite of the considerable reduction in total circulatory capacity of the right foot he was able to walk ten miles over rough country in June 1948 while following the T. T. in the Isle of Man. Throughout the period of observation there has been a slight increase in the total possible blood flow through the right foot, doubtless owing to the development of collateral channels and recanalization of vessels in the manner already described.

The other cases in the series have not had serial determinations made over such a long period and have been under observation for from two to ten months. In one it was not possible to continue plethysmographic studies; he continued smoking, the disease advanced rapidly and amputation was finally necessary. In the other cases the subjects have all ceased smoking, but during the time of observation there has been little significant change in the circulatory capacities.

The collateral channels appear to develop more readily in cases of thromboangiitis obliterans than in other types of vascular disease which appear in more elderly individuals. These collateral channels have been shown to be long and tortuous (fig.16) and it is accordingly not surprising in long standing cases of thromboangiitis obliterans to find evidence that the pressure in the arteries of the affected extremity is considerably reduced below normal levels. This fact may be appreciated clinically by noting the extreme pallor appearing on elevation of the affected feet. The reduction in blood flow on elevating either the foot of the couch or the affected limb has been measured in several cases, using the technique described in the previous section. The following case may be studied as an example of this technique:-

A. W. aged 40 years, a valet, first noticed pain and numbness in the right leg during route marches in 1942. The pain on exertion gradually became more severe and in 1946 he was experiencing pain in the right foot even while at rest. Later a similar more severe pain developed in the left foot. He has habitually smoked 15-20 cigarettes a day.

On examination the circulation in both feet was obviously grossly impaired. There was a dusky cyanosis of the foreparts of both feet more noticeable on the left side. Marked pallor developed on elevation of the feet. No arterial calcification was present radiologically.

<u>Pulses</u>	<u>Right</u>	<u>Left</u>
Femoral	+ +	+ +
Popliteal	+ +	+
Dorsalis pedis	+ +	-
Posterior tibial	-	+ (very faint)

After soaking both feet in warm water no capillary pulsation was visible in any of the toe pulps. Reactive

hyperaemia tests showed a considerable delay in return of circulation to the whole of the left foot, but in the right foot the return was prompt down to the bases of the toes but thereafter was markedly retarded. Saline and histamine wheal tests showed evidence of severe ischaemia in the left foot.

A diagnosis of thromboangiitis obliterans was made in view of the age of the patient, the peripheral distribution of the lesions, the absence of any radiological evidence of arterial calcification, and the negative tests for diabetes mellitus and other contributory diseases.

In June 1948 the maximal circulatory capacity of the right foot was determined plethysmographically at 44°C. and found to be 9.7 c.cs./100 c.cs./min. That of the left foot could not be determined at 44°C. owing to the severity of the disease and the danger to the life of the foot at such a temperature. At 34°C. the blood flow to the left foot was 3.8 c.cs., at 38°C. 4.3 c.cs. and at 40°C. 4.4 c.cs. During reactive hyperaemia the maximal flow was 4.3 c.cs./100 c.cs./min. The maximal circulatory capacity of the left foot was thus regarded as between 4.2 and 4.4 c.cs./100 c.cs./min. A left lumbar sympathectomy was carried out later in the month but had no effect on the resting blood flow or total circulatory capacity which both remained in the range of 3.8 to 4.2 c.cs. showing that the vessels were incapable of further dilatation.

After bilateral sympathectomies postural tests were carried out as previously described to determine the effects of reduction of blood pressure on blood flow. The brachial artery pressure during the investigation was 115/80, giving a mean pressure of 95 m.m. of mercury. Assuming that this mean pressure holds throughout the arteries the anticipated decrease in mean pressure on raising the feet would be 16%, and from a study of figure 10 the decrease in blood flow

anticipated would be approximately 25%. In actual fact the decrease in blood flow in the right foot was 28% and in the left foot 40%. The actual reduction in blood flow in the right foot thus corresponded to about an 18% decrease in mean pressure. In other words the effective mean pressure in the arteries of the right foot was about 90 m.m. of mercury. A large reduction was obviously not to be expected in this foot as the dorsalis pedis artery was pulsating freely. In the left foot on the other hand, where only a very faint posterior tibial pulse was palpable, the decrease in blood flow was much greater and beyond the range encountered in normal subjects. For such a decrease in flow to occur the actual mean arterial pressure in the arteries of the left foot was probably approximately 75 m.m. of mercury.

The above case illustrates many of the fundamental features of the physiopathology of thromboangiitis obliterans. In both feet the maximal circulatory capacity was reduced below that of a normal subject of his age. The arteries in the left foot were considerably affected and even in the resting state were obviously carrying blood at full capacity. There was thus virtually no response on heating the limb, under the stimulus of reaction to complete ischaemia, or after a lumbar sympathectomy. In other words the large normal reserve of the arterial circulation had been completely lost. The blood was reaching the left foot mainly through collateral channels and the pressure in these arteries was considerably reduced leading to a slow rate of blood flow and a diminished exchange of fluids between the capillaries and tissue spaces as shown by the saline and histamine wheal tests. In the right lower limb the popliteal and dorsalis pedis arteries were pulsating strongly and with this free channel there was accordingly little reduction in the arterial pressure in the right foot. The right posterior tibial pulse was absent accounting for his

symptom of intermittent claudication in the right calf. The smaller digital arterioles were affected on both sides as shown by the reactive hyperaemia test.

It will be realised that by a combination of methods described above a very full picture can be constructed of both the anatomical and functional changes that develop in thromboangiitis obliterans. In this way it has been possible to demonstrate a great deal of the mechanism of the disease. Unfortunately this throws little light on the aetiology. Tobacco smoking undoubtedly hastens the progress of the condition but seems unlikely to be the sole determining cause of the onset. It can be shown that smoking a cigarette causes a temporary reduction in the blood flow to the foot as measured plethysmographically but this reduction is only temporary. The reduction in thromboangiitic subjects is no greater than that in normal individuals. Nevertheless the present study has shown that the most important measure in the treatment of the condition is to persuade the patient to abandon entirely the tobacco habit.

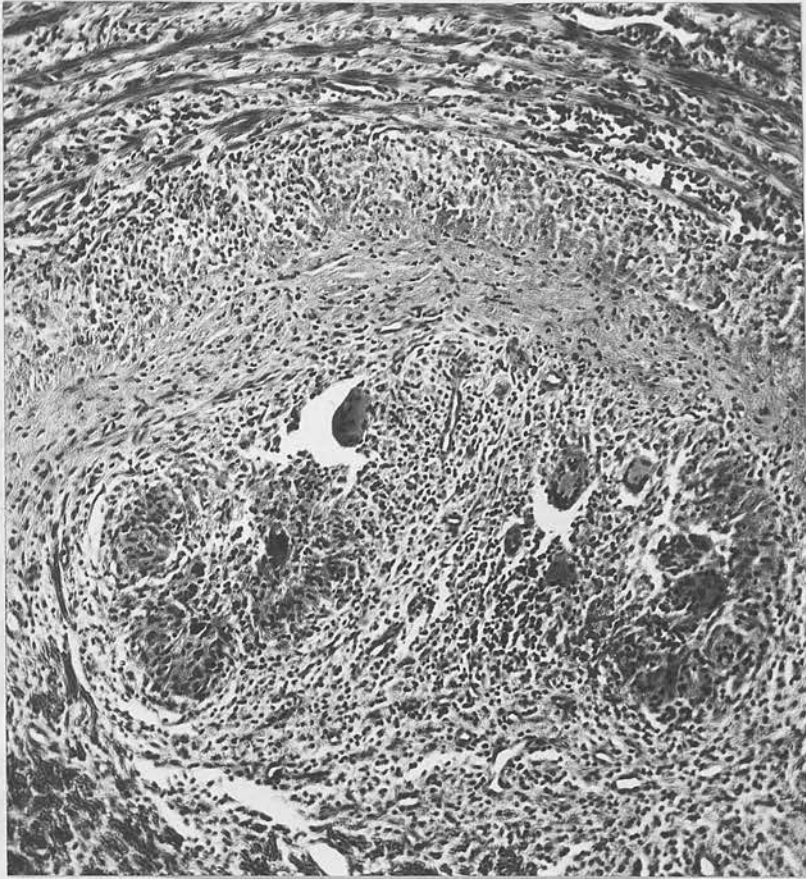


Fig. 11. Biopsy of a superficial vein from a case of thromboangiitis obliterans. Several giant cell formations of the "tuberculous" type are shown. The richly cellular organization of the thrombus is apparent. There is an infiltration of small round cells in all the coats but few polymorphs are present. Stain haematoxylin and eosin. X 120.

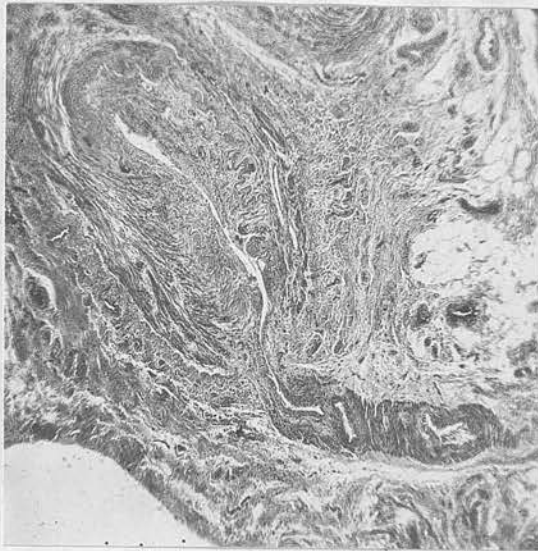


Fig. 12. Transverse section of an artery from a case of thromboangiitis obliterans. The continuity of the channel in the thrombosed main vessel with a small patent side branch is clearly shown. The condition is long-standing and the original thrombus has been replaced by fibrous tissue which shows no features characteristic of the disease. Stained haematoxylin and eosin. X 40.



Fig. 13. Transverse section of an artery from another case of thromboangiitis obliterans. Three episodes of thromboangiitis have obviously occurred. The last attack has also involved a small branch which has been serving as a collateral channel until a relatively late stage in the disease. Weigert's elastic stain. X 40.

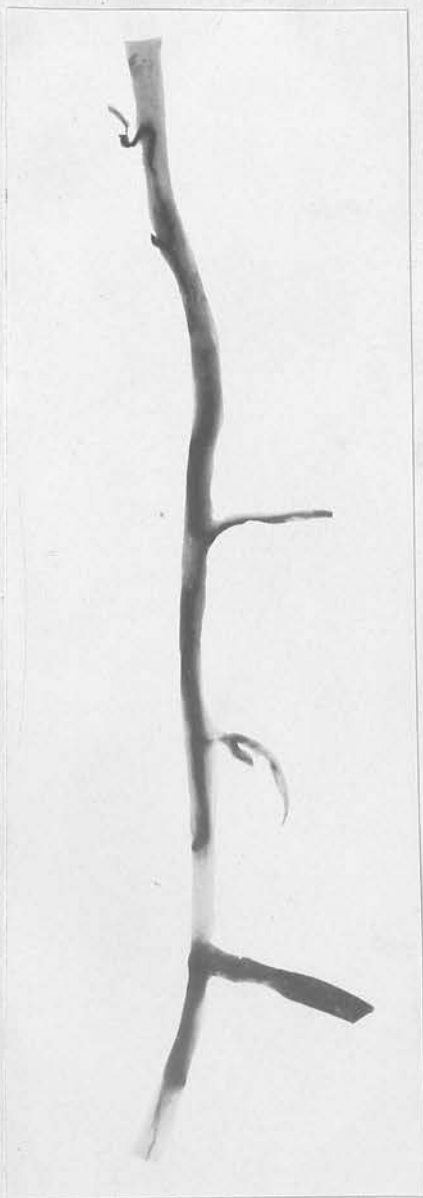


Fig. 14. A portion of the peroneal artery from a case of thromboangiitis obliterans, injected with lead phosphate coloured with trypan blue and cleared by the Spalteholz method. The relation of the patent channels in the main vessel to the side branches is clearly demonstrated. Natural size.



Fig. 15. Portions of arteries taken from cases of thromboangiitis obliterans showing patent arterial channels injected with India ink suspended in celloidin. The connections of new or persisting channels with the side branches is demonstrated. Subsequent microscopic sections demonstrated that the non-injected portions of the arteries were entirely blocked with thrombus and contained no new elastic coated channels. Natural size.

thromboangiitis obliterans after injection of India ink. The principal artery and its bifurcations are seen to be unobstructed by the disease. The patent channels of the distal arterial tree are seen in the upper part of the image and are completely filled with India ink. The distal arterial tree is seen to be filled with thrombus and the patent channels are seen to be unobstructed. The course of many of the arteries is seen to be unobstructed.

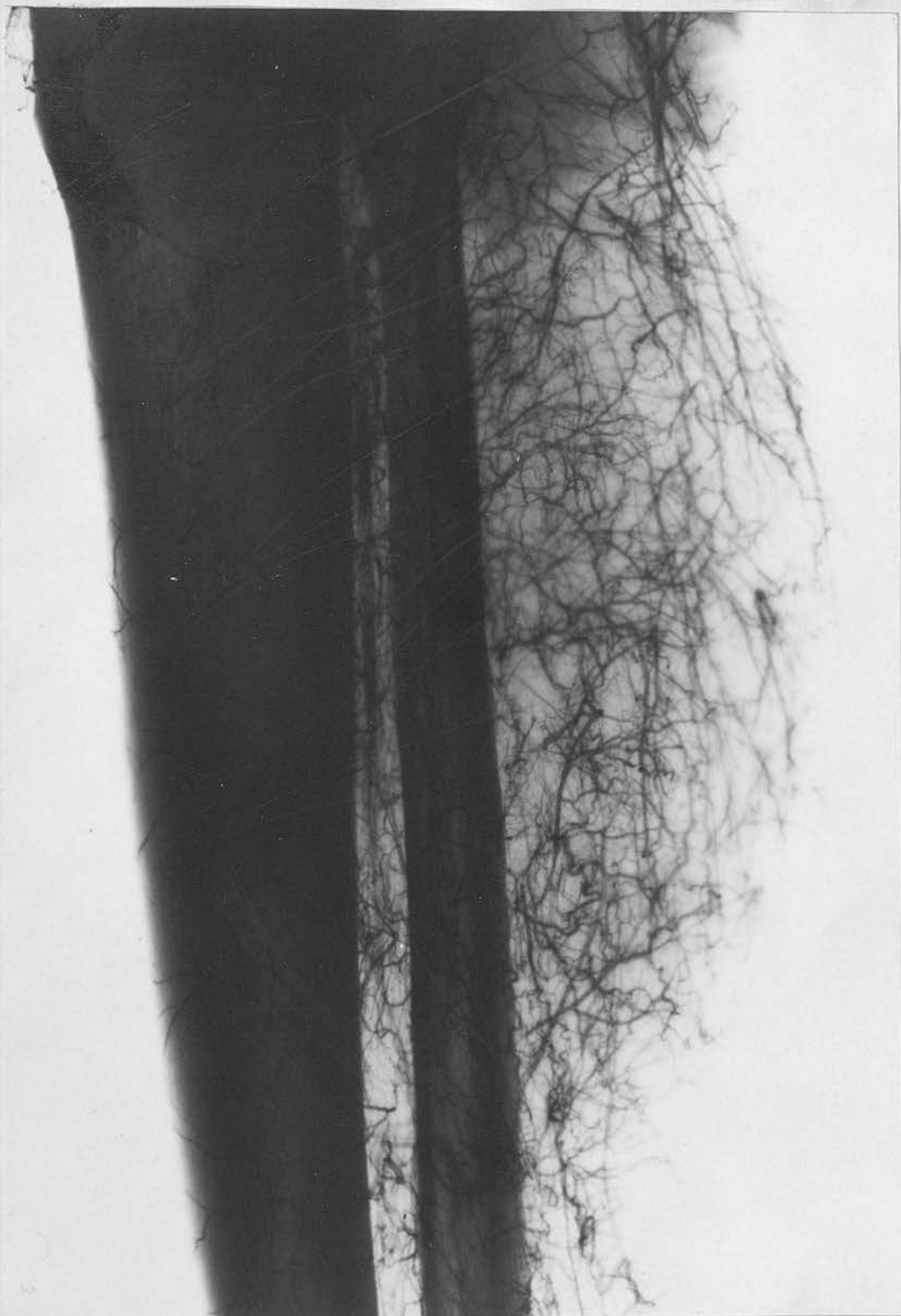


Fig. 16. A lateral view of an amputated limb from a case of thromboangiitis obliterans after injection of lead phosphate. The popliteal artery and its bifurcation are seen to be unaffected by the disease. The patchy nature of the condition can be seen in the upper parts of the anterior and posterior tibial arteries. On close inspection recanalized passages filled with lead phosphate can be discerned lying in the course of the obturated tibial arteries and their relation to the well filled muscular collaterals traced. The exceedingly tortuous course of many of the collateral arteries is also noticeable.

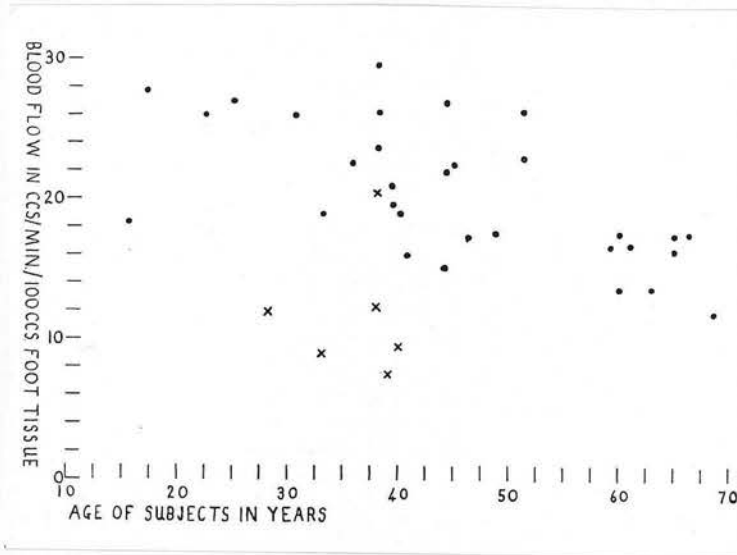


Fig. 17. Maximal circulatory capacities of feet of normal subjects (•) and of those suffering from thromboangiitis obliterans (x) at the time when the disease was first diagnosed. In five of the thromboangiitic cases the disease had affected the major arteries of the feet and the maximal possible blood flow was greatly reduced. In the sixth case the circulation was only markedly impaired in one toe and the total circulatory capacity of the foot was accordingly not noticeably affected. In all the thromboangiitic cases the circulation in the more affected limb only has been plotted. In the normal subjects it will be noted that the maximal circulatory capacity tends to become reduced with advancing years.

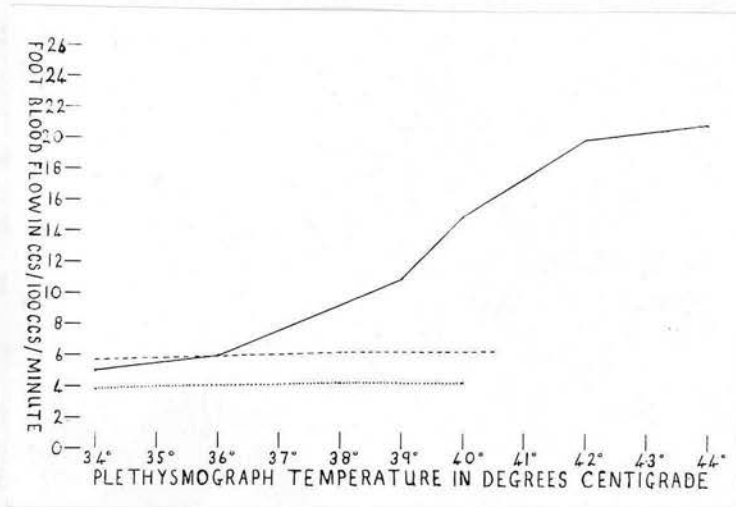


Fig. 18. Response of the circulation in the foot to local heat. The continuous line represents the changes observed in a normal subject. The interrupted and dotted lines are taken from two severe cases of thromboangiitis obliterans in whom the circulatory reserve was almost entirely abolished as shown by the insignificant increase in blood flow on heating the water in the plethysmograph. It was not considered advisable to raise the local temperature in these cases to 44°C. The blood flow during reactive hyperaemia did not exceed that obtained at 40°C. and the flows at this temperature were accordingly taken as the maximal circulatory capacities of the feet.

PART IV.

Atherosclerosis.

The lesions associated with the development of atherosclerosis are exceedingly complex and still occasion much dispute as to their interpretation. It is not proposed to enter into a discussion of the nature of the earliest lesions and it is sufficient to state these are the atheromas, the small slightly elevated yellow plaques and streaks which can be seen on the intimal surface of the arteries. These elevations constitute definite thickenings of the intima and consist of connective tissue and fat-laden phagocytic cells. As the disorder progresses these yellow patches grow larger and tend to become confluent, developing particularly on one side of the artery rather than concentrically. These early atheromatous lesions have little effect on the function of the arteries, but they are almost invariably present to some degree in all male subjects beyond middle age. As they become more extensive in older age it is possible to demonstrate a corresponding reduction in the maximal circulatory capacity of the foot (fig. 26). Similar observations have been made on the reduction in the blood flow through the hand with advancing years (Pickering 1936). In spite of this reduction in the blood flow the features of arterial disease do not usually appear until the atheromas become complicated by superimposed thrombus formation. The patient thus usually first becomes aware of symptoms following the obstruction of one of the larger arteries in the lower limb.

In all the amputated limbs there were advanced atherosclerotic lesions but as the features were so varied it is difficult to give an all-embracing description. It is accordingly proposed to concentrate on certain features that aroused special interest. In the intima the advanced atheromatous lesions consisted of large areas of relatively

acellular substance having a somewhat hyaline appearance with irregular deposits of cholesterol and fatty acids, occasional patches of fibroblasts and irregular collections of foamy lipophages in various stages of degeneration. Small capillary channels, often surrounded by lymphocytes, were frequently seen in the deeper parts of the intima and sometimes they attained a relatively large size, particularly when the original lumen was greatly reduced in calibre. Haemorrhages in the deeper part of the intima were frequently seen arising from these small vessels. They were only seen in advanced cases and were apparently late manifestations and not concerned with the original development of the atheromatous lesions. They were important in that on occasion they were seen rupturing inwards through the degenerate intima and had thus paved the way for the development of thrombosis.

Thrombosis was an almost invariable accompaniment of atherosclerosis of any degree of severity. The earliest thrombi appeared to be of the mural type and in some fortunate sections their origin could be traced to haemorrhages deep within the intima. In many cases however these appearances were deceptive. The organization of thrombus within atherosclerotic vessels was extremely slow and irregular, and the thrombus usually became agglutinated and fused into a hyaline mass long before organization tissue had penetrated at all deeply. It was often difficult to determine how much of the occluding mass was old thrombus and how much atheroma, as the histological appearances were essentially similar. A small island of thrombus, which had undergone fusion unduly slowly, might persist in the midst of the hyaline material and consequently give the appearance of an intimal haemorrhage. Duguid (1946) drew attention to the appearances resulting from mural thromboses in the coronary arteries and pointed out that many of the lesions classified as atheromatous were really arterial thrombi which by ordinary processes of organization

eventually became transformed into fibrous plaques. Certainly in the cases studied many instances of what were at first sight intimal haemorrhages proved on further investigation to be the results of irregular fusion of the thrombus. These thrombi were undoubtedly prone to softening with fatty degeneration, while the intimal haemorrhages underwent similar changes. The latter could only be diagnosed with certainty by their deeper position in the intima and their relationship to an intimal capillary vessel. Many of the atheromatous patches found in the arterial thickenings appeared to be a result of a combination of both these processes. The thrombus and intima were usually relatively poor in cellular tissue even in old-standing cases in which recanalization had occurred. This was the characteristic difference between atherosclerosis and thromboangiitis obliterans, but it was not always present (fig. 20)

Changes in the internal elastic lamina were characteristically present especially beneath the deeper atheromatous plaques. In such positions the alterations consisted in fragmentation, interruption, or fraying of the lamina into several thin layers which frequently united again at the other side of the plaque. The fragmentation of the internal elastic lamina was occasionally associated with spread of the atheromatous process into the media.

The medial coat of the artery often showed surprisingly little change when it was in relation to a relatively early stage of the formation of an atheromatous plaque. However in the more advanced lesions changes were frequently observed in the media of the arteries of the amputated limbs - a marked contrast to the features often found in the coronary arteries in the cases of myocardial infarctions. The muscle of the media was frequently fragmented or thinned with replacement by fibrous tissue or calcium deposits. More striking were the inflammatory changes that were often present around the degenerating muscle. These consisted in focal accumulations of

lymphocytes and occasional polymorphs usually aggregated around dilated vasa vasorum that had developed in the media (Fig. 19). The significance of these changes has been difficult to assess, but they were observed especially in relation to obliterated arteries, though not restricted to this condition entirely. However, when the lumen was patent the lymphocytic collections were not so marked. In the thrombosed arteries, the foci of small round cells typically had a perivascular distribution in that a small vessel was found within their midst. Such foci were traced extending in rows of cells between the more centrally placed muscle fibres of the media and separating them considerably. In addition there was often an increased number of migrating cells scattered here and there throughout the middle coat.

Most authors have described these leucocytic infiltrations in atherosclerosis of the arteries of the lower limbs and remarked on the fact that they are not nearly so commonly observed in atherosclerosis of the visceral arteries. None has expressed any definite opinion as to their significance. Gery et al (1939) described leucocytic infiltrations and giant cells (fig. 21) in such conditions, but stated that they had no specific character and were found at all ages and in every type of constricted artery. In the present series of cases these medial inflammatory lesions were particularly noticeable in one case in which extensive infection had been present, but they were later found in cases in which the skin was entirely intact. The possibility arises that they might be due to a mild infection, but this seemed unlikely for several reasons. An infection from an ulcerated area would presumably have spread by the perivascular lymphatics and would have involved at least equally severely the adventitial coat. Furthermore, no continuity of inflammatory reaction could be traced along the arteries from any ulcerated area, and, as previously mentioned, these changes occurred quite apart from infected

cutaneous lesions. The possibility that infection might be conveyed by the blood stream must also be considered. If it were from within the lumen the absence of inflammatory lesions in the intima is difficult to explain. If it were by way of the vasa vasorum the escape of the adventitia seems strange. In short, the evidence is against the inflammatory infiltrations of the media being regarded as a response to bacterial infection. It might be possible to observe experimentally in animals the response of an artery to infection with non-virulent organisms. In this connection, however, it should be noted that the arteritides that sometimes develop in subacute bacterial endocarditis are of quite a different nature, being essentially a panarteritis.

The collections of lymphocytes were always most noticeable around degenerate muscle fibres or in the region of plaques of medial calcification. The function of the lymphocytes is not fully known and, apart from infection, it is difficult to afford an explanation for their presence. Nevertheless it seems that necrosis of the musculature might attract them in much the same way as when they appear in a myocardial infarct after a few days. Thrombosis within the lumen may well affect the nutrition of the arterial wall, hasten the degeneration and necrosis of the musculature of the media, and thus lead to the attraction of the lymphocytes. Another possibility is that the lymphocytic infiltrations may be concerned rather with the development of the thrombosis but, though lymphocytes in smaller numbers have been observed in the media of patent arteries, there is little to support this view. The truth is that little is known about the reason for, or the function of, these collections of lymphocytes. A study of the cases has indicated that they are in some way connected with the thrombotic process which is such a vital factor in determining the onset of gangrene. They may thus be of considerable importance and are certainly worthy of further study.

The adventitia in atherosclerosis frequently showed no definite changes, but in a proportion of cases, especially those with thrombosis, there were irregular patches of fibrosis and small collections of lymphocytes around markedly congested vasa vasorum. The fibrosis was never marked and did not extend out to include the veins or nerve.

The veins in the cases of atherosclerosis did not all show consistent changes, but a common finding was a mild endophlebitis with thickening of the intimal coat, due to connective tissue hyperplasia. Cases in which venous changes were marked were complicated by purulent infections in the feet or by subcutaneous thrombophlebitis in the atrophic skin over the tibia.

The above remarks have applied chiefly to the main vessels of the lower limb down to the dorsalis pedis and plantar arteries, but mention must also be made of the changes in smaller arteries such as the digital and its branches. In some cases the digital artery showed changes characteristic of the disease in the main vessels. Often however the lesions in these small vessels were not specific, and if they alone were available for examination, the diagnosis was difficult. In such circumstances, the lesions were reactions to a slowed blood flow, a type of endarteritis obliterans showing definite proliferation of the intimal cells with occasional small collections of lymphocytes in isolated portions of the artery where cellular proliferation was most marked. In the adventitia, there were also sometimes small collections of lymphocytes around the vasa vasorum.

In studying the present series of cases special attention has been paid to the popliteal segment of the arterial tree as there are many indications of its importance in the development of obliterative arterial disease. Buerger (1924) in particular has emphasised its key position with regard to

the blood supply of the limb and his observations have been confirmed by numerous subsequent authorities, e.g. Allen et al (1946), Learmonth et al (1944). With these points in mind it is profitable to consider the cases in which there was definite evidence of obstruction at this level either in the amputation specimens or on unequivocal clinical grounds.

Out of the 35 cases regarded as atherosclerotic vascular disease there were 18 amputations performed at the mid-thigh. Of these three were complicated by diabetes and will not be considered at present. In sixteen of the amputation cases there was definite evidence of recent obstruction of the popliteal segment as shown by the presence of adherent red thrombus. This acute blocking of the artery was the event that necessitated the amputation. In the majority this was a simple thrombosis developing within the lumen of a grossly atherosclerotic artery and the process could usually be traced proximally, either from old atheromatous obstruction at the bifurcation of the artery, or from a bulging atheromatous plaque at a slightly higher level (fig. 23). In these cases of recent obstruction by blood clot, it is frequently impossible to decide whether the lesion is either entirely a primary thrombosis or embolism complicated by secondary thrombosis. This point particularly arose when auricular fibrillation was present, as in four of the cases studied. In those coming to amputation it may be possible, if the occlusion is very recent, to dissect out a definite embolus, but if it has been present for more than a few days this is usually impossible. In none of the amputation specimens was it possible to isolate an embolus and as local arterial disease was present at the site of obstruction it was thought that the lesion was thrombotic in all the cases.

In two only of the atherosclerotic amputation cases no acute obstruction was found, though in all the lumen was

grossly narrowed by disease. In one of these there was a spreading suppurative cellulitis in the foot which was the chief factor determining amputation. In the other, though no recent thrombosis was found on dissection of the vascular tree, it was noted at operation that the artery at the point of division was not pulsating, but that a femoral pulse was present in the groin. As there had been a recent severe increase in ischaemic pain all the available evidence pointed to an acute thrombotic event in the femoral artery somewhere immediately above the point of section. From a study of the atherosclerotic series of cases it was thus apparent that when a limb succumbed to the mortifying process, the usual finding in the vascular tree was a recent thrombosis which acted as the final precipitating factor. When such a finding was absent there was invariably some other explanation which frequently took the form of a marked increase in the circulatory demands of the limb resulting from infection. Depressed circulation, either as a result of a cardiac disorder such as auricular fibrillation or surgical shock following operation, may also play a part in determining the onset of ischaemic gangrene.

The development of aneurysms of the popliteal artery is a well recognised complication of advanced atherosclerosis. Thrombosis is a common event in aneurysms and such an event may well prove the precipitating factor in the development of gangrene. It was noted in two of the cases in this series. In one the condition was not suspected clinically but on dissection of the amputated limb recent thrombosis was found in a popliteal aneurysm. (Fig. 22). In the other an aneurysm was palpable during life, at first pulsating, but later the sudden cessation of pulsation was noted by the patient and signs of ischaemia in the leg and foot became apparent. The limb however survived and measurement of the maximal blood

flow through the affected foot two years later gave a figure of 6.5 c.c./100 c.c./min. Syphilis as a cause of aneurysm was excluded in both these cases. Atherosclerosis is indeed practically the sole cause of aneurysm in the popliteal artery in those more than sixty years of age (Allen et al 1946). In this connection it is interesting to note that in the second case mentioned above the patient had multiple cholesterolomata on the bony prominences, hypercholesterolaemia, and a past history of thromboses in the coronary and cerebral arteries. The first case came to post mortem examination and advanced atherosclerosis of all the larger arteries with aneurysms on the internal iliac arteries were found. It is difficult to understand what determines the site of development of these aneurysms. The artery in the popliteal space has less protection by muscles than the arteries in other regions of the lower extremity and also it is subjected to frequent bending. It is possible that this repeated strain on a diseased artery is a factor in weakening the wall to the stage at which dilatation takes place. Thrombosis is the common complication in such aneurysms; rupture is rare.

In many of the cases on gross dissection of the arterial tree small haemorrhages were visible in the intima. In some it was possible to trace a continuity through a rupture in the intima between the haemorrhage and thrombus within the arterial lumen. In one amputation specimen this appearance was very striking and was the apparent cause of an acute obstruction in the popliteal artery. This intimal haemorrhage had spread over a distance of about 5 cm. and had formed in reality a small dissecting aneurysm. The elevated intimal layer almost completely blocked the lumen. Another interesting point concerning this finding was that the patient had been receiving anticoagulant therapy in the form of dicoumarin shortly before the amputation. This is the only case in the

series of amputation specimens in which dicoumarin had been given, though a few had previously been treated with heparin. Obviously it is a theoretical possibility that dicoumarin might increase the liability to large intimal haemorrhages which play a part in the development of atheromatous plaques and arterial thromboses. It is accordingly highly important to have precise information on the action of dicoumarin in this respect, but no definite conclusions can be drawn from a study of this one case. Wright (1946), in studying coronary arteries in cases of myocardial infarction treated with dicoumarin, found no evidence of increase in number, severity, or extent of intimal haemorrhages as a result of the therapy.

The importance of the popliteal segment of the arterial tree in the final development of gangrene of the extremity has been fully demonstrated. The difficulties in circumventing an obstruction in this artery have long been known from surgical and experimental practice and have been fully studied. In the 18th century John Hunter observed the changes that ensued in the circulation after experimental ligation of an artery. Porta in 1845 demonstrated the development of collateral avenues from small pre-existing channels and in 1919 Bolognesi confirmed and extended these observations by experimental ligation of the external iliac artery of dogs. The animals were killed after varying periods of time and the vascular systems of both ligated and control limbs were studied by dissection and X-ray arteriography. Even at that time this was no new method, for arteriography is almost as old as radiology itself, as it was only about eleven weeks after Roentgen's discovery that Haschek and Lindenthal in 1896 reported the radiographic visualization of the arteries of an amputated forearm following the injection of a radio-opaque substance. It has provided one of the chief methods for the study of the development of a collateral circulation in obliterative arterial disease. The amputations

necessitated by the development of atherosclerosis of the popliteal artery were performed at the mid-thigh and the proximal origins of possible collateral arteries were not included in the specimens. It was thus not possible to investigate in any detail by an injection method the response of the vascular system to obstruction in the popliteal artery. In many cases in life however it is possible a few weeks after an acute obstruction of the popliteal artery to detect an accessory pulse present at the medial side of the patella due to enlargement of the small artery accompanying the saphenous nerve. Anatomy text books describe the circumpatellar anastomoses in the region of the knee joint. These channels, though sufficiently large for anatomical dissection in a normal subject are few in number and often do not suffer when sudden occlusion of the popliteal artery occurs. Multitudinous small muscular branches appear to be more important in obliterative vascular disease in forming collateral channels than the larger and discrete anastomotic branches nourishing tendons, fascia and bone. The popliteal artery, lying in the midst of tendons has practically no muscular branches and, when obstructed, cannot easily be bypassed. Surgical experience acquired from dealing with wounds of arteries has shown that in healthy adult males it is possible to tie off the common femoral artery without much risk to the limb. Ligation of the femoral below the profunda branch is dangerous, while ligation of the popliteal artery is frequently followed by gangrene.

While the dangers of a complete obstruction of the popliteal artery are thus obvious the significance of this segment in the early development of atheromatous lesions is not so apparent. Is this artery the site of predilection for the development of atheromatous degeneration in the lower limb? It has been suggested that the point where the artery passes

through the adductor hiatus might be peculiarly exposed to trauma and consequently predisposed to the development of disease in this region. The localization of arterial degeneration is usually patchy and difficult to assess. Concerning the sequence and frequency in which this process affects the arteries there seems to be little or no unanimity of opinion and the degree and site of involvement of the several arteries of a limb appear to follow no known laws. This distribution was studied to a limited extent by dissecting out the femoral and popliteal trunks in 40 routine autopsies irrespective of age and sex. Special attention was directed to the vessel wall in the region of the adductor hiatus. In four cases early atheromatous degeneration was found in this region while the rest of the arterial tree in the limb was free from disease and in particular no abnormalities were present in the femoral arteries. In five cases no atheroma was apparent, whilst in the others one quite definitely gleaned the impression that the lower part of the popliteal, especially immediately above its bifurcation, was more heavily involved in the degenerative process than the upper part of the popliteal and femoral arteries. This is in agreement with the views of Buerger (1924). In this small series there was no evidence that the tendinous margins of the hiatus played any part in the production of the lesions.

The lower part of the popliteal artery presents certain features that may well predispose to the development of atheromatous degeneration. The artery, by passing over the knee joint, is exposed to stress and possible trauma during locomotion. It is relatively unsupported by muscular tissue, passing through a predominantly tendinous region. The femoral artery where it is buried in muscles tends to escape. There is some evidence that the support of muscular tissue may tend

to retard the development of atheroma. Thus the surface of coronary arteries suffer heavily from atheroma while the branches within the myocardium are relatively free from involvement. The subclavian artery, not surrounded by muscle, is a common site of atheroma while the brachial usually escapes. In these instances there is of course the additional factor of differences in calibre. Nevertheless the relatively high incidence of atheroma in the more distal and narrower popliteal artery in comparison with the femoral is thus all the more striking.

It is noteworthy that the lower part of the popliteal artery has relatively few small branches in comparison with the upper part, and, as the vasa vasorum arise from these branches, there may more readily develop some abnormality in the nutrition of the vessel wall. The mechanism of blood supply to an arterial wall is still in dispute, but the conflicting views since 1875 have been fully summarized by Ramsey (1936). Now, as in 1875, three possible mechanisms must be recognized: namely nutrition through the vasa vasorum; nutrition from the lumen of the vessel: or nutrition by way of a canal system communicating directly or indirectly with the vasa vasorum or the lumen. It is still impossible to state categorically which of these mechanisms or what combination of them are operative, or what role is played by the lymphatics. The general opinion is that the intima is nourished from the lumen and the outer part of the media and the adventitia by way of the vasa vasorum, but there is an increasingly firm conviction that none of the "rigid theories is entirely adequate and that the mechanism of nutrition may conceivably vary in different types of vessel and under physiological and pathological conditions. Winternitz and his associates (1938) drew attention to the importance of haemorrhages from small vessels in the intima in the production of

atheromatous lesions. It is now, however, generally considered that these haemorrhages are not prime aetiological factors in the development of atheroma, but only secondary features consequent on the degenerative changes (Hueper 1944).

Following the Winternitz technique of injection and clearing, a study was made of the vasa vasorum of the popliteal artery from the point of view that possibly either localized pressure from the margins of the adductor hiatus or exposure to trauma in the popliteal space might have led to the development of abnormal intimal vessels before the gross lesions of atheroma appeared. The injections were carried out by the technique previously described in detail on 15 specimens of femoral-popliteal trunks. Seven of these specimens showed naked eye atheromatous patches of varying degrees of severity and in all of them it was possible to demonstrate numerous intimal and medial capillary channels (fig. 25). By contrast eight apparently normal femoral popliteal segments taken from subjects varying in age from 15 to 63 years contained no demonstrable capillary channels in the intima and media. In this small series the results did not indicate any abnormality in the vasa vasorum of the popliteal artery which might account for its increased liability to atherosclerotic disease.

From a study of the pathological anatomical material available it appeared that the earliest lesions developed at the bifurcation of the popliteal artery. These atheromatous changes, however, did not usually at their onset occasion any symptoms. It was development of thrombosis spreading proximally up the popliteal artery that commonly necessitated the amputations. This complication was responsible for the majority of the clinical features. The disturbances in the circulation occasioned by the development of atherosclerosis and thrombosis remain to be considered.

In general a deficiency of blood supply to a lower extremity is manifested by either the development of intermittent claudication or cutaneous lesions which fail to heal. It is now generally agreed that intermittent claudication is due to the accumulation of muscle metabolites owing to defective blood supply (Lewis 1932). A similar mechanism applies in the case of angina pectoris and in these cases it is often possible to demonstrate pathologically a fibrosis of the myocardium secondary to the disordered coronary blood flow. The question naturally arises as to whether a similar fibrosis may develop in the muscles of a lower limb in which the pain of intermittent claudication has been experienced. With this in view a small portion of the extensor digitorum brevis was taken for histological section from limbs amputated on account of atherosclerotic gangrene. In all cases it was possible to detect minor changes similar to those described by Blackwood (1944). These consisted in slight swelling of the muscle fibres and loss of the sarcolemma nuclei. Occasionally some slight replacement of the muscle cells by fibrous tissue was noted but this was not a prominent feature in any of the cases. All the available evidence pointed to the conclusion that intermittent claudication might be a prominent feature in the limb without any resulting fibrosis of the muscular tissue as revealed by a study of the extensor digitorum brevis. It might be objected that claudication pain is not commonly referred to the region of this muscle and that accordingly it was not suitable for such a study. It is however a small and convenient muscle for study in that a representative and comparable part in different cases can readily be taken. Moreover being situated in the distal part of the extremity it was considered more likely to show histological changes than the more proximally placed calf muscles from which it would be difficult

to choose a representative portion.

The principles of measuring blood flow in the lower limb by the plethysmographic method have already been described and discussed. The necessity for measuring the maximal possible flow through the part has been stressed, for if the flow through the foot is determined at the usual resting level no significant difference is found between normal and moderately affected feet. As it is known that atheromatous disease increases in severity with advancing age a determination of maximal foot blood flows were accordingly made in male subjects of differing ages. It was found that in elderly men there was an appreciable reduction in the circulatory capacity of the foot even though no clinical features of vascular insufficiency were present (fig. 27). As the blood pressure in these subjects was within the normal range it was concluded that the reduction in maximal flow with advancing age was due to narrowing of the arteries consequent on atherosclerosis. No subjective or objective features of arterial insufficiency were noted in individuals with a maximal circulatory capacity greater than 13 c.cs./100 c.cs. of foot tissue/min. (Fig. 26).

As has been described above in the account of the pathological anatomy the most important complication of atherosclerosis in the lower limbs is thrombosis in the popliteal artery. If the thrombotic process is restricted to one limb, the unaffected limb, provided that it is free from features of arterial insufficiency, can be used as a control for estimations of blood flow. It is frequently surprising how large the circulation through such a limb may be though it also is presumably affected by atheromatous disease. The major factor in the reduction of the circulation in the affected limb is thus the thrombosis, an event usually evident from the clinical history. These points are well illustrated in the

following case:-

J. G., age 49 years, a tailor by occupation, developed typical intermittent claudication in the right leg 1½ years before being seen. The onset was relatively sudden, coldness and cyanosis appearing in the foot one evening. The pain on exertion has continued in the leg. No angina pectoris. No symptoms referable to the left leg. On examination he was obese. Heart normal, B.P. 160/85.

<u>Pulses</u>	<u>Right</u>	<u>Left</u>
Femoral	+	+
Popliteal	-	+
Posterior tibial	-	+
Dorsalis pedis	-	+

No glycosuria; normal glucose tolerance curve.

Blood cholesterol 210 mgm.%. Blood Hb. 110%. X-ray legs no calcification of arteries.

Diagnosis: Right popliteal thrombosis secondary to atherosclerosis.

Plethysmography: Maximal blood flows (averages of 20 readings. Coefficient of variation 4%).

Right foot 10.8 c.cs./100 c.cs. foot tissue/min.

Left foot 17.0 c.cs./100 c.cs. foot tissue/min.

It is to be noted that the blood flow in the left foot is probably at the lower limit of normal for a man of his age, while that in the right foot is considerably reduced consequent on the popliteal thrombosis.

Three other similar cases have been studied and in all of them the maximal blood flow in the symptom-free limb was within normal range while in the limb with the thrombosis it was considerably reduced (fig. 27). Atheromatosis is usually fairly uniformly distributed in corresponding lower limbs and in these cases it has caused little reduction in blood flow.

The reason for the development of ischaemic features has been the complicating thrombosis superimposed on an atheromatous plaque. In cases with clinical evidence of ischaemia in both lower limbs it seems probable that a similar mechanism is at work, the reduction in blood flow being chiefly caused by thromboses developing on atheromas, but in them it is impossible to ascertain the state of the circulation before these complicating thromboses occurred. No case in an atheromatous individual has yet been studied in whom a definite thrombosis has appeared at a later date than the initial plethysmographic readings. It will readily be seen that these conclusions drawn from these plethysmographic studies confirm the opinions formed as a result of dissection of the amputated limbs in which popliteal thrombosis was the usual reason for the development of gangrene.

It sometimes happens that clinical features of vascular disease of the lower limbs develop though the peripheral pulses are palpably entirely normal. Nutritional cutaneous disorders may appear in the toes of individuals suffering from thromboangiitis obliterans and diabetic vascular disease in the presence of normal pedal pulses. In such cases the lesions are confined to the smaller distal arteries and arterioles. In my experience such entirely distal lesions do not occur in pure atherosclerosis. In elderly subjects free from diabetes, gangrene of a toe is invariably due principally to disease high up in the limb and not to local digital artery obstructions.

On the other hand intermittent claudication in the calf muscles may occasionally develop in atherosclerotic subjects without any definite abnormality in the popliteal, posterior tibial, and dorsalis pedis pulses. In these cases the mechanism is apparently a thrombosis either in the large peroneal branch of the posterior tibial artery or in the posterior tibial artery

itself with the establishment of a collateral filling of the artery at a lower level before the ankle region with its palpable pulse is reached. It must be emphasised that the pulsations in an artery are no indication of the amount of blood that is flowing through the artery. Thus in coarctation of the aorta the lower limb pulses are either absent or grossly diminished and yet the maximal blood flow in the foot is at a high normal level (fig. 7). Conversely in these cases of vascular disease the presence of pedal pulses does not necessarily imply that the foot circulation is normal. In all cases of individuals suffering from intermittent claudication in the calf, whatever the state of the pedal pulses, it has been possible to demonstrate a reduction in the circulatory capacity of the calf blood vessels. The resting blood flows are usually within the normal range but, when the reactive hyperaemia test is applied, the defect is readily revealed. These points are well shown in the following case in which the claudication was confined to one limb:-

C. J. P., age 50 years, a corn merchant, developed in June 1947 a sudden aching pain in his right calf, like cramp, while walking up a steep bank on the golf course. The pain was promptly eased by stopping, but recurred every time he walked fast or up an incline. He had never had this pain before and had had no pain earlier on the course, though the first part was equally hilly. Nothing abnormal was noted in the foot. He has had the pain ever since, the amount of effort to precipitate an attack remaining fairly constant.

He smokes 15 cigarettes a day. He has had attacks of myocardial infarction in 1937 and August 1947 and since the second incident has experienced angina pectoris on exertion. During the late war he was diagnosed as an alimentary glycosuria

His mother died at 52 years of a stroke and his father at 76 years of coronary thrombosis.

On examination he was a man of medium size, moderately well nourished, who showed no abnormal signs in the heart. The blood pressure was 155/90. The legs were of normal appearance and of equal temperature. The femoral and popliteal pulses were strong and readily palpable. Both dorsalis pedis pulses were felt but the posterior tibials were both absent. The X-ray of the heart was normal in shape and size, but the aorta was calcified. A glucose tolerance curve was normal and there was no glycosuria. On 17.11.48 the blood flow was estimated plethysmographically through the two calves at 34°C. The averages of the observations were:-

	<u>Right Calf</u>	<u>Left Calf</u>
Resting	2.5 c.cs./100 c.cs./min.	2.0 c.cs./100 c.cs./min
Reaction after 5 min. circulatory arrest.	29.2c.cs./100 c.cs./min.	19.0 c.cs./100 c.cs./min

A diagnosis of thrombosis on an atheromatous plaque in one of the larger left calf arteries was made.

It is noteworthy that the lower limb pulses were equal on the two sides and that the two limbs both presented no abnormal appearances. No significance can be attached to the bilateral absence of posterior tibial pulses as this may well occur in entirely healthy young adults. The plethysmographic observations however show that the circulatory capacity of the left calf was considerably reduced. There was no significant difference between the blood flows in the two calves at rest and symptoms in the limbs did not arise apart from exertion. The defect can only be demonstrated by the demands imposed by the reactive hyperaemia test.

It will be realised that in ischaemic limbs the blood flow through a vessel is not the sole factor in determinin

adequate nutrition of the tissues. On the arterial side it is essential that the pressure is sufficiently great to overcome the osmotic pressure of the plasma proteins so that fluid may pass out into the tissue spaces. The dehydration of tissues in incipient gangrene has long been recognised and has been demonstrated by the intradermal saline wheal test. Under such conditions the saline is unduly rapidly absorbed by the dehydrated tissues (Cohen et al. 1926), the wheal disappearing more rapidly in the ischaemic as compared with normal skin. It seems probable that this dehydration is due both to the reduced blood flow and to the low pressure within the arterioles.

There is no reliable or safe method of measuring the pressure in arteries distal to an obstructed popliteal artery, but, as has previously been explained, it is possible to ascertain the mean pressure within these vessels by measuring blood flow changes in response to elevation of the leg. These differences are most clearly revealed when in an individual one limb has a normal circulation which may be studied at the same time as the affected limb. The following case illustrates how this method of investigation may be used:-

R. P. age 51 years, a waiter, developed intermittent claudication in the left calf about $1\frac{1}{2}$ years previously. The pain is promptly relieved by rest, but develops readily after walking about 200 yards. No cutaneous lesions have appeared in the feet. He has suffered from chronic bronchitis for many years. On examination he had signs of emphysema and bronchitis and clubbing of the fingers and toes. Both femoral pulses were present and in the right lower limb the popliteal and posterior tibial pulses were readily felt, but not the dorsalis pedis. In the left lower limb no pulses were felt distal to the femoral. The condition was regarded as a left popliteal thrombosis secondary to atherosclerosis

and the following measurements were made on 22.9.48:-

Average maximal blood flow limbs horizontal.

R.foot 26.4 c.cs./100 c.cs./min. L.foot 8.6 c.cs./100 c.cs./min.

Average maximal blood flow limbs elevated.

R.foot 21.5 c.cs./100 c.cs./min. L.foot 5.1 c.cs./100 c.cs./min.

Percentage decrease in blood flow on elevation 20 cms.

R.foot 20%.

L.foot 40%.

Blood pressure in arm at heart level 160/110 mm. Mean pressure (diastolic + $\frac{1}{3}$ pulse pressure) 127 mm.

Decrease in arterial pressure in foot on elevation of limbs 15 mm, that is $\frac{15}{127} \times 100\%$ or 12%.

Thus a 12% reduction in hydrostatic pressure in the limb with a normal maximal circulation led to a decrease of 20% in the blood flow, while in the limb with the obstructed circulation the decrease in flow was 40%. The mean pressure proximal to the obstructed arteries was 127 mm., but in the left foot distal to the obstructed popliteal artery the pressure was much lower, probably in the region of 70-80 mm. from a study of figure 10.

Similar results have been obtained in ten other cases of peripheral vascular disease studied by this method and it has thus been demonstrated that there is a considerable drop in mean pressure in the arteries of the affected limbs. This is to be associated with the passage of the blood through devious collateral channels. The importance of this diminution in pressure will be readily recognised, for not only is the total blood flow reduced, but such blood as does pass through the vessels will not be able to play its full part in the nutrition of the foot owing to a reduction in the filtration fraction passing into the tissue spaces.

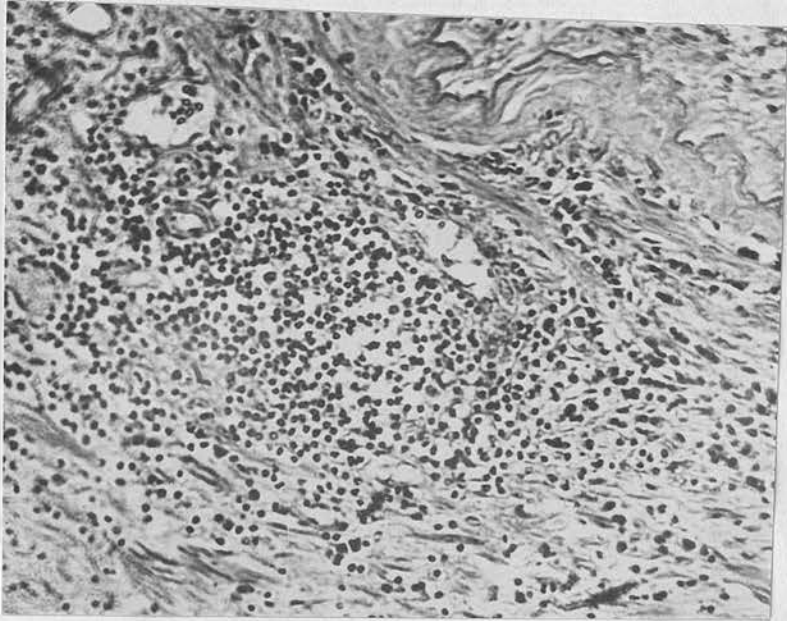


Fig. 19. A section of the wall of the popliteal artery from a case of atherosclerosis. The internal elastic lamina is shown partially disrupted at the top right corner. The media seen in the centre is densely infiltrated with lymphocytes and there has been considerable destruction of muscular tissue. The intima shows typical atheromatous degeneration. No medial calcification is present. In this case the lymphocytic infiltration was associated with recent thrombosis within the lumen of the popliteal artery. Stain haematoxylin and eosin. X 400.

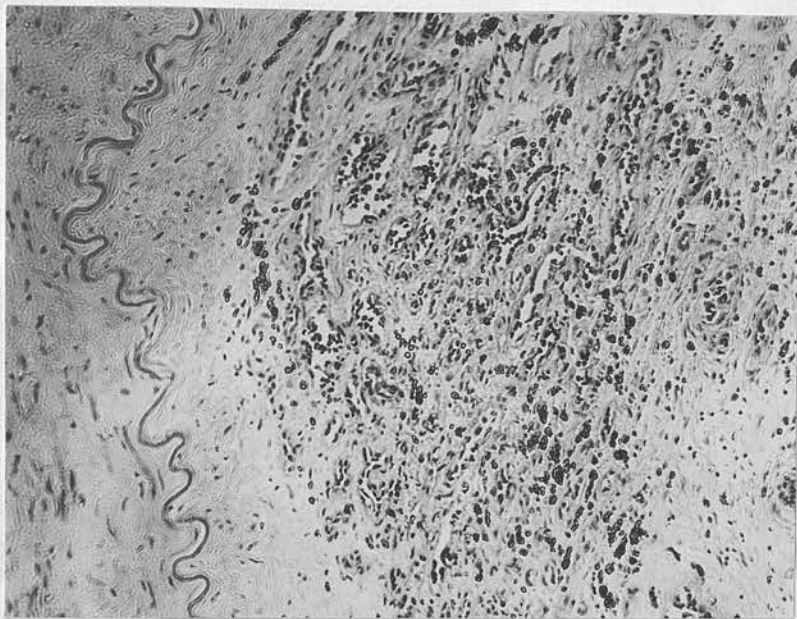


Fig. 20. A section of the peroneal artery from a case of atherosclerosis. The thrombus within the artery has been invaded by highly cellular granulation tissue and numerous haemosiderin deposits are present. The inflammatory changes within the thrombus and the preservation of the internal elastic lamina are suggestive of thromboangiitis obliterans. The degenerative changes within the intima and media however point to atherosclerosis and more typical atheromatous lesions were present in other arteries. Stain haematoxylin and eosin. X 300.

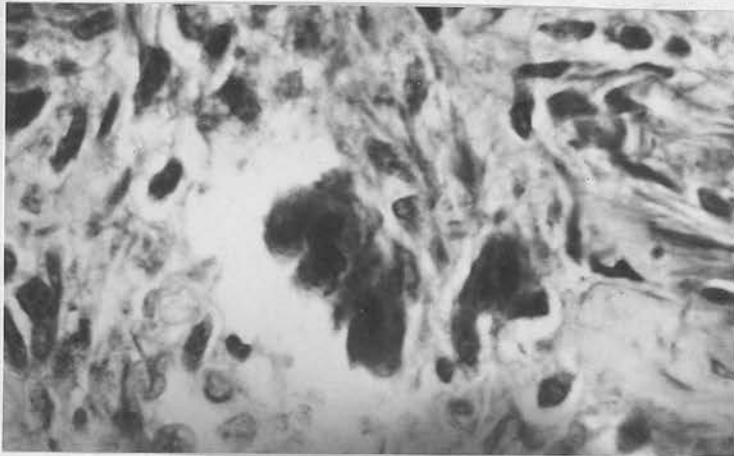


Fig. 21. A section of a portion of organizing thrombus in the posterior tibial artery of a case of atherosclerosis. Two giant cells of the foreign body type are seen. This richly cellular type of organization was present in many of the cases of atherosclerosis complicated by thrombosis. Stain haematoxylin and eosin. X 750.

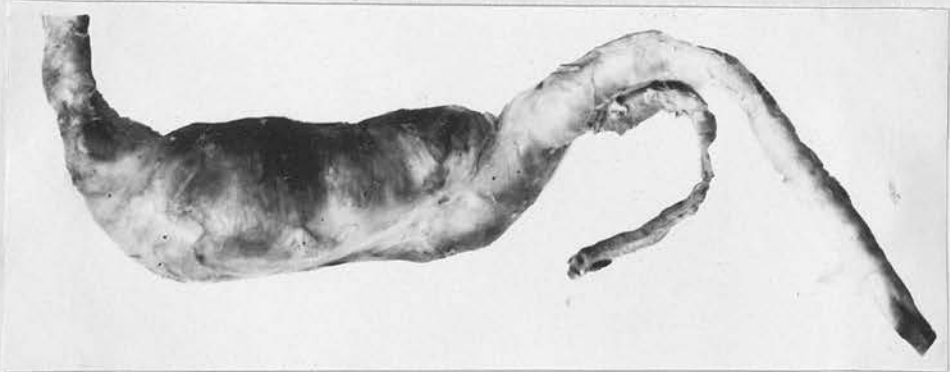


Fig. 22. An aneurysm of the popliteal artery from a case of severe atherosclerosis with considerable destruction and inflammatory changes within the media. The bifurcation of the popliteal artery is seen to the right. Complete thrombosis within the aneurysm had determined the onset of gangrene within the limb. $\frac{1}{2}$ natural size.

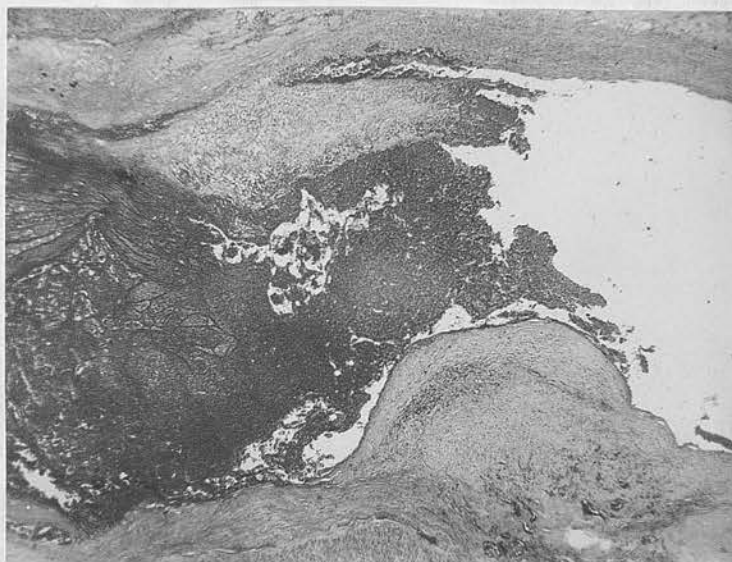


Fig. 23. A longitudinal section of an atherosclerotic popliteal artery. A large atheromatous plaque is shown and thrombosis developing proximal to this obstruction caused the development of gangrene of the limb. The lumen immediately distal to the plaque was patent. Several small vessels can be seen within the tissue of the plaque, while in the upper portion uneven organization of the thrombus leads to a picture that might easily be taken for an intimal haemorrhage rupturing into the lumen. Stain haematoxylin and eosin. X 60.



Fig. 24. X-ray of portion of leg amputated on account of atherosclerotic gangrene. The limb was injected with lead phosphate through the popliteal artery. The posterior tibial artery can be seen lying between the tibia and fibula. The anterior tibial artery is less clearly shown behind the tibia. The filling of these major arteries is intermittent and indistinct owing to atheromatous and thrombotic obstruction, but by contrast many of the side branches arising from these arteries are distinctly and uniformly filled with injection mass and are obviously serving as collateral channels.

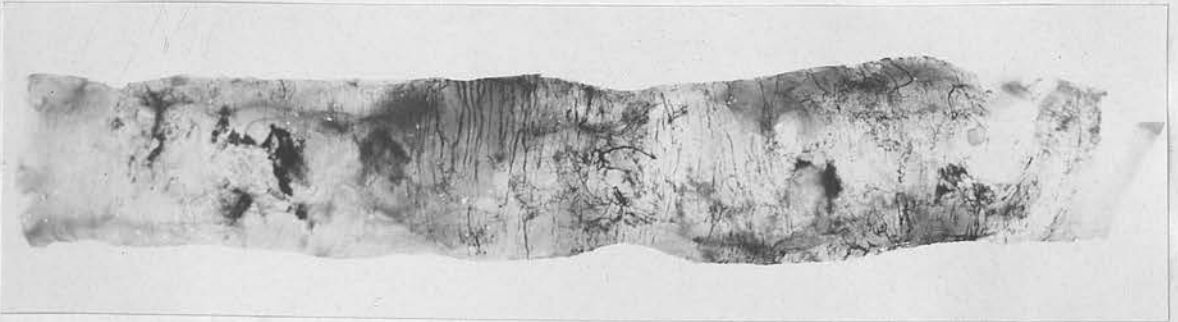


Fig. 25. A segment of the femoral-popliteal arterial trunk in the region of the adductor hiatus from an autopsied male aged 53 years suffering from a moderate degree of peripheral atherosclerosis and slight medial calcification. Numerous vasa vasorum are seen in the cleared specimen, outlined by India ink. The adventitia was completely stripped before clearing and these vasa accordingly lie in the media and intima. It is not possible to demonstrate these channels in normal arteries. The transverse distribution of the vasa in relation to an area of medial calcification is of interest. The vessels of the intima are more irregular in their arrangement and often lead into relatively large sinuses. X 4.

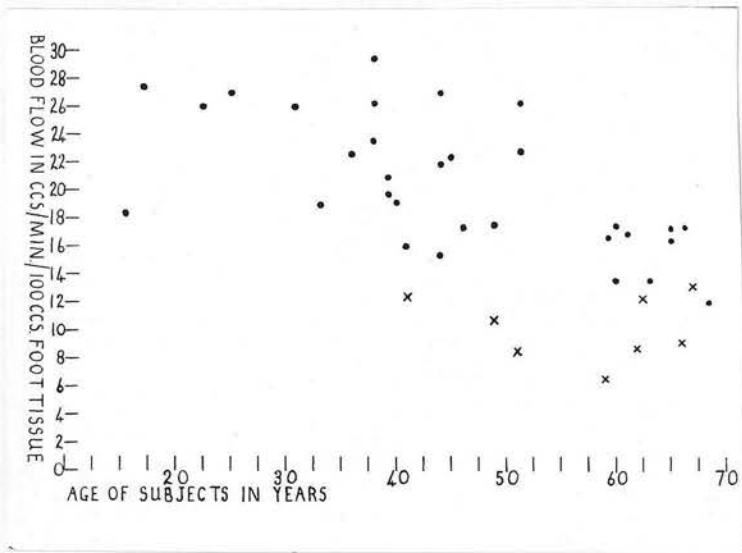


Fig. 26. Maximal circulatory capacities of the feet in normal subjects (•) and these affected with manifest atherosclerotic vascular disease (x). The readings in the latter subjects were made when they first reported on account of ischaemic features. A considerable reduction was found in the majority of these cases, but in the oldest subjects there tended to be little difference between those affected and symptom-free. In all the cases with symptoms the main obstruction was located in the popliteal artery and the reduction in the foot was fairly uniform. No clinical features suggestive of ischaemia appeared in any subjects with a maximal capacity greater than 13 c.cs./ 100 c.cs. foot tissue/min.

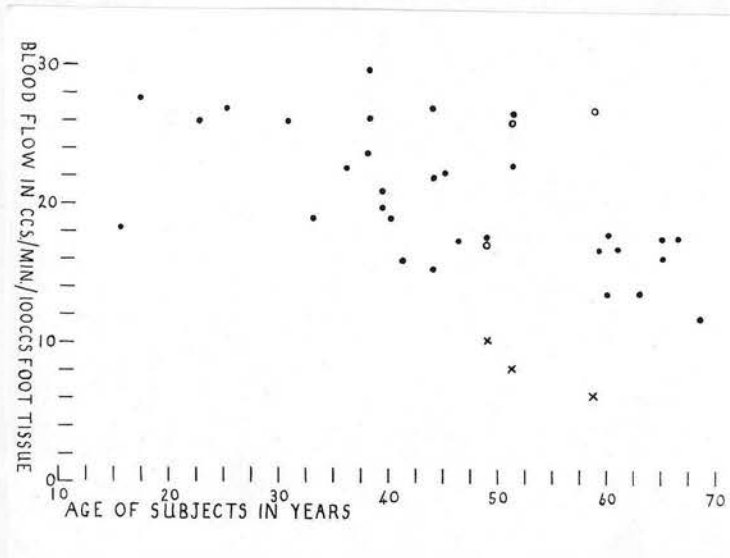


Fig. 27. The maximal circulatory capacities of three subjects with unilateral popliteal thrombosis. Normal subjects •. Affected limb x. Unaffected limb o. The thrombosis has obviously been the factor responsible for the development of ischaemic features, as the circulation in the limbs unaffected by thrombosis is within normal limits though the extent of purely atheromatous degeneration is probably roughly the same in the two limbs.

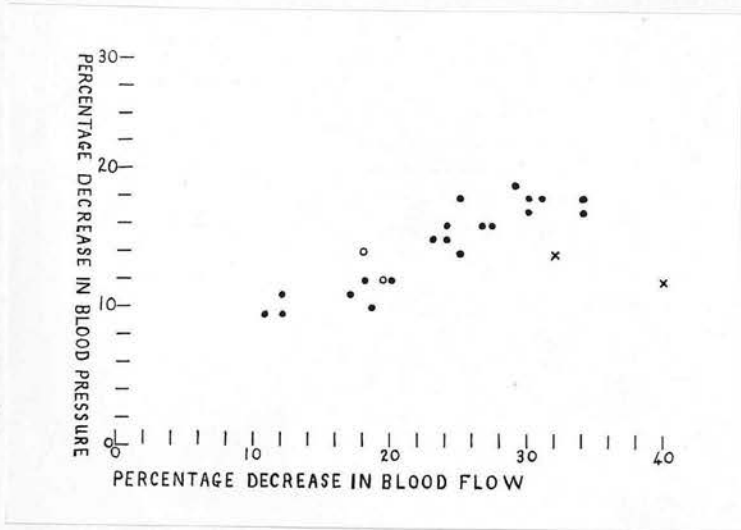


Fig. 28. Relation between blood flow and blood pressure in two subjects with obliterative vascular disease associated with unilateral popliteal thrombosis. Normal subjects •. Affected limb x. Unaffected limb o. The blood pressure was measured in the arm at heart level. The unaffected limbs give normal responses to elevation, but the affected limbs show an excessive decrease in blood flow demonstrating that the arterial pressure distal to the thrombosis is considerably reduced in comparison with the brachial arterial pressure.

PART V.

Diabetic Vascular Disease.

The association between the presence of diabetes mellitus and the development of arterial disease in the lower extremities has long been recognised. The existence of diabetes mellitus is generally regarded as a predisposing factor to severe and premature atherosclerosis. Numerous surveys of the incidence of this condition have been published and these undoubtedly show that atherosclerosis sufficient to produce clinical features of ischaemia develops on the average a decade earlier in diabetic men and two decades earlier in diabetic women as compared with non-diabetic subjects (Dry and Hines 1941). Pearl and Kandel (1939) found definite evidence of atherosclerosis in fifty of 100 diabetic patients taken at random, while Joslin (1946) found that in 749 cases of diabetes mellitus commencing in childhood and with a duration of fifteen or more years nearly 50% of those studied have shown radiologically calcified arteries in the legs.

The present study consists in a review of 20 cases of diabetic vascular disease in the lower limbs. In 10 cases amputations above or below the knee were carried out and these limbs have been studied by gross dissection, injection and histological methods. In the remaining cases the pathological physiology has been investigated by plethysmographic and other methods previously described. Though, as has been pointed out above, the association between diabetes and atheroma of the larger vessels has long been recognised, it was felt from a clinical study that disease of the larger vessels alone could not account for all the disturbances of the circulation seen in the lower limbs in diabetic vascular disease. The intention thus is to investigate the view that diabetes merely causes a premature atherosclerosis of the arteries and to ascertain

whether any other factors are present in this type of vascular disease. In addition to the above cases of definite vascular disease a group of patients who had suffered from diabetes for over five years was also investigated with regard to the circulation in the lower limbs.

In the gross dissection of the amputated limbs a considerable degree of atheroma was noted in the popliteal, posterior, and anterior tibial arteries. Particularly noticeable was the extent of medial calcification. It is however extremely difficult to form any accurate estimate of the extent of degenerations of this type in the peripheral arteries, as no precise method of measurement is available. There was, however, no doubt that a relatively severe degree of atheromatosis was present in all the amputated limbs of the diabetic subjects. One striking feature was the relative scarcity of complete arterial obstruction. In the purely atherosclerotic cases a recent thrombosis in one of the major vessels was an almost constant finding and was regarded as the final factor in precipitating the onset of ischaemic gangrene. This was not so in the diabetic cases. The amputations carried out may be grouped as follows:- Mid-thigh 5 limbs, Below knee 5 limbs.

In this small series of 10 cases it is interesting that in half it was possible to carry out below knee amputations and in every case satisfactory healing of the stump took place. This lower level of amputation was chosen wherever there was evidence that the popliteal artery was patent as demonstrated by palpable pulsation in the fossa or by the reactive hyperaemia test. It will be noted that in not nearly so high a proportion of the atherosclerotic cases was it possible to carry out amputations at this lower level. On dissection of the five limbs amputated at the midthigh recent thrombosis was found in the popliteal artery

in two instances, while in the other three this artery was patent though moderately narrowed by atheromatous plaques. In the latter three cases the higher level of amputation had been chosen on account of extensive cellulitis in the foot. In the cases amputated below the knee infection was not a marked feature and peripheral ischaemia alone was the condition that necessitated amputation. It is a point worthy of particular note that severe ischaemia of the toes may develop in diabetic subjects without any definite clinical or pathological evidence of obstruction in the larger arteries of the thigh and leg. It was this feature which first excited interest and suggested that in these cases the circulatory lesions were not solely atheromatous in nature and that vessels smaller than arteries were also involved. In the clinical study of diabetic vascular disease it has also been frequently noted that relatively circumscribed ischaemic lesions may develop on the toes even though both the dorsalis pedis and posterior tibial pulses are present. Similarly the presence of intermittent claudication in the calves on exertion has been noted personally in three diabetic subjects in whom the popliteal and pedal arteries were all palpably pulsating. Such observations as these seemed to indicate that diabetes mellitus not only predisposed to the development of atheroma in the larger arteries of the lower limbs but also to obliterative disease in the smaller branches of these arteries, a condition not usually seen in uncomplicated atherosclerosis.

Confirmatory evidence of this view was obtained from injection studies. Thus in a case of diabetic vascular disease in which ischaemic lesions of the first and fourth toes with a relatively normal circulation elsewhere had been the chief features, amputation of the first toe had been unsuccessful owing to failure of wound healing. An injection

of radio-opaque lead phosphate showed marked obliteration of the arteries around the amputation site and a slight deficiency in the vascular network of the fourth toe.

(Fig. 30)

A different approach was also made by studying the maximal circulatory capacity of the feet in subjects who had had diabetes for over five years and comparing the results with those obtained in normal subjects. The numbers of diabetics who have been studied so far are small, but the results show a striking decrease in the circulatory capacity of the feet (Fig. 31). It should be emphasised that these subjects had no definite symptoms of vascular disease and that at least one of the pedal arteries was pulsating. It must also be remembered that in many young normal subjects only one of the pedal arteries may be palpable. It thus seems probable that the reduction in the circulation in the foot in these diabetics was largely due to small vessel damage. Confirmatory evidence of this view was also obtained in three of these subjects on ophthalmoscopic examination as they presented in the fundi tiny spindle haemorrhages of the type found in diabetics. Such haemorrhages were not seen in the purely atherosclerotic types of peripheral vascular disease uncomplicated by hypertension.

On histological examination of the arteries typical atheromatous lesions and medial degenerations similar to those reported in the previous section were observed. There were no histological features in the arteries peculiar to the diabetic state and it was not possible from a study of the sections alone to determine that the case had been complicated by diabetes mellitus. It was however noticed that the inflammatory lesions previously noted in the atherosclerotic subjects were often very prominent in the diabetic cases, particularly in the female subjects (Fig. 29).

Indeed some of the slides presented a picture in many respects similar to that found in thromboangiitis obliterans. The only cases of peripheral vascular disease in the lower limbs seen in females were all complicated by diabetes and it is interesting to note that they showed histological lesions reminiscent of those seen in younger men.

Estimations with the plethysmographs of the maximal blood flow in the feet of those with features of peripheral vascular disease all showed a decrease below the normal level. While the figures were extremely variable it was found that in some cases the reduction of blood flow was slight, especially when the only features were small healed cutaneous lesions in the toes. Here again there was thus strong evidence that diabetic vascular disease might be localised to small areas such as one or two toes and that the rest of the circulation in the foot might be relatively little affected. Symptoms of vascular disease in the foot might thus appear with only a slight reduction in the total blood flow to the foot as a whole - a condition similar to that seen in the peripheral form of thromboangiitis obliterans.

From the above considerations, particularly with regard to the possibility of extremely localised lesions, it will be anticipated that it will be extremely difficult to state at what level of reduction of blood flow to the foot definite ischaemic features become apparent. In one subject with diabetes mellitus over a period of 12 years small gangrenous patches appeared on two of the toes and these subsequently became infected. With conservative treatment in bed these lesions healed. Subsequent plethysmographic observations showed that the maximum circulation possible in the foot was 5 c.c./100 c.c. foot tissue/min. Yet, even with this figure of about one quarter of the normal, healing of infected lesions was able to take place - a demonstration of the enormous reserve of circulatory capacity

normally present in the foot.

Estimation of the blood pressure in the arteries of the affected feet showed that the pressure gradient fell off markedly distal to the obstructions, as demonstrated by the leg raising technique. The same features with regard to the circulation passing through tortuous collateral vessels were thus demonstrated in the diabetic cases as in other kinds of vascular disease (Fig. 32).

In spite of much investigation little is known about the mechanism of the development of vascular disease in diabetic subjects. The occurrence of vascular disease depends primarily on the duration of the presence of the diabetes. Even strict control of the diabetes with insulin will not prevent the onset of this disturbance (Groom and Scott 1949), and there is little reliable evidence as to the frequency of vascular disease in those with glycosuria strictly controlled and in those treated on the "free diet" system. Diabetes mellitus is recognised as a generalised metabolic disturbance not restricted solely to carbohydrate metabolism. The blood cholesterol level is frequently raised and in view of the experimental work on hypercholesterolaemia and atheromatosis in rabbits this elevation may possibly be a factor in the development of the vascular lesions. As has been shown diabetic vascular lesions are not restricted to the larger arteries. Small vessel lesions are frequently seen in the retina in old diabetics and the present study has shown that the small vessels in the foot may be involved. The development of the atheromatous lesions in the larger arteries may possibly be related to disturbances in the vasa vasorum caused by the diabetes on the lines of the hypothesis suggested by Winternitz et al (1938). Investigation of the condition of capillaries by either injection or histological methods is difficult, but it is hoped to carry out further work on the

condition of the vasa vasorum in diabetic subjects. It is noteworthy that in these individuals there is also evidence of damage to the vasa nervorum (Jordan 1936).

The sex incidence of the different types of vascular disease in the lower limbs is of considerable interest. No cases of thromboangiitis obliterans or uncomplicated atherosclerosis going on to amputation were seen in females. The only amputation cases seen in females were in diabetic subjects, and in them the histological appearance of the arteries was reminiscent of that seen in the younger or middle aged groups of male subjects. In other words inflammatory changes as shown by cellular infiltrations were relatively prominent and the lesions seen in an older group of diabetic women corresponded to the types seen in a younger group of men. The whole process of the onset and development of arterial disease is thus retarded several decades in women.

It will be apparent that diabetic arterial disease occupies a position intermediate between thromboangiitis obliterans and atherosclerosis. The distinction between the different types of arterial disease is often extremely difficult and on many occasions not possible as the features of one type merge into the next. Several reports have appeared of thromboangiitis obliterans of patients with diabetes (Horton and Allan 1934), but these cases will not stand critical survey, the diagnosis of thromboangiitis obliterans being based on the presence of small vessel involvement which at that time was not regarded as occurring in uncomplicated diabetes. Obviously the classification on pathological grounds of the different types of arterial disease occurring in the lower limbs is extremely difficult, as the histological appearances range from frankly inflammatory lesions seen in acute thromboangiitis obliterans to typically degenerative atheromatous features seen in elderly subjects without any clear dividing

lines. Diabetes mellitus is the one condition in human subjects which is clearly recognised as predisposing to the development of vascular disease, and a study of the mode of onset of the arterial disturbances in this condition is one of the more promising avenues of approach to the largest problem confronting medicine to-day.

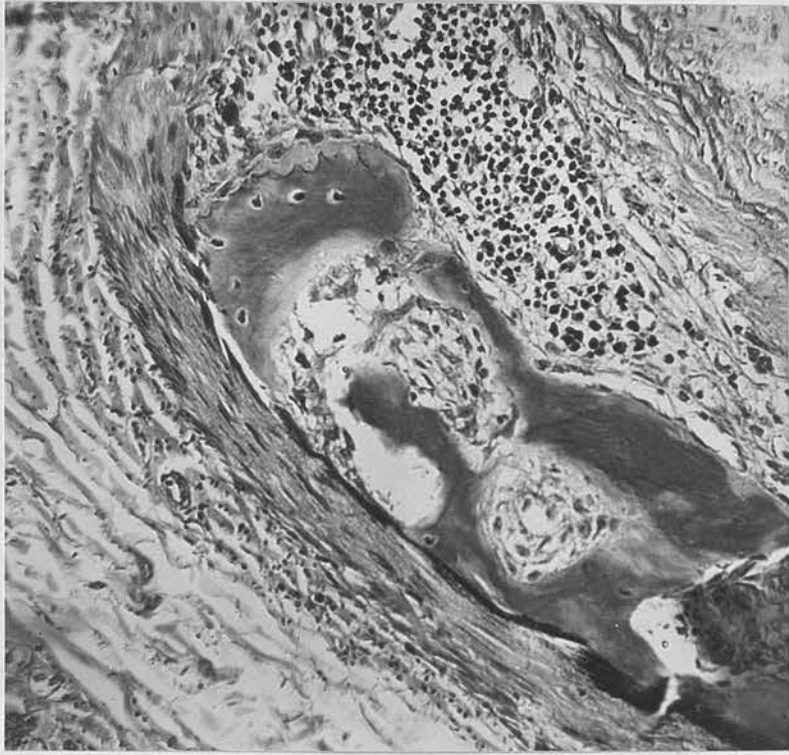


Fig. 29. Section of the posterior tibial artery from a female case of diabetic vascular disease. An area of bone formation is apparent in the media and this is partially surrounded by a dense collection of small round cells. The musculature of the media has been considerably destroyed. The thickened intima and the fragmented internal elastic lamina are situated in the top left corner. The adventitia contains numerous small round cells. Stain haematoxylin and eosin. X 450.

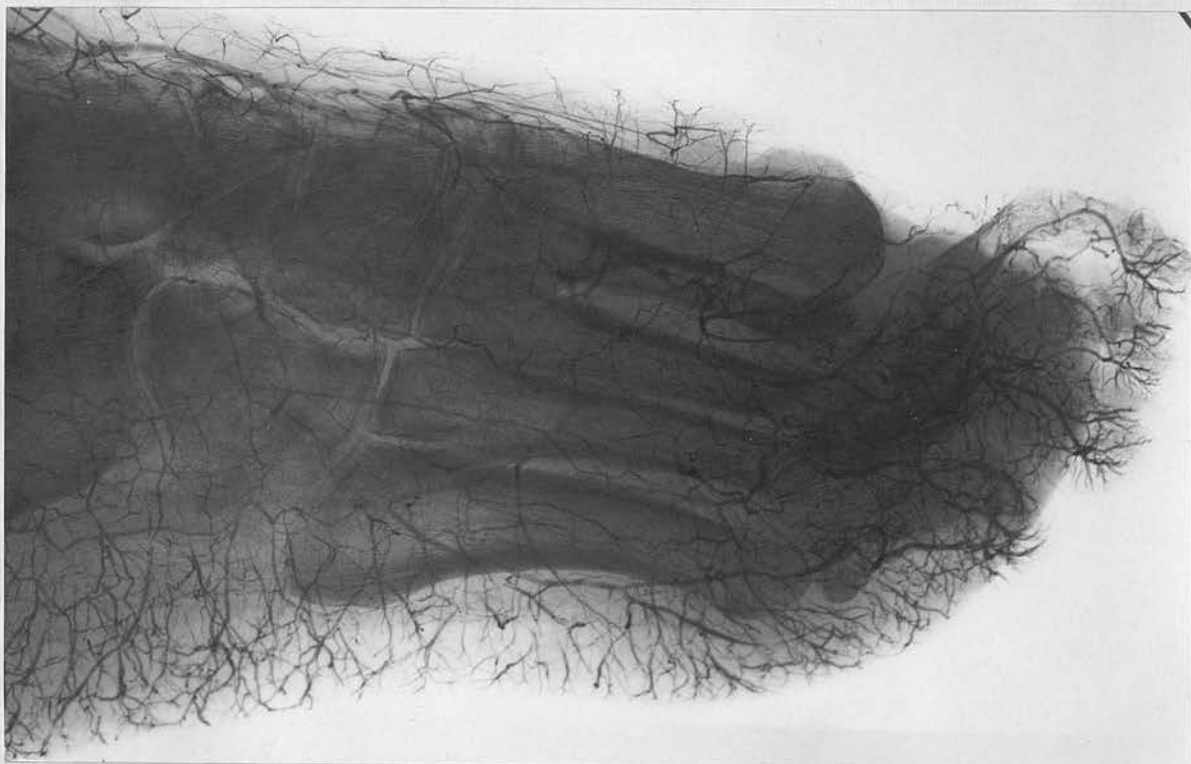


Fig. 30. Lateral and dorsal X-rays of a foot amputated on account of diabetic vascular disease and injected with lead phosphate. The great toe had previously been amputated but the wound had failed to heal. The marked obliteration of small vessels around the head of the first metatarsal is clearly shown. There is also some deficiency in the arterial network around the fourth toe.

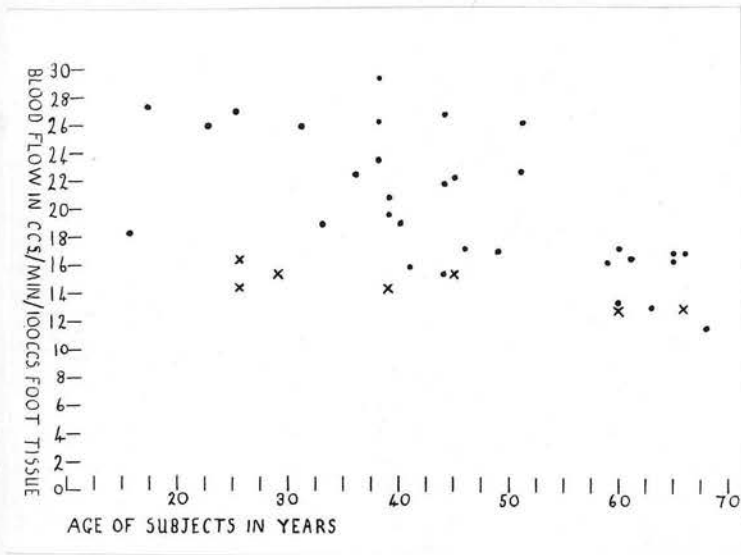


Fig. 31. Maximal circulatory capacities of normal subjects (•) and of those with diabetes mellitus of five or more years standing (x). All the diabetic subjects had palpable popliteal pulses and at least one palpable pedal pulse, and were free from clinical features of ischaemia. Nevertheless their blood flows were all at the lower limits of normal.

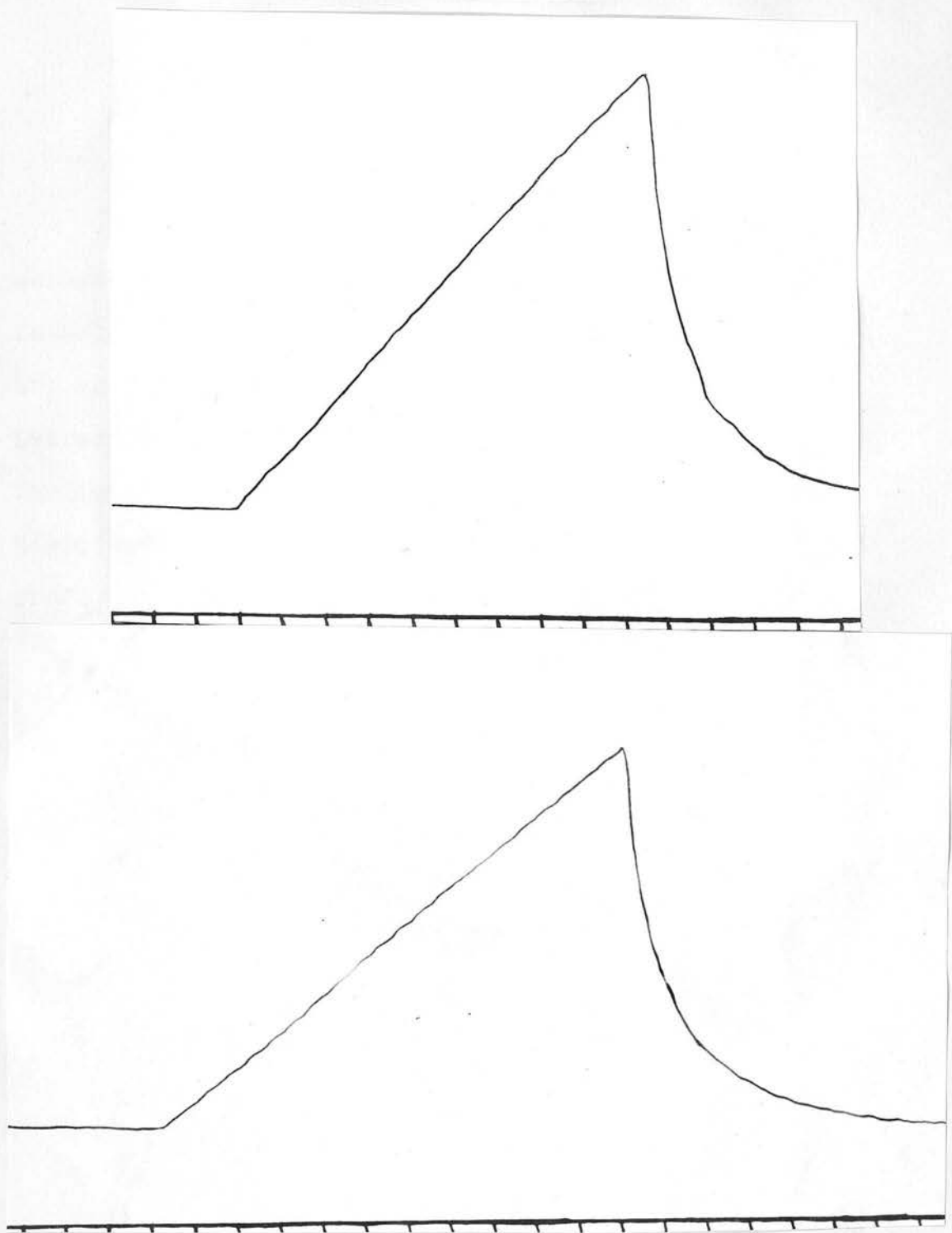


Fig. 32. Blood flow tracings from the foot in a case of diabetic vascular disease with brachial B.P. 130/90. Plethysmograph 44°C. The popliteal and dorsalis pedis pulses were not palpable but a weak posterior tibial pulse was present. No pulsations are present in the tracings. The upper tracing was with the limb horizontal and represents 12.7 c.cs./100 c.cs./min. The lower tracing is taken with the limb raised 20 cm. and represents 9.3 c.cs./100 c.cs./min. The decrease in blood flow is 27% while the decrease in mean arterial pressure on raising the limb is about 14%. The decrease in flow is thus rather greater than normal, doubtless owing to the arterial obstructions and the development of devious collateral pathways.

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