

STUDIES OF THE PATHOLOGICAL  
ANATOMY AND PHYSIOLOGY OF SOME  
PERIPHERAL CIRCULATORY DISORDERS

A thesis submitted for the degree of  
Doctor of Medicine  
in the  
University of Edinburgh  
by

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February 1950



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## INTRODUCTION

The first part of the work described in this thesis was connected with the pathological anatomy of arterial disease in the lower limbs. However, this study afforded only a static picture of what were essentially dynamic disturbances. Hence, further investigations were carried out on the disorders of blood flow resulting from the presence of structural disease. After studying the effects of local disease on the circulation in the limbs, it was a natural step to investigate the blood flow to the lower limbs in the presence of a coarctation of the aorta. The observations later made in a case of aneurysm of a peripheral artery threw considerable light on the pathogenesis of clubbing of the fingers. This condition appeared to be essentially a peripheral circulatory disorder and was studied in its general aspects, but as this investigation has not been long in progress the mechanism has not yet been elucidated in every detail. The hypothesis and results to date do, however, appear to afford a complete explanation of the development of clubbing and are thus of considerable interest. Finally an opportunity presented to make some observations on the circulatory disturbances associated with phaeochromocytomata. This also involved a study of the circulatory actions of noradrenaline and of the relation of that drug to the development of arterial hypertension.

The thesis thus consists of a series of articles on disorders of the peripheral circulation. Some have already been approved by the Journal of Pathology and Bacteriology and by Clinical Science and are in the press. Others have been accepted by Clinical Science or are in course of preparation for submission for publication. A summary is included at the end of each section. The results are shown so far as possible in graphs, tables and illustrations. The actual plethysmographic tracings



rather than reproductions have been included in many cases in order that the standard of the work may be assessed.

My thanks are due to many who have at various times encouraged and assisted me in this work: to Professor Sir James Learmonth who first aroused my interest in disorders of the peripheral circulation: to Professor A.M. Drennan who provided facilities in his department for the early anatomical studies; and especially to Professor G.W. Pickering who throughout all the later work gave much helpful criticism and advice. Many of the experiments could not have been carried out without assistance, especially when multiple observations of blood flow, blood pressure, and heart rate had to be made at the same time. For assistance on various occasions I am grateful to Dr. Y.Y. Akrawi, Dr. A.J. Barnett, Dr. R.B. Blacket and Dr. K.W. Cross. Help with the construction of the first forearm plethysmograph was given by Dr. R.T. Grant and Dr. H.E. Holling. The charts and diagrams have all been entirely prepared by myself, but for assistance in the photography I am indebted to Dr. G.A.C. Summers, Dr. P.A. Cardew and the technical staffs of the Pathological Department at the University of Edinburgh and of the Medical Unit at St. Mary's Hospital Medical School. I should also like to thank the senior staff at St. Mary's Hospital for permission to investigate cases under their charge and the patients and students for their cooperation throughout the observations.

... to investigate the pathology of the ...

SECTION I

METHODS OF INVESTIGATION OF THE PATHOLOGICAL ANATOMY.

... the long-standing effects of vascular disease. Following this general inspection various further methods of investigation are used. These are described as follows: -

1. General dissection of the vascular tree.
2. The method of injection of the vascular tree with various dyes and solutions.
3. The method of injection of the vascular tree with various oils.
4. The method of injection of the vascular tree with various solutions.
5. The method of injection of the vascular tree with various solutions.
6. The method of injection of the vascular tree with various solutions.
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9. The method of injection of the vascular tree with various solutions.
10. The method of injection of the vascular tree with various solutions.

... a study of the different types of disease. ...

## METHODS OF INVESTIGATION OF THE PATHOLOGICAL ANATOMY.

1

As the study included the investigation of the condition of the blood vessels in both amputated limbs and biopsy specimens a considerable variety of methods was used. 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 which could be attributed to the long-standing effects of vascular disease. Following this external inspection various further methods of investigation were used. 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 radioopaque 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 more complex 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 how adequately the various vascular channels had been filled. This was particularly helpful in tracing out the course of the small vessels canalizing occluded arteries. Gross dissection and histological study were carried out in all the limbs received for examination and in eight limbs a successful injection of a coloured radioopaque substance was also performed. These last eight limbs do not however represent all that were injected 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 an amputated 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 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 this 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. This was a considerable advantage in the further investigations. Better results were obtained if the fixation was 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 taken from the popliteal, anterior and posterior tibial, dorsalis pedis and



plantar arteries, and designed to include the veins and nerve together with the surrounding connective tissue were taken for microscopic study.

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 connections of the new channels recanalizing thrombosed arteries. Thirty segments that showed complete occlusion and recanalizing vessels were serially sectioned at five microns thickness. Every fifth section was mounted and stained by Weigert's method for the demonstration of elastic tissue. In this series a few representative sections were stained by haematoxylin and eosin to illustrate more clearly the cellular reaction. In this way between one hundred and fifty and two hundred sections of each vessel segment were examined. Those stained specifically for elastic tissue were of particular value in demonstrating the changes in the vessel walls and the stages of obliteration and recanalization of the lumen. 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 arterial segment, 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 by the method described by Winternitz and his associates (1938). About 10 cm. of the artery centred on the hiatus were dissected out, care being taken to include the small side-branches and some surrounding tissue. The proximal end was cannulated and the distal clamped with artery forceps. India ink was 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 artery was 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 concerning the technique. 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 was essentially similar to that described by Pettigrew (1934). The leaks from the side branches of the artery during the injection often caused considerable trouble, 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 difficulty 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. The same problem was encountered 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, but in man it is not possible to demonstrate these channels using a lower pressure (Winternitz and others, 1938). A 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 it would be a great advantage to obtain a picture of the arterial tree as a whole throughout the affected 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 aroused as to 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 - to inject either a coloured substance and display the arteries by dissection or digestion of the surrounding tissues, or a radio-opaque substance and radiograph the result. Various attempts were made with injections of a suspension of India ink in celloidin (fig.30) and certain information was obtained in this way regarding the significance of side branches and the recanalized main vessels, but little further knowledge could be obtained by this method regarding the circulation to the limb as a whole. The injection of celloidin coloured with 1% alkanid 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 demonstration of 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 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.

The ideal method was to develop a technique whereby radiological and dissection with clearing and histological studies might be performed on the same limb. Arteriography of a limb 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 visualisation of the arteries of an amputated forearm following the injection of a radio-opaque substance. It has subsequently provided one of the chief methods for the study of the development of a collateral circulation consequent on arterial obstruction. Various substances such as barium sulphate and mercury have been used to form the contrast injection mass. For investigation of the lower limb a satisfactory solution was found by modifying Schlesinger's method (1938) for coronary arterial injection. The modified injection mass was prepared as follows:-

Solution A: Lead acetate 60 gm.

Distilled water 172 ml.

Dissolve by heat, filter and allow to cool.

Solution B; Anhydrous disodium hydrogen phosphate

24 gm.

Distilled water 190 ml.

Dissolve by heat, filter and allow to cool.

Preparation:-

1. 1.5 gms. agar-agar in 2000 ml. flask.
2. Add 100 ml. of solution A and boil till frothing ceases.
3. Add 1 ml. of 0.06% phenol red as indicator.
4. Add 70 ml. of solution B.
5. Add by pipette 10% sodium hydroxide till indicator

changes pink.

6. Add distilled water till total is 250 ml.
7. Boil 10 mins. till agar is fully dissolved.
8. Add 2 gm. trypan blue.
9. Heat for 1 min. and stir.
10. Strain while hot through gauze.
11. Preserve at room temperature.

The mass now consisted of about 8% precipitated lead phosphate which was found 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 half an hour in a water bath maintained at 42°C. The popliteal artery was cannulated and the vessels were irrigated with 200 ml. physiological saline at 40°C. The lead phosphate, previously warmed to 40°C, was injected at 400 mm. pressure, the bottle being agitated during the whole time to prevent any settling of the precipitate. About 150 ml. were 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 limb 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.

As the work progressed and further experience was gained in the injection technique several criticisms, improvements and modifications became apparent. Thus the pressure of 400 mm. mercury was excessive, but the high pressure was used originally on account of difficulty in injecting some of the atherosclerotic arteries. In these the popliteal artery was usually grossly obstructed, while the site of amputation was



at the junction of the middle and lower thirds of the thigh. In many specimens the block was thus only a few centimetres below the tip of the cannula and, as the popliteal artery has no large side branches to carry a collateral circulation round the site of the obstruction, 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 however high a pressure is used. The collateral vessels to circumvent the obstruction in the popliteal artery arise from the femoral 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 that the popliteal artery has been completely thrombosed. This probably explains why so little has been written on the injection of amputated lower limbs. The only previous account is that of Horton (1930). He, using mercury as the radio-opaque material made no mention of this difficulty but his series included no cases of popliteal artery thrombosis. 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. 34). Similarly in the cases 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

uncertainty regarding the level 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, but owing to the legal position regarding subsequent removal of the limb this was not possible.

Several minor points in the technique deserve 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 demonstration 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 Reeve's 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 serial naked eye sectioning and the nature of the obstruction was determined. 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 40 microns. (Schlesinger 1938). The obvious fallacy arising from any injection technique is that filling of a vessel may be incomplete owing to the presence of post mortem thrombus not dislodged by the preliminary saline irrigation. The investigation of any region in which the vessels were not injected was thus an essential step to ensure that the failure of the lead phosphate to penetrate was due to obliterative vascular disease and not to artefacts. It is hardly necessary to mention that after injection and fixation of vessels conclusions should only be drawn with regard to organic obstructions and that it is essential to demonstrate that they were present before amputation. No studies by an injection method after amputation can be regarded as in any way reflecting the functional state of patent vessels during life.

#### SUMMARY.

The methods used in the investigation of the pathological anatomy of amputated limbs have been described. These included:-

1. Gross dissection of the arterial tree down to the distal part of the foot and subsequent fixation in formalin.
2. Macroscopic serial transverse or longitudinal sectioning of all the major vessels.
3. Microscopic examination of selected portions of the vessels.
4. Detailed investigation of occluded arterial

segments by serial microscopic sections and specific staining for elastic tissue.

5. Injection of the femoral-popliteal artery with India ink to demonstrate the vasa vasorum.

6. Injection of the whole arterial tree through the popliteal artery with precipitated lead phosphate coloured with trypan blue and subsequent radiography dissection, and microscopy.

The Winternitz method of displaying the vasa vasorum in atherosclerotic arteries is criticized as the 400 mm. of mercury pressure required may cause artefacts. Even in pathological arteries these channels cannot be demonstrated by injection at a lower pressure.

The chief difficulty encountered with injection of the whole limb was that the site of obstruction of the artery was frequently immediately below the level of amputation and a free entry of lead phosphate into the distal part of the limb could not accordingly be obtained. After injection checking of the filling of all patent lumina with the lead phosphate by macroscopic and microscopic sectioning formed an essential step in the investigation to avoid drawing fallacious conclusions.



The problem of coronary atherosclerosis is a complex one, involving many factors. It is not yet clear whether the disease is primarily atherosclerotic in nature or whether it is a distinct entity. The evidence is conflicting, but it is generally agreed that the disease is atherosclerotic in nature. The evidence is based on the fact that the disease is characterized by the presence of atherosclerotic plaques in the coronary arteries. These plaques are composed of lipids, fibrous tissue, and cellular debris. The plaques are usually found in the inner wall of the artery, and they can lead to the narrowing of the artery. This narrowing can lead to the development of atherosclerotic heart disease, which is a leading cause of death in the United States. The disease is characterized by the presence of atherosclerotic plaques in the coronary arteries. These plaques are composed of lipids, fibrous tissue, and cellular debris. The plaques are usually found in the inner wall of the artery, and they can lead to the narrowing of the artery. This narrowing can lead to the development of atherosclerotic heart disease, which is a leading cause of death in the United States.

SECTION II

METHODS OF INVESTIGATION OF THE PATHOLOGICAL PHYSIOLOGY.

The methods of investigation of the pathological physiology of the heart are numerous and varied. They include the study of the gross anatomy of the heart, the study of the histology of the heart, the study of the physiology of the heart, and the study of the pathophysiology of the heart. The study of the gross anatomy of the heart involves the dissection of the heart and the study of its various parts. The study of the histology of the heart involves the study of the microscopic structure of the heart. The study of the physiology of the heart involves the study of the normal function of the heart. The study of the pathophysiology of the heart involves the study of the changes in the function of the heart that occur in disease. The methods of investigation of the pathological physiology of the heart are numerous and varied. They include the study of the gross anatomy of the heart, the study of the histology of the heart, the study of the physiology of the heart, and the study of the pathophysiology of the heart. The study of the gross anatomy of the heart involves the dissection of the heart and the study of its various parts. The study of the histology of the heart involves the study of the microscopic structure of the heart. The study of the physiology of the heart involves the study of the normal function of the heart. The study of the pathophysiology of the heart involves the study of the changes in the function of the heart that occur in disease.



The problem of accurately assessing the dynamics of the 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 investigations and their significance has been discussed by numerous authorities (Pickering (1933), Lewis (1936), Allen et al (1946)). 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) 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. To perform this test it is essential that the limb is first warmed to eliminate vasoconstrictor tone. This is best done by soaking in water at  $40 - 44^{\circ}\text{C}$  for ten minutes, but, if this is inconvenient, hot bottles or a heating cradle may be used. After elevating the limb to drain the skin vessels, the arterial circulation is excluded by a pneumatic cuff round the thigh inflated to 300 mm. of mercury pressure. After five minutes of occlusion the pressure is released and the spread of the flush caused by the returning arterial circulation is watched. It is possible to time the spread to various anatomical levels comparing the two sides, and to notice any general or localised delay. Similar information can be obtained by injecting fluorescein into an arm vein and watching under ultra-violet irradiation the spread of a green

fluorescence down the limbs (Sicher, 1943). The fluorescein test was found particularly useful in assessing the efficiency of a tourniquet on a limb during the performance of some experiments on intermittent claudication. Obviously if the tourniquet is completely obstructing the arterial flow, no fluorescence should develop in the distal part of the limb. In using both the reactive hyperaemia and the fluorescein tests, it is important to control carefully the conditions under which the observations are made. This is essential if comparative results are required and, in these circumstances, the circulation times were always measured with the limb vessels at full vasodilatation.

In patients complaining of intermittent claudication, accurate assessment of the exercise tolerance is extremely valuable. In all cases this was done by walking the patients over steps similar to those described by Wayne and La Place (1933) in their investigations of angina pectoris. A record was kept of the number of circuits performed and the time before pain was felt. The subject was allowed to walk at his own natural pace and this rate was found to be remarkably constant. The amount, duration and rate of exercise were thus calculated, and, provided that care was taken to ensure similar conditions with regard to clothing, previous meals, and room temperature and that an adequate period of rest was given before testing, reproducible results were obtained. This test was used to assess the severity and the progress of the disease and also to investigate the nature of intermittent claudication. Tests performed in this way sometimes gave results at variance with the patients' statements, particularly with regard to improvement. Obviously any test relying for

its end point on a subjective sensation experienced by a patient may be of doubtful validity. The patient may count the number of circuits but he is always given to understand that the time recorded by the stop watch, of which he is unaware during the performance of the test, is the important feature. In spite of these possible faults an exercise tolerance test performed in this manner gives information considerably more valuable than can be obtained by an assessment of the patient's statements. As, however, there are spontaneous fluctuations in exercise tolerance even under the most carefully controlled conditions, it is essential that numerous and frequent tests are carried out before any conclusions are drawn. This is particularly important when assessing the results of therapy and in this connexion it is far more valuable to examine regularly and often a small series of patients than a large series only once or twice before and after treatment. The first essential is to collect information about the natural course of the disease.

For the measurement of blood flow in a limb, only two reasonably accurate methods are available, namely the use of either a Stewart's calorimeter or a plethysmograph. The recording of skin temperature by thermocouples has been used extensively in the past for measuring blood flow but this is a method of limited accuracy and not suitable for the investigations described later. The results obtained from skin temperature records in the study of peripheral vascular disease have been disappointing (Richards (1946)). Calorimetry and plethysmography give more detailed quantitative information and have been used extensively in this work. An excellent comparison and review of these three methods of measuring peripheral blood

flow has been carried out by Cooper et al. (1949), and their methods have been extensively followed.

Calorimetry has been used by the writer for the determination of blood flow through the hands. The method was originally described by Stewart (1911) and depends essentially on the rate of transfer of heat from the hand to the water within the calorimeter. It is thus primarily a measure of the cutaneous blood flow which constitutes the greatest part of the circulation through the hand. The result is expressed as calories per minute. Stewart translated this into blood flow in millilitres per minute per gram of tissue but Sheard (1926) subsequently showed that this calculation was probably unsound. Accordingly, all the results will be expressed as calories per minute. In the original pattern the considerable loss of heat to the exterior involved a cooling correction at the end of the period of the observation. This, however, has been avoided by using as the water container a large vacuum flask as described by Greenfield and Scarborough (1949). The writer built a calorimeter of such a pattern and it has been used in all the clinical observations and experiments.

The instrument consisted of a large vacuum flask of one gallon capacity, a stirrer driven by an electric motor and a small 6.0 volt electric bulb mounted within the calorimeter. For use, 3,500 ml. of water were added to the calorimeter and the hand to the level of the distal carpal bones was inserted into the water through a sponge rubber cuff which sealed the opening. The hand was allowed to soak for at least 15 minutes before observations were begun in order to exclude any fallacies due to the previous environmental circumstances



of the hand. The temperature of the water was measured at minute intervals with a Sutton thermometer graduated to  $0.01^{\circ}\text{C}$  and observed through a lens. The heat eliminated by the hand is taken up not only by the water, but also by the stirrer and its case, the inner lining of the thermos flask and the portion of the thermometer immersed in the water. It was thus essential to ascertain the water equivalent of these structures for the calculation of the result. That of the stirrer and flask was calculated by adding rapidly to the calorimeter with the thermometer and a known amount of water in place, further water of known volume and temperature. The resultant change in temperature of the water in the calorimeter was measured and with these data it is a simple matter to calculate the water equivalent of the calorimeter (Stewart 1911). From an average of five observations made in this manner the water equivalent of the writer's calorimeter was found to be 300 ml. The heat elimination from the hand was thus calculated as  $((3,500 + 300) \times \text{rise in thermometer in degrees C per minute})$  small calories per minute. No allowance can be made for the water equivalent of the thermometer which was used unchanged in all the experiments. This slight error has thus been a constant value.

In order to obtain accurate observations with a calorimeter several precautions must be taken. It is essential to make sure that the slight heat loss to the exterior from the vacuum flask is exactly balanced by the heat generated by the parts immersed in the water. These sources of heat are the friction at the bearings of the stirrer and the small electric bulb, the current passing through which was controlled by a variable resistance. The speed of the stirrer



motor and the brightness of the bulb were adjusted so that, with the opening for insertion of the hand, closed, water in the calorimeter at  $32.00^{\circ}\text{C}$  remained at a constant temperature.

This was ascertained by leaving the calorimeter at the conclusion of an experiment with the motor running and the hand opening closed with a layer of sponge rubber. Under such circumstances the temperature after half an hour did not change by more than  $0.05^{\circ}\text{C}$  and no cooling correction was thus necessary in readings made at minute intervals. Working in a room temperature between  $19^{\circ}$  -  $23^{\circ}$  it was found that in the calorimeter constructed by the writer the frictional heat of the stirrer was just sufficient to balance the external loss and no additional heat from the bulb was usually required.

Using the calorimeter in this way on one hand and simultaneously a plethysmograph on the other, it has been shown that the results are strictly comparable (Cooper et al. (1949)).

The calorimeter may be used to determine either the resting heat elimination or the maximal heat elimination of the hand. To measure the latter, the opposite hand and forearm were immersed in water at  $45^{\circ}$  and the subject was wrapped in blankets. With the subject sweating freely the rate of heat elimination was calculated during the period required to raise the temperature of the calorimeter bath from  $31.00^{\circ}$  to  $32.00^{\circ}$  centigrade (Pickering 1936). Obviously the rate of transfer of heat depends partly on the temperature gradient between the immersed extremity and the calorimeter bath. It is possible to apply a correction for observations made in a different temperature range (Arnott and Macfie (1948), Greenfield and Scarborough (1949)) and this has occasionally been necessary. As, however, quite apart from the purely

physical considerations, changes in bath temperature may also affect the tone of the cutaneous vessels maximal heat elimination in the present study has normally always been observed over the range  $31^{\circ}$  to  $32^{\circ}\text{C}$ .

Special precautions are required when the heat elimination is to be measured in the same individual on successive occasions. It is then most important that the same volume of hand is immersed in the water at each observation. This was ensured by marking with a silver nitrate pencil a level around the forearm which subsequently acted as a guide to the amount to be inserted into the calorimeter. When serial records were being made, the volume of the hand was measured by displacement on each occasion and the heat elimination was expressed as calories per minute per 100 ml. of hand tissue. As however, the blood flow per unit volume is much greater in the finger than in the hand as a whole (Goetz, 1946) expression of the result in this manner does not compensate for differences in the volume of hand inserted.

In the past the calorimeter has not been extensively used for the measurement of blood flow but results obtained in the study of circulatory disorders have been reported by Brown (1926) Pickering (1943) and Arnott and Mathew (1939). In the older models the hand stirrer and cooling correction were troublesome features, but the present vacuum flask type of instrument has been found by the writer to give reliable results and to be of great assistance in clinical investigation.

A plethysmograph consists essentially of a chamber into which an organ or extremity may be inserted. The entrance is 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 closed system to a Brodie's bellows or a miniature paraffin spirometer. The plethysmograph was first described and named by Mosso (1879) who used his instrument to record changes chiefly in pulse volume and did not make any direct observations on blood flow. Brodie and Russell (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. They 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 hand, forearm, calf and foot plethysmographs. These instruments were constructed chiefly out of celluloid which made them light and convenient for use on patients. It should be added that all the equipment apart from the kymograph was made by the writer. When these investigations were begun no time marker was available and one was accordingly constructed out of an ex-service electric clock. As the only suitable wheel for carrying the electrical contacts revolved once in 1.5 secs. this accounts for the unusual time interval in the earlier tracings. The venous occlusion cuffs were made out of bicycle inner tubing. The volume recorders were of the microspirometer paraffin float type and were constructed of thin tin plate. They were of various sizes designed to give a displacement of 0.3 cm. to 1.2 c.m. per 1.0 ml. increment of volume. An ink-writing device was constructed out of glass

capillary tubing and thus the use of smoked paper, troublesome in clinical investigation, was avoided. The calibration was carried out after each experiment by adding water through a burette inserted into the aperture designed for the thermomoter. With the recorders commonly used, the calibration was not absolutely linear (fig 10). Complete linearity may be obtained by using a long-angled writer at the end of the lever. This however, increases the mass of the moving parts which is an undesirable feature and writers of this type were only used when simultaneous plethysmographic records of the blood flow in two limbs were desired. Optical systems with photographic recording are more accurate but have the great disadvantage that the results cannot be seen during the experiment.

The first forearm plethysmograph was made according to the method of Holling (1947). To avoid the necessity of a water tight seal between the skin and plethysmograph which is difficult and tedious to make, a sleeve made of thin latex rubber sheeting was fitted inside the instrument. For use it was then only necessary to slip the plethysmograph onto the forearm and to fill it with water. Bulging at the ends was prevented by adjustable sliding celluloid plates. This type of instrument has a double advantage. Firstly, it can be assembled for use within five minutes and, secondly, as no tight seal is required at either end, there is no danger of producing venous congestion. It is of course essential that the sleeve is loose fitting and made of extremely thin rubber so that the water presses it into firm apposition to the skin. The calf plethysmograph was constructed on the same principle. Fitting of a foot plethysmograph in the past has always been regarded as troublesome owing to the difficulty of constructing



an instrument of reasonable size into which the extremity with its right angled bend may be inserted. All previous instruments for the foot have used a water tight seal to the skin of the leg (Stead and Kunkel (1938), Landowme and Katz (1942), Abramson (1944)). A watertight seal at the ankle joint with the hollow behind the malleoli has usually been impossible and so-called foot plethysmographs have usually included the distal end of the leg. These difficulties were overcome by manufacturing a thin sock of latex rubber sealed at the proximal end through a thicker rubber diaphragm to the celluloid of the instrument. The construction of the apparatus is shown in the diagrammatic illustration (fig. 1) and in the photograph (fig. 2). The thin rubber sock is collapsed firmly and completely by the water onto the skin of the foot and into the crevices between the toes. The outer surface of the celluloid was covered with a quarter-inch-thick cork sheeting to act as a heat insulator. Subsequent observations showed that it was highly essential that the local temperature surrounding the part was kept constant throughout the experiments. Small variations in local temperature produce considerable fluctuations in blood flow. For this reason the plethysmograph was always filled with water, though Berry and others (1948) have recommended air as the natural and most suitable medium. Their compensating plethysmographs working in duplicate on two limbs would not be suitable for the type of work envisaged, as the two limbs were often not comparable and the second limb was frequently required for blood pressure estimations and for intravenous infusions. It is also much simpler to keep water rather than air at a constant temperature within the plethysmograph. In the author's plethysmograph,

water at the desired temperature entered at the bottom of the instrument and escaped at the top, thus ensuring that the limb was maintained at a constant temperature up to the time of the readings. The extremity 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. Hand plethysmographs were constructed on the same basis as the foot model, but thin surgical rubber gloves were used in place of socks.

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 reliability 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 or imposed variations, 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 found 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 these extremities, 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, but, even so, a reliable mean measure of the circulation through the feet can only be obtained from a large series of observations. The fluctuations in vasomotor tone and thus in blood flow to the periphery are determined by many factors. The flow may 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 readily be appreciated. It will also be understood that under resting conditions the functions of the circulation to the leg and forearm and the foot and hand differ considerably. Thus the upper part of the forearm or leg, the region normally chosen for the fitting of plethysmographs, consists chiefly of muscle; the skin in this area usually plays a relatively small part in heat elimination (Grant and Pearson (1938)). Waves of vasomotor activity indicating rapidly changing degrees of vasoconstrictor tone are not seen in tracings from these parts (fig. 3). The circulation is chiefly going to skeletal muscle and large fluctuations in a series of readings are not found. Ten consecutive inflow tracings of calf blood flow determined with the water in the plethysmograph at  $34^{\circ}\text{C}$ . gave the following figures:- 2.8, 2.9, 3.0, 3.1, 2.9, 3.2, 3.1, 2.8, 3.0, 3.0; mean 3.0 ml./min/100 ml. of calf tissue; standard deviation 0.1 ml. and coefficient of variation 3.3%. It has been found that after calculating the standard deviation of several series of resting calf and forearm blood flows, the coefficient of variation has not exceeded 10% and in the majority of cases it has been under 5%.

In the hand and, to a lesser degree, the foot, the circulation performs two main functions, namely nutrition of the tissues, and elimination of heat from the skin surface (Grant and Pearson (1938)). 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  $34^{\circ}\text{C}$ . the blood flow readings at half minute intervals

fluctuated greatly. The figures under such circumstances were: 4.8, 4.5, 5.4, 4.3, 6.0, 4.5, 7.0, 4.5, 5.5, 5.3; mean 5.2 ml./min/100 ml. of foot tissue; standard deviation 0.8 ml. and coefficient of variation 15%. An average of ten such readings is obviously of less statistical significance for comparative purposes. The variations in the hand blood flow observed under similar circumstances are considerably greater. If however, a similar series of readings is made with the water in the plethysmograph at  $44^{\circ}\text{C}$ . to ensure full local vasodilatation there is considerably less variation in successive readings (fig. 4). Thus in the same patient the figures for the blood flow in the foot at full vasodilatation were 20.4, 21.4, 20.7, 21.2, 21.4, 20.0, 20.7, 20.2, 20.5, 20.3; mean 20.7 ml./min/100 ml. of foot tissue. The coefficient of variation under these circumstances was 2.4% and in a series of observations on 33 normal feet at full vasodilatation the coefficient of variation has lain between 2% and 12%. It will thus be appreciated that fairly consistent results can be obtained in measuring the blood flow at minute or half minute intervals in the calf and forearm at  $34^{\circ}\text{C}$ . and in the foot at  $44^{\circ}\text{C}$ . The inflow tracings obtained under these conditions are satisfactory. In the case of the muscular parts, a long straight inflow is the rule provided that the plethysmograph is at or slightly above heart level (fig. 5). Even at full vasodilatation in the foot, the venous bed is sufficiently great to permit an even rate of filling over enough pulse beats for an accurate straight line representing the initial inflow to be drawn (fig. 6).

The extreme variability of plethysmographic blood flow determinations in the hand has already been mentioned. These



fluctuations are most pronounced when the bath temperature is at about  $34^{\circ}\text{C}$ . and the subject is kept comfortably warm so that his vessels are neither fully constricted or dilated. Under these conditions a series of readings will show the utmost irregularity. The fluctuations occur in both hands coincidentally (fig. 63) and thus in a simultaneous comparison of two hands from minute to minute these changes are immaterial. They do however, render difficult the calculation of a reliable average blood flow and obviously a very large series of readings must be made. The fluctuations are due to waves of vasomotor activity (fig. 7), partly determined by respiration, and are not seen in sympathectomised hands. With the hand at full vasodilatation the variability of readings is much less, as in the foot, and several readings have been made satisfactorily under these conditions. The venous bed in the hand, however, is relatively small and the period of the tracing that shows a straight line inflow is thus short (fig. 8). In many cases even the first part of the inflow is not straight for more than two pulse waves and no satisfactory line representing the initial arterial inflow can be drawn. It was on account of considerations such as these that the writer always chose, wherever possible, to use a calorimeter for measurement of hand blood flow, as this instrument averages out the fluctuations due to rapidly varying vasomotor tone.

The above conclusions have only been drawn with regard to blood flow determinations made in rapid succession, usually at 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 subjects the readings on the

foot at  $44^{\circ}\text{C}$ . 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 some the flow rose to a maximum in 45 mins. 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 or forearm measured at  $34^{\circ}\text{C}$ . is more constant and this is generally accepted as the best temperature at which to make these determinations (Barcroft and Edholm (1943)). All the results presented have been the average of at least ten and usually fifteen or more readings. In conducting an experiment the variability that may occur in individual readings is illustrated in fig. 9. In all cases the standard deviation (using  $n - 1$ , as the numbers of readings are small) has been calculated, and the results statistically analysed according to the methods of Chambers (1940).

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, but 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 limb, it has been found that in the case of the foot at full vasodilatation the figures on different days agree to within  $\pm 20\%$ . Similarly the heat elimination of the hand at full reflex vasodilatation is remarkably steady in the same individual. Day to day variations in resting forearm blood flow are however more variable even when every precaution is taken to reproduce similar basal conditions.

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  $44^{\circ}\text{C}$  to ensure full vasodilatation.

The readings <sup>in</sup> ml./ min./ 100 ml. of foot tissue were:  
9.9.48. Right foot. 10.4, 10.7, 11.2, 11.3, 11.9, 11.0, 10.7, 10.4, 10.1, 11.0.

Mean 10.9; standard deviation 0.4; foot volume 1,185 ml.

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

Mean 16.2; standard deviation 0.7; foot volume 1,220 ml.

10.9.48. Right foot. 10.7, 10.4, 10.9, 10.2, 10.7, 10.7, 10.8, 11.5, 11.2, 11.5.

Mean 10.9; standard deviation 0.4; foot volume 1,195 ml.

Left foot. 17.9, 16.2, 16.5, 17.2, 18.3, 19.2, 19.0, 17.4, 17.0, 20.4, 18.0.

Mean 17.9; standard deviation 0.8; foot volume 1,200 ml.

The results of blood flow determinations have always been expressed as ml. of blood per minute per 100 ml. 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 ml. on one day and 900 ml. on the following day and to compare the results by dividing the total blood flow in 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 low blood supply, while the toes with their relatively large cutaneous surface and the presence of numerous arteriovenous anastomoses have a large supply. In investigating the foot the upper end of the plethysmograph has been fixed at the level of the ankle joint. When a series of observations has 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. If the two feet are to be compared, corresponding marks are made at the ankle joints after measuring the correct distance above the tip of each medial malleolus. In many of the observations on blood flows 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/100 ml. of tissue. 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 distally a higher proportion of bone and tendon is included and this invalidates the results.

The above points with regard to plethysmography have been stressed particularly with regard to making comparative observations. There are, of course, many other considerations which merit attention if accurate reproducible results are to be obtained. These have been emphasised on many occasions (Lewis and Grant, (1926) Grant (1938), Abramson et al (1939), Wilkins and Eichna (1941), Landowne and Katz (1942)). The warnings of these authorities will not be repeated in detail but they have been carefully studied. The fact that the blood flow is actually expressed in ml. per minute should not blind the investigator to the fact that the results may be extremely inaccurate if all precautions are not rigidly observed. Thus the part being examined must be supported comfortably on sandbags and must preferably be slightly above heart level so that the venous bed is relatively empty. In the forearm and calf the distal circulation must be excluded by a cuff inflated above arterial pressure. If properly applied this does not affect the validity of the results (Kerslake (1949)). The position of the venous occlusion cuff at the proximal side of the plethysmograph is of the greatest importance. If placed near or in contact with the plethysmograph the sudden inflation of the cuff from the air reservoir causes an artefact by displacement of tissue during the initial period of the inflow tracing. If

removed further from the plethysmograph the artefact is largely avoided but the record of the arterial inflow is less as the blood is partly contained in the tissue between the plethysmograph and cuff. In measuring finger blood-flow, Goetz (1946) found that with the venous occlusion cuff at the wrist the value was only a quarter of that obtained with the cuff around the base of the finger. If the necessary observations can be made in one experiment the position of the venous occlusion cuff is not changed. If, however, serial measurements are required on successive days or at longer intervals the position of the cuff becomes of great importance. In such circumstances it was placed 3 cm. proximal to the upper end of the plethysmograph irrespective of any artefact. The blood flow was then calculated from the straight line portion of the inflow tracing immediately beyond any distortion caused by the inflation of the cuff. Several of the original untouched tracings have been included in the thesis. The straight lines drawn through along the inflow plethysmogram and the vertical line for the calculation of the result by the method of Barcroft and Edholm (1943) have also been left to illustrate more fully the method of measurement and to allow assessment of its accuracy.

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 is to shorten the period of the tracing which is a straight line, 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 mm. 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 in mm.Hg.</u>	<u>Blood flow readings in ml. / min. / 100 ml.</u>
90 mm.	21.9, 25.4, 22.0, 20.4.
80 mm.	24.8, 22.5, 24.7, 25.0, 23.3
70 mm.	25.8, 23.9, 24.2, 24.6, 25.2
60 mm.	23.0, 23.4, 22.6, 25.8, 24.6
40 mm.	23.9, 24.2, 24.6, 22.0, 22.4
20 mm.	19.0 (unsatisfactory tracing owing to shortness in 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 mm. 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 mm. 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). The writer always used a venous occlusion pressure of 70 mm. of mercury. In the severest case of arterial disease studied the inflow tracings were similar with venous occluding pressures at 50 and 70 mm. of mercury (fig. 10). As will be shown later there is no doubt that the pressure in arteries distal to an obstruction is 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. This was probably largely due to the fact that the physiological investigations were restricted to the less severe cases of vascular disease. Thus no patients in whom there was any immediate danger of the onset of gangrene were investigated in the plethysmograph. On general grounds it is undesirable to expose an ischaemic limb to a



temperature of  $44^{\circ}\text{C}$ , but in the type of case studied no harm resulted from this procedure. The constancy of readings at full vasodilatation has already been mentioned, but there is another reason why this temperature should be used in the investigation of peripheral vascular disease.

In many investigations the writer has confirmed the observation of Sharpey-Schafer (1949) that the resting blood flow at  $34^{\circ}\text{C}$  may be the same or even slightly higher in a diseased limb than in a relatively unaffected fellow. A possible explanation is that in a case of mild ischaemia an additional blood supply may be provided with the limb at rest to repay debts incurred by previous activity. The main feature of arterial disease is 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  $44^{\circ}\text{C}$  to ensure full vasodilatation the flow may be found to have increased fivefold above that at  $34^{\circ}\text{C}$ . 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  $43 - 44^{\circ}\text{C}$ , 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. The maximal blood flow into the foot after release of the circulation is recorded and measurements are subsequently made at half minute intervals. 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 is repaid (Abramson et al., 1941). The writer has also confirmed the observations of Eichna and Wilkins (1941) that a small change of temperature has relatively little effect on the magnitude of the reactive hyperaemia blood flow. This was accordingly always determined at a local temperature of  $34^{\circ}\text{C}$ . The blood flows in the foot measured at  $44^{\circ}\text{C}$  and during the height of reactive hyperaemia were usually similar. As both measurements were made at full vasodilatation, this was regarded as the maximal circulatory capacity of the foot (Landowne and Katz, 1942). Whenever possible, in investigating the foot the writer has preferred the method of measuring the maximal circulatory capacity at  $44^{\circ}\text{C}$ . Several successive readings are then

possible and an average may be taken. Using reactive hyperaemia it is only possible to repeat the observations once or twice owing to the discomfort caused the patient by the period of arterial occlusion and the delay between the readings. Similar considerations apply in measuring the calf blood flow in cases of vascular disease. Even in patients complaining of severe intermittent claudication on exertion the resting blood flow through the calf, measured plethysmographically at  $34^{\circ}\text{C}$ , may be found to be within normal limits. In these cases it is not satisfactory to make the measurements at  $44^{\circ}\text{C}$ , as this will not bring about full vasodilatation in the deeper arteries supplying the muscle. The greatest stimulus to dilatation of these vessels is exercise, and accordingly measurements have been attempted after a standard period of exercise consisting in contracting the calf muscles to plantar-flex the foot against a known weight once per second. The investigation was technically difficult. The results have been found very variable and it has not been possible to draw any satisfactory conclusion (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 has consistently shown a reduction in the maximum flow attained in comparison with a healthy fellow limb, and is more easily carried out than the test after exercise. Recent improvements in technique by Shepherd (1950) and by Barcroft and Dornhorst (1949) may simplify blood flow investigations during and after exercise.

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 maximal circulatory capacity of the part. In other words, the first feature of the pathological physiology of vascular disease is a reduction in the circulatory reserve of the limb. As the disease progresses, the reserve circulatory capacity is steadily decreased, 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 et al., 1935) and the results do not represent the maximal circulatory capacity of the



part. The development of pain may be very troublesome while attempting to measure the circulation in feet at  $44^{\circ}\text{C}$ . 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 the maximal circulatory capacity can be ascertained either by applying the reactive hyperaemia test with the plethysmograph at  $34^{\circ}\text{C}$  <sup>or</sup> by raising the temperature in the plethysmograph in a series of steps. Thus the initial observations are made at  $34^{\circ}\text{C}$ . The temperature is then increased to  $38^{\circ}$  and further readings are taken. Thereafter rises are made to  $40^{\circ}$  and  $42^{\circ}$ . 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 or no increase after the steps to  $38^{\circ}$  and  $40^{\circ}\text{C}$ . The blood flow at the stage beyond which no further increase is apparently possible may be considered the maximal circulatory capacity of the foot. The level attained by this method should be compared with the reactive hyperaemia flow. The gradual raising of temperature is only satisfactory when there is a general reduction in blood flow to the foot. If the pain arises from a small ischaemic part such as a toe the maximal circulatory capacity can only satisfactorily be estimated by the reactive hyperaemia test.

The blood flow through an artery depends chiefly 39  
on the calibre of the vessel, the pressure within it  
and the viscosity of the blood. Changes in viscosity  
are probably not of great importance in obliterative  
vascular disease. According to the law of  
Poiseuille (1843) the volume of the blood flow varies  
as the product of the effective pressure and the  
fourth power of the radius of the artery. While  
this forms the essential basis for determining the  
circulation to a part, it must be realised that there  
are numerous other factors (Bradley, 1948). In a  
study of the pathological physiology of obliterative  
arterial disease it is desirable to know not only  
the flow but also the pressure within the affected  
vessels. The latter quantity is difficult to  
determine. Beyond an obstruction the flow is  
frequently non-pulsatile and methods dependent on a  
cuff are thus completely unreliable. Direct  
measurements by inserting a needle into the artery  
have been attempted (Sharpey-Schafer, 1948), but it  
is difficult to be certain as to how representative  
a reading they afford as the needle-tip may be  
partially embedded in thrombus, and the proximal and  
distal connexions of the chosen artery are unknown.  
Furthermore, it was not considered desirable to  
attempt to insert needles that might cause further  
damage to already unhealthy arteries. These  
considerations led the writer to seek an alternative  
method of indirect measurement of the effective  
pressure within the arteries of the foot as a whole.

The conspicuous pallor that may develop on elevating feet supplied by partially obstructed arteries has long been recognised as a clinical sign. This change is presumably due to a greater relative drop in the effective perfusing pressure in the arteries of the feet of patients with disease. This feature and the observation of the rapid onset of gangrene in an ischaemic limb when the foot of the bed was raised on ten-inch blocks to drain oedema fluid promoted the idea of studying the reduction in blood flow brought about by postural changes. A series of experiments was accordingly designed to measure the decrease in blood flow in the normal foot effected by elevating the lower limb a known amount. A relationship between flow and pressure might thus be established and the method extended to the study of peripheral vascular disease.

It can be shown that by raising the feet to a height of 190 mm. above the heart level the blood pressure in the arteries of the feet will be reduced by the effects of gravity by a known amount provided that the blood pressure in the aorta remains constant. The pressure in the brachial artery was measured before and after this manoeuvre. Assuming that the specific gravity of blood is 1.06 and that of mercury 13.6 the reduction may be expressed as  $190 \times \frac{1.06}{13.6}$  or 15 mm. of mercury. The observations of the blood flow were made with a local temperature of  $44^{\circ}\text{C}$  in order to ensure constant full vasodilatation. Five readings were obtained with the

leg level; the foot was then raised 19 cm. and a further ten tracings were recorded; finally, five readings were again made with the leg 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 thus available and the percentage decrease of the blood flow in the elevated position was calculated. Equally satisfactory inflow tracings could be obtained in the level and elevated positions (fig.11). 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. It involves the assumption that the pressure in the artery at the root of the lower limb is similar to that in the brachial artery. This is almost certainly not the case as the femoral artery pressure is usually higher. These studies were carried out before the capacitance manometer was available for the direct measurement of femoral arterial pressure. Nevertheless, except in cases of



coarctation of the aorta there is probably a fairly constant relation between brachial and femoral artery pressures (Green et al. 1947). The percentage reduction in blood flow was plotted against the calculated percentage reduction in arterial blood pressure using measurements obtained in normal and hypertensive patients without evidence of occlusive vascular disease (fig.45). It will be appreciated that if the arteries and arterioles behaved as rigid tubes the decrease in blood flow would be exactly proportional to the decrease in pressure and the points would lie on a straight line at  $45^\circ$  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 rather less. It is probable that their arteriolar walls are considerably thickened. The evidence at present available suggests that the proportionately greater fall in blood flow is due to a passive collapse of the arteriolar walls with the decrease in pressure. The flow of a fluid through a rigid tube varies as the fourth power of the radius of the lumen so that even a small decrease in the calibre of the arterioles on raising the feet would account for a considerable fall in blood flow.

In this investigation the feet were always elevated a standard amount to produce a fall of approximately 15 mm. of mercury in pressure. The

experiments were repeated in five subjects raising the feet to different heights. A height of above 25 cm. was not possible with the plethysmograph. A similar distribution of points was obtained, except that with the lesser degrees of elevation a rather greater decrease in flow was obtained. As these experiments were carried out in normal subjects this presumably represented a greater degree of passive arteriolar collapse than occurred in hypertensive subjects. In studying cases of peripheral vascular disease the standard technique of raising the foot 19 cm. was used in most investigations. In these cases it will be obvious that if the pressure in the arteries of the foot is disproportionately low owing to disease the observed flow on elevating the foot will be decreased below the normal. The results obtained under these circumstances will be described in the next section.

A modified plethysmograph may be used in a different manner for the determination of digital artery pressure. Information of this nature was required in an investigation of unilateral finger clubbing. The systolic pressure was determined in the digital arteries at the bases of the fingers by using a pneumatic cuff and a small finger tip plethysmograph. Cuffs 2 cm. in width were fitted around the proximal phalanges, and air-containing plethysmographs over the distal two phalanges. The pulsations in the finger tip were transmitted through

an entirely air-conducting system constructed from wide bore rubber tubing to a soap bubble volume recorder, and photographed (Greenfield, 1948). The principle is thus similar to that in Goetz's plethysmograph which, however, with its low frequency heavily damped spirit-column recording system cannot give accurate information regarding pulsations (Wiggers, 1947). The soap bubble system with its high frequency response is considerably more reliable. By inflating the cuffs above systolic pressure and then reducing the pressure slowly it was possible to determine the level at which pulsations first appeared in the soap bubble. This was taken to represent the systolic pressure in the digital arteries at the base of the finger. As it was not possible to photograph records from two soap bubble volume recorders simultaneously the following procedure was adopted. Both plethysmographs were connected by tubing of equal length and bore (1 cm. in diameter), through a Y-piece to one bubble recorder, and clamps were fitted to shut off each finger in turn. To change the reading from one finger to the other required about 10 seconds. The pressure in the cuff controlled from an air reservoir was reduced until pulsations were seen and recorded on one side. Switching over to the opposite side where the pressure was thought to be lower it was possible to demonstrate complete absence of pulsations, but on returning to the first side to show that pulsations were still present.

The observations were repeated at lower cuff pressures until pulsations were recorded from both fingers. By this method records were obtained of the digital artery pressures in the two hands. This was the only occasion on which an air-conducting plethysmographic system was used. It should be appreciated that the physical properties desirable for the measurement of pulsations are more exacting than those required for the determination of a steady increment in volume.

Plethysmography has many applications in clinical research and, provided always that proper precautions are taken, it can provide detailed and accurate information regarding peripheral blood flow. It is, however, a tedious and time-consuming technique. The estimation of the maximal circulatory capacity of 33 normal feet required the registering and subsequent measurement of approximately 1,000 inflow tracings. Estimations of blood flow are not readily made outside the laboratory where the kymograph and the rest of the equipment are kept. The calorimeter, on the other hand, is readily transported to the ward. Plethysmography is thus essentially a method for research and not for routine clinical use.

In the majority of the experiments and observations the blood pressure has been measured in the brachial artery by the ordinary cuff sphygmomanometer. This is a convenient method but has the disadvantages of giving no graphic record



of the results and of interfering with the flow of blood while the reading is made. Accurate assessment of the diastolic pressure is difficult especially when there is considerable peripheral vasodilatation. During infusions of adrenaline it was often found impossible to obtain any reliable readings as sounds were audible over the brachial artery even when the pressure in the cuff was zero. For these reasons and in order to obtain a graphic record of the pulse wave form, direct methods of arterial pressure recording were developed. The first attempts were made with a modified Hamilton manometer (Hamilton et al, 1934) and the equipment constructed in the laboratory was tried out on an anaesthetised cat. This model was, however, not considered satisfactory for use on a human subject. An attempt was then made to construct a Wigger's manometer (Wigger, 1926) but this was no more satisfactory and it was felt that neither type of instrument was suitable for the experimental observations lasting an hour or longer which were essential in some of the work contemplated. These membrane manometers were fitted with mirrors and the moving beam of light was photographed. The difficulties and objections with regard to them may be summarised as follows:-

1. The manipulation of the mirrors in order to direct the light beam onto the camera is extremely tedious and difficult even with fine screw

adjustments. The arterial wall. It was thus

2. The fitting of a front surface mirror to the metal (Hamilton) or elastic (Wiggers) membrane tended to interfere with the performance of the instrument.

3. A membrane sufficiently stiff to give the high frequency response necessary for adequate measurement of pressure (Wiggers, 1926) always gave too low a sensitivity with a beam of light of convenient length for easy manipulation in a clinical laboratory.

4. The alteration in volume with pressure changes tended to be high and led to an increased moving mass within the hydraulic system. Blood thus entered into the needle with the consequent danger of clot formation. A good manometer should accordingly be designed to have a high volume modulus of elasticity to prevent these complications.

5. The needle penetrating the artery had to be connected to the membrane manometer by piping which could not conveniently be reduced below 50 cm. in length. The hydraulic system was thus unduly great in volume, a fact which interfered with the accurate registration of the pulse wave pattern. The lead tubing formed a relatively rigid system allowing the subject practically no movement throughout the period of the experimental observations. Any slight change of position might lead to displacement of the needle out of the artery

or damage to the arterial wall. It was thus considered unsafe to use either the Hamilton or Wiggers type of manometer for the rather long observations required in the study of experimental hypertension.

Two other methods for direct recording of arterial pressure have been described, using either the Statham strain gauge (Green et al, 1947), or a variable electrical capacitance system. The writer has no personal experience of the former method and his efforts have been entirely directed to the development of a suitable capacitance manometer. The principle of this method is that a diaphragm acts as the movable plate of an electrical capacitance; changes in pressure thus bring about alterations in the capacity of the condenser. The parts of the manometer may be grouped as follows:-

1. A hydraulic system with a needle for arterial puncture at one end and the metal diaphragm at the other.
2. A radiofrequency oscillator.
3. A differential voltage amplifier.
4. A cathode ray oscillograph.
5. A recording camera.

Manometers of this type were first developed for measuring pressure in engine cylinders (Brookes-Smith and Colls, 1939), and later for arterial pressure pulse records (Lilly, 1942; Buchtal and Warburg, 1943; Skouby, 1945; and Peterson et al, 1949) It will be noted that while the original

application in engineering was British in origin the subsequent development of its use in human subjects has been entirely in American and Danish hands. Its introduction to British medical science is thus long overdue.

The arrangement of the electrical side of the apparatus was entirely in the hands of Mr. D.A. Tanfield of the Physics Department, St. Mary's Hospital Medical School and of Mr. C.H. Brookes-Smith of Southern Instruments Ltd. This part of the apparatus will not be described in detail. The hydraulic system was designed and constructed by the writer in conjunction with Dr. R.B. Blacket. The condensor gauge was connected through a three-way tap with an 18 gauge record needle which was inserted into the artery. The membrane of the condensor gauge was thus only 8 cm. from the tip of the needle. The gauge itself, being extremely compact and cylindrical in shape, measuring 2.5 cm. x 1.5 cm. in diameter, was readily supported by a small wedge-shaped block on the thigh. The third limb of the tap was connected by rubber tubing through a bottle containing heparin-saline solution to a hand pressure bulb and a mercury manometer. The condensor gauge was linked by a flexible cable to the oscillator.

Before use the whole hydraulic system must be filled with saline solution containing heparin. It is highly important to exclude any air bubbles as their presence will entirely invalidate the pressure tracings. The gauge was filled from a syringe



fitted with a fine hypodermic needle which could be swept around all the crevices to dislodge any bubbles. It was then screwed onto the three-way tap while fluid was actually flowing through the tap from the bottle. Subsequent testing for the absence of air bubbles and leaks was carried out by immersing the tap and needle in sterile saline and applying a negative pressure to the bottle. Changes in the shape of the pulse wave and in the response to sudden pressure alterations also reveal the presence of air bubbles as they lead to a considerable lowering of the volume modulus of elasticity. The hydraulic chamber of the condensor gauge was sterilized by exposure to formalin vapour and the rest of the hydraulic system by boiling. The needle was inserted under local anaesthesia into either the brachial or femoral artery. The latter was the easier procedure. The form of the pulse wave was studied on the oscillograph screen and the position of the needle adjusted until the greatest amplitude of the wave was obtained. This observation was essential as the commonest source of error was found to be displacement of the needle, so that the aperture lay against the arterial wall and the pulsations were thus considerably damped. Once the needle was shown to be well within the lumen the gauge was fixed to a suitable wedge on the thigh with adhesive strapping and left undisturbed till the conclusion of the observations. The needle

was periodically flushed from the saline reservoir by raising the pressure in the bottle above systolic and placing the tap openings in the appropriate position. This precaution, however, was found to be hardly necessary as the calculated volume displacement coefficient was approximately  $10 - 6$  ml. / 100 mm. of mercury and the movement of blood into the tip of the needle during systole was thus minimal. On no occasion was any trouble experienced with clotting, and immediately after flushing no difference was noticed in the pulse pressure wave form showing that no thrombus was developing. Before and after each experiment a static calibration of the instrument was carried out against the mercury manometer, the precaution being taken to have the gauge and the upper level of the saline at the same height. Ascending and descending calibration points were recorded to detect any hysteresis in the gauge. A typical calibration curve is shown in figure 12. It was essential to check for zero drift due to temperature changes at the end of the series of observations, but this was not a troublesome feature as the temperature coefficient of capacitance was less than  $4 \times 10 - 6$  per degree C.

The absolute accuracy of a capacitance manometer system for determining and following rapid changes in blood pressure is extremely difficult to assess. Ideally it requires study of the response to square



pressure waves, but these are difficult to generate and an opportunity to attempt this test was not open to the writer. Arrangements are, however, being made for this to be done in the laboratories of Southern Instruments Ltd. From the physical point of view it was accordingly necessary to rely on the information obtained from the calculation of the free period of the instrument. With the hydraulic system entirely filled with saline the 18 gauge needle was inserted into the lumen of a piece of rubber tubing also filled with saline and connected to a mercury manometer. The pressure in the tubing was raised to 200 mm. of mercury and with the camera running at its maximum speed the tubing was sharply withdrawn from the needle point. The pressure at the needle tip was thus suddenly reduced to atmospheric. A 50 cycle per second ripple introduced into the record was used as a time marker and it was thus possible to calculate the free period of the instrument and the duration of the period of decline of pressure (fig.13).

The free period of the instrument determined with the 18 gauge record needle in position was about 100 cycles per second. Experiments with a variety of needles showed that the bore and length of the needle were the chief factors in limiting the free period. The wider and shorter the needle the more accurate are the records obtained but in actual practice it was not considered advisable to use a needle larger than the 18 gauge record pattern for the arterial puncture.

The influence of the length and diameter of the passage between the needle tip and the condenser on the performance of the instrument has not been realised by many workers though it was demonstrated clearly by Lilly (1942). The use of a long length of fine polythene tubing or lead piping will detract from the desirable physical properties of the manometer.

Such were the purely physical tests carried out on the instrument. It is, however, obviously possible to check the readings of the capacitance manometer against other blood pressure recording instruments. In human subjects the needle was inserted into one brachial artery and an ordinary cuff sphygmomanometer was applied to the other arm. The readings obtained in such experiments were comparable within the range of variation obtained between right and left arms. The capacitance manometer, however, was more conveniently used for recording femoral artery pressure, which was usually slightly above brachial artery pressure. The instrument was also used in cats in which the carotid pressure, measured directly by mercury manometer, and the mean femoral, determined by the capacitance manometer, were compared. These were shown to be similar at varying levels of pressure produced by different drugs.

The capacitance manometer has numerous advantages over other methods of intra-arterial pressure recording. No rigid tube fixes the patient to the electrical side of the equipment. The movement of fluid within the



needle is so slight that it can be left in place for an hour or longer without any danger of clot formation. Only very occasional flushings with heparin saline solution was required. The inclusion in the d - c amplifier of a low pass filter which can be switched into the circuit as required provides a convenient method of recording the mean intra-arterial pressure by continuous electrical integration (fig. 14).

The instrument used by the writer was largely constructed from parts designed primarily for engineering use. Many improvements on the technical side became apparent during the experiments, particularly with regard to the design of the gauge for easier filling and sterilization. The cable link and position of the oscillator also required reconsideration. The construction of a suitable cable is one of the greatest problems in this type of work. It has to be reasonably light and flexible, but yet of low and constant capacity. The connecting cable itself inevitably has a certain capacity and bending may increase its capacity and cause an error as great as 5 per cent of the mean pressure. In the apparatus used by the writer it was thus essential that the patient lie relatively still and that the condenser gauge and oscillator were not moved during the observations. It is intended to build a small oscillator which can be attached directly to the condenser gauge and mounted on the thigh or forearm. The difficulty with the capacity of the cable could

thus be overcome and the instrument be used for recording pressure during graduated exercise.

The instrument was developed in conjunction with Southern Instruments Ltd. who kindly lent some of the recording equipment. This firm is now attempting to produce commercially, on the lines described above, a capacitance manometer suitable for human use.

#### S U M M A R Y.

The methods of performing the reactive hyperaemia and fluorescein tests have been described. Adequately controlled conditions for measuring the circulation times were essential and the tests were best performed at full vasodilatation.

The exercise tolerance test performed by walking the patient over steps till claudication developed should be repeated frequently as spontaneous fluctuations are common.

The construction and use of a calorimeter suitable for the hand has been described. The precautions necessary in the use of this instrument have been listed in detail. If serial observations are to be made the same volume of hand must be inserted on each occasion.

Plethysmographs were constructed for the forearm, leg, foot and hands. The necessary measures for ensuring accurate readings on different occasions were outlined. In investigating vascular disease it is essential to determine the maximal circulatory capacity

of the part as the first sign is a reduction in this reserve. The maximal flow in the foot may be measured either by ensuring full vasodilatation by local heat or during reactive hyperaemia. In the calf the reactive hyperaemia test is a simpler method than measuring the flow after exercise.

The blood flow in the foot at full vasodilatation was measured with the leg in horizontal and elevated positions. The decrease in the foot blood flow was due to a drop in intravascular arterial pressure and to secondary passive collapse of the arterioles.

A finger air-conducting plethysmograph designed for measuring digital arterial pressure was described. The pulsations were transmitted to a soap bubble volume recorder.

An electrical capacitance manometer was constructed for the measurement of intra-arterial pressure. Its use, advantages and limitations were outlined.

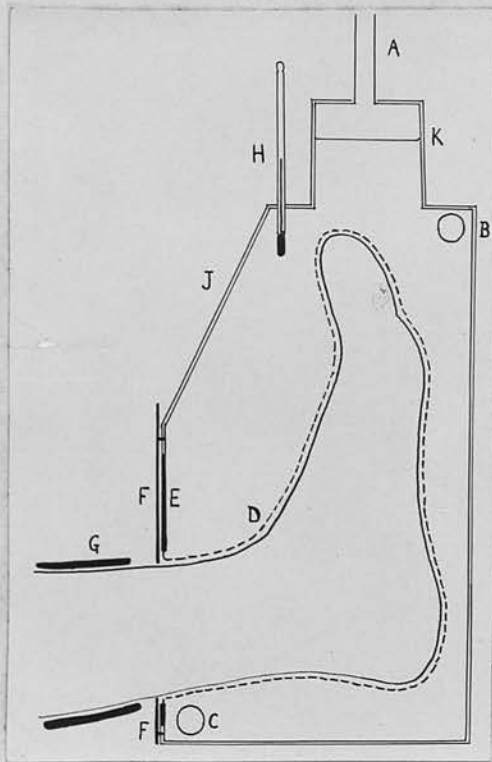


Fig. 1. Diagram of foot plethysmograph.

A. connexion to volume recorder.

B. water outlet.

C. hot water inlet.

D. rubber sock collapsed onto skin of foot.

E. rubber diaphragm.

F. adjustable sliding plate to prevent bulging of diaphragm.

G. venous occlusion cuff.

H. thermometer.

J. celluloid wall of plethysmograph; the layer of cork insulation outside the celluloid is not shown.

K. upper level of water.



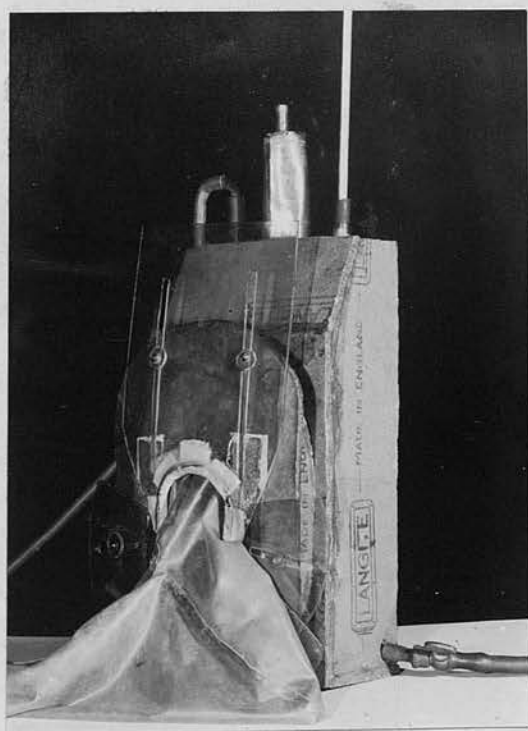


Fig. 2. Photograph of foot plethysmograph. The rubber tubing with brass taps is connected to the inlet for water. The rubber sock is turned inside out in front of the plethysmograph. The adjustable celluloid plates can also be seen.

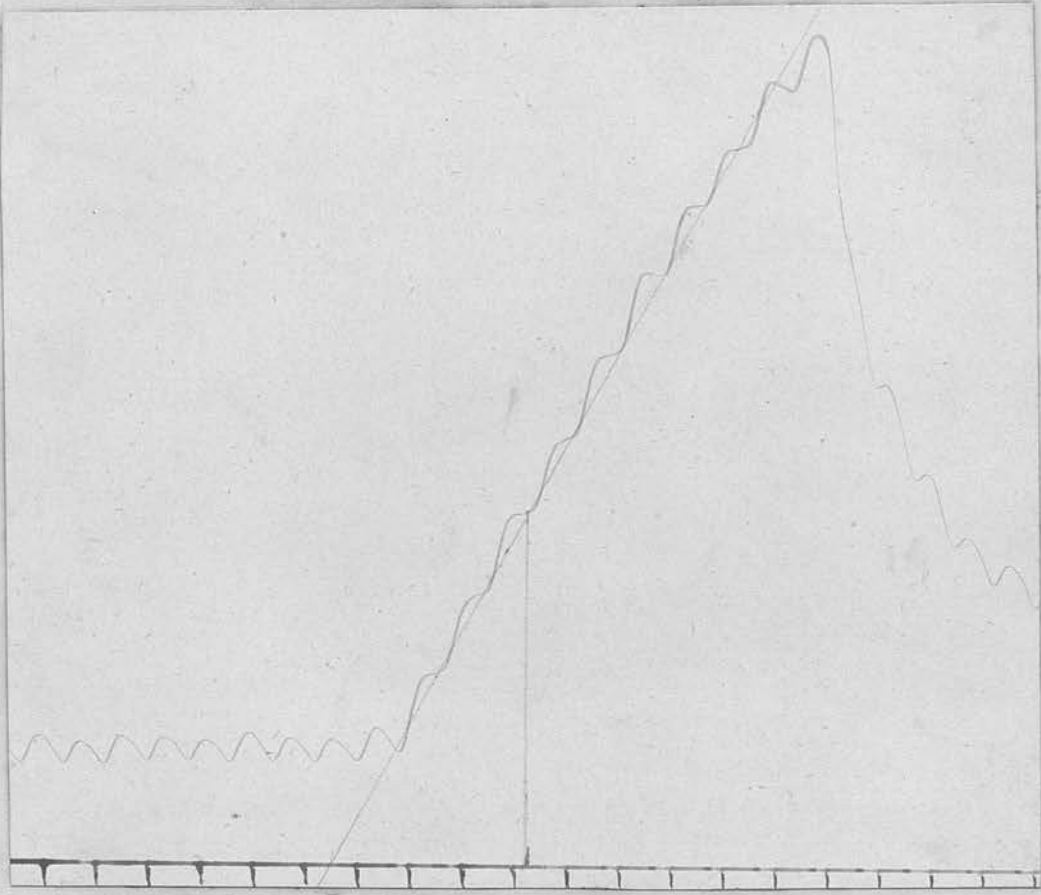


Fig. 3. Forearm arterial inflow tracing. The long straight base line before inflating the venous occlusion cuff shows no evidence of fluctuating vasomotor activity with the plethysmograph bath temperature at  $34^{\circ}\text{C}$ . Blood flow 4.5 ml./min./100 ml. Time marker 1.5 sec.

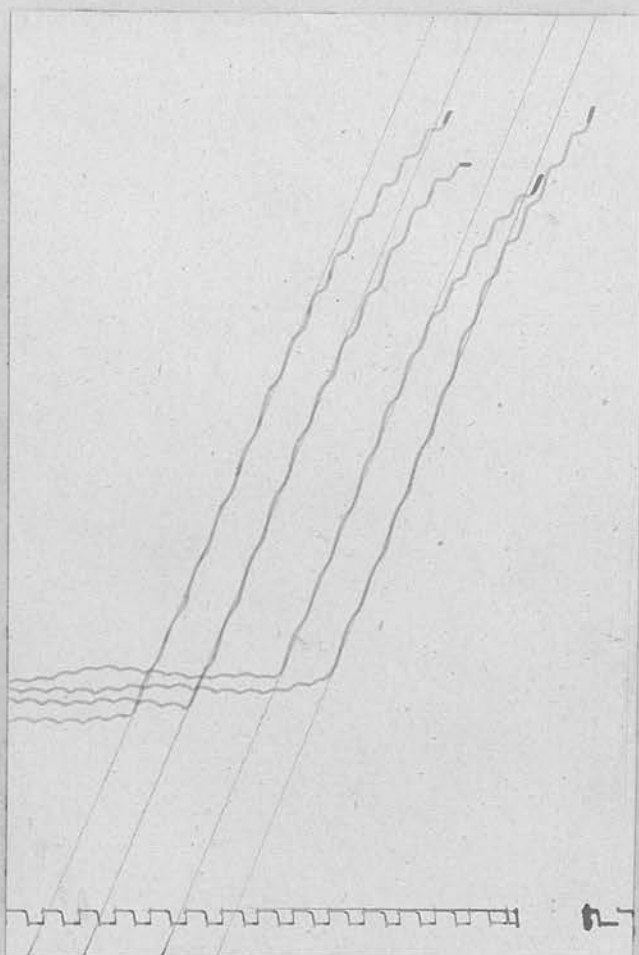


Fig. 4. Foot arterial inflow tracings as obtained by venous occlusion plethysmography with the water bath temperature at  $44^{\circ}\text{C}$ . to ensure full vasodilatation. The tracings have been obtained in close proximity by rewinding the kymograph to allow comparison. The rate varies from 19.6 to 20.5ml. At full vasodilatation the rate of blood flow is relatively constant and reproducible results are usually readily obtained. time marker 1 sec.

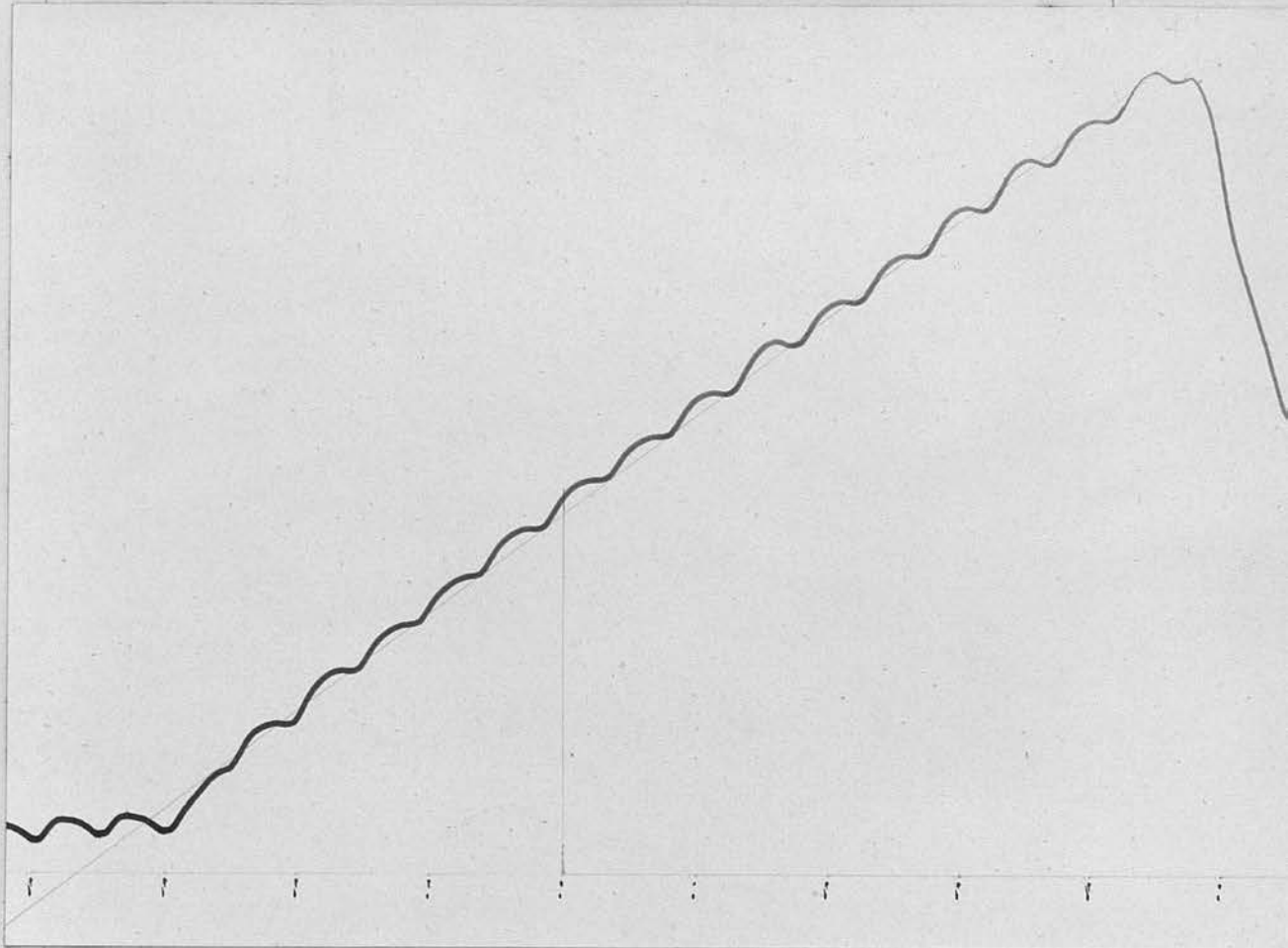


Fig. 5. Typical forearm arterial inflow tracing as obtained by venous occlusion plethysmography. Inflow rate 4.7 ml./min./100 ml. Note the long straight inflow allowing an accurate straight line to be drawn through the tracing for measurement. Time marker 1.5 sec. Plethysmograph water bath temperature 34°C.



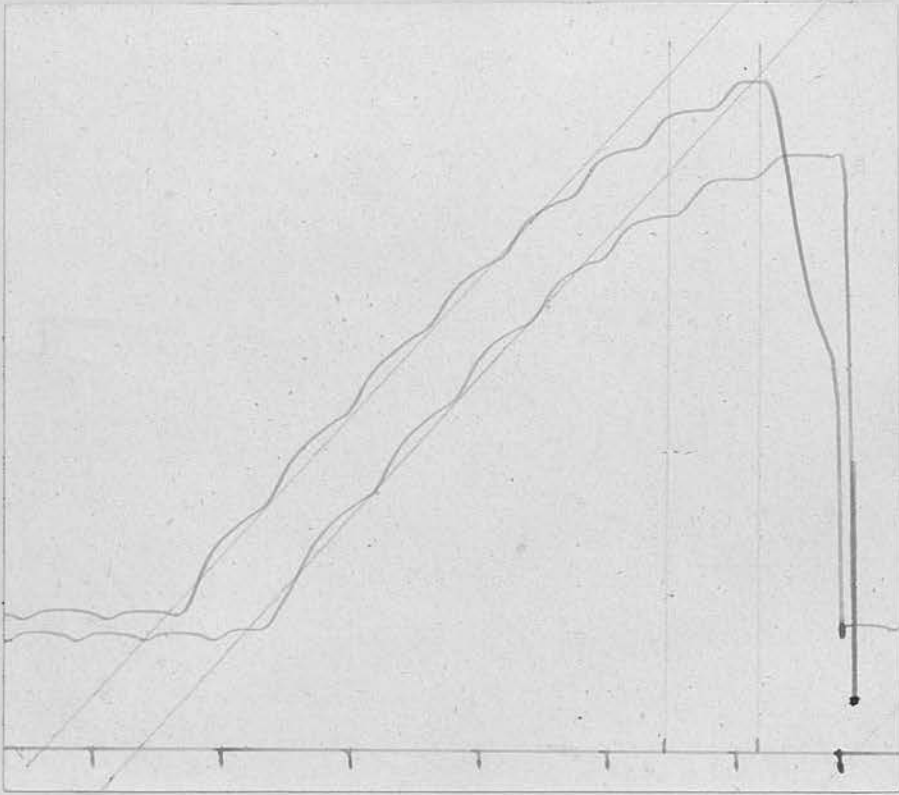


Fig. 6. Two foot inflow tracings with the plethysmograph bath at  $44^{\circ}\text{C}$ . At full vasodilatation it is possible to draw a long straight line through the first three or four pulse beats before the venous bed is filled to capacity. Blood flow 17.9 and 17.8 ml./min./100 ml. of foot. Time marker 1.5 sec.

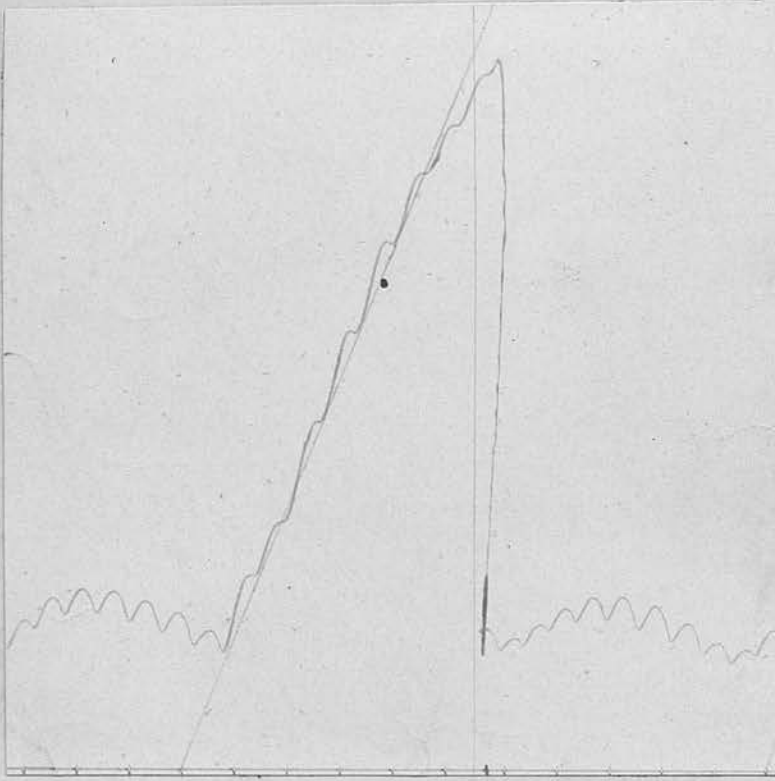


Fig. 7. Typical hand arterial inflow tracing as obtained by venous occlusion plethysmography. Plethysmograph temperature  $34^{\circ}\text{C}$ . Waves of vasomotor activity can be seen on the tracing accounting for the variability of readings at this temperature. Blood flow  $20.0 \text{ ml./min./}100 \text{ ml. of hand.}$  Time marker  $1.5 \text{ sec.}$

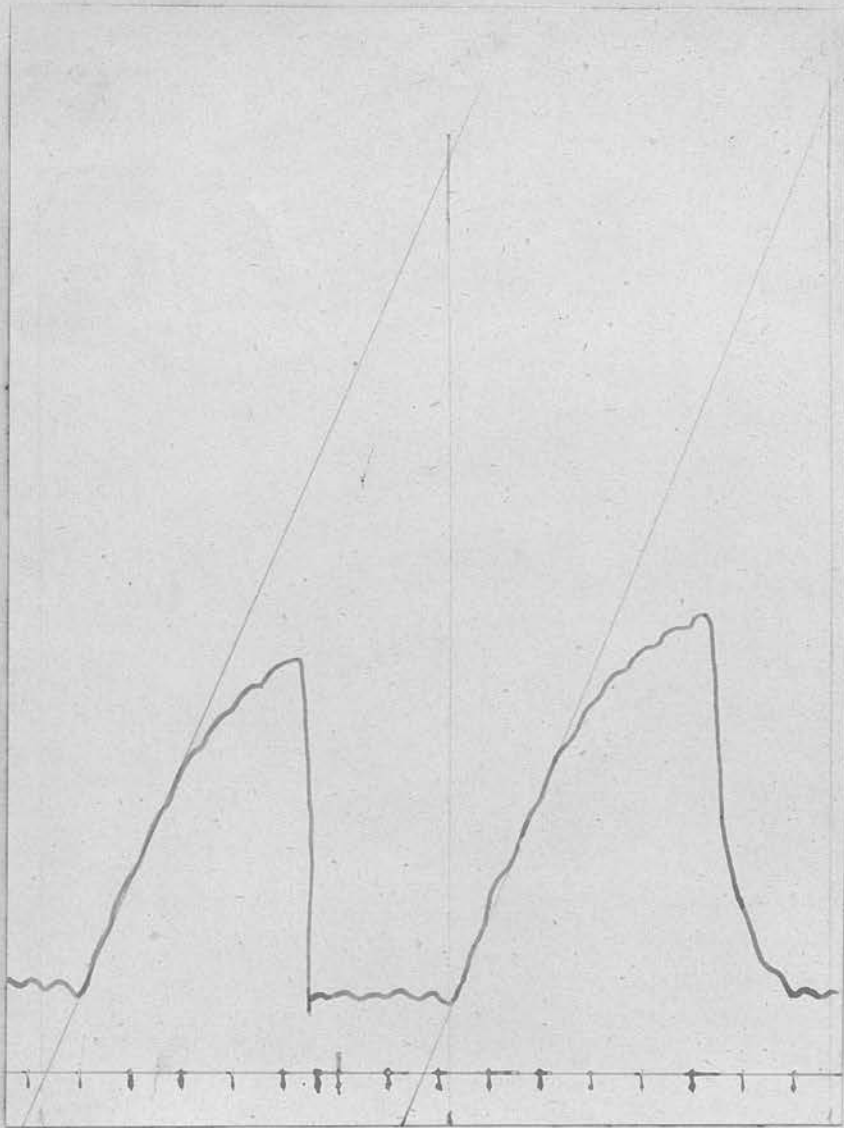


fig. 8. Typical hand arterial inflow tracings as obtained by venous occlusion plethysmography. Hand at full vasodilatation obtained by plethysmograph water bath temperature at  $44^{\circ}\text{C}$ . First tracing inflow rate 25.2 ml./min./100 ml. Second tracing 26.9 ml./min./100 ml. Note straight line inflow for the first three or four pulse beats. Time marker 1.5 sec.

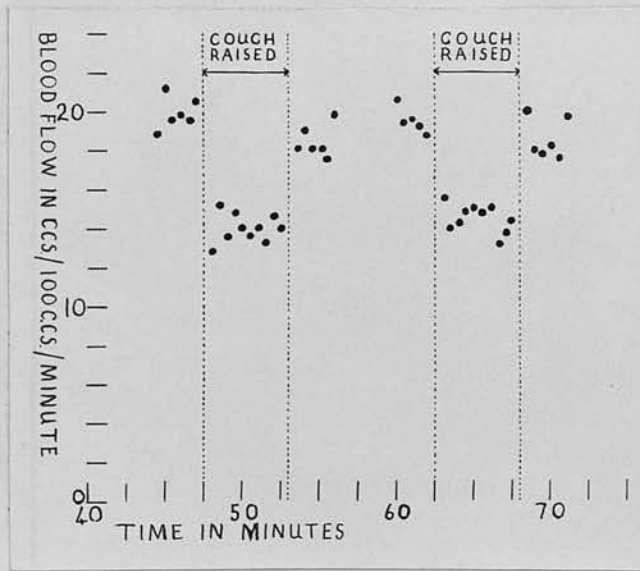


Fig. 9. An experiment on a normal subject showing the effect on the blood flow of raising the foot 19 cm. above heart level. The individual readings as measured in the plethysmograph at  $44^{\circ}\text{C}$  are plotted. In this experiment the whole examination couch was tilted by raising the end on blocks. A similar decrease in flow is obtained by raising the leg alone.



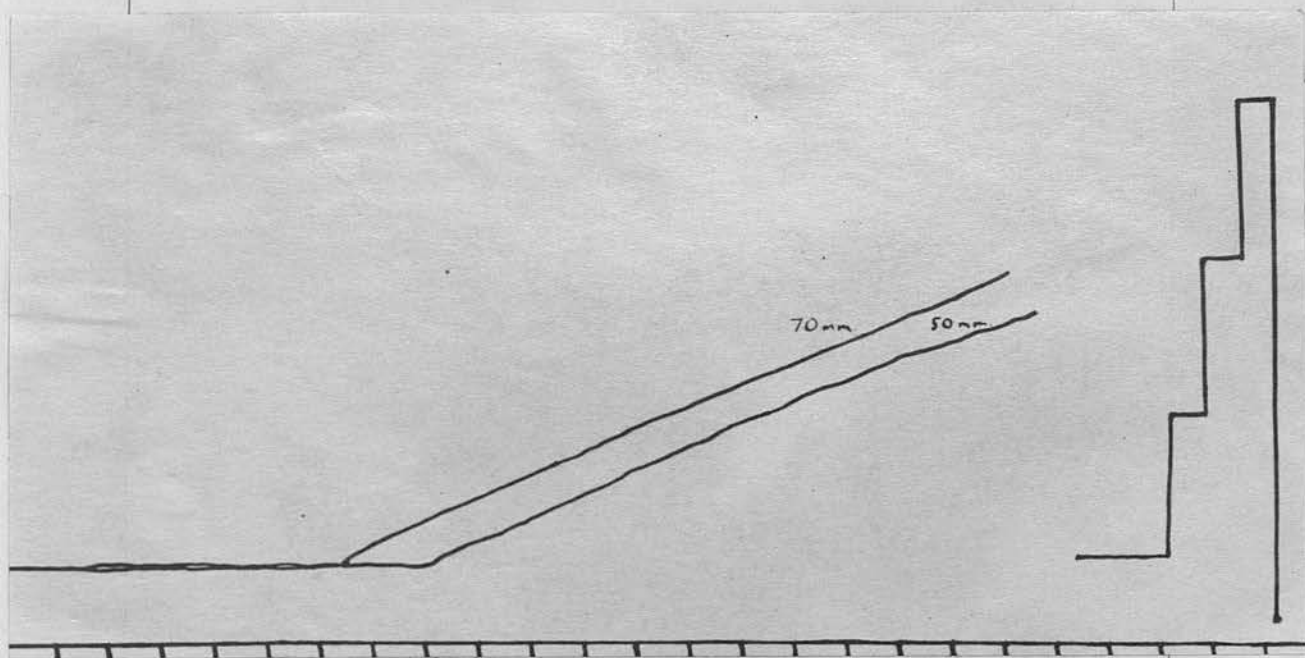


Fig. 10. The blood flow in the foot of a patient with advanced thromboangiitis obliterans in whom sympathectomy had been performed. The tracings were made using 70 mm. and 50 mm. of mercury pressure in the venous occlusion cuff with similar results. Plethysmograph temperature  $34^{\circ}\text{C}$ . Time marker 1.5 sec. The calibration of the volume recorder shows increments of 5 ml. The blood flow was 3.8 ml./min./100 ml. of foot.

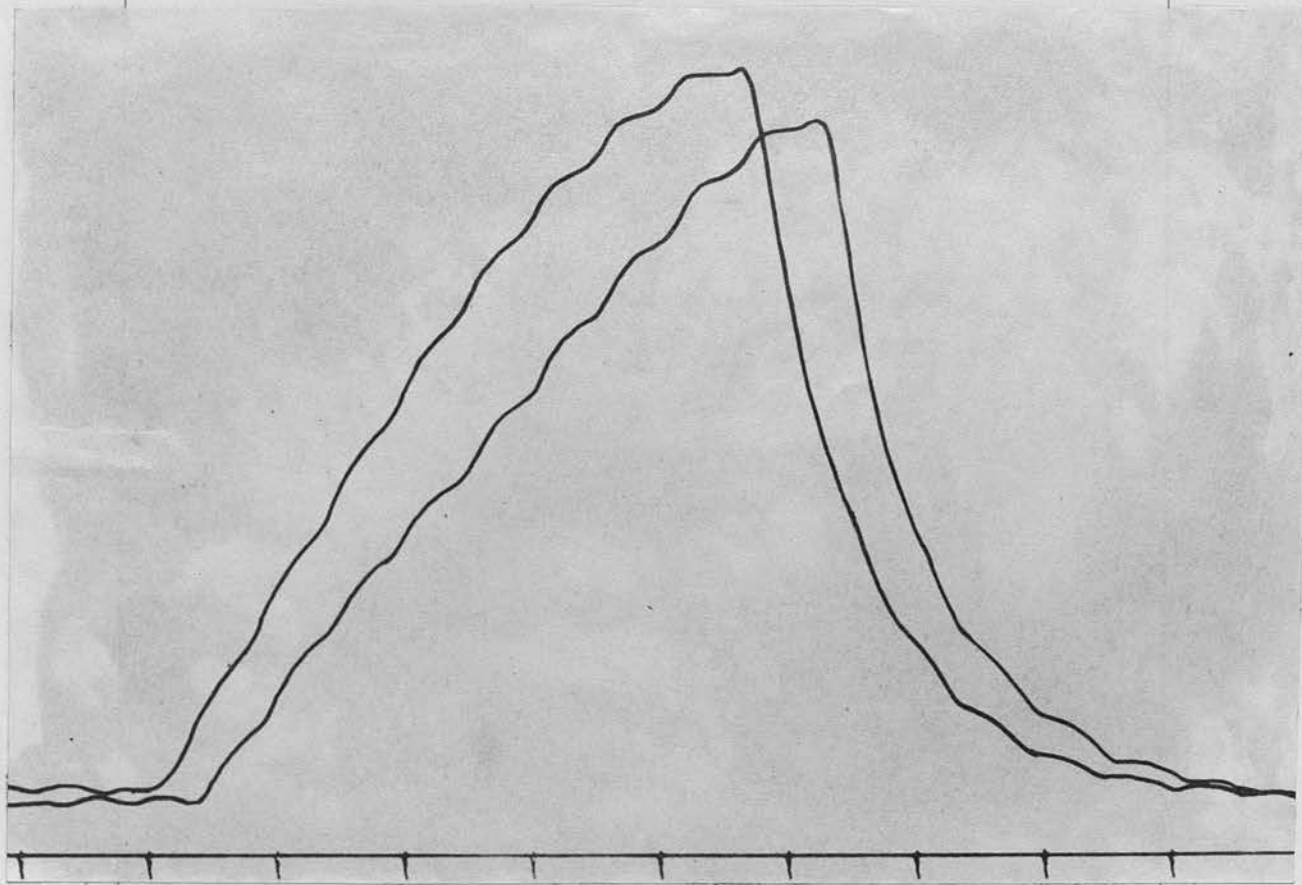


Fig. 11. Arterial inflow tracings with the leg in the horizontal and elevated positions. Foot blood flow 19.8 and 14.1 ml./min./100 ml. Plethysmograph temperature 44.0°C. Time marker 1.5 sec. In second tracing foot elevated 19 cm.

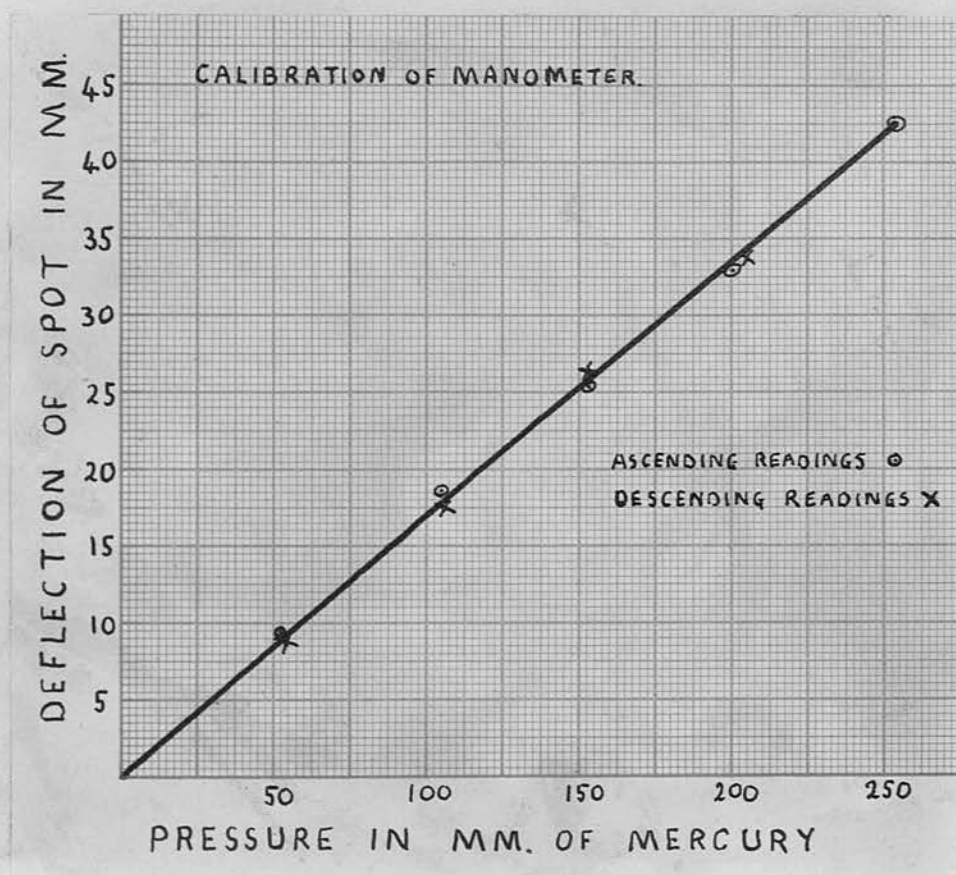


Fig. 12. Calibration of capacitance manometer against a mercury manometer. Ascending and descending readings are recorded to detect any hysteresis. The calibration is almost linear to 250 mm. but falls off beyond that point.

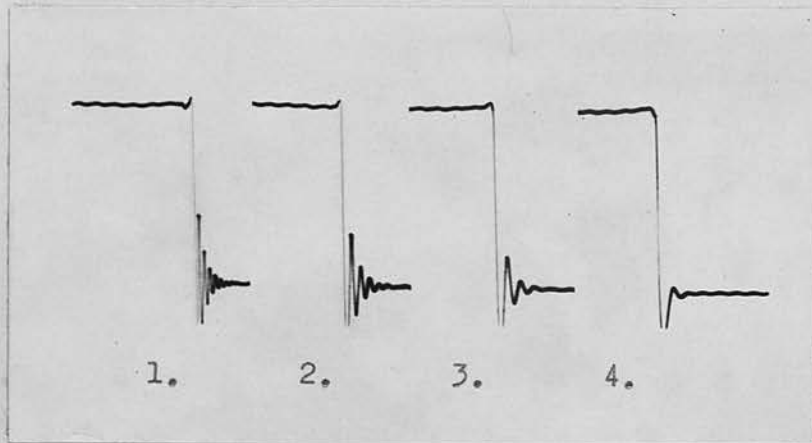


Fig. 13. Determination of the natural frequency of the capacitance manometer using needles of different gauge. The pressure in the system was suddenly dropped from 200 mm. of mercury to zero and the free period was determined from the subsequent oscillations. The 50 cycle per second ripple in the base line served as a time marker. The natural frequency with the different needles was:

1. 16 s.w.g. needle 200 cycles per second.
2. 18 s.w.g. needle 100 cycles per second.
3. 22 s.w.g. needle 75 cycles per second.
4. 26 s.w.g. needle 50 cycles per second.

For all the arterial pressure records an 18 gauge needle was used.



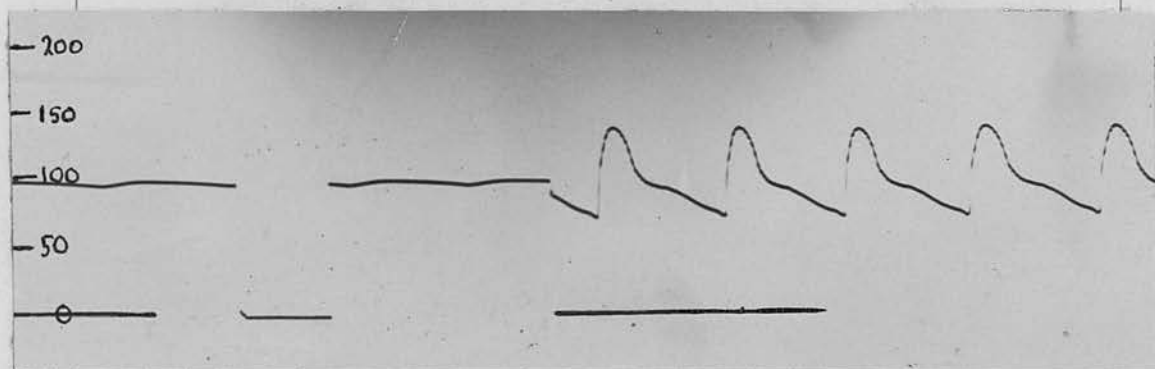


Fig. 14. Femoral arterial pressure record showing on the left the mean pressure determined by continuous electrical integration and on the right the pulse waves. A zero tracing was automatically introduced every tenth second to provide a base line for measuring and a time marker for the continuous record. Mean pressure 96 mm.; systolic 148 mm.; diastolic 70 mm.

SECTION III

THE PATHOLOGICAL ANATOMY AND PHYSIOLOGY OF  
ARTERIAL DISEASE IN THE LOWER LIMBS.

The lower limb has been divided into two groups...

The only satisfactory classification of disease is on an aetiological basis. Unfortunately little is known about the causation of any type of arterial disease in the lower limbs and it is for this reason that there is so much discussion about classification which has to be based largely upon pathological anatomy. Since Buerger's description in 1908 of the histological features of lesions seen in young male patients it has been customary to divide cases of primary arterial disease of the lower limbs into two main categories, namely thromboangiitis obliterans and atherosclerosis. This of course is only done when more general causes such as, for example, syphilis or embolism from a primary source in the heart have been excluded. While the pathological features seen in the arteries of young and elderly men may be quite different and easily distinguished, difficulty is frequently experienced in the examination of specimens taken from patients in the fourth and fifth decades. At this age the features of both types appear to mingle and no clear-cut distinction is possible; the one disease merges imperceptibly into the other. The change is not abrupt at any age, for atheromatous change may be apparent in thrombosed arteries of subjects still in their twenties. On the other hand inflammatory reactions may be present in the arteries of patients over fifty years of age. Nevertheless from a clinical and descriptive point of view it is convenient to attempt to separate the two groups.

Aetiology and Classification of Obliterative Vascular Disease.

The cases that have been studied have been divided into two groups entirely on an age basis. No

aetiological classification is possible and an opportunity to study fully the pathological anatomy is only present in those who have suffered major amputations. The course of the disease is so variable that no reliable classification can be made on clinical grounds. Thus no alternative was left but to separate out the cases according to the age at which definite and clear-cut features of vascular disease first became apparent. The age of 35 years was chosen on entirely arbitrary grounds. Those whose illness certainly began before this age were regarded as cases of thromboangiitis obliterans. The remainder were classified as atherosclerosis. It is not to be understood by this that the writer regards these two conditions as being either of a different nature or aetiology. For this reason it is perhaps better to use the terms juvenile and senile obliterative arteritis (Boyd et al. (1949) ). The older terms however have been used as they are well established in clinical practice and a change of nomenclature will not help until more is known of the aetiology.

78 cases of obliterative vascular disease have been studied in detail. Thirteen, all male, first had undoubted signs of vascular disease present before they had attained 35 years of age and were accordingly designated cases of thromboangiitis obliterans. Five of them were seen by the writer before they were this age; the ages of the others were between 36 and 41 years when first examined by him. In this group six major amputations were carried out, three biopsy specimens of cutaneous veins were taken and in seven patients plethysmographic studies were possible. Little can be said with regard to the aetiology of the disease in this group.



In none did the onset appear to be due to trauma and no patient fell into the group described by Boyd and his associates (1949) as primary popliteal thrombosis. This latter condition must be rare; it accounted for only one per cent in Boyd's series. In all the writer's cases careful investigation showed the presence of disease in other arteries in addition to the popliteal. There was no definite family history of arterial disease; indeed such a history was less frequent in this younger age group than in the older. None were hypertensive. The racial distribution is of some interest. Of the four cases seen in the Edinburgh area none were Jews, while of the remainder seen in Paddington where a large number of refugees have congregated seven out of the nine were Jews from the continent of Europe. This suggests strongly that race plays little specific part in the genesis of the disease and that the racial incidence depends largely on the site of the hospital. The low incidence of Jewish blood in the Edinburgh cases has been confirmed in a large series by Lynn and Burt (1949). The effect of tobacco-smoking on the course of the disease will be mentioned later. Two features were seen in this group but not in the other groups. Involvement of the arteries of the upper limbs was present at an early age in two of the cases and finally necessitated amputation. In no other cases at any age did this occur. Localised inflammatory venous lesions were seen in three patients. These distinctive features possibly suggest that thromboangiitis may have an inflammatory basis and be of entirely different origin from the type of disease seen in more elderly patients even though clear-cut histological distinctions cannot be made. The remaining 65 cases, whose symptoms began after 35

years of age, have been divided into two groups, those without and <sup>those</sup> with diabetes mellitus. There were 45 in the group without diabetes and their ages when first seen ranged from 40 to 72 years. There was one female in this series. In eighteen, major amputations were carried out and in twentyfour, the blood flow in the calf or foot was measured with plethysmographs. In the group with diabetes mellitus there were 20 patients; five of them were female. In ten cases there were major amputations and in eight blood flow determinations were carried out. There is little to be said about the aetiology of the disease in the atherosclerotic group. In the case of the one female patient with vascular disease without diabetes there was gross hypertension, her blood pressure constantly being about 270/150; her age was 48 years. In the other cases hypertension was by no means a constant factor, for of these remaining patients only five had pressures above 170/100, the highest being 196/108. It did not thus appear to play much part in the genesis of the disease. In the diabetic group of twenty patients only one had a high blood pressure; it was 180/100. The part played by diabetes in the production of vascular disease and the nature of this disease will be discussed later.

The cases studied were not selected on any definite basis except that the blood flow examinations were restricted to patients with the milder degrees of vascular disease. This means that up to the present it has not been possible to carry out physiological and anatomical observations in the same patients, as those due to have amputations obviously were not suitable for study in plethysmographs. No attempt was made to collect a large series of cases, but the material collected was examined in considerable

detail which would not have been possible if it had been necessary to deal with a big number of patients. A representative number of amputation specimens and of physiological investigations was examined in each group by the methods detailed in the earlier sections.

Appearances on Dissection of the Limbs.

In the cases of thromboangiitis obliterans the major vessels were usually dissected free from the surrounding structures without difficulty. In no case was a neighbouring nerve firmly bound to the vascular tree as described by Buerger (1924). The venae comitantes were, however, often closely adherent to the artery and were not separated with any ease. This finding was commonest when the disease was of long standing and had been accompanied by cutaneous infections. The lymph nodes were always enlarged in such cases and it seemed probable that the fibrosis around the vessels was largely due to secondary infection. These features were equally common in the older age group and were not in any way peculiar to thromboangiitis obliterans. The view expressed by Boyd and others (1949) that the degree of fibrosis around the vascular bundle was determined by the duration of infection in the perivascular lymphatics was strongly supported by these dissection studies. The gross characteristics of the arteries 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 often strangely localised, the transition from apparently normal to obliterated artery being singularly abrupt. In all these cases the oldest lesions were in the more distal parts of the limbs, though it was often impossible to find any clinical features associated with obviously old



occlusions of small arteries in the feet. If any symptoms were produced by a limited thrombosis in these sites their significance was probably realised by neither doctor nor patient. A collateral circulation would quickly be developed and the disturbance forgotten. These small thromboses in plantar and digital arteries were only detected by serial sectioning of the vessels after fixation. They appeared as firm yellowish or white occlusions within the centre of the artery and were easily distinguished from post mortem thrombus. Definite and persistent symptoms only arose from thromboses in small vessels when these were exceedingly numerous and extensive. The involvement of the proximal portions of the tibial arteries and popliteal artery was, from the pathological point of view, a late feature. On the other hand they frequently provided the first clinical signs, as obstructions at this level are not so readily circumvented by the collateral circulation. Clinically, proximal and distal types of the disease have been described (Kinmonth 1948). Pathologically, in two cases in which the earliest clinical signs appeared to indicate a proximal onset of the disease, the oldest lesions were found in the distal arteries, though these were only few and widely scattered. In the recent arterial occlusions the obturating mass was red or brown and was centrally placed in a vessel that otherwise appeared healthy. In the amputated limbs involvement of the arteries was considerably commoner than of the veins. In the cases where fibrous tissue spread out from the adventitia to involve the veins the latter were often patent, even though the artery were blocked by long 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 old organized thrombus. This strange distribution of lesions within the vascular bundle suggested that the perivascular fibrosis and the intravascular lesions were independent conditions.

In the older age group the major arteries were often hard, brittle and tortuous. Between the hardened areas which were affected with calcification of the media the artery often seemed to be dilated. This was especially noticeable when it was occluded with thrombus, and was frequently seen in the popliteal segment. Two cases in which definite aneurysm formation occurred will be described in a later section. Widespread medial calcification was often present in segments where the arterial lumen was completely patent and it did not appear to determine in any way the site of a thrombosis. The atheromatous changes in the intima formed the chief features in the disease. They were widely scattered in the larger arteries and were frequently associated with thrombosis. Often only a small clot was present on the edge of an atheromatous plaque; in these cases it sometimes appeared that the thrombus actually spread into the wall of the intima and it was impossible to decide macroscopically whether this represented an intimal haemorrhage rupturing inwards, or old intravascular thrombus with the margins already converted into amorphous atheromatous material. These points will be discussed in greater detail when the histological appearances are described. The atheromatous lesions were commonest in the larger arteries of the limbs and were not seen in the small arteries. Occlusive disease in the latter was rarely seen in the older age group of purely atherosclerotic cases in contrast to what was seen

in the younger age group. If thrombosis was found in these small arteries it appeared to be secondary to older lesions in the tibial arteries. The veins were often not involved though their walls sometimes seemed unduly thick; when cutaneous lesions were present a secondary thrombophlebitis was frequently found spreading proximally. The cause of such a venous thrombosis was thus usually apparent and it was obviously a different process from the phlebitis seen in the cases designated thromboangiitis obliterans. When septic cutaneous lesions had been present for a considerable time perivascular fibrosis was a common finding. In cases with frank sepsis in ulcerated areas, the vascular bundle was manifestly swollen with a tense gelatinous type of oedema. Subsequent histological study in such cases confirmed the presence of infection in the tissue surrounding the vessels.

In the cases complicated with diabetes mellitus, advanced atheromatous lesions and calcification of the media frequently were present. On the other hand it was often noticed that small cutaneous lesions were present in the toes without any definite gross obstructive lesions being present in the larger arteries. This was unlike what had been observed in the uncomplicated cases of atherosclerosis. Further dissection of the smaller arteries showed that they were frequently involved in the diabetic cases. As a result of this observation an investigation into the nature of diabetic vascular disease in the lower limb was undertaken and will be described later.

#### Histological Features of Obliterative Vascular Disease.

In all types of the disease a careful selection of blocks was made to include portions of artery in

which it was reasonable to expect to find the earliest histological features of the disease. It had been hoped, particularly in cases labelled thromboangiitis obliterans, to detect some abnormality in the intima or endothelium that had led to the development of the thrombosis. It must be admitted that this search in the arteries was of no avail in spite of the fact that many hundreds of sections were examined. In the amputated limbs the earliest changes as described by Buerger (1924) were not found in the arteries. Possibly one should not expect to find them in amputated limbs as, naturally, in such cases the disease has been present for some time. Nevertheless in these limbs it was always possible to find portions of artery recently thrombosed - indeed it was usually the extension of such a thrombosis that necessitated amputation. Microscopic sections from such areas showed remarkably little in the way of any acute inflammatory reaction even though numerous serial sections were cut. The earliest change appeared to be a simple thrombosis in an otherwise healthy artery; a section of the vessel immediately beyond the area of thrombosis never showed any definite inflammatory reaction. The cellular infiltration of the wall of the artery appeared to follow rather than determine the thrombosis and was thus the beginning of the repair process. It seemed that the factor that determined the thrombosis produced no specific inflammatory changes. This inability to find in arteries lesions which from Buerger's descriptions might be regarded as the earliest changes, has been described by other investigators (Allen et al. (1928), Gery et al. (1939) ). Buerger regarded the earliest change as an acute polymorphonuclear infiltration of all the coats of the artery. In the peripheral



portions of the clot he described focal collections of leucocytes - the so-called "purulent foci". He did admit, however, that these 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, especially as 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 (1924) no illustrations of "acute lesions" in arteries appear, even though he has described them. All the "acute" illustrations are confined to veins.

An opportunity of studying the earliest changes in affected veins was afforded by biopsy specimens taken from three 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 contribute outstanding features. More prominent were the giant-cell formations which are often regarded as typical of the condition (Fig.15). These giant-cell formations were also more rarely found in some of the sections of arteries in the amputated



limbs, but they were not so common as in the veins, and Leriche's observation can be confirmed that many sections have to be cut in order to demonstrate them (Leriche 1946). The resemblance of the giant-cell formation 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 15. 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 conspicuously 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. 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 (Fig.22). 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 often 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 swollen lining endothelial cells. A perivascular infiltration of lymphocytes was often 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 leucocytes were present there was frequently considerable tissue necrosis or 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 (Fig.22). 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 interpretation of the changes seen in the earliest stage of the development of atheromas is exceedingly difficult and still causes much dispute. These small slightly-elevated plaques and streaks could be seen scattered on the intimal surface of most of the larger arteries of the amputated limbs. The elevations constituted definite thickenings of the intima and appeared to consist of connective tissue and amorphous fatty material. The plaques tended to become confluent and to develop particularly on one side of the artery rather than concentrically. In all the amputated limbs of the older age-group there were advanced atherosclerotic lesions, but the histological features were extremely varied. It is proposed to concentrate on certain features that aroused special interest. In the intima the fully-developed lesions consisted of large masses of relatively acellular substance having a somewhat hyaline appearance with irregular deposits of cholesterol and fatty acids, occasional collections of fibroblasts and foamy lipophages in various stages of degeneration (Fig.28.). Small capillary channels often surrounded by a few lymphocytes were frequently seen in the deeper parts of the intima and appeared to arise from the vasa vasorum in the media. They attained a relatively large size particularly when



the lumen of the major artery was greatly reduced in calibre (Figs. 18 and 38). Blood partially fused with atheromatous material was frequently seen in the deeper part of the intima and in close relation to these small vessels. This blood would be regarded by Winternitz and his associates (1938) as intimal haemorrhages but Duguid (1949) has pointed out that they may equally well arise from intravascular thromboses. In fortunate sections it was possible to trace a continuity of this deeply-situated blood with definite thrombus within the arterial lumen.

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 early deposits could be seen deep within the intima. 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 (Fig. 28). 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 changes resulting from mural thrombus 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. 71  
These thrombi were undoubtedly prone to softening  
with fatty degeneration, with the result that in any  
isolated section it was usually impossible to  
distinguish on histological grounds whether an  
atheromatous plaque had arisen from an intimal  
haemorrhage or intravascular mural thrombosis. The  
fact that it was frequently possible to demonstrate a  
connexion between the deep incompletely organized  
blood and thrombus within the lumen (Fig.21) provided  
no definite evidence either way as it has been  
suggested that an intimal haemorrhage may rupture  
inwards and that the consequent damage to the intima  
and endothelium was responsible for the thrombosis  
within the vessel (Paterson 1939, 1941). It is also  
quite conceivable that such haemorrhages may play a  
part in the formation of dissecting aneurysms as  
the longitudinal split develops in the deeper part  
of the intima. Such a condition was seen in one  
popliteal artery in which the elevation of the  
intima by the blood had led to complete occlusion of  
the arterial lumen. On the other hand the vessels  
around the thrombus are usually small capillary  
channels. There is no elastic tissue around their  
walls and they are the kind of new vessel that is  
commonly seen in tissue that is being organized. They  
are therefore not the type of vessel that would  
lead to a haemorrhage rupturing inwards against the  
intraarterial pressure. In the earlier cases these  
collections of blood in the deeper parts of the  
intima were reported as haemorrhages, as it frequently  
had not been possible to trace any connexion with  
the lumen. Reinvestigation however showed that some  
of the blood might conceivably be the result of  
intraarterial thromboses. Though no final statement

is possible, the balance of evidence resulting from the study of the growth of these atheromatous lesions strongly supported the views of Duguid (1946, 1948). In the older lesions the thrombus was always completely fused into a hyaline mass and cholesterol clefts were often apparent. Calcification occasionally occurred in the deep parts of the intima close to the invading capillaries. The thrombus and intima in this older age-group were typically relatively poor in cellular organizing tissue. This was certainly the characteristic distinction that might be made between atherosclerosis and thromboangiitis obliterans. It was, however, not always present and, occasionally, cellular organizing tissue was found in an elderly subject with typical atheromatous lesions elsewhere (Fig. 20). In middle age either type of lesion might be seen.

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 (Fig. 29).

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. The muscle of the media might be 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.17). 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. These inflammatory reactions were frequently associated with calcification or even bone formation in the media (Fig.19).

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 have expressed any definite opinion as to their significance. Gery and others (1939) described leucocytic infiltrations and giant cells (Fig.16) in such conditions, but stated that they had no specific character and were found at all ages and in every type of obstructed artery. It is difficult to say whether the inflammatory reactions are secondary to changes in the lumen and intima of the artery or are a primary disturbance of the media associated with the development of a sclerosis of the



Mönckeberg type. 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. In this connexion 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 it is difficult to offer an explanation for their presence. Nevertheless it seems that necrosis of the musculature might attract them in much the same way as 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 presence of the lymphocytes. Another possibility is that the lymphocytic infiltration 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 suggested 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 distal ulceration and infection, there were irregular patches of fibrosis and small collections of lymphocytes around markedly congested vasa vasorum. The fibrosis, as described earlier, occasionally extended out to include the veins.

The veins in the cases of atherosclerosis did not all show consistent changes, but a common finding was a mild 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. Rarely the digital artery showed changes characteristic of the disease in the main vessels. Often 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 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 the cases complicated by diabetes mellitus the histological appearances were essentially similar. Occasionally it was thought that the digital arteries in these cases showed a greater degree of intimal hyperplasia but no clear-cut evidence on this point was available. Certainly it can be said that by studying a section it was impossible to tell whether diabetes had been present or not. In this connexion it should be emphasised that changes in the calibre and walls of small arterioles and capillaries are extremely difficult to detect by histological examination.

#### Recanalization of Thrombosed Arteries.

In the occluded arteries seen in all the amputation cases new vascular channels constituted a prominent feature in thrombi which had undergone organization. These channels have long been recognized and were described in many of the early works on arterial disease (von Winiwarter (1879)). Virchow (quoted by Tannenberg and Fischer-Wasels (1927)) showed that the channels present inside an organized thrombus did not communicate directly with the patent functioning parts of the vessel lumen above and below the occluded segment. Leriche (1946)

considered that the vascular passages within the thrombus were of little functional significance. It is, however, known that vessels in which blood is flowing under arterial pressure develop elastic tissue within their walls. It was accordingly hoped that further information regarding the function of these new vessels might be obtained by studying their connexions and the mode of formation of the elastic tissue (Akrawi and Wilson (1950) ).

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 (Heuking 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 (Fig.22). 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 (Figs.23 and 24). 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 (Figs. 25, 26 and 27).

In the cases of atherosclerosis complicated by occlusion of the artery similar types of new vessel formation were seen, but the organization of the thrombus was not so highly cellular as in the thromboangiitis cases. Nevertheless as far as new vessels within the thrombus were concerned the sequence of events followed a course closely similar to that described in the previous paragraph. The small capillaries led from elastic-coated channels to non-elastic blood sinuses which were shallow and lined only by endothelial cells. The latter channels penetrated into the media and joined some of the venous vasa vasorum. The elastic-coated channels ran in the longitudinal axis of the lumen and, after intercommunicating, led into side-branches coming off the main vessel (Figs. 28 and 29).

In both types of occlusive arterial disease the elastica surrounding these channels was continuous with the internal elastic lamina of the side-branches which they joined (Fig.29). 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 (Fig.27). The side-branches were also either fully patent, partially obstructed, 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 Xray 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 (Fig.35). 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 (Fig.30). 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 Xray photographs (Figs.34 and 36). 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 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 function of these channels 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 effected 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 (Figs. 26 and 27). 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 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 seemed 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 Development of the Collateral Circulation.

The demonstration of the part played by the small channels recanalizing thrombi naturally leads to an examination in general of the response of the arteries



in a limb when occlusions develop in the major vessels. 82

This subject has for long aroused interest, as the first observations were made in the well-known experiments of John Hunter. Later 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 in dogs. The animals were killed after different periods and the vascular systems of both ligated and control limbs were studied by dissection and arteriography. Later still the circumvention of obstructions in main arteries has been studied extensively in the living subject by arteriography (Dos Santos et al. (1931) Allen (1933)). The general mechanism is thus well known but, as in this series of cases it was possible to examine the amputated limbs by a variety of techniques, the results will be briefly presented.

The development of collateral avenues was largely studied in the leg, as the anterior and posterior tibial arteries were injected from above their origin and they were readily found in dissections. The methods of establishing a collateral circulation observed in the amputated limbs may be described under the following headings:

1. By a dense network of small arteries. This was seen particularly in the younger subjects and to its greatest degree in a patient who had undergone sympathectomy (Fig. 34). In a normal limb many of the small arterial branches probably only function intermittently except when exertion demands an additional supply of blood. They are thus not seen in injections when the main arteries of the leg are intact (Fig. 31). In a young subject, when enlarge-



ment of these small arteries is still possible, gradual obstruction of the main vessels leads to the development of a thick network. In this manner many small arteries attempt to take over the function of the obliterated anterior and posterior tibial arteries (Fig.32). The most extensive networks were seen in young sympathectomised subjects, but as youth and sympathectomy in the writer's series of amputation cases were invariably associated the relative role of each could not readily be distinguished.

2. By circumvention of an obstructed segment. When an artery was partially or totally occluded a collateral was often found arising from it a short distance above the point of occlusion. This collateral artery passed more or less at right angles from the parent trunk for a short but variable distance and then turned, often abruptly, to run roughly parallel to the obstructed artery. Distal to the occlusion it turned in to rejoin the parent trunk at right angles (Fig.33). The pattern of such by-passes was often complex and was best elucidated by dissection of the vessels after injection of a coloured mass and radiography (Fig.37).

3. By extension and dilatation of the vasa vasorum. This was a method particularly seen in the older patients in whom a more generalised network of vessels did not develop. Enlarged vascular channels were frequently seen in the outermost parts of the intima, the media and the adventitia (Fig.38). These channels frequently communicated with vessels in the perivascular sheath and with the recanalizing passages within the thrombus. It is difficult to assess exactly what part they played in the collateral circulation, as their function was obviously partly to

do with organization of the thrombus. In thromboangiitis obliterans such large intravascular vessels were not seen in obstructed arteries and it accordingly seemed in older subjects that they were developed out of proportion merely for local organization.

4. By recanalization of the thrombus as described in the previous part.

It should be realised that these are not separate and isolated events but that the collateral circulation is provided by a complex interweaving of all the new vessels. The system was always found most fully developed in cases where the obliterative process had been slowly advancing over many years. Hence it was most conspicuous in young subjects with symptoms of long standing and was never well developed in cases where thrombosis in a large vessel had necessitated early amputation.

The exact mechanism that prompts the collateral arteries to develop is not known. The release of metabolites from ischaemic tissue possibly provokes a vaso-dilatation analogous to that seen in reactive hyperaemia (Lewis and Grant (1925) ). The enormous surface area occupied by small arteries in the sympathectomised limbs invited the question as to the part played by sympathectomy in bringing about this increase. There is evidence of the existence of a great many arterial branches which are not visible in the arteriograms of living subjects as they are not conveying blood at the time of the examination. Sympathectomy may increase the number of permanently patent arteries. Evidence for this view is afforded by Horton and Craig (1930) who made arteriograms of the hind legs of dogs on some of which sympathectomy had been performed. The surface area occupied by

arteries was much greater in the limbs without a sympathetic nerve supply than in the normal control limbs. Mulvihill and Harvey (1931) demonstrated that sympathectomy greatly accelerated the development of the collateral circulation after ligation of the external iliac artery in dogs. There is thus considerable evidence that the release of vasomotor tone effected by sympathectomy encouraged the permanent opening and growth of small arteries to compensate for the occlusion in the main arterial tree.

#### The Role of the Popliteal Artery in Vascular Disease.

In studying the present series of cases special attention has been paid to the popliteal segment of the arterial tree, as there were many indications of its importance in the development of obliterative arterial disease. Buerger (1924) emphasised its key position with regard to the blood supply of the limb and his observations have been confirmed by subsequent investigators (Learmonth et al (1944), Allen et al. (1946) ). With this point 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.

In the series there were 20 amputations performed at the mid thigh and in sixteen of them 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 all it was probably a thrombosis developing within the lumen of a grossly atherosclerotic artery and the process could usually be traced proximally either from atheromatous lesions at the bifurcation of the artery or from a plaque at a slightly higher level (Fig.21).



In these cases of recent obstruction by blood clot it was occasionally difficult to decide whether the condition was entirely a thrombosis or embolism complicated by spreading thrombosis. This point particularly arose in four cases, as auricular fibrillation was present. In none of these cases was it possible to isolate an embolus and, as local arterial disease was present at the site of the obstruction, it was concluded that the lesion was probably thrombotic.

In three only of the midhigh amputation cases was no acute obstruction found in the popliteal artery. In one of these there was a spreading suppurative cellulitis in the foot which was the chief factor determining amputation. In the second there was extensive disease and obliteration of the tibial arteries, though the popliteal itself had escaped. (Fig. 34). In the third, 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 probably at the origin of the profunda branch. From a study of these 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 precipitating factor. When such a finding was absent there was invariably some other explanation, usually infection, which led to a marked increase in the circulatory demands of the limb. Depressed circulation, either as a result of a cardiac disorder such as auricular fibrillation or shock following operation, also played



a part in determining the onset of ischaemic gangrene.

The common method of obstruction was a thrombosis developing on an atheromatous area of the intima. In general it was quite impossible to understand what had precipitated the local thrombosis. Often the degree of atherosclerosis elsewhere in the limb was not gross and it was not always on what appeared to be the most grossly diseased areas that the clotting developed. Similarly, in autopsies it was frequently observed that a greatly roughened intimal surface was free of recent thrombosis. There is considerable evidence that atherosclerotic disease is episodic in nature. The presence of small atheromas has little deleterious effect on the circulation. They are present in all older male subjects the majority of whom are entirely free from symptoms of circulatory deficiency. The key to understanding this problem lies not so much in determining the primary cause of atheromas which are seen in all adults, but rather the factor that leads to the superimposition of massive thrombosis which causes the loss of limb and life.

The importance of the popliteal segment of the arterial tree in determining the final onset of gangrene of the extremity has been fully demonstrated. The difficulties of circumventing an obstruction in this artery have long been known from surgical practice. Sudden obstruction or ligation of this artery is usually followed by gangrene of the extremity. An obstruction of more gradual onset may be circumvented by the enlargement of the anastomotic arteries around the knee joint. An accessory pulse at the medial side of the patella is frequently felt in such cases. The anatomical position of the popliteal artery is of some importance in this respect. Lying in a fibrous sheath surrounded by loose fatty tissue

and tendons it has no large muscular branches and only gives off a few discrete arteries for the supply of the relatively avascular surrounding structures. Multitudinous small muscular branches appear to be more important in obliterative vascular disease in forming collateral channels. 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.

Though the dangers of a complete obstruction of the popliteal artery are 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 of this process affecting 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 50 routine autopsies irrespective of age and sex. Special attention was directed to the vessel wall in the region of the adductor hiatus. In 4 cases early atheromatous degeneration was found in this region while the other large arteries in the

limb were free from disease. In 5 cases no atheroma was apparent, whilst in the others one quite definitely gained 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, buried in muscle, tends to escape. There is other evidence that the support of muscular tissue may tend to retard the development of atheroma. Thus the surface 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. 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 might 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 recognised; 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 are at the most 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.39). 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.

The part played by these small vessels within the wall of the artery in the development of arterial disease is difficult to assess. There are grave objections to the Winternitz method of demonstrating these channels, the chief being that they can only be filled by using a pressure of about 400 mm. of mercury. It is thus quite possible that they may be artefacts developing only in diseased arterial walls. On the other hand the channels which are demonstrated have the appearance of small vessels. It is of interest that they tend to encircle the artery in a ring fashion in the medial coat. This may be associated with the arrangement of the calcium deposits in Monckeberg's sclerosis. Histological sections of the walls of atherosclerotic arteries also show numerous small vascular channels (Fig.18). They were not, however, apparent in the earliest lesions of either thromboangiitis obliterans or atherosclerosis. It would, accordingly, seem that they are secondary features and not of prime aetiological

importance. As to whether they may give rise to haemorrhages and thus to progress of the disease is an open question. The views of Duguid (1949) in this respect have already been mentioned. From his studies the writer has no doubt that deposition of thrombus from the blood within the arterial lumen is the most important factor leading to either gradual or sudden complete obstruction. It is often possible to see quite clearly the development of this process in the popliteal artery (Fig.21). On the other hand the appearances often suggest that an intimal haemorrhage has taken place, as blood is found deep in the intima or even outside the internal elastic lamina. In such circumstances in the earlier case records the condition was described as an intimal haemorrhage. As the investigation proceeded, doubt on this point increased, the difficulty being that it was never possible to find an intimal vessel from which the haemorrhage might have occurred. Furthermore, the greater number of sections that were examined in series the more often was it possible to trace a connexion between the deeply-placed blood clot and the intimal surface. It is also possible that blood may rupture outwards from the lumen of the artery through the degenerate intima to the internal elastic lamina and then spread longitudinally, forming a dissecting aneurysm. A lesion of this nature was seen in one of the amputated limbs, the elevation of the intima having led to complete obstruction of the lumen of the popliteal artery.

In summary it may be said that the distal part of the popliteal artery appears to be unduly susceptible to the development of vascular disease and that thrombosis developing in this region is a great danger to the life of the limb. The arrangement of

the vasa vasorum did not appear to play any part in this increased liability to disease. Haemorrhage from small vessels in the arterial wall may occur but increasing experience suggests that this is an improbable explanation of blood seen deep in the intimal coat. In the popliteal artery as elsewhere the main event leading to development of obstruction is the intraarterial deposition of thrombus either gradual or sudden..

The Distribution of Arterial Lesions in relation to Blood Flow.

The extent to which the blood flow is decreased naturally depends on the sites of the obstructions in the arteries. It has already been explained that in the younger subjects with thromboangiitis obliterans the earliest lesions appear in the distal part of the extremity. They may be extremely localised and cause ischaemia of only a relatively small area. These cases are frequently misdiagnosed, as there may be no change in the general appearance of the limb and the peripheral pulses may not be noticeably altered in comparison with healthy individuals. The disease may advance very slowly over several years; only the smaller arteries may be affected, and, in a young subject, an efficient collateral circulation is developed so that even though the condition has been present many years there is little decrease in the maximal circulatory capacity of the limb. The following case illustrated many of these points.

M.M. aged 38 years, a tailor of Polish Jewish parentage, born and educated in England and first seen on 7.6.48 had noticed pain in the right calf about 10 years previously. The pain developed after walking about half a mile and subsided promptly on resting.

The attacks occurred for 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. 3 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  $45^{\circ}\text{C}$  capillary pulsation was demonstrated in all the toe pulps except in these two. 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  $44^{\circ}\text{C}$  gave the following figures for maximal circulatory capacity: Right foot 20.5ml./min./100 ml. (average of 22 readings; standard deviation 0.7ml. and coefficient of variation 3%). Left foot 21.7ml./min./100 ml. (average of 21 readings standard deviation 0.8 ml. and coefficient of variation 3%).

In this case it would be tempting to regard the slightly lower figure in the right foot as due to the



disease which has symptomatically been confined to the right lower limb. However the difference between the two sets of figures is not statistically significant, for a difference as great as 1.5ml/min./100 ml. may be found on comparing an entirely normal right and left foot. The blood flow through toes at full vasodilatation is probably about 40ml/min/100 ml. (Goetz (1946) ). The volume of this patient's first and second toes was calculated as 25 ml. The foot volume on the two sides was 950 ml. The total flow to the right was thus 195ml./min. and to the left 206ml./min. If the circulation to the right first and second toes had been entirely cut off the difference in total flow on the two sides would be expected to be only 10ml. (i.e. one quarter of 40ml./min./100 ml. as the volume of the toes was 25 ml.) It will thus become apparent that the foot plethysmograph is not a suitable instrument for revealing changes in circulation to only a small localised area. A toe plethysmograph would of course confirm the local deficiency in circulation demonstrated by the reactive hyperaemia test. After twelve weeks the circulation to the right second toe was apparently normal as judged by the reactive hyperaemia test and it was not possible to produce claudication on exercising the patient over the steps. In this case the disease had been localised to a few small arteries in the calf and foot and there was no appreciable decrease in the maximal circulatory capacity of the foot (Fig.42).

If the arteries in the feet become more widely involved the circulatory capacity may be greatly decreased even though the popliteal artery is patent and there are no symptoms referable to the calves. The following case is of interest in this respect.

H.E. aged 39 years, a garage proprietor, first

noticed pain on walking in the right great toe in November 1943. The disturbance was transient lasting only a fortnight. During 1945 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 was no 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 high on the dorsum of the foot presented the typical features described in thromboangiitis obliterans. A few giant-cell formations were seen in serial sections. At that time the following observations on the circulation in the lower limbs were made.

<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 secs.	3 secs.
Heel	14 secs.	10 secs.
Base of toes	50 secs.	19 secs.
Tips of toes	80 secs.	25 secs.

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.

Right foot 7.8ml/min/100 ml. Left foot 17.0ml/min/100 ml.

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

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.	Right foot 8.0ml./min/100 ml.
23.3.48.	Right foot 8.2ml./min/100 ml. Left foot 16.6ml./min/100 ml.
19.5.48.	Right foot 8.3ml./min/100 ml. Left foot 18.6ml./min/100 ml.
16.6.48.	Right foot 9.3ml./min/100 ml.
2.2.49.	Right foot 10.5ml./min/100 ml. Left foot 17.5ml./min/100 ml.

In this case the vascular lesions are apparently confined to the right foot. There was no evidence of involvement of the arteries supplying the right calf. It is of interest that in spite of the considerable reduction in the total circulatory capacity of the foot he was able to walk ten miles over rough hilly country in June 1948 without experiencing any claudication in the calf or foot. Throughout the

period of observation there has been a slight increase in the total possible blood flow through the right foot, probably owing to the development of collateral channels and recanalization of vessels in the manner already described.

The determinations of the maximal circulatory capacity of the foot in six patients who were regarded as suffering from thromboangiitis obliterans are shown in figure 42. These estimations were carried out when the patients first reported to hospital. In two severer cases it was not possible to expose the feet to  $44^{\circ}\text{C}$ . They were accordingly investigated by slowly raising the temperature in the plethysmograph from  $34^{\circ}\text{C}$ . The results are shown in figure 47 and it will be seen in such cases that there is practically no reserve circulatory capacity.

In all the cases so far described the arterial lesions have been situated chiefly in the feet and the age of the subjects when symptoms first began was under 35 years. In older subjects a similar reduction in blood flow can be demonstrated consequent on obstruction of the larger arteries. It must, however, first be realised that in the series there was a slight decrease in the maximal circulatory capacity of the foot in the older subjects even though they had no symptoms of arterial disease. This may be seen in figure 46. The results for the normal subjects were statistically analysed with regard to the effect of age. These subjects were selected from patients who gave no history of cardiovascular disease and who on examination presented no evidence of cardiac disease or hypertension. All had at least one palpable pedal pulse. It has been claimed that in healthy limbs there is no decrease in blood flow in the foot with increasing age (Kunkel and Stead (1938) )



As it has, however, been shown that there is a decreasing hand blood flow with age (Pickering (1936)) the observations on the 29 normal subjects over 30 years of age were analysed statistically. Assuming that the blood flow at each age was distributed normally about a straight line it was found that the line which gave the best fit was blood flow =  $(31.17 - (0.235)\text{age})\text{ml./min./100 ml.}$  That is to say that for an increase in age of 10 years the average decrease in maximal blood flow was  $2.35\text{ml./min./100 ml.}$  This decrease with age was significant at the  $P = 0.001$  level ( $t$  with 27 degrees of freedom equals 3.85). The standard error of the regression coefficient 2.35 is  $0.61\text{ml./min./100 ml.}$ , so the mean decrease in average maximal blood flow with 10 years of age almost certainly lay in the range  $2.35 \pm 1.22 \text{ ml./min./100 ml.}$

If the clinical features pointed to an obstruction of the popliteal artery and the limb survived there was always a gross reduction in the maximal circulatory capacity of the foot (fig.46). In these cases the decrease was secondary to an obstruction high in the arterial tree and there was not usually any definite evidence that the arteries in the foot were involved. These measurements thus indicated to what extent the collateral circulation can circumvent an obstruction in the popliteal artery. The results are most clear-cut when only one popliteal artery has been thrombosed and the arteries in the other limb are pulsating freely. In such circumstances the other foot is available for comparison, as is illustrated in the following case.

J.G. aged 49 years, a Jewish tailor, developed a sudden pain in the right leg one evening while sitting in his chair. The foot, at first white, became later cold and cyanosed. The colour changes

and the pain in the foot while at rest gradually disappeared, but he has subsequently always experienced pain in the right calf on exertion, promptly relieved by resting. There were no symptoms referable to the left leg at any time. He was otherwise entirely fit. He was first seen  $1\frac{1}{2}$  years after the thrombosis on account of the claudication.

He was a slightly obese individual. The heart was normal and the blood pressure was 160/85.

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

There were no accessory pulses felt on the right side. There was no glycosuria and he had a normal glucose tolerance curve. Blood cholesterol 210 mgm%. Hb 15.4 gms %. Xray of legs showed no arterial calcification.

The clinical diagnosis was a right popliteal thrombosis secondary to atherosclerosis.

The maximal blood flows in each foot were measured in plethysmographs with the water at  $44^{\circ}\text{C}$ . The results (averages of 20 readings; coefficient of variation in each case 4%) were:

<u>Foot</u>	<u>Volume</u>	<u>Blood flow.</u>
Right	1190 ml.	10.8ml/min./100 ml.
Left	1205 ml.	17.0ml/min./100 ml.

It is to be noted that the blood flow in the left foot is probably within the normal range for a man of his years. That in the right foot was considerably reduced owing to the popliteal thrombosis.

Two other similar cases have been studied. In both, one limb was clinically entirely normal while in the other there was a popliteal thrombosis. The results

are shown in figure 43. The maximal blood flow in the symptom-free limbs was within the normal limits, while in the limbs with the thrombosis it was considerably reduced. Atheromatosis is usually fairly uniformly distributed in corresponding lower limbs and in these cases it had apparently not reduced the circulatory reserve as long as massive thrombosis had not occurred. The reason for the development of ischaemic features was invariably 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 of blood flow being occasioned by thrombus superimposed on the atheromas. In bilateral cases the only possible comparison is with healthy subjects (fig.46) as 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 however readily be seen that these plethysmographic studies confirm the opinions formed as a result of dissection of the amputated limb in which popliteal thrombosis was the usual reason for the sudden reduction in the circulation necessitating amputation.

#### The Nature of Intermittent Claudication.

It has been generally accepted that the pain of intermittent claudication is due to a reduction in blood flow so that the requirements of exercising muscle are not forthcoming. The association between arterial disease and the development of pain on exercise has long been recognised (Boyd and others (1949) ) and the view of Lewis and his associates (1929) that intermittent claudication was due to inadequacy of blood flow through muscles during exercise has not been seriously challenged. The

deficiency of arterial inflow leads to the accumulation in the tissue spaces of a pain factor which stimulates the sensory nerve endings.

This reduction in blood flow has been demonstrated in the limbs of all subjects examined with intermittent claudication. In such subjects the maximal circulatory capacity of the feet has usually been diminished (fig.55). This has invariably been the case when the arterial obstruction causing the claudication is situated in one of the major arteries of the limb. However it sometimes happens that clinical features of arterial insufficiency develop though the peripheral pulses are palpable and appear entirely normal. In such cases the lesions are confined to the smaller distal arteries and arterioles. These lesions, in the writer's experience, are more commonly seen in cases of thromboangiitis obliterans or diabetes mellitus and are rare in pure atherosclerosis. In elderly subjects free from diabetes, gangrene of a toe, for example, is usually principally due to disease high up in the main arteries of the limb rather than to local digital arterial 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 or 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.

no



In all cases of 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 deficit is readily revealed. These points are illustrated in the following case in which the claudication was confined to one limb.

C.P. aged 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 necessary 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 faint. The Xray 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.

The blood flow through the two calves was measured in plethysmographs at 34°C. The resting flows were the mean of 12 readings. The flows during reactive hyperaemia (Fig. 50) were repeated twice. The averages of the observations were:

	<u>Right Calf</u>	<u>Left Calf</u>
Resting	2.4ml/min/100 ml.	2.1ml/min/100 ml.
After 5 min.	29.2ml/min/100 ml.	19.0ml/min/100 ml.

circulatory arrest.

In this case the results were as anticipated. Though the resting blood flows showed no significant differences on the two sides the circulatory reserve of the left calf was considerably diminished. Similar observations have been made on three other cases with apparently normal pulses but suffering from pain on exercise. It has thus been confirmed that a restriction in blood flow is an essential factor for the production of the pain of intermittent claudication.

During the performance of exercise tolerance tests on subjects whose symptoms were confined to one calf it was decided to ascertain how much exercise could be performed with the circulation to the leg totally excluded before the onset of pain. For this purpose one of the subjects with a popliteal thrombosis on one side and an apparently normal circulation on the other side was chosen. The arterial inflow on the sound side was excluded by wrapping a rubber bandage type of tourniquet round the thigh. Compression was thus applied over a distance of 25 cm. and the peripheral pulses were entirely obliterated. The subject then exercised over the steps. The pain of claudication

first developed on the side with arterial disease and not on the side with the circulation excluded by the tourniquet. This observation was repeated on five occasions in this patient. A similar result was obtained on testing the other two patients with a unilateral popliteal thrombosis. It was also shown in these three patients that applying the tourniquet to the limb with the thrombosed artery either reduced or did not materially alter the amount of exercise required to bring on the pain. The effect of the tourniquet was then investigated, generally in patients with claudication predominantly on one side though the arterial disease was bilateral. In them it was also shown that it was not possible to bring on with a tourniquet the pain of claudication earlier in the limb with the normally better circulation. The pain was always first experienced in the limb with the greater degree of arterial disease even though the other limb obviously had its circulation reduced to a much lower level by the tourniquet.

These results were contrary to expectation and the following factors were accordingly considered:

1. The tourniquet may not exclude the arterial circulation during exercise. No measurements of the blood flow were of course possible during the actual performance of the test. Immediately after exercising the pulses beyond the tourniquet were impalpable.

The efficiency of the tourniquet was also investigated with fluorescein injected into the arm. A small amount always got past the tourniquet however tightly it was applied. The quantity was minimal in comparison with the side of the popliteal thrombosis. This test was carried out before and after exercise.

2. The volume of blood may be greater in the limb with the healthy arterial system and may enable

the patient to carry on for a longer period with this leg in spite of the tourniquet. The results in the experiments were similar whether the tourniquet was applied with the limb elevated or dependent.

3. The tourniquet may interfere with the function of the nerves carrying the sensation of pain. It was shown that the appreciation of pain (pin pricks) and of light touch (cotton wool) was retained after the period of exercise.

4. In normal subjects it was demonstrated that it was possible to produce the typical pain of intermittent claudication by exercising in the manner described after application of the tourniquet. The number of circuits before the onset of pain varied between 20 and 40. In the subjects with arterial disease the usual number of circuits was 10 to 30.

It would thus appear that intermittent claudication may be caused entirely by arterial insufficiency as produced by a tourniquet. The presence, however, of arterial disease appears to decrease the degree of ischaemia necessary for the production of the pain. It has not been possible to show that the tourniquet prevents entirely the flow of blood in the femoral artery during exercise. Such a tourniquet left in position an hour or longer would certainly produce gangrene. In contrast the opposite limb with the arterial disease showed no sign of incipient gangrene. It is thus extremely difficult to imagine that during the period of exercise the limb with the tourniquet received a greater supply of blood than the limb with the popliteal thrombosis. The amount of exercise done by each limb was also equal, as each step was of the same height and the weight was carried by the limbs alternately. Similar observations have



apparently not been made previously, but Professor Sharpey-Schafer at the October 1949 meeting of the British Cardiac Society mentioned a case of thrombosis of the brachial artery in which claudication appeared in the forearm muscles. The claudication was produced in this forearm by a lesser amount of exercise than was required in the opposite forearm with the circulation excluded by a cuff. The arterial circulation was shown to be entirely excluded in this case.

The mechanism whereby the presence of arterial disease aids the development of intermittent claudication other than by reducing blood flow, is entirely obscure. The threshold for pain may be reduced in the affected limb, or the diseased segments in the arteries may initiate some pain sensation. Adequate evidence on both these points is lacking. The origin of pain has been studied by Seifert (1931) who concluded that in cases of embolism the sensation of pain was initiated locally in the artery. Leriche (1946) has advanced the hypothesis that the artery at the site of occlusion may act as a trigger area for the production of pain and vasomotor disturbances. Freeman and others (1949) have reported improvement of painful symptoms after arterectomy which was considered due to the interruption of some nervous reflex from the region of thrombosed arteries. It is accordingly conceivable that the presence of arterial thrombosis in one limb may explain the earlier development of pain even though the degree of ischaemia on exercise is less than in the artificially occluded limb. It is, however, obvious that there is still much to be learnt regarding the origin of the pain of intermittent claudication.

The Development of Ischaemia.

In all the cases of obliterative vascular disease it has been shown that obstructions in the main arteries lead to a decrease in blood flow. The extent of this decrease is variable and depends on the rapidity of the development of the obstruction and the ability of the collateral arteries to dilate. It must be realised, however, that it is not solely the reduction in blood flow that produces the features of ischaemia. If the pressure in the arteries distal to a block is low, the effective filtration pressure in the arterial limbs of the capillary loops may be decreased to such an extent that the osmotic pressure of the plasma cannot be overcome. In such a case fluid would not pass out of the vessels and the tissues of the limb become dehydrated. That this dehydration occurs was demonstrated by Cohen and others (1926) who showed that saline injected intradermally was more rapidly removed in ischaemic limbs. This observation has been confirmed in ten cases with incipient gangrene, the less affected leg being used for comparison. The injected fluid is quickly absorbed by the dehydrated tissues. Similarly there is a feeble response to intradermal histamine (Starr (1928) ) presumably owing to the low pressure in the arterioles. The wheal is small in extent and there is little flare.

A desire to ascertain the extent to which the pressure in arteries might be reduced by obliterative disease led to the measurement of blood flow in the horizontal and elevated positions. The effect of this manoeuvre on the blood flow in healthy subjects has already been described. In vascular disease the results are clearest when only one limb is grossly

affected and the other is available for comparison. The results in two such cases are shown in figure 45. It is apparent that the pressure in the arteries of the foot distal to the thrombosis is considerably reduced in comparison with the relatively unaffected limb. This test was repeated in ten patients with atherosclerotic vascular disease affecting both lower limbs, and the percentage decrease in pressure in them was shown usually to be greater than that in normal subjects. It should be emphasised that the blood flows are measured at  $44^{\circ}\text{C}$  so that full vasodilatation is ensured in both the horizontal and elevated positions. If the blood flows are measured with the arteries partially constricted there is a dilatation on elevation and the decrease in blood flow is thus not so great. It was found only to be possible to investigate in this way patients with an extremely mild degree of obliterative vascular disease as pain readily developed in more severely affected limbs on elevation with the water at  $44^{\circ}\text{C}$ . It is, however, possible to make observations on patients who have had sympathectomies with the plethysmograph at  $34^{\circ}$ , as reflex changes in local arteriolar tone due to posture cannot occur. In this way subjects with severer degrees of vascular disease were investigated. The method is illustrated in the following case.

A.W. aged 40 years, a valet, first noticed pain and numbness in the right leg during route marches in 1940. 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; 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 cc/min/100 ml. 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 3.8ml. at 38°C 4.3ml and at 40°C 4.4ml. (Fig.47). During reactive hyperaemia the maximal flow was 4.2ml/min/100 ml. (Fig.48). The maximal circulatory capacity of the left foot was thus regarded as between 4.2 and 4.4ml/min/100 ml. 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 3.8 to 4.2ml. 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 95mm of mercury. Assuming that this mean pressure holds throughout the arteries the anticipated decrease in mean pressure on raising the feet 19 cm. would be 16%, and, from a study of figure 45, the decrease in blood flow anticipated in a normal foot 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 90mm 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. The tests were repeated with the feet only elevated 10 cm. and after several observations the mean pressure in the arteries of the left foot was calculated as approximately 70mm. of mercury. This method obviously only affords a rough estimate of the mean pressure but it does demonstrate the considerable decrease in a limb with severe vascular disease.

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, after a period of 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. In the right lower limb the popliteal and dorsalis pedis arteries were pulsating strongly and, with this unobstructed channel, there was, accordingly, little reduction in the mean arterial pressure in the right foot. The right posterior tibial pulse was absent, which was in keeping with his complaint of claudication in the right calf. The smaller digital arterioles were affected on both sides as shown by the reactive hyperaemia test.

There is obviously no entirely satisfactory method of measuring the blood pressure in arteries with obliterative disease. Direct measurements with a needle in an artery, even if successful, would not necessarily afford a representative picture of the mean pressure in all the arteries of the foot. The changes in blood flow on raising the leg do reflect in a general manner the pressure in the arteries of the feet. A reduction in pressure profoundly affects the nutrition of the tissues and, together with the decreased blood flow, is responsible for the development

of the signs of ischaemia.

It remains to consider to what extent the reserve of the circulation is reduced before symptoms of vascular disease appear and to correlate this reduction with structural changes in the limb. It is only possible to do this using the plethysmograph, in cases where the reduction in blood flow is generalised over the calf or leg. The most favourable cases were thus those in whom the major incident had been a thrombosis in the popliteal artery leading to a decrease in the circulatory capacity of the leg and foot. Selecting such cases it was shown that in them there was usually a 50 to 70% decrease in the maximal blood flow before there was any complaint of claudication. This figure is slightly above that of Kunkel and Stead (1938), but such conclusions are not probably of great value as the onset of symptoms is obviously related to the amount of exertion in which the patient is accustomed to indulge. Thus a commercial traveller who habitually hurried uphill to the railway station carrying a heavy suitcase complained of claudication, though his maximal foot blood flow was 15.5ml/min/100 ml. which is at the lower limit of normal. On the other hand elderly patients who did not indulge in any undue exertion had blood flows below this level (Fig.55). With regard to such complaints as delayed healing of cutaneous lesions, the maximal circulatory capacity of the feet was always below 10ml/100ml/min. Three cases were investigated after delayed healing of cutaneous lesions. The maximal circulatory capacity of these feet ranged from 4.3 to 8.2ml/min/100 ml. It is interesting to note that satisfactory healing of infected ulcers can be obtained at these low levels. For obvious reasons it is impossible to

measure how low the flow becomes before the onset of ischaemic gangrene. The patient with the maximal foot blood flow at 4.3ml/min/100ml. was regularly at work as a valet and the onset of gangrene obviously was not immediately imminent.

Generalised osteoporosis of the bones of the foot was only seen radiologically in one of the cases examined with the plethysmograph. The maximal circulatory capacity of this foot was 5.1ml/min/100ml. Osteoporosis was not seen in other feet having a similar or lower maximal circulatory capacity. In these cases, however, severe ischaemia had not been present for longer than two years, while in the case with osteoporosis, judging from the clinical history, the blood flow had been at a low level for at least eight years.

It has not been possible to correlate the blood flow measurements with findings on dissection of the limb. Changes in the structure of muscle were investigated in the dissected limbs. In cases of angina pectoris it is often possible to demonstrate a fibrosis of the myocardium secondary to the ischaemia. The question naturally arises as to whether a similar fibrosis may develop in the muscles of a lower limb in which intermittent claudication has been experienced. With this in view portions of the calf muscles and of extensor digitorum brevis were taken for histological section. In many of the sections of the extensor digitorum brevis 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. Only very rarely was any displacement of the muscle cells by fibrous tissue noted. Changes in the calf muscles were not



conspicuous. 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 muscle. The changes in extensor digitorum brevis were slightly more prominent, presumably on account of its more distal situation and greater ischaemia.

No histological studies were carried out on the nerves and little information was obtained regarding the degree of ischaemia necessary to produce disturbances in their function. Blunting of sensation of light touch, but not of pain, was present in two cases with the circulation reduced below 5ml/min/100ml. of foot. Evidence from one case of femoral arterial embolism also suggested that regeneration of nerve might occur with the maximal circulatory capacity reduced to about that level.

#### The Nature of 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. 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 showing that atherosclerosis sufficient to produce clinical features of ischaemia develops 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 and 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. Although, 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 extensive vascular disease a special group of patients who presented features of lesions in the small vessels 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 observed in the popliteal, posterior, and anterior tibial arteries. Particularly noticeable was the extent of medial calcification. It is extremely difficult to form any accurate estimate of the extent of degeneration 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<sup>1</sup> obstructions. 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. There were five amputations at the mid thigh and five below the knee. In this small series of ten 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 whenever there was evidence that the popliteal artery was patent as demonstrated by palpable pulsations 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 mid thigh recent thrombosis was found in the popliteal artery in three instances, while in the other two this artery was patent though narrowed by atheromatous plaques. In these two cases the higher level of amputation had been chosen on account of extensive infection in the foot. In the cases amputated below the knee infection was not a marked feature. It is a point of particular note that severe ischaemia of the toes may develop in diabetic patients without any clinical or pathological evidence of obstruction in the larger arteries of the thigh and leg. It was this feature which first aroused 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 frequently been noted that relatively circumscribed ischaemic lesions may develop on the toes even

though the dorsalis pedis and posterior tibial pulses were 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 tibial pulses were all felt. Such observations as these seemed to indicate that diabetes mellitus not only predisposed to the development of an atheroma in the larger arteries of the lower limb 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, but only slight deficiency in the fourth toe and none in the foot. (Figs. 40 & 41) It is not possible to demonstrate this involvement of small vessels in all cases of diabetes going on to amputation and in some the process is similar to that in uncomplicated atherosclerosis. Gangrene is then due to thrombosis in large arteries spreading up to cut off the collaterals as previously described.

A group of seven patients who presented features suggestive of damage to small vessels was also studied. All had suffered from diabetes for at least ten years. One was blind on account of a severe retinitis. Four others had small spindle shaped haemorrhages in the optic fundi. The other two had had occasional septic



infections around the toe nails. In none were there any symptoms of claudication and all had popliteal and both tibial pulses, felt after soaking the feet in hot water. The maximal circulatory capacity of these feet was measured plethysmographically. In the seven cases this was found to lie at the lower range of normal. In them it seemed probable that this low maximal flow was due to generalised involvement of the small vessels (Fig.51).

On histological examination of the arteries, typical atheromatous lesions and medial degenerations similar to those reported above 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 described in the atherosclerotic subjects were often very prominent in the diabetic cases, particularly in the female subjects. Indeed, some of the slides presented a picture in many respects similar to that found in thromboangiitis obliterans. The only amputations 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 as the organization of thrombosed arteries was usually cellular.

Estimations with the plethysmograph of the maximal blood flow in the feet of those with the 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 strong evidence that diabetic vascular disease might be localised to small areas, chiefly the 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 early thromboangiitis obliterans. A preliminary report of similar conclusions has recently been published in America (Megibow et al (1949) ). These authors obtained full vasodilatation by using tetraethyl ammonium bromide in diabetic subjects. With a microplethysmograph they showed a decrease in the amplitude of the volume pulsations and a decrease in the rate of peripheral blood flow. The association of a normal oscillometric index and an abnormal microplethysmogram suggested that the fundamental peripheral vascular lesion in diabetes mellitus was a specific alteration of the smaller blood vessels analogous perhaps to the vascular change found in diabetic retinopathy or in the nodular variety of intercapillary glomerulosclerosis.

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 5ml/min/100 ml.

foot tissue. 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.

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 (Dolger (1947) ) 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 (Leary (1936) ). 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 and calf 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 might be profitable to examine 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 occurred 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 shows features intermediate between thromboangiitis obliterans and atherosclerosis. The distinction between the different types of arterial disease is difficult and on many occasions not possible as the features of one type merge into the next. Several reports have appeared of thromboangiitis obliterans in patients with diabetes (Horton and Allan (1934), Collens and Wilensky (1939)) 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 cellular lesions



seen in 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 today.

#### Conclusion.

The investigation of the limbs amputated from subjects in the younger age group did not reveal the pathological changes in the arteries described in detail by Buerger (1914). The earliest lesion seen in these cases was always a thrombosis in an artery with a wall that showed little or no sign of inflammation. Such has been the experience of many other investigators (Allen et al. (1946)). Buerger (1939) however has reiterated his original concept of thromboangiitis obliterans. Inflammatory lesions in superficial veins were readily found.

In the atherosclerotic cases the feature of chief importance was the deposition of thrombus on the atheromatous plaques. By this process the arteries finally became completely occluded. A similar mechanism was at work in diabetic vascular disease, but this condition was also complicated by the presence of lesions in the minute vessels. It was not possible to ascertain the nature of these small lesions.

Though something was learnt of the mechanism of the disease process, no light was thrown on the aetiology of arterial disease. The cases were followed and the progress of the disease was observed.

By exercise tolerance tests at monthly intervals and by repeated plethysmographic observations it was possible to show that cessation of smoking was the most valuable measure in checking spread of the disease and in aiding the development of the collateral circulation. This view is now widely accepted particularly with regard to the younger age-groups (Freeman (1947) ). Lampson (1935), using a hand plethysmograph, showed that the vasoconstriction induced by smoking cigarettes and inhaling lasted for about one hour. This vasoconstriction has also been confirmed in the foot by the writer. Though it aggravates the condition it is apparent that smoking alone does not cause arterial disease.

In all the cases of arterial disease studied it was apparent that the deposition of thrombus on the intima was the event of major importance. Whether this is determined by an abnormality primarily in the blood or in the arterial wall it is impossible to say. The distribution of the early lesions suggests that local factors in the arterial wall must at least play a part. The observations also suggested that these depositions of thrombus were episodic in nature both in the younger and older subjects. Sudden changes in exercise tolerance and the finding in dissected limbs of discrete localized areas of thrombosis of similar age in different arteries favoured this view. Holman (1949) has reached a similar conclusion. It thus appears that the key to the problem lies essentially in elucidating the mechanism of the intraarterial deposition of thrombus.

#### Summary.

1. The classification of arterial disease on an aetiological basis is impossible and on a

pathological basis difficult as there is no clear-cut distinction between the groups. For convenience thromboangiitis obliterans may be regarded as a form of arterial disease occurring in young male subjects, being characterised by a peripheral distribution of the early lesions and the occurrence of venous thromboses. Cases with an onset of symptoms after the age of 35 years were invariably regarded as atherosclerotic.

2. The histological features of thromboangiitis obliterans were studied in amputated limbs and in biopsy specimens of veins. In the arteries the earliest change appeared to be a bland thrombosis with little inflammatory reaction in the wall. The organization of the thrombus was a highly cellular reaction. The early lesions were usually first seen in the smaller arteries.

3. In atherosclerosis the larger arteries were typically involved. The principal feature was the deposition on the atheromatous areas of thrombus which became fused into an amorphous hyaline mass. There was usually no cellular organization of this tissue. Haemorrhages from vessels deep in the intima might occasionally occur, but the appearance was often deceptive and more suggestive of old deposition of thrombus which had not completely fused with the atheromatous material.

4. The recanalization of occluded arteries was studied in detail and it was shown that the new elastic-coated passages developed from and connected with patent side-branches. They thus formed part of the collateral circulation which was also formed by the enlargement of small pre-existing arteries and by dilatation of the vasa vasorum.

5. The popliteal artery was shown to be a frequent

site for early atheromatous change. The reason for this predilection was obscure, though, the artery is unprotected by muscular tissue and is exposed to the stress of movement. Vasa vasorum in the media and intima of the healthy artery could not be injected but they were readily filled if atherosclerosis were present. Recent thrombosis in this artery was the usual cause for midhigh amputations.

6. The decrease in blood flow in different types of arterial disease was measured with the plethysmograph. A considerable diminution in circulatory reserve occurred before any major symptoms appeared. A major thrombosis in an artery, rather than the steady development of atheromas with increasing age, was the chief cause of this loss of circulatory reserve.

7. Experiments on cases of intermittent claudication showed that in arterial disease the reduction in blood flow was not the only factor contributing to the development of the pain.

8. The presence of ischaemic lesions was due to a decreased blood flow and to a diminished pressure in the arteries, which led to an inadequate supply of fluid and nutriment to the tissues. The relation of the reduction of blood flow to the development of features of ischaemia was discussed.

9. Diabetic vascular disease was shown not to be only a premature atherosclerosis, as there was also evidence of damage to the small vessels of the limb. In many cases the latter predominated and were mainly responsible for the features of the disease.

#### Summary of Investigations.

In the 78 cases of obliterative vascular disease all the standard clinical investigations were carried



out. These case notes and the records of the special physiological and pathological examinations run into several hundred pages. They cannot, accordingly, be presented here. The conclusions reported in the text, however, have been chiefly based on the results of plethysmographic determinations, exercise tolerance tests, and pathological examination of amputated limbs. Exercise tolerance tests were only carried out when the patient was able to attend regularly at fortnightly intervals in the first instance. It was thus not possible to examine frequently in this way all who had plethysmographic determinations.

The numbers and investigations in each group were as follows:

Group 1 Thromboangiitis obliterans.

13 cases. (All male).

Blood flow determinations in 8 cases.

Exercise tolerance tests in 4 cases.

Amputated limbs 6 (3 in thigh: 3 in leg).

Amputated fingers and toes 3.

Biopsy of veins 3 cases.

Group 2 Atherosclerosis.

45 cases (1 female).

Blood flow determinations 24 cases.

Exercise tolerance tests 20 cases.

Amputated limbs 18 (16 in thigh: 2 in leg).

Group 3 Diabetic vascular disease.

20 cases (5 female).

Blood flow determinations 8 cases.

Exercise tolerance tests 4 cases.

Amputated limbs 10 (5 in thigh: 5 in leg).

(In addition 7 patients with long-standing diabetes but without evidence of lesion in the large vessels were included as described in the text).

Short notes on all the cases of obliterative vascular disease are given in the appendix (Cases 6-33). In the two tables that follow are results of experiments showing the alteration in blood flow consequent on raising the foot.

TABLE A

The effect of raising the foot 19cm. on the blood flow in the foot in subjects with high and normal blood pressures but without obliterative vascular disease. All the determinations were carried out at 44°C.

Subject	Age	Sex	Side	Blood Pressure	Maximal Blood Flow Horizontal ml./min./100 ml.	Maximal Blood Flow Foot elevated 19 cm. ml./min./100 ml.	Percentage decrease in blood flow.	Percentage decrease in mean blood pressure due to gravity.
S.B.	39	M	Right	210/135	22.0	19.7	10%	9%
M.L.	45	F	Right	200/140	26.5	23.4	12%	9%
R.C.	37	F	Right	155/110	29.8	25.6	14%	12%
M.G.	67	F	Right	174/102	16.1	13.7	15%	12%
F.B.	44	M	Right	136/90	15.8	11.3	28%	14%
J.F.	40	M	Right	132/88	18.8	14.2	24%	15%
J.J.	45	M	Right	124/78	22.0	15.7	27%	15%
H.O.	46	M	Left	115/82	17.4	11.9	31%	16%
C.N.	62	M	Right	110/70	16.8	12.6	25%	18%
C.R.	16	M	Right	114/70	18.3	12.2	33%	18%
F.H.	65	M	Right	110/70	16.4	11.0	33%	18%
E.W.	66	M	Right	102/68	17.1	12.1	29%	19%
J.A.	28	F	Right	102/70	15.5	10.7	31%	19%



TABLE B

The effect of raising the foot 19cm. on the blood flow in the foot in patients with obliterative vascular disease. The blood flow has been determined at 44°C. except in the case P.S. in whom a lumbar sympathectomy had been performed.

Patient	Sex	Age	Brachial B.P.	Side	Maximal foot blood flow. Horizontal ml./min./100 ml.	Maximal foot blood flow. Elevated 19 cm. ml./min./100 ml.	Percentage decrease in blood flow	Percentage decrease in mean pressure due to gravity.
G.K.	M	41	110/76	Right	15.9	11.2	29%	17%
				Left	12.4	8.4	32%	
R.P.	M	51	160/100	Right	26.4	21.5	19%	13%
				Left	8.6	5.1	41%	
J.G.	M	49	150/92	Right	10.9	7.8	27%	13%
				Left	16.2	13.2	19%	
P.S.	M	49	120/78	Right	5.5 <sup>x</sup>	3.5	37%	16%
C.P. <sup>xx</sup>	F	38	130/80	Left	13.0	9.7	26%	15%
E.S.	M	60	140/95	Right	13.3	9.3	30%	14%
E.F.	F	48	135/85	Right	14.7	10.7	27%	15%
A.F.	M	56	130/85	Left	13.2	8.9	32%	15%
W.V.	M	62	195/100	Right	12.2	10.0	22%	11%
				Left	9.0	5.5	28%	

<sup>x</sup> Sympathectomised. Measured at 34°C. Maximal circulatory capacity 6.3ml/min./100ml.

<sup>xx</sup> Popliteal embolism.



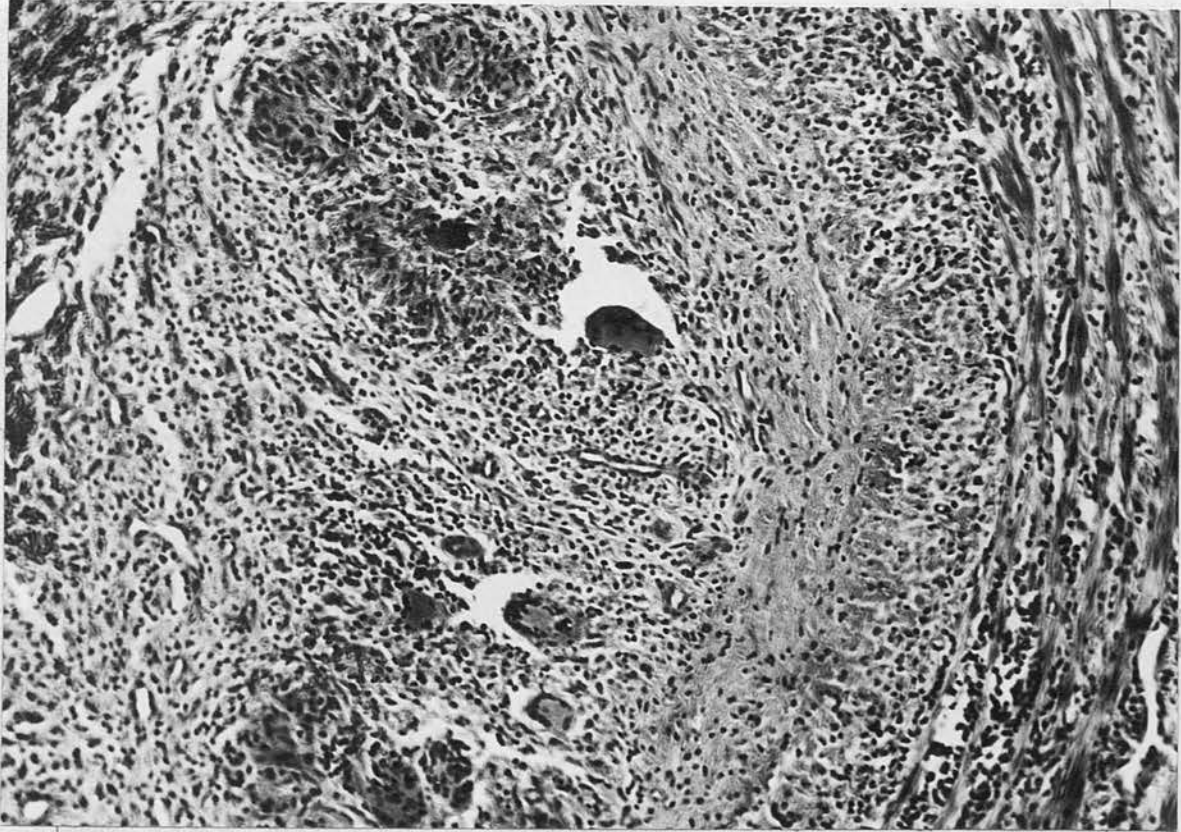


Fig. 15. Biopsy of the saphenous vein from a case of thromboangiitis obliterans (age of subject 34 years) showing several giant cell formations of the tuberculous type. The richly cellular organization of the thrombus is apparent and there is an infiltration of small round cells in all the coats. The arrangement is typical of an early stage in the evolution of the disease in a vein. Stained haematoxylin and eosin x 200.

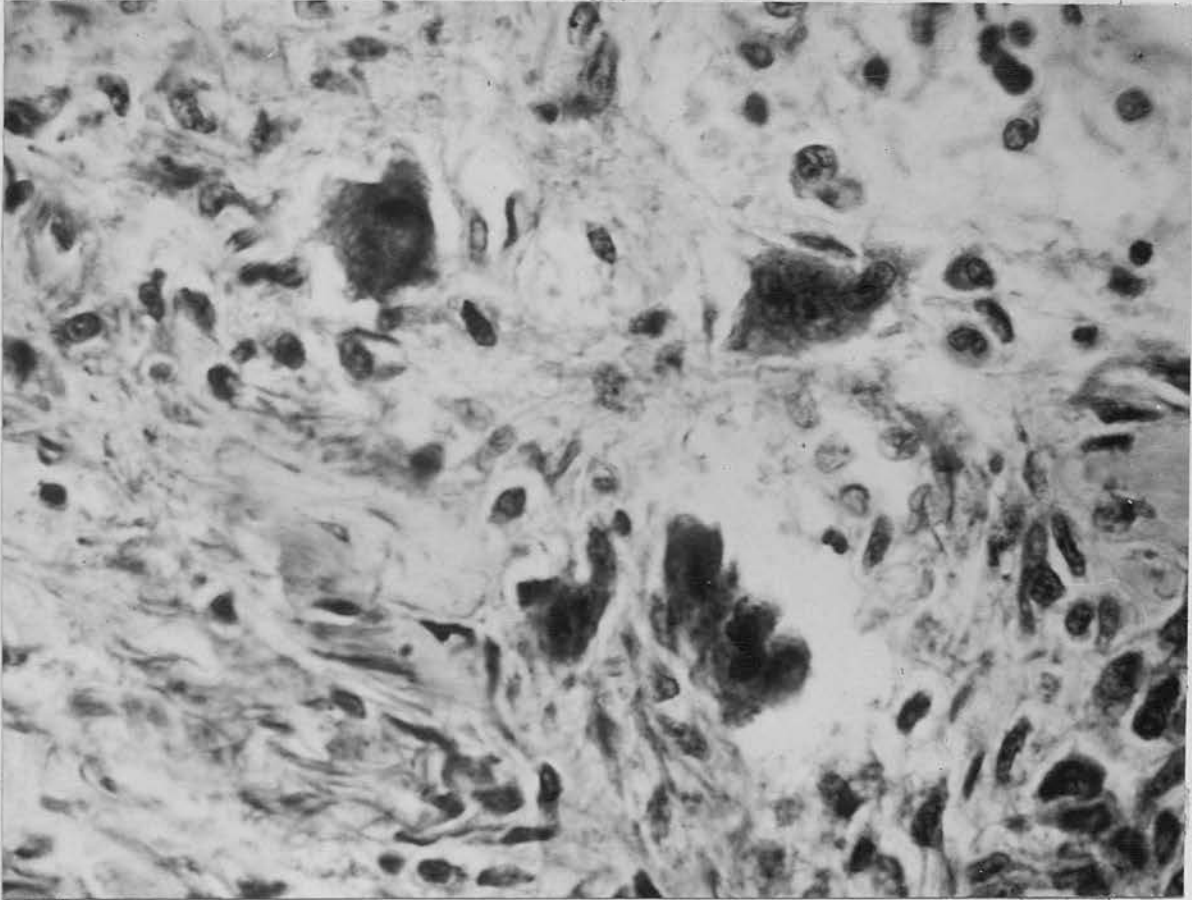


Fig. 16. Section of a part of organized thrombus in the posterior tibial artery in a case of atherosclerosis (age of subject 74 years). The organization is more cellular than usual and several giant cells are seen. Similar giant cells may be seen in all types of arterial disease. Stain haematoxylin and eosin x 750.

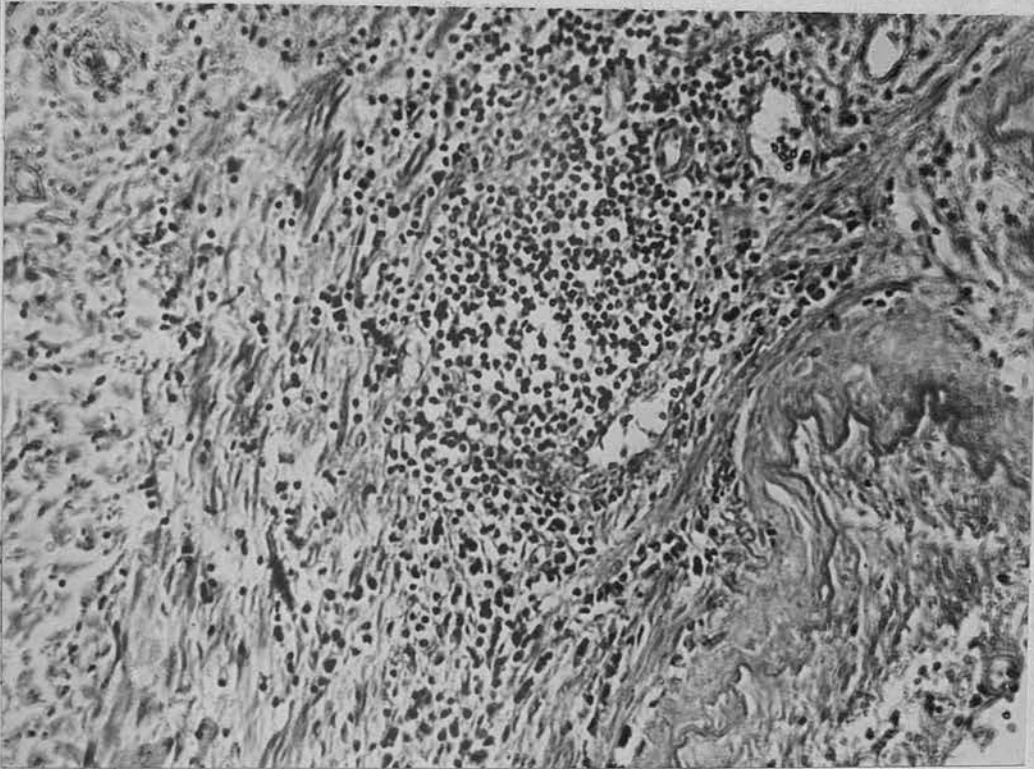


Fig. 17. Section of the wall of the popliteal artery from a case of atherosclerosis (age of subject 59 years). The internal elastic lamina seen towards the bottom right corner is preserved relatively intact. The media is densely infiltrated with lymphocytes and there has been considerable destruction of muscular tissue. The intima shows some atheromatous change. No medial calcification is present but there is a recent thrombosis within the lumen of the popliteal artery. Stain haematoxylin and eosin x 400.





Fig. 18. Section of the wall of the popliteal artery from a case of atherosclerosis (age of subject 58 years). A recent thrombosis had occurred in the artery. Numerous vascular channels are present in the media and there is a slight infiltration with small round cells. The internal elastic lamina is split into several layers and there is considerable intimal thickening. Stain haematoxylin and eosin x 250.

The architecture of the media has been extensively destroyed. Stain haematoxylin and eosin x 450.





Fig. 19. Section of the wall of the posterior tibial artery from a case of atherosclerosis complicated by diabetes mellitus (age of subject 70 years). The lumen of the artery was greatly reduced by old thrombosis and atheromatous tissue. An area of bone formation is present in the media and there is a conspicuous aggregation of small round cells in this region. The musculature of the media has been extensively destroyed. Stain haematoxylin and eosin x 450.

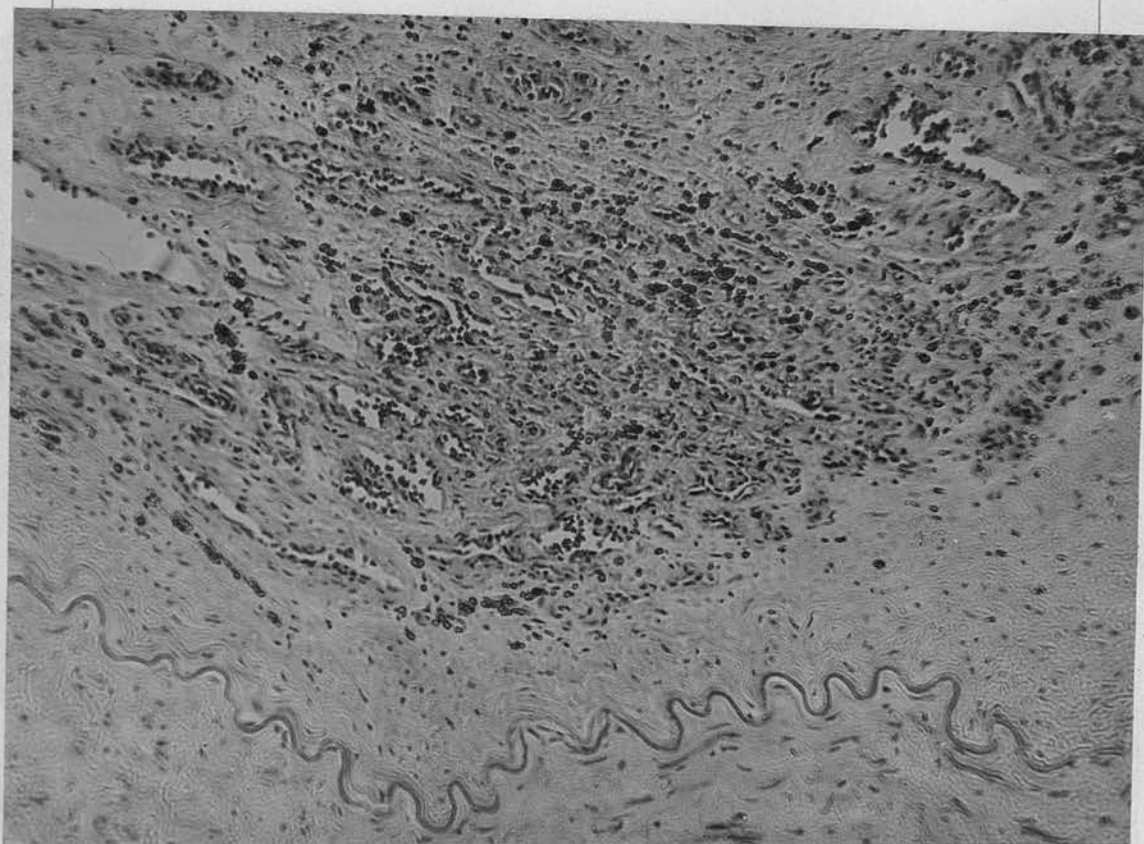


Fig. 20. Section of the peroneal artery from a case of atherosclerosis (age of subject 72 years). The section shows the thrombus has been invaded by highly cellular tissue in spite of the age of the subject. Some atheromatous changes in the intima and media are apparent but the internal elastic lamina is preserved intact. The picture is reminiscent of that seen in much younger subjects. Stain haematoxylin and eosin x 350.

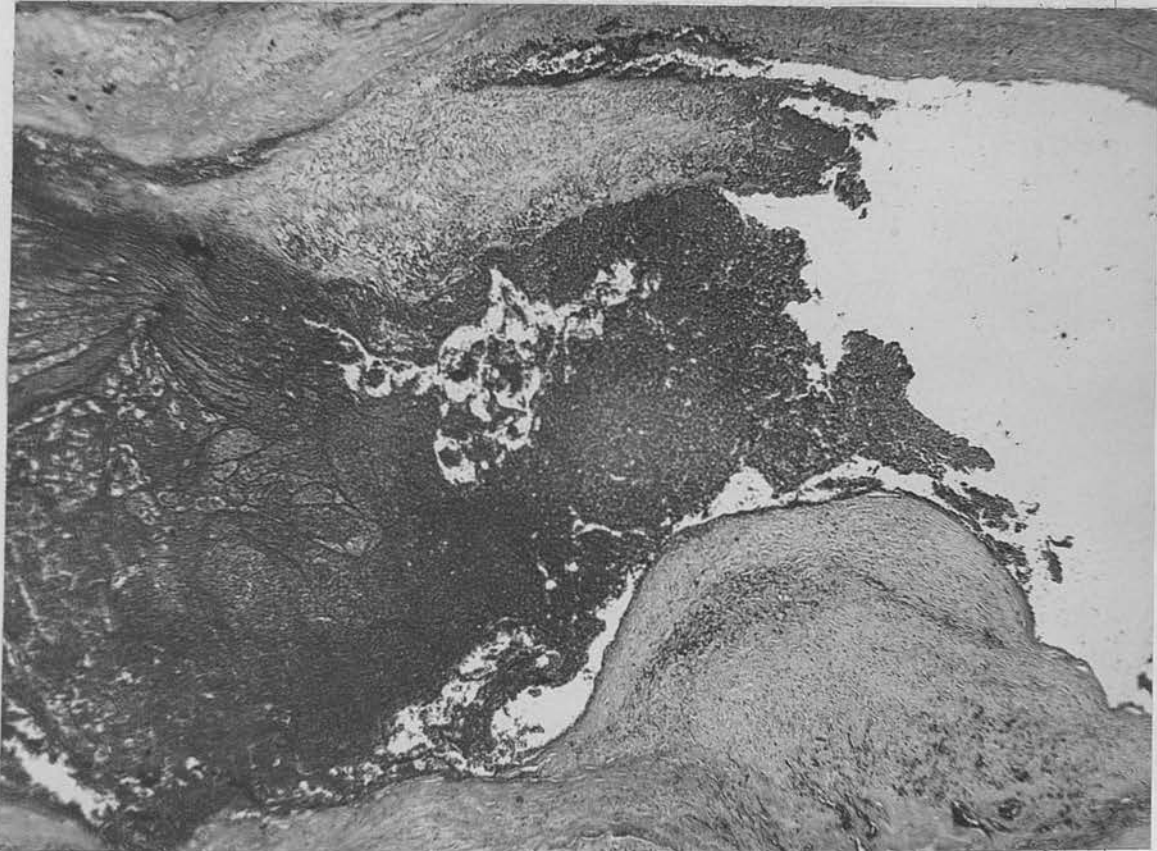


Fig. 21. Longitudinal section of the popliteal artery from a case of atherosclerosis (age of subject 71 years) showing part of the intima and the lumen occluded by recent thrombosis. In the lower atheromatous plaque small vessels can be seen deep in the intima. In the upper plaque the fusion of thrombus into atheromatous material can be seen. Some of the thrombus lies deeply but obviously is continuous with that in the lumen. Stain haematoxylin and eosin  $\times$  150.



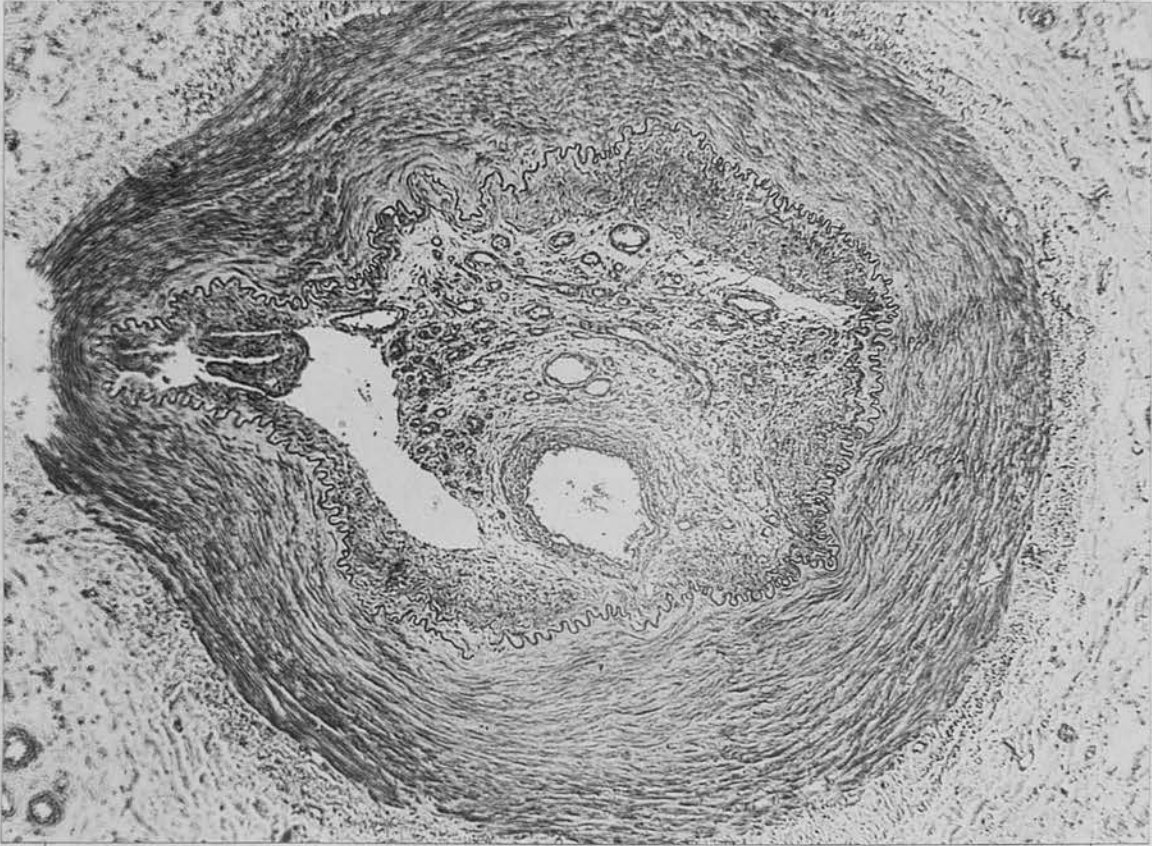


Fig. 22. Section of the anterior tibial artery from a case of thromboangiitis obliterans (age of subject 27 years). The lumen is occluded with organized thrombus in which numerous vascular channels are apparent. Some of the latter have acquired an arterial structure; others are thin-walled and are apparently serving as venous channels. The internal elastic lamina is preserved intact and there are no inflammatory changes in the media or adventitia. Stain haematoxylin and eosin x 50.



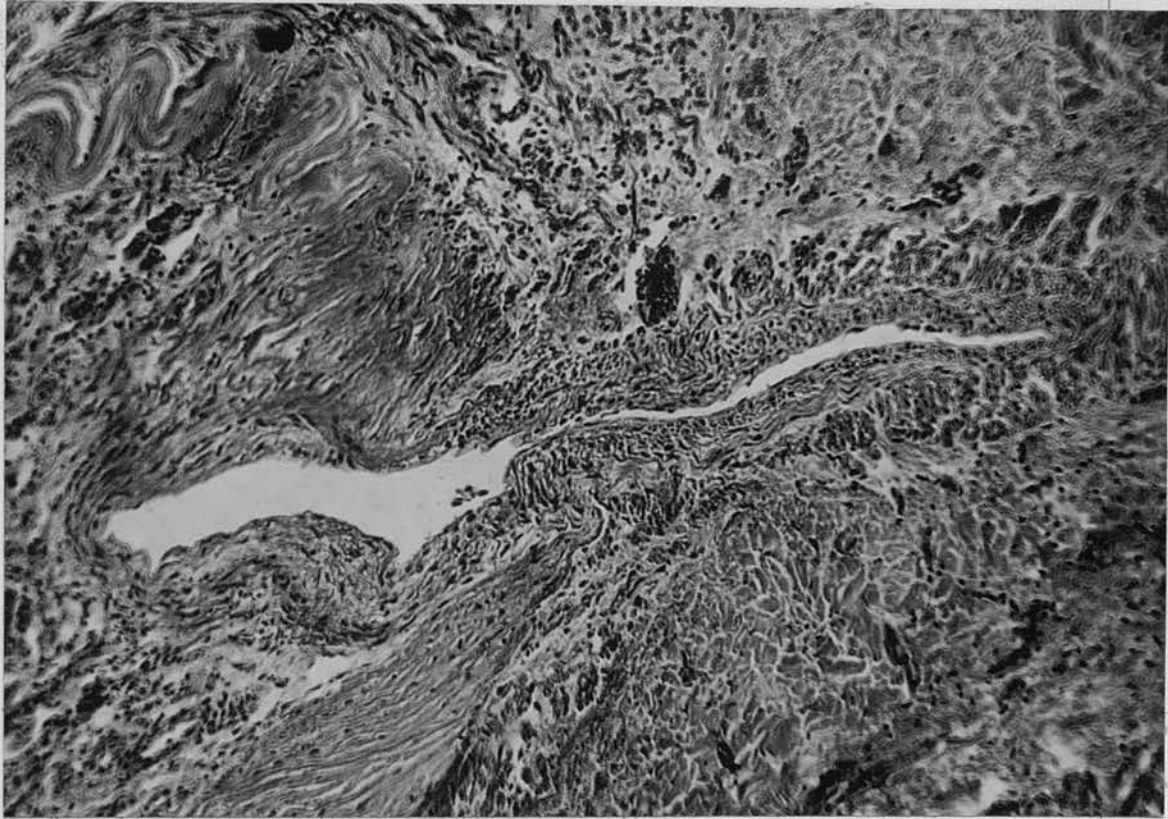


Fig. 23. Section of the dorsalis pedis artery from a case of thromboangiitis obliterans (age of subject 27 years). A vessel with an elastic coat and arterial structure is shown in the thrombus, communicating with a small patent branch. The cellular nature of the thrombus can be seen. There is a sparse infiltration of small round cells. Stain haematoxylin and eosin x 200.

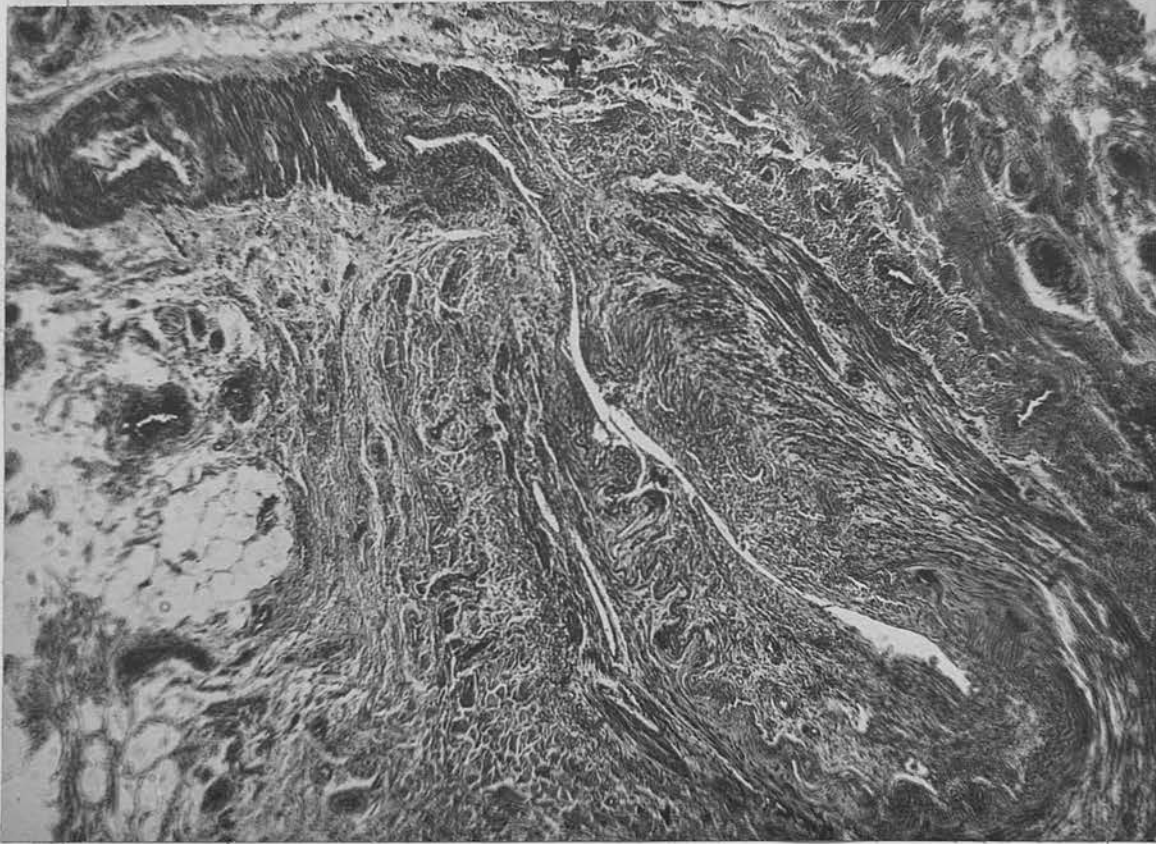


Fig. 24. Section of the vessel in fig. 23 cut from the same block at a lower level. The recanalizing vessel in the thrombosed artery is shown communicating with another patent branch. Stain haematoxylin and eosin x 100.

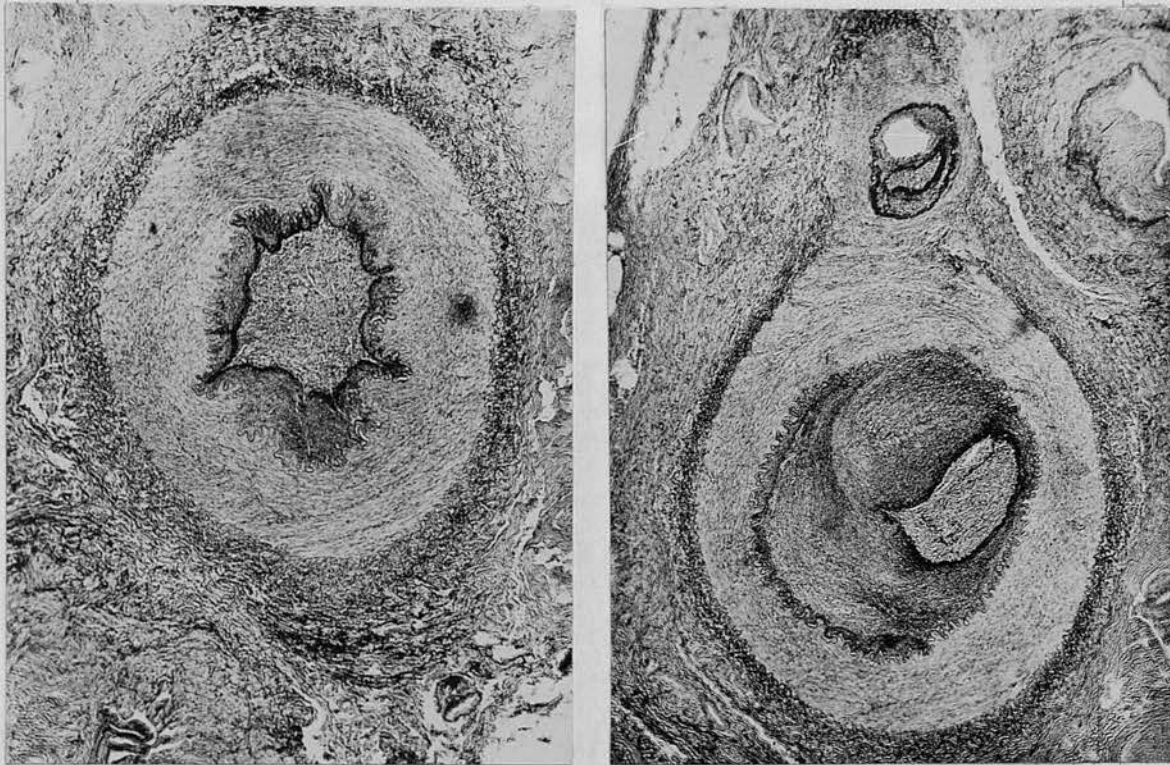


Fig. 25. Serial sections of the anterior tibial artery from a case of thromboangiitis obliterans (age of subject 43 years).

(a) The lumen is occluded with organized thrombus of recent origin. The original internal elastic lamina can be seen and also an elastic coat laid down round a later channel which subsequently became thrombosed.

(b) The same artery at a lower level showing more clearly the successive thrombotic incidents. A patent side branch is approaching. Weigert's elastic stain x 50.





Fig. 26. Same artery as fig. 25 at lower levels.  
(a) The elastic tissue is shown spreading out into the thrombus from the patent branch.  
(b) The patent branch enters the most recently thrombosed part of the main artery. Weigert's elastic stain x 50.





Fig. 27. Same artery as figs. 25 and 26 at lower levels.

(a) A recanalizing channel with early elastic tissue formation around it formed from the patent branch shown in fig. 26 (b).

(b) The recanalizing channel communicates with another patent branch at a still lower level. A further patent branch is seen entering at the bottom right corner. Weigert's elastic stain x 50.

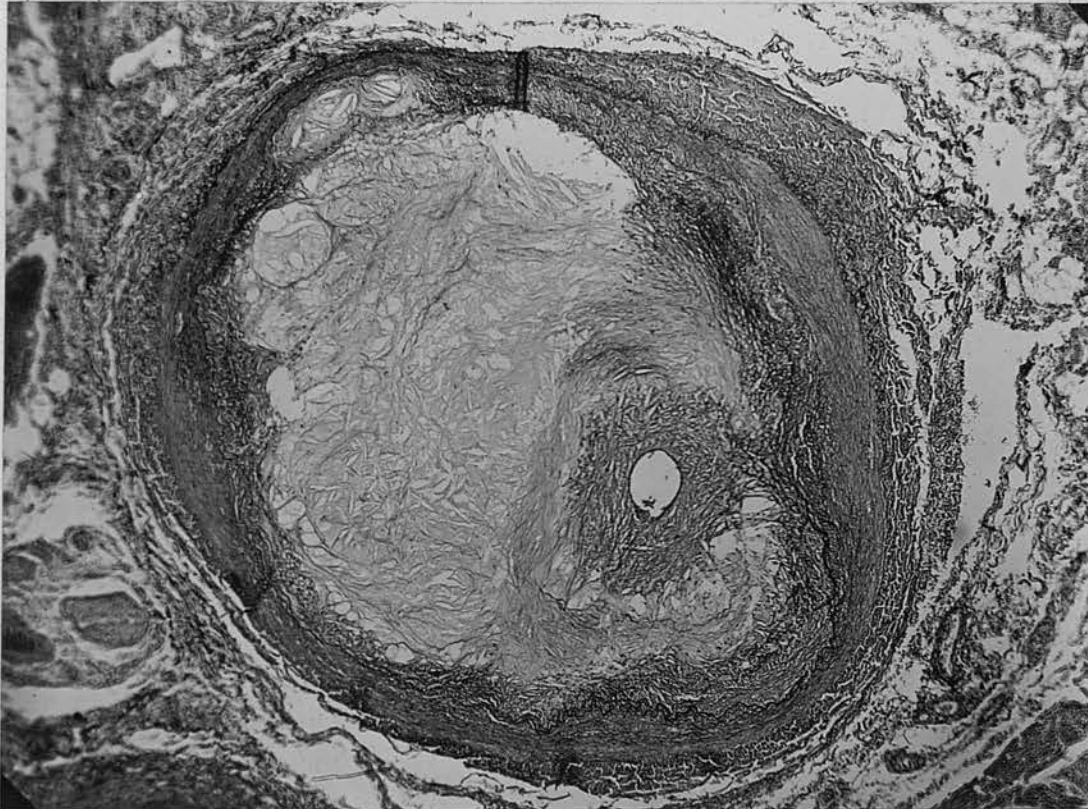


Fig. 28. Section from the posterior tibial artery in a case of atherosclerosis (age of subject 60 years). The artery is occluded with thrombus which has undergone atheromatous change. Numerous cholesterol clefts are present in the thrombus. A recanalizing vessel is seen surrounded by a condensation of elastic tissue. Weigert's elastic stain x 50.

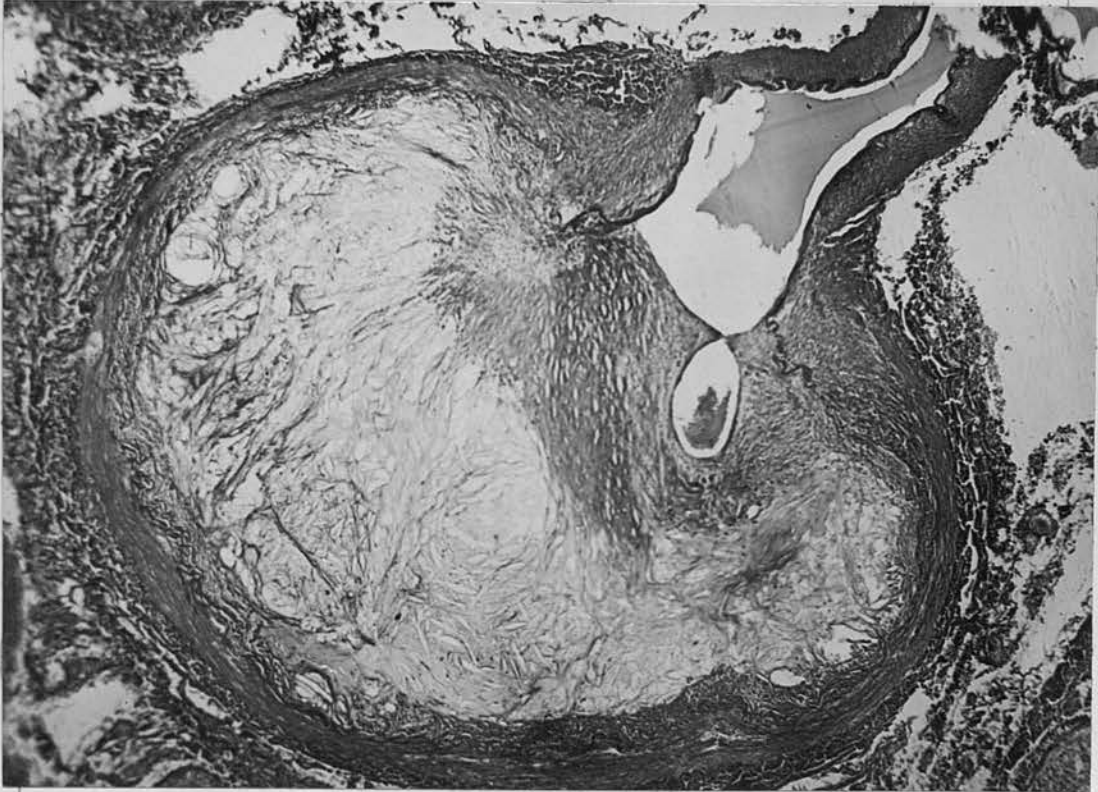


Fig. 29. Same artery as fig. 28 at a lower level after cutting serial sections. The recanalizing vessel is seen communicating with a patent branch. The elastic tissue in the thrombus can be seen spreading out from the internal elastic lamina of the patent branch. Weigert's elastic stain x 50.





Fig. 30. Portions of the tibial arteries from a case of atherosclerosis (age of subject 57 years). The limb was injected with a suspension of India ink in celloidin. Selected parts of the arteries were cleared by the Spalteholz method. The relations of the side branches to the recanalizing channels in the obstructed parts of the artery are shown. Subsequent microscopic sections showed that the portions of arteries not filled by the India ink contained no elastic-coated channels. Natural size.





Fig. 31. Radiograph of the leg of a healthy subject aged 23 years. The amputation was carried out on account of severe injury to the lower part of the thigh involving the popliteal artery. Injection has been carried out through the anterior and posterior tibial arteries. The main arteries have been filled but little has passed into the branches.

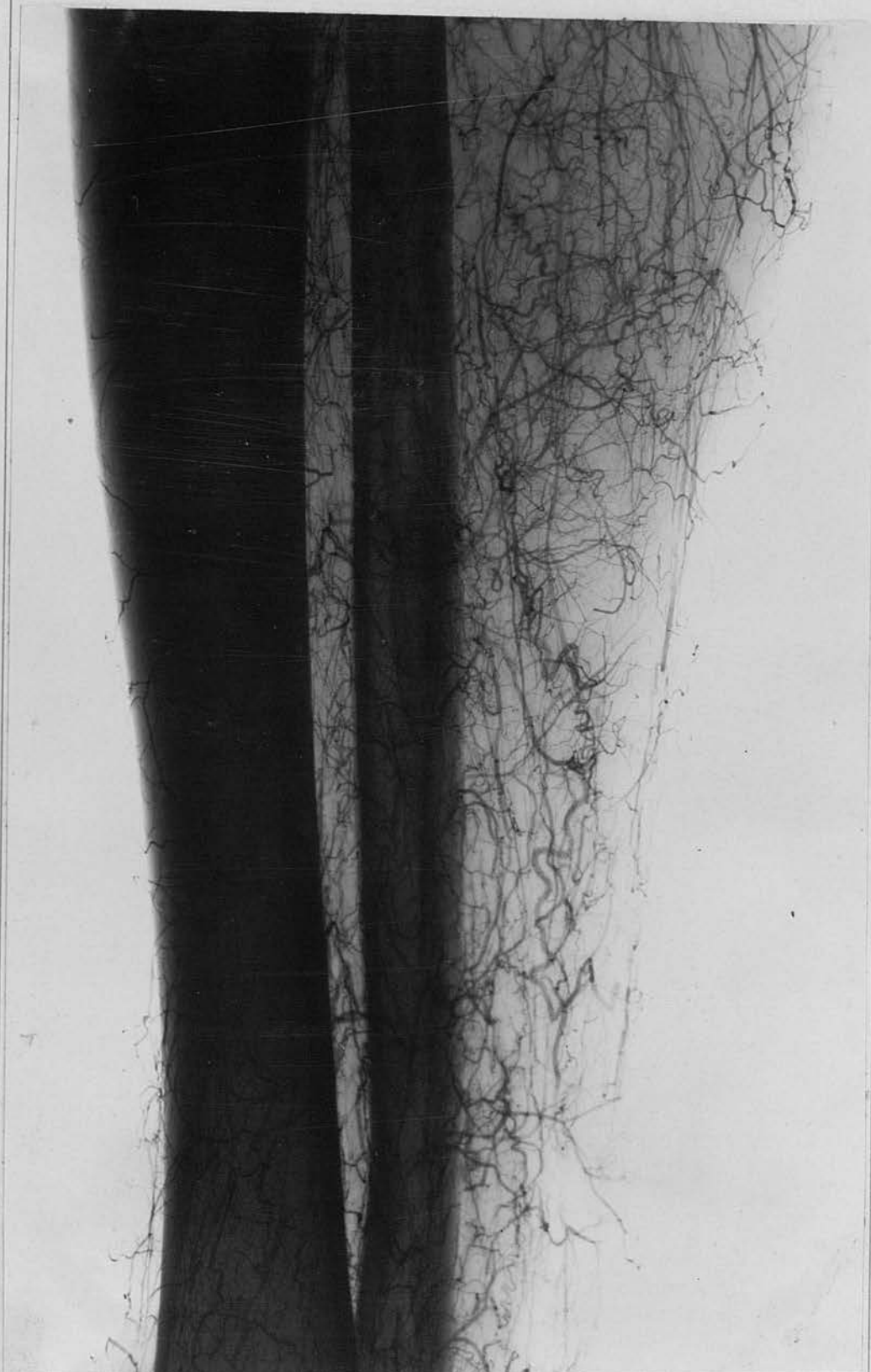


Fig. 32. Radiograph of the leg of a case of thromboangiitis obliterans (age of subject 43 years) injected through the popliteal artery (see fig. 34.). Lumbar sympathectomy had been carried out 16 months before amputation. The main arteries in this part of the leg are obliterated but there are a great number of small collateral vessels, many presenting the typical corkscrew appearances.



Fig. 33. Radiograph of the leg of a case of atherosclerosis and diabetes mellitus (age of subject 70 years). The filling of the anterior and posterior tibial arteries is intermittent owing to the presence of numerous obstructions from old thromboses. A few patent well filled branches are shown.

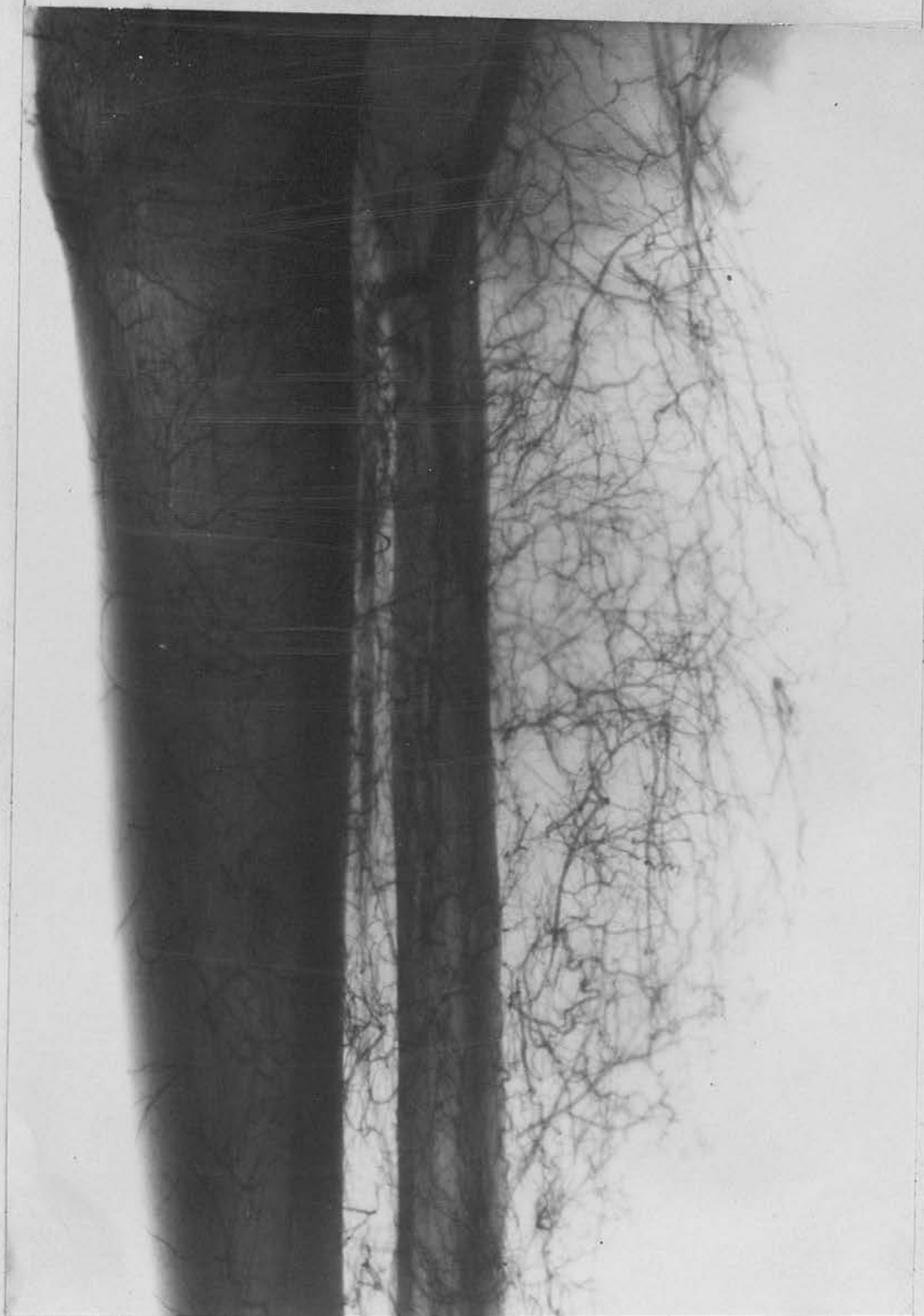


Fig. 34. Radiograph of the upper part of the leg of a case of thromboangiitis obliterans (same subject as figure 32). Though there was a history of the disease being present in this limb for 15 years the popliteal artery was not affected and is shown uniformly filled down to its bifurcation. The intermittent obstruction of the upper parts and the complete obliteration of the lower parts of the tibial arteries are apparent.





Fig. 35. Radiograph of the leg of a case of atherosclerosis (age of subject 71 years). The injection was through the popliteal artery which was only obstructed in its upper part. The posterior tibial artery is seen lying between the two bones and is only filled intermittently and incompletely. Several evenly-filled branches are seen communicating with the artery and with each other forming collateral pathways.

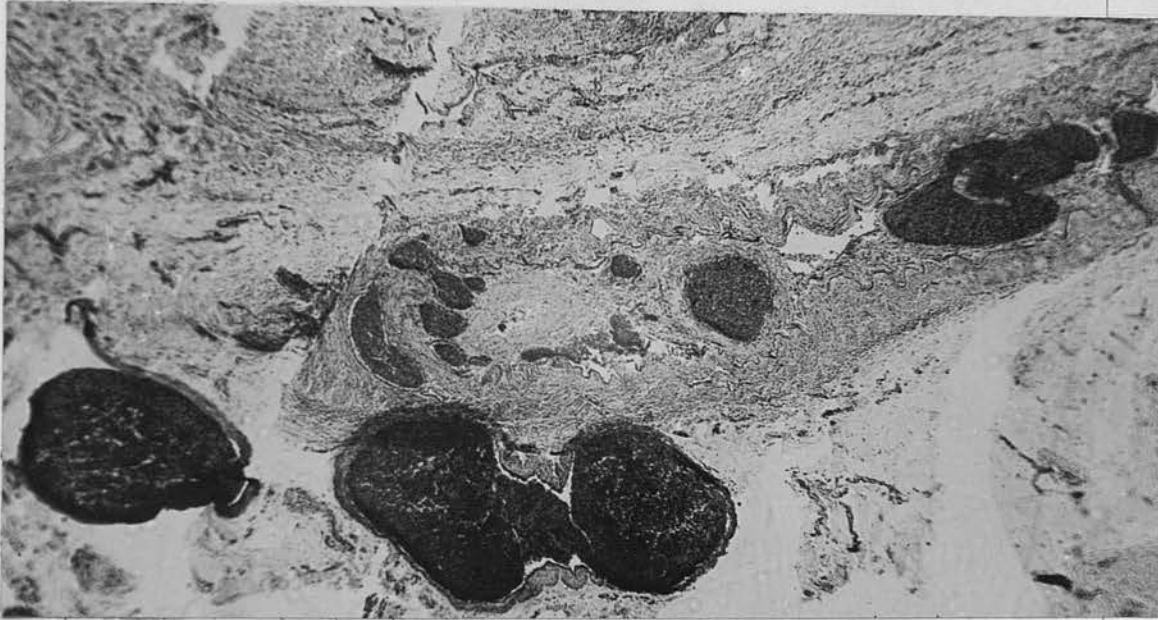


Fig. 36. Section of posterior tibial artery from a case of thromboangiitis obliterans (same case as figs. 32 and 34). The section is slightly oblique but shows that the elastic coated channels within the thrombosed artery have all filled with the lead phosphate which has also passed into the venae comitantes. Stain haematoxylin and eosin x 100.

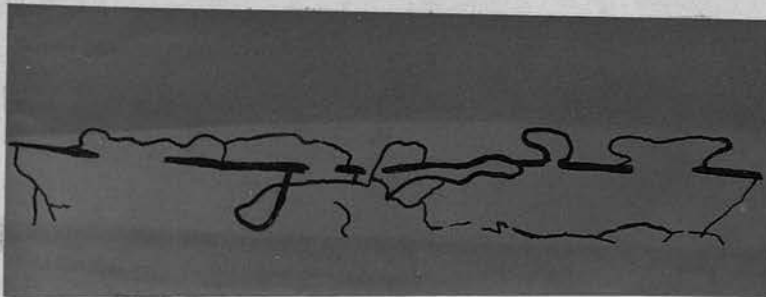


Fig. 37. Diagrammatic illustration of the development of the collateral circulation as seen in the posterior tibial artery of a case of atherosclerosis (age of subject 65 years). The reconstruction is based on a radiographic and dissection study. The absence of elastic coated channels in the unfilled portions of the posterior tibial artery was confirmed histologically.



Fig. 38. Section of the posterior tibial artery from a case of atherosclerosis (age of subject 70 years). The lumen is greatly narrowed by advanced atheromatous change. Calcification is present in the intima and media and there is a considerable infiltration of the latter coat with small round cells. Numerous widely dilated vascular channels are present in both of these layers. Stain haematoxylin and eosin x 50.





Fig. 39. A segment of femoral-popliteal artery in the region of the adductor hiatus from a male aged 53 years suffering from a moderate degree of peripheral atherosclerosis but having no symptoms of vascular disease during life. Numerous vasa vasorum are seen in the cleared specimens, outlined by India ink. The adventitia was completely stripped before clearing and these vasa accordingly lie in the media and intima. The transverse distribution of many of the vasa in the media is shown; those in the intima are irregular in their arrangement. x 4.

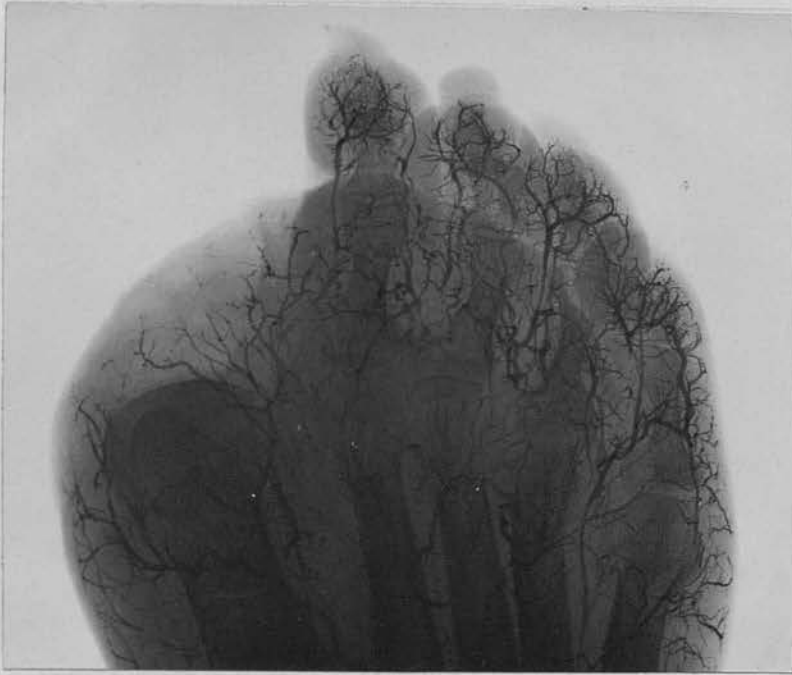


Fig. 40. Radiograph of the dorsal view of the forepart of the foot of a female case of diabetic vascular disease (age of subject 56 years). The great toe was amputated on account of ischaemic gangrene but the wound failed to heal. A below knee amputation healed without difficulty. The injection was carried out through the tibial arteries which though atherosclerotic were not grossly occluded and the injection mass flowed freely into the foot. The deficiency in arterial supply around the head of the first metatarsal is clearly shown. Subsequent histological sections in the region showed marked intimal hyperplasia in the small arteries and complete obstruction of the arterioles.



Fig. 41. Lateral view of the foot shown in fig. 40. The deficiency of arterial filling around the head of the first metatarsal is again demonstrated.

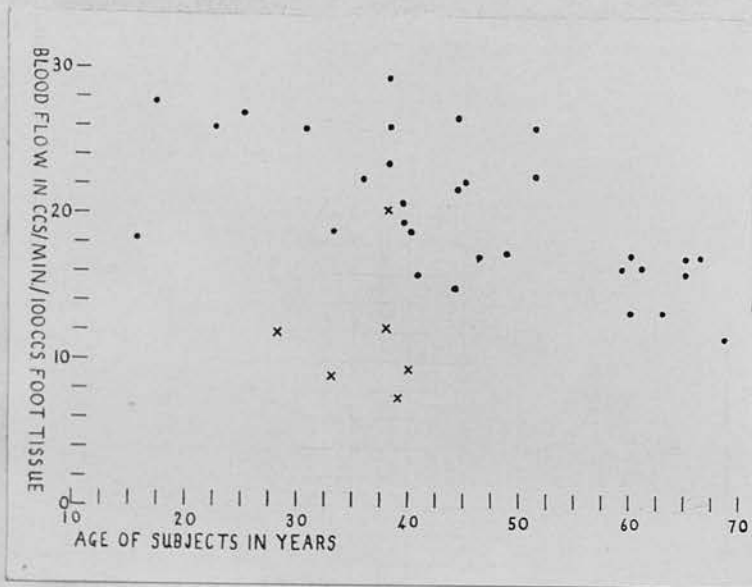


Fig. 42. Blood flow in normal subjects (black circles) and in cases of thromboangiitis obliterans (crosses). The blood flow was measured with the plethysmograph bath temperature at  $44^{\circ}\text{C}$  and thus represents the maximal circulatory capacity of the foot. In each case the more severely affected foot reading is plotted. In one case (M.M. in text) only two toes were conspicuously affected and the flow is thus in the normal range. In the five other cases the arteries in the foot were widely affected. In two cases with severe disease the flow could not be measured at  $44^{\circ}\text{C}$  and the results obtained with them are shown in fig. 47.



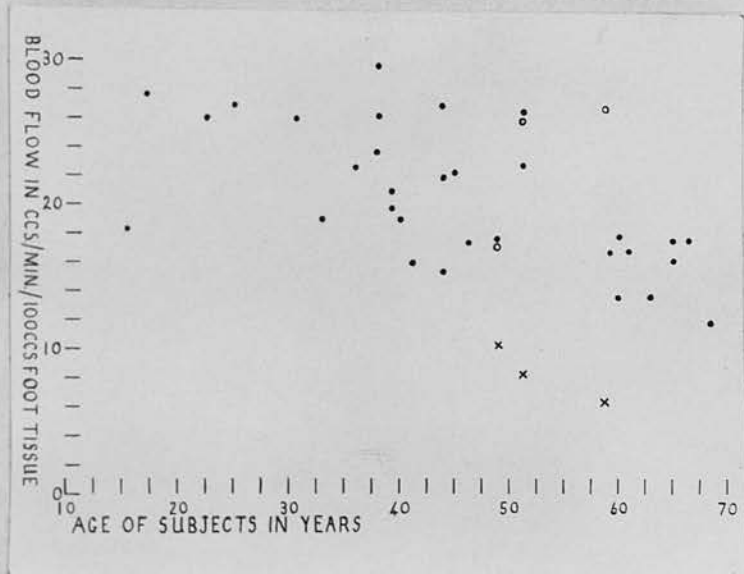
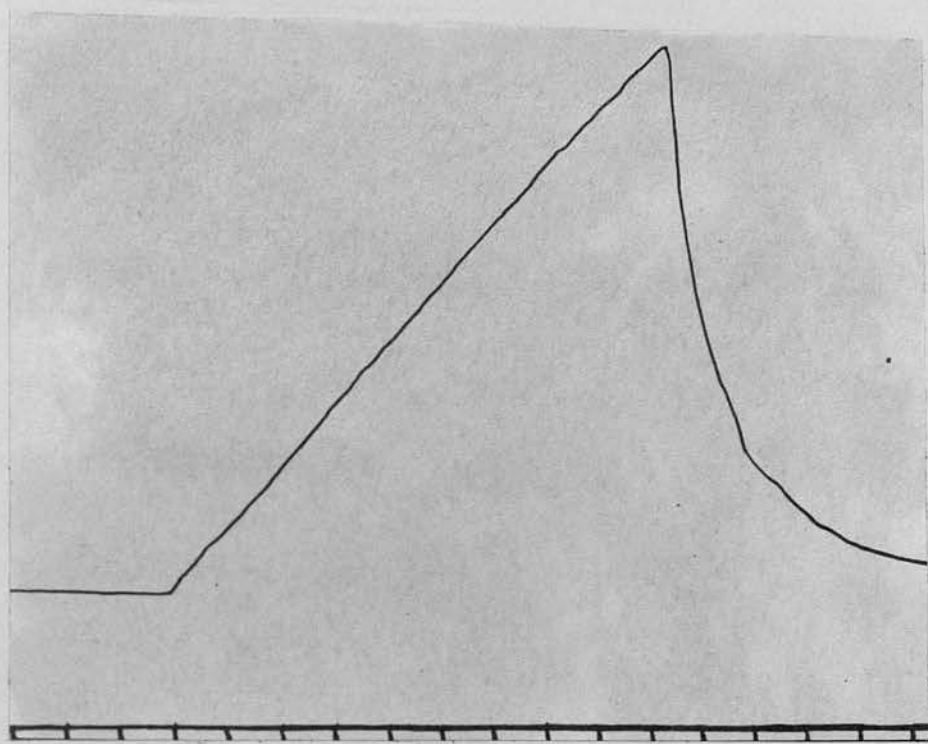
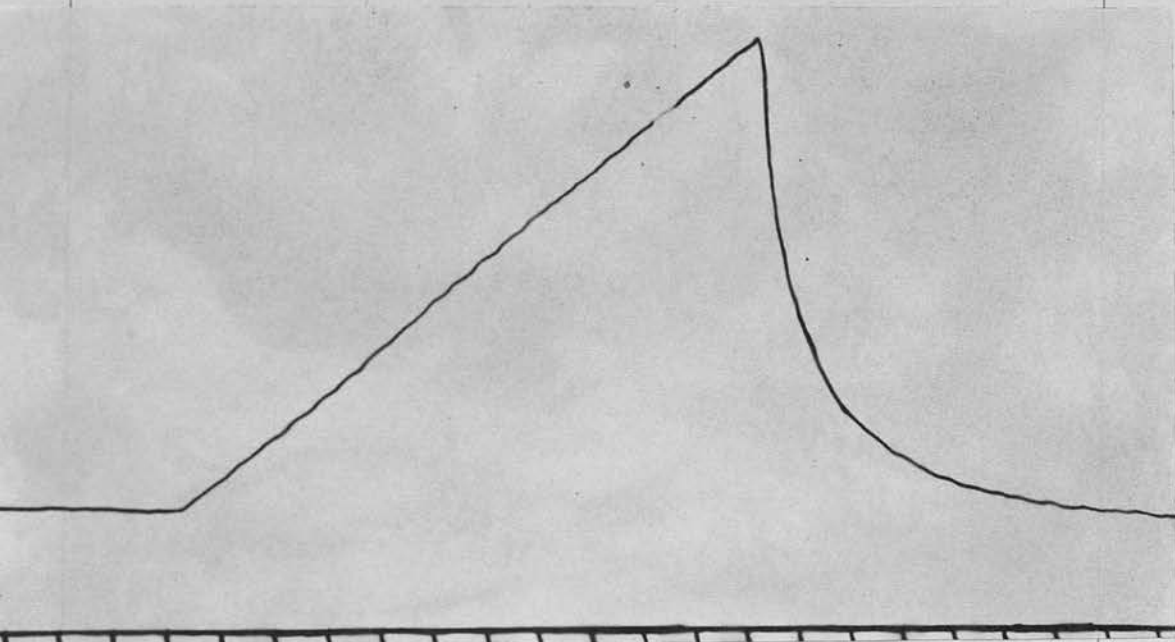


Fig. 43. Maximal blood flows in normal subjects (black circles) and in three cases of popliteal thrombosis (unaffected limb, open circles; affected limb, crosses). In the unaffected limbs the peripheral pulses were all present and the maximal blood flow was in the normal range. In the limbs with the thrombosis the maximal blood flow was greatly reduced; the thromboses had been present for at least one year at the time of the measurements.



(a)



(b)

Fig. 44. Maximal blood flow tracings from a case of atherosclerosis (age of subject 56 years). No pulses were present below the femoral artery and no pulsation is seen in the plethysmograms. (a) Inflow tracing in horizontal position 12.7 ml./min./100 ml. (b) Inflow tracing with foot elevated 19 cm. 9.3 ml./min./100 ml. Time marker 1.5 sec.

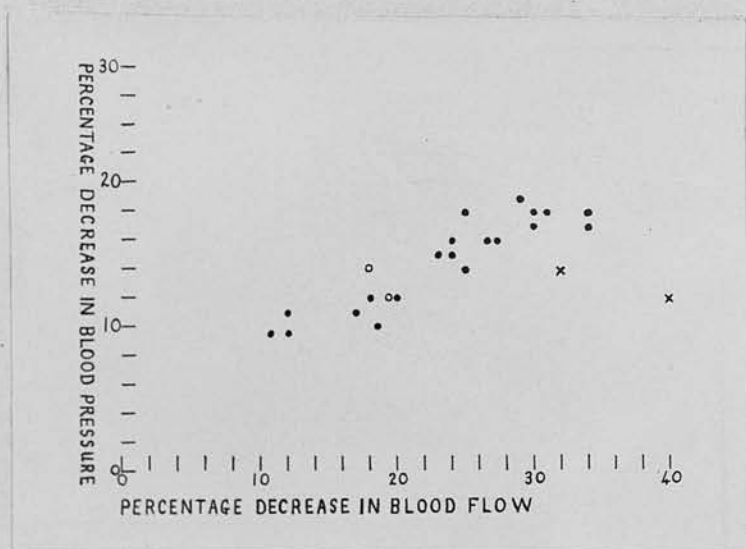


Fig. 45. Relation between maximal blood flow in the foot and mean intra-arterial pressure. Black circles represent subjects without obliterative vascular disease. On decreasing arterial pressure by elevating the foot there is a proportionately greater decrease in blood flow indicating that a passive collapse of arteries and arterioles has occurred coincidentally with the decrease in pressure. All the points charted have been obtained by elevating the foot 19 cm. The three points with the least percentage decrease in pressure were in grossly hypertensive subjects in whom less passive collapse occurred. The open circles represent unaffected limbs in two subjects with a unilateral popliteal thrombosis and the crosses, the results in the affected limbs. The results show that there was a considerable drop in the arterial pressure distal to the thrombosis.

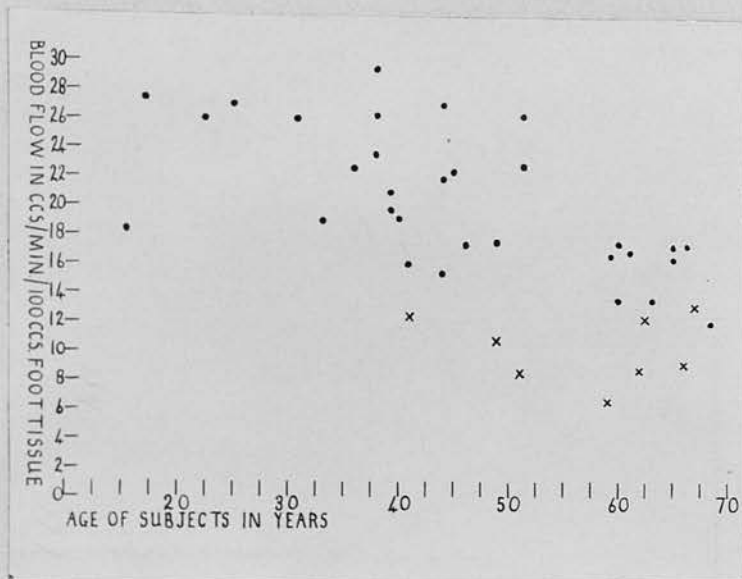


Fig. 46. Maximal blood flow in the foot in normal subjects (black circles) and subjects with thrombosis of the popliteal artery (crosses). The plethysmograph bath was maintained at  $44^{\circ}\text{C}$  and it was thus only possible to investigate subjects in whom a good collateral circulation had developed. These points accordingly represent the greatest extent to which the obstruction can be overcome. In the majority of the cases of sudden popliteal thrombosis the life of the extremity is in danger and the maximal foot blood flow cannot be measured in a plethysmograph.



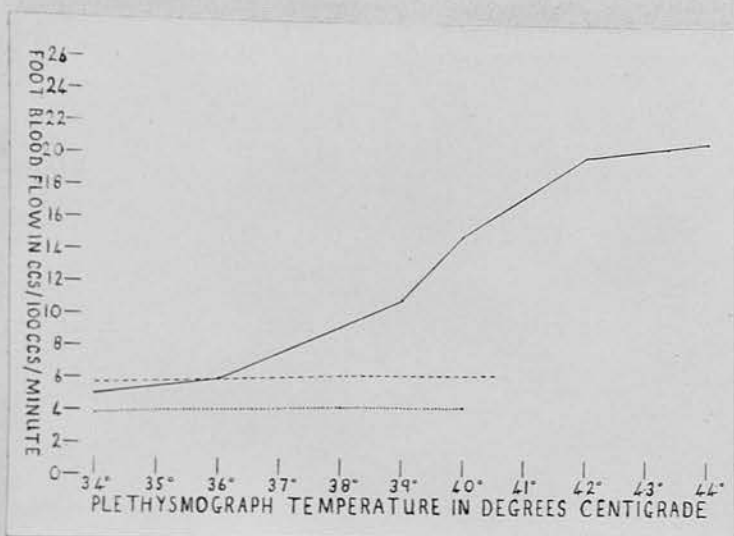
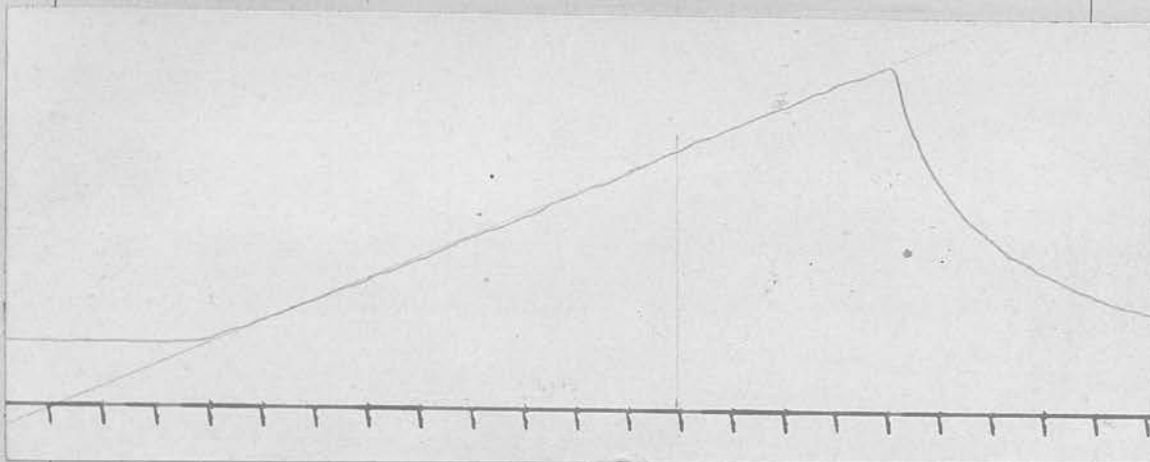
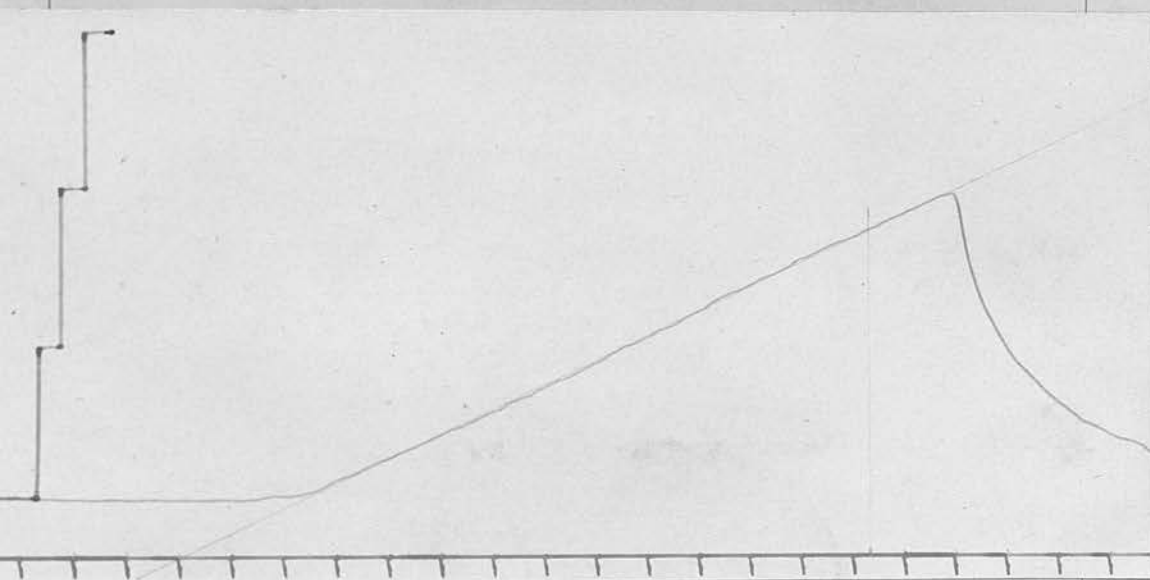


Fig. 47. Response of the blood flow in the foot to local heat.

In a normal subject (continuous line) there is a steady increase in blood flow as the plethysmograph temperature is raised indicating the reserve circulatory capacity of the arteries of the foot. The response of two subjects with advanced thromboangiitis obliterans is also shown (interrupted and dotted lines). In them the reserve circulatory capacity has been almost entirely lost and the resting blood flow is practically the total possible blood flow.



(a)



(b)

Fig. 48. Foot blood flow tracings in the more severe case of thromboangiitis obliterans shown in figure 47.

(a) Resting blood flow 3.4 ml./min./100 ml.

(b) After 5 min. arterial occlusion during height of reactive hyperaemia blood flow 4.2 ml./min./100 ml.

Calibration in 5 ml. increments. Plethysmograph

temperature  $34^{\circ}\text{C}$ . Time marker 1.5 sec. The figure

obtained by this method for the maximal circulatory agrees

closely with that obtained by the local heating method.

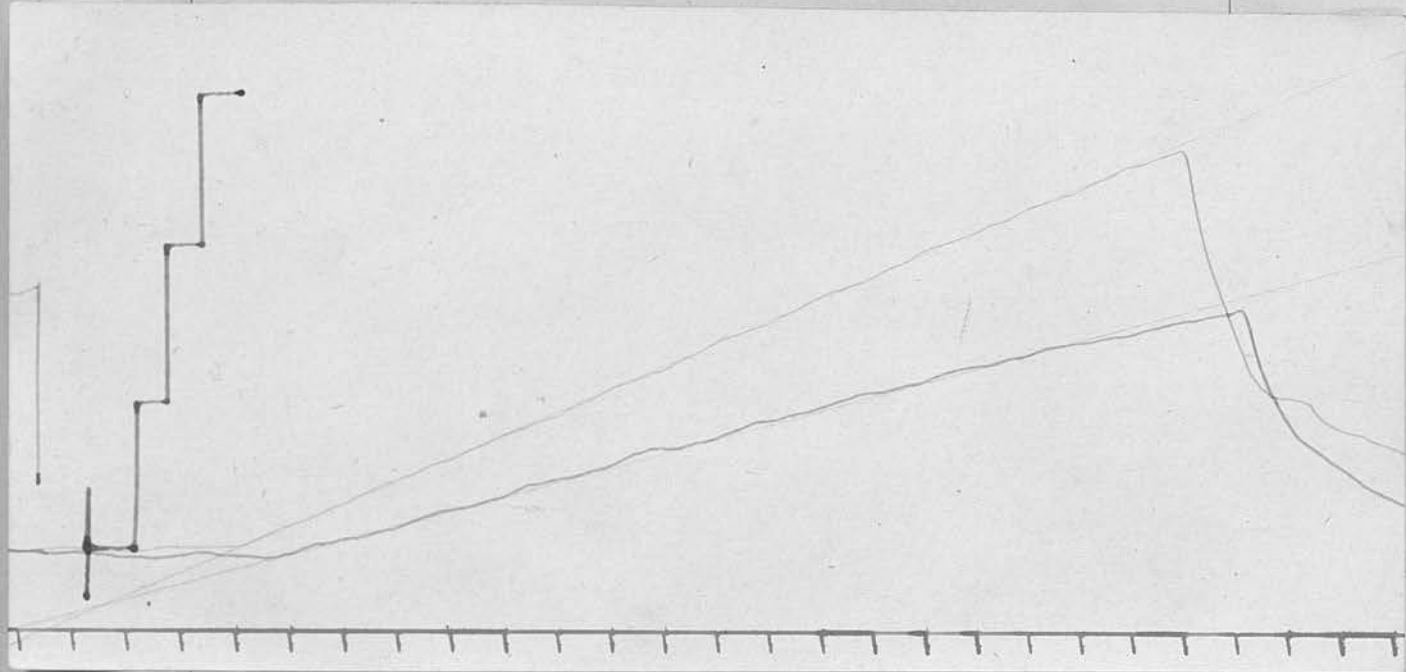
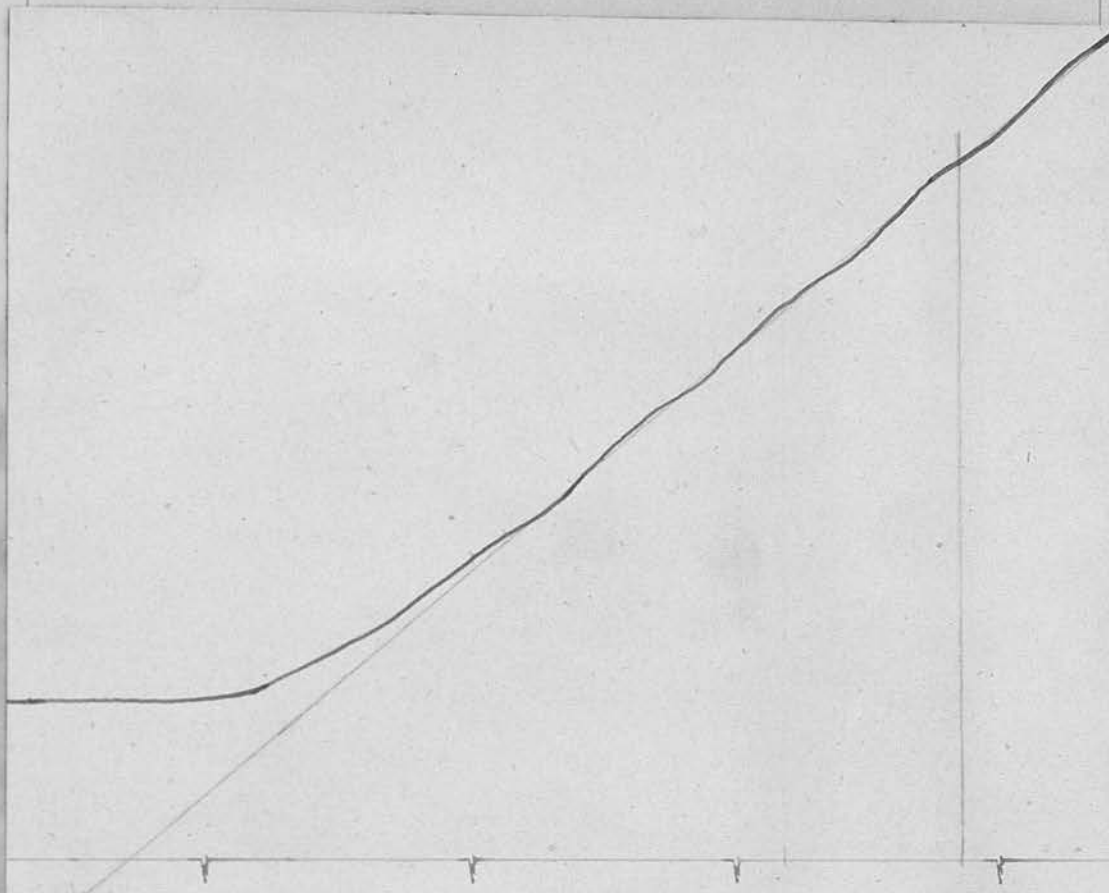
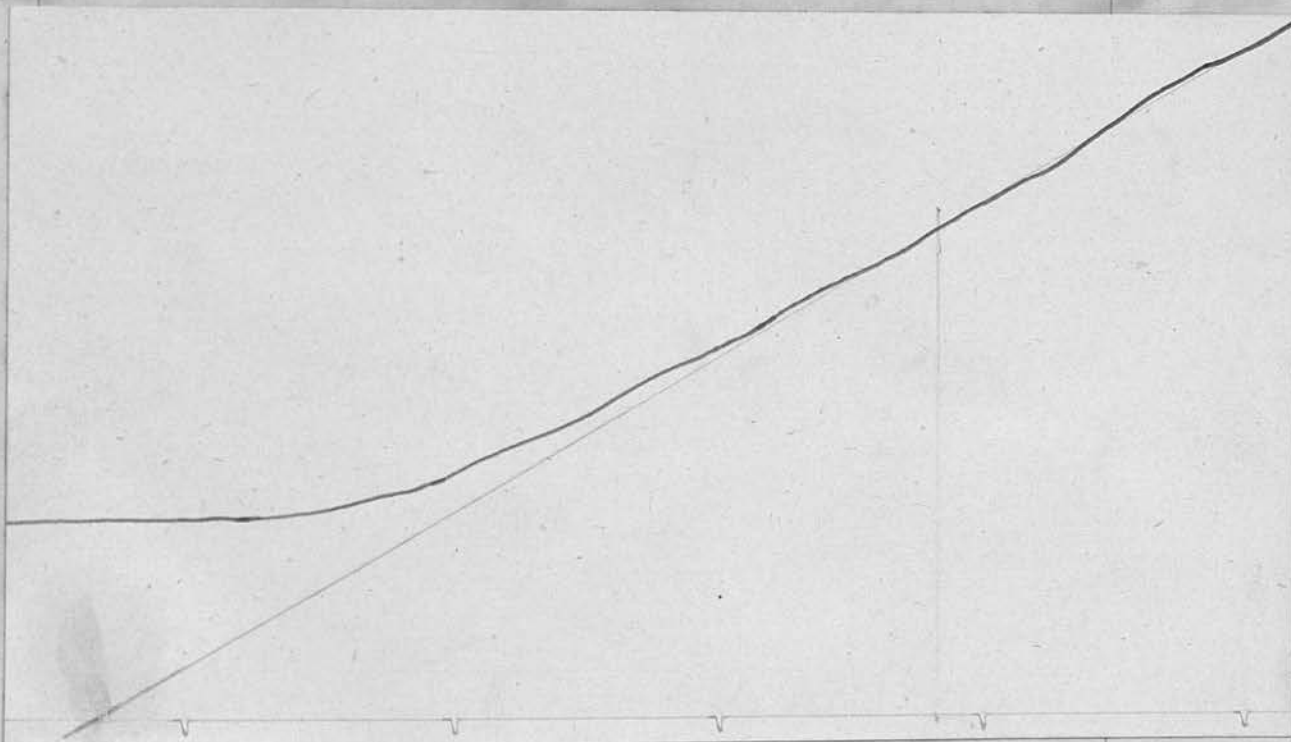


Fig. 49. The effect of elevating the foot 19 cm. on the blood flow in the same case as shown in figures 47 and 48 after sympathectomy. Upper tracing limb horizontal, blood flow 3.7 ml./min./100 ml.; lower tracing limb elevated, blood flow 2.1 ml./min./100 ml. Calibration in 5 ml. increments. Plethysmograph temperature  $34^{\circ}\text{C}$ . Time marker 1.5 sec.



Right calf. 29.2 ml./100ml./min. Time marker 1.5sec.



Left calf. 19.0 ml./100ml./min. Time marker 1.5sec.

Fig. 50. calf blood flows during reactive hyperaemia in a case of left-sided intermittent claudication.



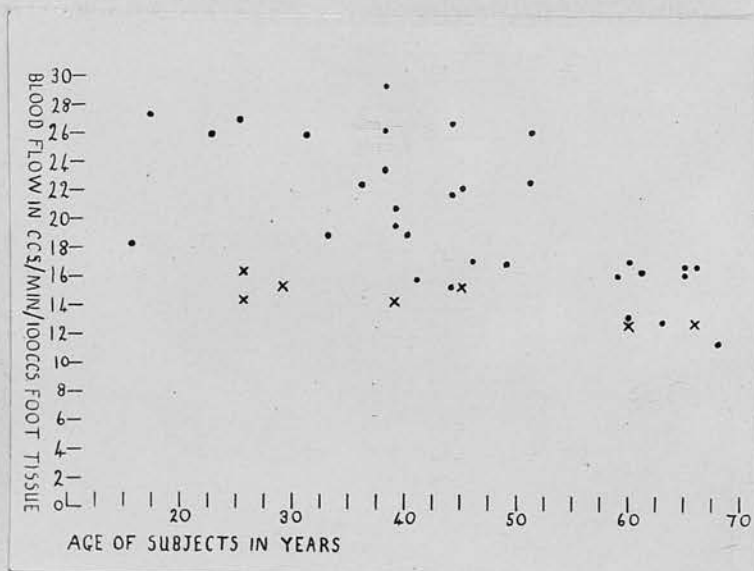


Fig. 51. Maximal foot blood flow in seven subjects with long-standing diabetes mellitus. Black circles, normal subjects; crosses, subjects with diabetes mellitus. The five younger subjects all had normal pedal pulses and no signs or symptoms of vascular disease in the lower limbs. The two older subjects had palpable pedal pulses but had had minor cutaneous lesions about the toes. The reduction in blood flow in these cases is attributed largely to disease of the small vessels.