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

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THE BLOOD FLOW DISTAL TO A COARCTATION OF THE AORTA.
In the investigations reported so far, attention has been chiefly paid to circulatory disturbances arising from local structural changes in the arteries of the lower limbs. The blood flow in the foot distal to an obstruction in, for example, the popliteal artery, has been studied and it has been shown that in these circumstances the peripheral circulation was considerably reduced. It was then decided to investigate the effect of a stricture considerably higher up and for this purpose a series of cases of coarctation of the aorta were chosen. In recent years as a result of successful surgical operations, increasing attention has been paid to the clinical features and pathological physiology of this disorder. Measurements of the blood flow in the limbs beyond a coarctation of the aorta have been reported by Lewis (1933), Wakim et al. (1948) and Bing et al. (1948). These investigations have all determined the resting blood flow in the leg and made no attempt to determine the circulatory reserve of the calf or foot. Clinical descriptions of cases of coarctation have occasionally referred to the development of intermittent claudication in the lower limbs (Eppinger and Middlefart (1933), Ejrup (1948)). This symptom, as has previously been shown, is essentially the result of a reduction in the circulatory capacity of the limb. The purpose of the present study is therefore to determine the maximal foot circulation possible in patients with a coarctation of the aorta and to compare these results with those obtained in normal subjects and in patients with intermittent claudication due to peripheral vascular disease. It has been possible to study six cases of coarctation of the aorta. They have not been selected
in any way and were referred to the writer after diagnosis in the hospital outpatient department.

Case Reports and Circulatory Measurements.

Case 1. H.R., a male aged 31 years complained of a slight cough with sputum during the three weeks immediately before he was seen. This was attributed to a cold which refused to clear up. Otherwise he had no complaints but was sent to hospital on account of a high blood pressure found at a life insurance examination. In childhood he had been told that he had a cardiac disorder and was advised not to play games. He disregarded this advice after the age of 14 years and subsequently took part regularly in cross-country running with considerable success. He served throughout the war with the Royal Engineers in the 8th Army.

On examination he appeared fit and well developed. The right carotid pulsations were conspicuously forceful and the left weak. The right subclavian pulse was strong but the left was greatly diminished. The left brachial and radial pulses were weak and delayed. The right suprascapular, intercostal and epigastric arteries were all prominent and pulsating freely. There were no palpable vessels on the left side of the chest wall. Weak femoral, dorsalis pedis and posterior tibial pulses were felt. The cardiac apex was 10 cm. from the midline in the 5th space. A systolic murmur was present at the apex and over the lower end of the sternum where it was louder. The blood pressure in the right arm was 160/100, in the left arm 120/105 and in the lower limbs 95 mm. by palpation, no auscultatory readings being possible. In the left infraclavicular region numerous fine crepitations were heard. No abnormality was found in the other systems.
Radiological examination of the chest showed moderate cardiac enlargement with some left ventricular hypertrophy. The transverse diameter was 14.0 mm. The aortic knuckle was not prominent. Rib notching was extremely conspicuous on the right third to ninth ribs but only minimal on the left side. Extensive pulmonary tuberculous infiltration with early cavity formation was present in the left upper lobe.

The clinical diagnosis was pulmonary tuberculosis and coarctation of the aorta between the origins of the innominate and left carotid arteries.

Blood flow determinations with the foot plethysmograph at 44°C centigrade showed the maximal circulation of the right foot to be 26.8 ml/min/100 ml. (average of 43 readings: coefficient of variation 3%). Pulsations were absent in the plethysmograms (fig52).

As the main arteries to the two upper limbs arose proximal and distal to the coarctation, the blood flow in the hands was also measured. This was done simultaneously in two calorimeters. The thermometers were calibrated against each other and the difference between them over the range 27-33°C was less than 3%. The heat elimination of the left hand was consistently slightly greater. In view of this surprising result the calorimeters and thermometers were changed to opposite sides and the investigation repeated with a similar result. Before each determination, both hands were soaked in the same basin of water for 20 minutes to exclude any external environmental difference between the two hands. The same volume of hand tissue was inserted into each calorimeter bath and all the precautions detailed in an earlier section were rigorously observed. The average resting heat elimination was
Right hand 4.1 cal./min./100 ml. and Left hand 4.9 cal./min./100 ml.

At full vasodilatation obtained after immersing the feet in water at 45°C, the heat elimination was Right hand 73 cal./min./100 ml. and Left hand 80 cal./min./100 ml.

Case 2. G.H, 24 years, a male tractor driver played games at school until stopped at the age of 11 years by the school doctor. Since then he has always been unduly breathless on exertion but habitually went on long bicycle rides up to 25 miles a day when aged 17 years without any apparent discomfort. When 18 years old he developed a pain outside the left nipple and a constricting sensation in the centre of the chest. This pain was associated with exertion but often persisted for several days after any severe effort. It occasionally occurred while at rest in bed. It was never promptly eased by resting. On running upstairs he has noticed a tingling sensation in the calves eased by resting, but he has never had any definite pain or constricting sensation in the legs.

On examination he was a muscular individual both in the upper and lower parts of the body. Strong arterial pulsations were obvious in the neck. The radial pulses were strong and equal in force. The femoral pulses were weak and delayed in comparison with the radial. Large collateral arteries were palpable on both sides of the chest wall. The cardiac apex was 11 cm. from the midline in the 4th space. A loud second sound was heard at the 2nd right costal cartilage and a harsh systolic murmur was present widely conducted over the precordium and in the interscapular region posteriorly. The blood pressure in the right arm was 195/75 and in the left 205/95. In the right thighs faint sounds were heard over the range 140 to 120 mm. No abnormality was found in the other systems.
Radiological examination of the chest showed slight left ventricular hypertrophy and a small aortic knuckle. The transverse diameter was 150 mms. Conspicuous rib notching was present on both sides.

The clinical diagnosis was coarctation of the aorta beyond the origin of the left subclavian artery and effort syndrome.

Blood flow determinations with the foot plethysmograph at 44°C showed the maximal circulation of the right foot to be 24.0 ml./min./100 ml. (average of 58 readings; coefficient of variation 5%). Pulsations were absent in the plethysmograms.

Case 3. E.S. a male aged 15 years remained well until aged 13 years, when he was admitted to hospital complaining of weakness of the hands and legs of two weeks duration. A diagnosis of coarctation of the aorta was made. After discharge from hospital he noticed a weak sensation after strenuous exertion such as running upstairs. This sensation departed after standing still for a minute or two. There was never any pain in the legs. He was able to indulge in considerable exertion, cycling and swimming without any symptoms.

On examination he was a well developed boy without any noticeable abnormality in the lower limbs. The radial pulses were equal and synchronous. The femoral pulses were feeble and delayed in relation to the radial. Pulsating vessels were palpable on both sides of the chest wall. The cardiac apex was in the fourth space 10 cm. from the midline. A loud systolic murmur was present all over the precordium maximal in the third left space. The blood pressure in the right arm was 155/85 and in the left 160/90; in the legs it was approximately 110/90. No abnormality was found in the other systems.

Radiological examination of the chest showed an enlarged
left ventricle and a small aortic knuckle. The transverse diameter of the heart was 150 mm. Considerable rib notching was present on both sides.

The clinical diagnosis was coarctation of the aorta beyond the origin of the left subclavian artery.

Blood flow determinations with the foot plethysmograph at 44°C showed the maximal circulation of the right foot to be 20.9 ml./min./100 ml. (average of 15 readings; coefficient of variation: 5%). Faint pulsations were present in the plethysmograms.

Case b. R.P., a female aged 19 years was admitted for treatment of a duodenal ulcer. She had no symptoms referable to the cardiovascular system but had been rejected for military service on account of a cardiac abnormality. She suffered from cold hands and feet during the winter but had never noted any colour changes or pain in the limbs. She had chorea when 9 years old and pneumonia in infancy. Her mother and several maternal relatives had goitres.

On examination, a moderate degree of thyroid enlargement was present. Conspicuous pulsation was noted in the carotid arteries. The radial pulse was of equal strength on the two sides. The femoral pulses were weak and delayed in comparison with the radial. The cardiac apex was felt in the 5th space 3 cm. from the midline. A systolic murmur was heard over the whole precordium and in the interscapular region. Pulsating intercostal and suprascapular arteries were felt on both sides of the chest.

The blood pressure was in the right arm 150/96, in the left arm 148/88, in the right thigh 125/110 and in the left thigh 120/104.

Radiological examination showed conspicuous bilateral rib notching, left ventricular enlargement and some fulness of the
ascending aorta (fig53). A barium swallow demonstrated a
double aortic impression and the site of constriction was
clearly shown opposite the disc space between T5 and T6 vertebrae.

The clinical diagnosis was duodenal ulcer, simple goitre and
coarctation of the aorta beyond the origin of the left subclavian
artery.

Blood flow determinations with the foot plethysmograph at
44° centigrade showed the maximal circulation of the right foot
to be 13.0 ml./min./100 ml. (average of 25 readings: coefficient
of variation 6%). Faint pulsations were present in the
plethysmograms (fig54).

Case 5. A.H. a female, aged 30 years, was found during her
first pregnancy to have a blood pressure of 150/95. There was
no albuminuria but the child was stillborn. She was again
pregnant in 1940 but this pregnancy was terminated and she was
sterilized on account of hypertension. In April 1949 she was
admitted to hospital because of swelling of the ankles and
increasing dyspnoea on exertion. The haemoglobin at this time
was 58%. She was subsequently treated with iron and the
haemoglobin rose to 96%. The breathlessness and swelling of the
ankles subsided. She has had no pain in the legs.

On examination she was a well developed woman with strong
arterial pulsation in the neck. Both radial pulses were of
equal strength but the femoral pulses were almost impalpable.
There was no venous congestion in the neck. The cardiac apex
was felt in the 5th space 10 cm. from the midline. A loud
systolic murmur was heard over the precordium and in the
interscapular region. Several collateral vessels were felt on
both sides of the chest wall.

Radiological examination of the chest showed slight left
ventricular enlargement, rib notching and a small aortic knuckle.

While in Hammersmith Hospital, direct arterial pressure readings were recorded simultaneously in the brachial and femoral arteries (Dr. J.F. Goodwin). The brachial pressures were systolic 190, diastolic 133, mean 154; and the femoral systolic 167, diastolic 133, mean 156.

She was referred to St. Mary's Hospital for blood flow determinations. With the foot plethysmograph at 44° centigrade the maximal blood flow was 22.4 ml./100 ml./min. (average of 30 readings; coefficient of variation 5%). Faint pulsations were present in the plethysmograms.

The coarctation was subsequently excised but the aortic suture broke down six weeks after operation and the patient died suddenly. No post operative blood flow determinations were thus possible.

Examination of the portion of the aorta resected showed a gross stenosis with the lumen reduced to a transverse diameter of 2 mm. over a distance of 2 mm. The blood flow to the lower limbs in this case was thus almost entirely through collaterals in the chest wall.

Case 6. M.H. a female aged 17 years, had no definite complaints but always noticed that she became breathless on exertion sooner than her comrades. Nevertheless, she played all games at school and had never experienced any pain in her legs. She was referred to hospital by her school doctor after a medical examination.

On examination she was a healthy well developed girl. There was conspicuous arterial pulsation in the neck. Both radial pulses were strong and equal. The femoral pulses were not felt. The blood pressure was 185/100 in both arms. The
cardiac apex was in the 5th space 9 cm. from the midline. A systolic murmur was present over the precordium and at the back in the interscapular area. Collateral vessels could be felt in the chest wall.

Radiological examination showed some left ventricular enlargement. The aortic knuckle was not unduly hypoplastic. There was faint evidence of bilateral rib notching.

The clinical diagnosis was coarctation of the aorta distal to the origin of the left subclavian artery.

Blood flow determinations with the foot plethysmograph at 44°C centigrade showed the maximal foot flow to be 19.1 ml./min./100 ml. (average of 24 readings; coefficient of variation 7%). Extremely faint pulsations were detected in the plethysmograms.
Statistical Analysis of Results

The results in the cases of coarctation of the aorta are shown in figure 55. They have been compared with those obtained in 33 normal subjects and in 16 subjects with intermittent claudication as the predominant symptom of obliterative vascular disease.

The mean maximal blood flow in normal subjects of all ages was 20.5 ml./min./100 ml. of foot tissue. In the cases of coarctation it was 21.6 ml./min./100 ml. of foot tissue. Comparing the cases of coarctation with normal subjects of similar age groups and using the t test the calculated value of t was 0.53; with P = 0.05 Fisher and Yates (1938) give t as 2.02. There is thus no significant difference between the normal subjects and those with coarctation of the aorta as regards foot blood flow.

The difference between the normal subjects and those with intermittent claudication has already been discussed. The patients with claudication fell into an older age group than those with coarctation, but even allowing for this the difference between the levels of blood flow was great. The mean maximal foot blood flow in those with intermittent claudication was 10.4 ml./min./100 ml. The calculated value of t was 8.15 and with P = 0.01 Fisher and Yates give t as 2.88. There was thus a highly significant difference between the flows of those with claudication and those with coarctation of the aorta.
DISCUSSION

The results show clearly that in the six cases of coarctation of the aorta the collateral circulation in the chest wall was adequate for the provision of a normal blood flow to the lower limbs. Even at full vasodilatation the blood flow was the same as in healthy subjects and there was no reduction in the maximal circulatory capacity. The blood flow in the two subjects with coarctation (Cases 2 and 3) who complained of symptoms in the legs on exertion were well above the levels seen in association with intermittent claudication secondary to arterial disease in the limbs. The clinical features of Case 2 were not typically those of claudication as the sole sensation in the legs as a result of exertion was described as "tingling". In Case 3 the complaint was of weakness in the legs on exertion and there was no mention of pain or cramp. The sensation quickly disappeared on resting, but obviously his description of the symptoms was not that of intermittent claudication. The other cases were entirely free of symptoms in the legs.

In Case 1 the stricture lay between the origins of the right and left subclavian arteries and it was possible to compare the blood flow in the two hands. The result was surprising for the flow in the hand proximal to the stricture both at the resting level and at full vasodilatation was the smaller. Every
precaution was taken to ensure that this was a fair comparison; the investigation was repeated after the calorimeters and thermometers had been changed to the opposite sides and a similar result was obtained. In this case all the collateral arteries to circumvent the aortic stricture were presumably arising from the right subclavian artery and there was thus a large diversion of blood at the origin of this artery through widely dilated channels leading to the lower part of the body. This circulatory readjustment may be partly responsible for the lesser blood flow to the right hand but it is difficult to draw definite conclusions as the exact arrangement of the anomalous arteries is not known and the case is moreover complicated by a left sided pulmonary tuberculosis.

It is interesting to note that collaterals restricted in their origin to the right side were able to circumvent entirely the aortic stricture and that this case of coarctation had the largest maximal blood flow in the group.

Though the volume of blood flow in the plethysmograms was entirely normal in the cases of coarctation the pulsations in the tracings were small or absent (figs. 52 and 54). This affords a clear demonstration that the strength of the pulsations in an artery is not necessarily an indication of the blood flow through the vessel. Ejrup (1948) demonstrated by tonoscillography after exercise that 35 out of 38 cases of coarctation of the
aorta showed an "inverse reaction" similar to that seen in peripheral vascular disease. This, however, is a feature rather of a non-pulsatile flow than of a reduction in the flow. Thus in Case 4 with the most conspicuous rib notching and the most readily felt lower limb pulses the blood flow through the foot was the smallest.

No previous investigators have measured the maximal circulatory capacity of any part of the lower limbs but Lewis (1933) and Wakim et al. (1948) agree that the blood flow in the resting calf is similar to that in normal individuals. This is the expected result as the muscular development and condition of the calf appears clinically normal in subjects with coarctation of the aorta. Bing et al. (1948), however, claimed that the resting calf blood flow was reduced and returned to normal after operation. Full details of their measurements were not given nor were the results analysed statistically. Furthermore the mean of the figures plotted in their graph and the mean given in the text were substantially different and made any reliable statistical investigation by the writer impossible. In only one of the present series of cases was the stricture removed surgically and as she did not survive, no post-operative measurements have been possible.

Several investigations of the renal clearances have been made in coarctation of the aorta (Friedman et al, 1941, Genest et al, 1948). Their findings
have all been similar, namely a normal glomerular filtration rate as measured by inulin and a lowered diodone clearance with a rise in the filtration fraction. This has been interpreted as indicating a decreased renal blood flow. It is important to note that the mean blood pressure in the arterial system distal to a coarctation is above normal. Furthermore, similar renal changes are found in hypertension due to any cause (see Section VII). The renal clearances only returned to normal in the cases where the blood pressure also fell after operation (Genest et al., 1948). The cause of the hypertension in the lower part of the body in coarctation of the aorta is of uncertain origin. It is also felt that the mechanism of the changes in the renal clearances is obscure. It should not be assumed that they indicate a reduced volume of blood flowing through the renal artery distal to a coarctation of the aorta.

Cases of coarctation of the aorta are of some rarity and in view of their interest attract considerable medical attention. The dangers of the development of an effort syndrome under such circumstances can readily be appreciated and the frequent palpation of the lower limb pulses may well direct the patient's attention to his legs. An effort syndrome is clearly present in Case 2, where a fit muscular individual was dissuaded from normal exertion by a school medical officer. It is accordingly important to appreciate that the presence of a stricture in the aorta does not necessarily
reduce the blood flow in the lower limbs to a level likely to give rise to symptoms. The present series of cases, however, is small and the writer has not had an opportunity of examining a patient with coarctation of the aorta and true intermittent claudication.

SUMMARY.

Six cases of coarctation of the aorta have been studied. The maximal circulatory capacity of the foot has been measured in all the cases and shown not to differ significantly from normal. On the other hand a group with intermittent claudication due to obliterative vascular disease had a significantly decreased blood flow in the foot at full vasodilatation. In one case the coarctation lay between the origin of the right and left subclavian arteries and the blood flow to the left hand was slightly the greater both at resting levels and at full vasodilatation. The conclusion was that in the cases available for study the collateral arteries in the chest wall were entirely adequate to circumvent the stricture and that no symptoms in the lower limbs could be attributed to a diminished blood flow.
Fig. 52. Foot blood flows at 44°C. Time marker 1.5 sec.

(a) Normal subject with pulsations. (b) Coarctation of aorta (Case 1) without pulsations.
Fig. 53. X-ray of chest of case 4 (coarctation of aorta) showing conspicuous rib notching.
Fig. 54. Maximal foot blood flow in Case 4. Faint pulsations were present in the plethysmograms. Blood flow 17.3 ml./min./100 ml. Time marker 1.0 sec.
Fig. 55. Maximal foot blood flows with plethysmograph bath temperatures at 44°C. Black circles normal subjects; open circles coarctation of aorta; crosses subjects with intermittent claudication due to obliterative vascular disease.
ANEURYSMS OF THE PERIPHERAL ARTERIES.

Aneurysm on the large arteries of the extremities are not rare and relatively few cases have been reported in recent years in comparison with the extensive literature of the previous century. Thus Harvey Cushing writing in 1935 (quoted by Berry 1940) described a patient who suffered from an aneurysm, which had to be removed surgically. The reason for this change in incidence is not immediately apparent. Treatment is now more actively and more efficiently employed and at the present time an infrequent cause of death. Potter et al. (1936) reported a case of aneurysm occurring in the aorta of a child. Aneurysms of the peripheral arteries (Miller and Section 1929) are often due to aneurysm under the periosteum of the radius and ulna. The incidence during the last century was in social life (Marx 1966). They occurred in soldiers. As no pathological works were available at that time an aorto-iliac artery may have been syphilitic, presently it has been suggested that atherosclerotic vascular aneurysms are more frequently associated with the conduction of syphilis. Increasing incidence of atherosclerotic vascular disease. Linton's (1949) statistics from the Massachusetts General Hospital support this view.

The aorta has been able to study in detail the cases of atherosclerotic popliteal aneurysm and the case of syphilitic aneurysm. Recent review (Lentini 1949, Linton 1949) have discussed fully the surgical treatment of these conditions. The consideration of the pathological basis of atherosclerotic aneurysms. The only measurements of the peripheral circulation instal
ANEURYSMS OF THE PERIPHERAL ARTERIES.

Aneurysms on the large arteries of the extremities are now rare and relatively few cases have been reported in recent years in comparison with the extensive literature of the previous century. Thus Bransby Cooper, writing in 1836 (quoted by Harley 1940), regarded popliteal aneurysm as a condition "which has ceased to bear any novelty". The reason for this decline in the incidence is not immediately apparent. Syphilis is now diagnosed earlier and more efficiently treated and is at the present time an infrequent cause of a peripheral aneurysm (Mills and Horton (1938) Wells et al. (1936)). Syphilitic aneurysms occur usually in the middle age group while aneurysms of atherosclerotic origin are seen principally in old age. Judging from previous records the chief age incidence during the last century was in middle life (Harley, 1940). Many occurred in soldiers. As no serological tests were available at that time it is uncertain how many were syphilitic. Recently it has been suggested that atherosclerotic popliteal aneurysms are more frequently seen owing to the greater expectancy of life and a consequent increasing incidence of degenerative vascular disease. Linton's (1949) statistics from the Massachusetts General Hospital support this view.

The writer has been able to study in detail two cases of atherosclerotic popliteal aneurysm and one case of syphilitic axillary aneurysm. Recent reviews (Leriche (1949) Linton (1949)) have discussed fully the surgical treatment of these conditions but considerably less has been written about the pathological basis of atherosclerotic aneurysms. The only measurements of the peripheral circulation distal
to an aneurysm in the lower limb have been made by the skin temperature method (Theis (1937), Hardy and Denham (1940), Richards and Learmonth (1942)). Study of the case of axillary aneurysm revealed some exceedingly interesting circulatory changes which have apparently never previously been investigated. This is not surprising, for at the time when syphilitic aneurysms were common satisfactory apparatus for measuring blood flow had not been devised. Now they are rare and it has only been possible so far to investigate one case. The information obtained from the cases of aneurysm in the lower limbs will be described and discussed first as this confirms and amplifies generally accepted views. The case of axillary aneurysm, which is a striking contrast to these two, will then be presented in detail.

1. Popliteal Aneurysms.

Two cases of popliteal aneurysm have been studied in detail and full reports will be found in the Appendix (Cases 4 and 5). Both are of considerable interest from the point of view of the physiology and anatomy of the condition as the writer was able to carry out in one blood flow measurements in the foot and in the other a full pathological investigation of the whole circulatory system. The information obtained from the study of these two cases may be briefly reviewed.

Synopsis of Case Reports.

Case 4. A.V.H., a male aged 55 years in 1947, gave a history highly suggestive of a cerebral thrombosis in 1926 and a coronary thrombosis in 1935. His right leg was amputated in 1943 below the knees as a
result of gangrene of sudden onset probably due to a popliteal arterial thrombosis. In November 1943 he developed a pain in the left calf and the foot became discoloured. He was admitted to hospital and the foot recovered after 16 days. No records of this admission or of the pathological examination of the right leg are available.

He was readmitted to hospital in May 1944 when he was found to have a pulsating left popliteal aneurysm about 5 cm. in diameter. No pedal pulses were felt. At this time, while the aneurysm was still pulsating, an accessory pulse was present on the medial aspect of the knee. He had a mild degree of hypertension, blood pressure 145/110, multiple cholesteatomata on the knees and elbows and a blood cholesterol of 310 mgm per 100 ml. He was kept under observation at St. Mary's Hospital and in January 1946 pulsation suddenly ceased in the aneurysm. The circulation to the foot remained adequate and no gangrene developed. He has however subsequently noticed claudication in the left calf on walking and the foot tends to be rather cool. The accessory pulse has persisted unchanged. The aneurysm can still be felt as a firm non-pulsatile swelling.

The resting blood flow in July 1948 as determined in the left foot with the plethysmograph bath temperature at 34°C was 3.5 ml./min./100 ml. (average of 20 readings). To measure the reserve capacity of the foot circulation a reactive hyperaemia test was carried out and after five minutes arterial occlusion in the thigh the flow rose to a maximum of 6.9 ml./min/100 ml. It is noteworthy that pulsations were visible in the plethysmograms even though the flow was greatly reduced and no pedal pulses were palpable (Fig. 5).
Case 5. J.A., a male aged 75 years in 1947 gave a history of intermittent claudication in both legs of several years duration. In July 1945 a left midthigh amputation was carried out following a sudden popliteal thrombosis. In the amputation specimen a recent thrombosis was found in the popliteal artery extending far down into the posterior tibial artery. There was no aneurysmal dilatation of the popliteal artery. Sections of the arteries of this limb prepared and examined by the writer showed advanced atherosclerotic changes which had led to severe destruction and thinning of the media.

In March 1947 there was a sudden onset of pain in the right leg which rapidly became gangrenous. The blood pressure was 190/120. The popliteal and pedal pulses were absent and a midthigh amputation was carried out. Dissection of the limb by the writer revealed the presence of a popliteal aneurysm measuring 8 cm x 2 cm, and occluded by recent thrombus (Fig. 57). The distal exit of the aneurysm was grossly narrowed by old atherosclerotic thickening.

The patient died six days after operation and autopsy revealed an exceedingly gross degree of atherosclerosis throughout the body with aneurysms on the internal and external iliac arteries. A recent myocardial infarction was the cause of death.

Histological sections of the walls of the popliteal and other aneurysms showed gross atheromatous degeneration of the intima with superimposed recent thrombosis and older partially organised blood clot in the deeper parts of the intima. The internal elastic lamina was considerably fragmented and disorganised. The media was thin and in parts consisted only of a few strands of extremely atrophic muscle fibres. Numerous small vascular
channels and pigment-laden macrophages were present in the media. The vasa vasorum were enlarged and numerous. (Figs. 58 and 59).

A detailed report of the examination of the other arteries and organs will be found in the appendix.

Discussion of Popliteal Aneurysms.

Although atherosclerosis is an extremely common disease it apparently seldom leads to the formation of definite aneurysms on the peripheral arteries. Obviously many cases of aneurysm of the popliteal artery must be overlooked, as the swelling, if not pulsating, will not easily be diagnosed and in these circumstances it will only be found on dissection of the limb (Wells et al. 1936). A certain degree of dilatation and elongation is not uncommon in atherosclerotic arteries but in all the amputated limbs dissected only one popliteal aneurysm was found. This comparative rareness naturally arouses curiosity as to the mechanism of the development of this complication.

From a consideration of the two cases it appears that a gross degree of atheromatous degeneration of the arteries is essential. In the first case there was clinical evidence of involvement of cerebral, coronary, and lower limb arteries. The arterial disease here was associated with a manifest disturbance of cholesterol metabolism as shown by the subcutaneous deposits and the persistent hypercholesterolaemia which is a recognised cause of atheromatosis (Hueper, 1944). In the other case one limb had already been lost as a result of arterial disease though at the time of the first amputation twenty months before death no aneurysm was present in the popliteal artery on that side. At autopsy,
however, severe widespread atherosclerosis and several aneurysms were found. The occurrence of multiple atherosclerotic aneurysms is not uncommon in the recorded cases of popliteal aneurysm. Bilateral aneurysms were present in the cases reported by Flemming (1939) and by Hardy and Denham (1940). Keynes and Morel (1943) recorded the incidence of atherosclerotic femoral and popliteal aneurysms in the same patient. It is thus apparent that these aneurysms reflect the presence of extensive atheromatous degeneration. It should be noted that in the writer's two cases and in those quoted above syphilis was excluded as a possible cause by serological tests.

In both cases a certain degree of hypertension was present, more severe in Case 5 and this presumably predisposed to aneurysm formation. Though hypertension is frequently mentioned as a cause, in many of the reports the blood pressure is not mentioned. Where a record is available the hypertension is usually only mild (Keynes and Morel 1943, Hufnagel 1943) and it is probably not an aetiological factor of much significance.

Local factors are certainly of greater importance. There is no doubt that aneurysmal dilatation is preceded by damage to the arterial wall through spread of the atheromatous degeneration. In all the aneurysms studied microscopically a conspicuous feature was the atrophy and thinning of the media which normally provided the chief muscular and elastic support of the artery. The histological changes in all the reported cases have been remarkably similar. Robb-Smith (1943) in particular has described the fragmentation of the internal elastic lamina and the extreme flattening, narrowing
and vascularization of the media which were all features seen in a marked degree in the aneurysms in Case 5.

Local trauma and strain have been cited by many writers (Oleson (1930), Baker (1934)) as factors in the production of popliteal aneurysms. In the writer's cases there was no history of any injury. Matas (1909) has suggested that movements at the knee lead to strain causing small tears in the elastic fibres of the media in diseased vessels. This may partially explain the frequency of the popliteal artery as the site of aneurysm formation but it is difficult to get any reliable evidence.

A factor which has not been considered by previous authors but which may be of some importance is the condition of the arterial lumen immediately distal to the aneurysm. It should be noted that in Case 4 while the aneurysm was still pulsating the pulses in the foot could not be felt and that a collateral artery was present on the medial side of the knee. In other words the evidence suggested that the popliteal artery was blocked immediately distal to the pulsating aneurysm. In Case 5 an old occlusion of the popliteal artery at its bifurcation was found, while the aneurysm itself, situated immediately proximal to this obstruction was filled with recent thrombus. Dornhorst and Sharpey-Schafer (1949) have shown that immediately proximal to an obstruction in the brachial artery produced by a cuff the pulse pressure waves become steeper and rise higher. These are both conditions which will obviously predispose to stretching of the arterial wall. The development of atherosclerotic aneurysms immediately proximal to a coarctation of the aorta is a well recognised complication (Abbot 1928). It
is accordingly suggested that in these two cases older obstructions situated at the bifurcation of the artery played a part in the formation of the aneurysms. In this connexion it is interesting to note that in Linton's (1949) series the aneurysms were pulsating in all 14 cases but in only two were both pulses felt in the foot.

The dangers resulting from the presence of a popliteal aneurysm have long been recognised and they consist chiefly in thrombosis, rupture and distal embolism. The sudden development of thrombosis in the aneurysm may lead to gangrene of the extremity. This complication was seen in Case 5 and numerous previous articles have drawn attention to this potential catastrophe (Wells et al. 1936). In Case 4 it seems that the occlusion at the bifurcation of the popliteal artery which probably developed in November 1943 was adequately circumvented by the collateral artery, for when the aneurysm itself thrombosed there was relatively little distal circulatory disturbance. The blood flow measurements in this case, carried out after the final thrombosis, indicated the maximal amount of blood that could be supplied to the foot, probably chiefly by the pulsating collateral artery though the number and size of other collaterals cannot be assessed. The maximal blood flow was about one third of the normal value. Theis (1937) has recorded skin temperature readings in cases of atherosclerotic popliteal aneurysms which were always associated with a diminished blood flow in comparison with the opposite side. The interesting observation by Richards and Learmonth (1942) in their case of a syphilitic popliteal aneurysm will be discussed in the next section when it will become apparent that
further plethysmographic studies should be carried out in these cases, particularly where the aneurysm is pulsating freely and the distal circulation unobstructed.

2. Axillary Aneurysm.

The cases of aneurysms of atherosclerotic origin investigated by the writer and reported previously have all shown evidence of a reduction in distal blood flow due to the occurrence of thrombosis within the aneurysm. The writer however was fortunate in being able to study a case of aneurysm of the axillary artery of syphilitic origin. Here the clinical features suggested strongly that the circulatory changes were of an entirely different order from those seen in the cases of popliteal aneurysm. It was accordingly decided to investigate the condition fully as no previous observations on blood flow in association with such an aneurysm had been recorded. Furthermore the case to be reported was associated with a conspicuous degree of unilateral clubbing of the fingers and it was considered that a detailed study of the peripheral circulatory disturbance might throw some light on the mechanism of the development of this condition. As the investigation required simultaneous observations with plethysmographs on the two upper limbs Dr. K. W. Cross kindly assisted with some of the instrumental readings (Cross and Wilson 1950).

Unilateral clubbing of the fingers is uncommon but extremely interesting in view of the information that may be gained concerning the circulatory changes associated with finger clubbing as the normal hand is available for comparison. Such a condition obviously
provides very favourable circumstances for making carefully controlled observations. Though several cases have been reported and reviewed recently (Rodgers, 1941; Sartor 1943) no detailed investigations have been made and no definite conclusion has been reached about the mechanism of the development of the clubbing. The present case and the associated circulatory disturbances are accordingly presented in detail.

**Case Report.**

A male aged 63 years, married with no children, served in the Royal Marines from 1903-1919 and subsequently was employed as a general labourer. In 1912 he developed a penile sore for which he received treatment with mercury over a period of several months. Thereafter he remained well until 1938 when a painless swelling appeared on the forehead. This was incised on several occasions, failed to heal satisfactorily, and was later diagnosed as a gummatous ulcer. The condition subsequently responded to antisyphilitic injections and healed with much scarring. In 1947 a lump was noticed one evening in the right armpit. There was no pain but the patient attributed the condition to straining himself a few hours previously by reaching up to lift a heavy box from a lorry. No weakness or any other disturbance was noted in the limb. The swelling has persisted unchanged to the present date. In January 1949, he noticed increasing abdominal distension and later swelling of the genitalia and legs. Abdominal paracentesis has subsequently been carried out repeatedly at intervals of two to six weeks. His general condition has recently considerably deteriorated, his appetite has been poor and he has lost weight in spite of fluid retention. He has had a cough and sputum for many
years especially during the winter months, and has become increasingly short of breath on exertion. There have been no other illnesses of note. He was formerly a heavy spirits drinker (up to a bottle a day) but has been moderate in recent years.

On examination there was an irregular depressed white scar over the right side of the forehead. A few telangiectases were present on the face and purpuric spots were present on both arms. There was no abnormal lymph node enlargement in the neck, axillae or groins. The fingers of the right hand were conspicuously clubbed with definite curving of the nails, fluctuation of the nail bed and bulbous swelling of the pulp of the finger tips. The fingers of the left hand showed changes suggestive of very early clubbing - a slight fluctuation of the nail bed and curving of the nails (Figs. 61 and 62). After exposure for half an hour to ward temperature the right hand was always warmer than the left. The veins of the dorsum of the right hand also appeared slightly more prominent. A firm pulsating swelling measuring approximately 5 x 4 cm. in diameter was present in the right axilla, and apparently arose from the third part of the axillary'artery. (Fig.60). The pulsation was abolished by compressing the subclavian artery, but the swelling was not thereby reduced in size. The brachial and radial pulses on the two sides were of equal force. No cardiac abnormality was detected. The chest was emphysematous with poor movement, faint breath sounds, generalized rhonchi and moist sounds at both bases. The abdomen was grossly distended with fluid. The upper limit of liver dullness was in the 6th space: the liver edge was not palpable even after drainage of the fluid. Rectal examination was normal.
Considerable oedema of the sacrum, genitalia and ankles was present. No abnormality was detected in the nervous system.

Radiological examination of the chest showed moderate bilateral basal emphysema. Diffuse fibrosis was present in both upper zones, the upper part of the right lower zone and the left midzone. The heart was not enlarged but a moderate prominence of the aortic knuckle was noted. X-ray of the right arm showed a soft tissue opacity in the axilla associated with minimal calcification. X-ray of the hands showed enlargement of the subungual cancellous tufts of certain of the terminal phalanges. These changes were much more conspicuous on the right side. No subperiosteal new bone formation was seen along the shafts of the metacarpals or distal forearm bones.

Urine. Albumen, nil; sugar, nil. Blood. Wasserman and Kahn reactions strongly positive. Thymol turbidity, 4 units. Serum bilirubin, 0.2 mg./100ml. Blood Hb, 13.4 g./100 ml. R.B.C. 4,400,000/cu.m. W.B.C. 6,500/cu.m.; polymorphs 70%, eosinophils 2%, lymphocytes 20%, monocytes 8%. Plasma protein, 6.5g./100 ml.; albumen 2.5 g.; globulin 3.8g./100 ml. Plasma prothrombin 67% of normal. Serum cholesterol 138mg./100ml.

The clinical diagnosis was cirrhosis of the liver, syphilitic aneurysm of the axillary artery and pulmonary fibrosis, possibly syphilitic in origin.

The opportunity was taken of making further detailed observations on the circulation in both upper limbs.

Results of Circulatory Investigations.

Brachial artery blood pressures were estimated on the two sides by similar sphygmomanometers. The
readings were made as far as possible simultaneously and half way through the determinations the observers changed sides. The brachial artery blood pressures with the patient at rest in bed, as determined from the averages of three sets of two independent observers was, right 133/85, and left, 130/80. No individual observer found any marked difference between the pressures on the two sides.

The pressure in the digital arteries of the middle fingers was determined, using cuffs round the proximal phalanges, finger plethysmographs, and a soap bubble volume recorder as previously described. Repeated observations on three different occasions were made with the patient sitting in a chair. The pressure on the right side was always found to be higher than that on the left. This finding was constant at different degrees of peripheral vasodilatation obtained by heating the patient. The average of these results showed the systolic digital pressures to be, right 145mm., and left 128.mm.

The venous pressures relative to the sternal angle were measured in two corresponding forearm veins with citrate manometers after the patient had been lying at rest for half an hour with the arms exposed. Between the readings the arms were placed in different symmetrical positions to reveal any changes due to local compression. The venous pressures on the two sides showed no consistent differences and the difference between the two readings was never greater than 2 cm. of citrate solution. The averages of the readings in different positions were, right +1.7 cm., and left +0.7cm.

Simultaneous forearm blood flows were measured at 34°C on two separate occasions. The flow through the right forearm in the tracings was slightly greater than through the left. The results were:
Of the 43 pairs of readings, 1 pair was identical, and in all the remaining 42 the flow was greater on the right side.

Hand blood flows as determined simultaneously by plethysmographs showed that in every tracing the blood flow through the right hand was considerably greater than that through the left (Fig. 63). The hands were inserted into the plethysmographs to corresponding anatomical levels, but the right with the clubbed fingers was slightly larger. The results were:

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<th>No. of readings</th>
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Heat elimination from the two hands was determined simultaneously in calorimeters. Before observations were begun both hands were soaked for 25 minutes in a basin of stirred water from which the calorimeters were subsequently filled. This procedure was designed to exclude temperature differences on the two sides due to external causes. The heat elimination was consistently greater from the right hand throughout the period of observation, both with the subject sitting at rest and with the feet in hot water to produce vasodilatation in the hands (Fig. 64). The results may be summarized:
Venous blood samples for gas analyses were taken simultaneously under paraffin from two corresponding antecubital veins. The limbs were exposed and at rest for one hour before the specimens were taken and congestion of the limbs avoided before and during withdrawal of the blood. The subsequent gas analyses were carried out in the manometric Van Slyke apparatus in duplicate by Dr. J. Hardwicke with the following results.

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<td>ml.</td>
<td>Cal/100ml/min</td>
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<td>70</td>
<td>320</td>
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No abnormality was demonstrable in the sympathetic nerves of the upper limbs. The vasomoter reflexes on the two sides were similar and entirely normal responses to placing the feet in hot and cold water were obtained. Sudomotor and pilomotor activity was also unaffected as was shown by normal sweating on the affected side and by the development of the "goose-skin" reaction on pinching the trapezius.

Discussion of case of axillary aneurysm.

The slight degree of clubbing in the left hand is probably to be attributed to the cirrhosis of the liver and to the pulmonary fibrosis, while the greatly increased clubbing in the right hand is largely a consequence of the axillary aneurysm. Several cases of unilateral clubbing of the fingers have been described in association with an aneurysm of either the subclavian or axillary artery. (Hogler, 1920; Rodgers, 1941). The majority of these
Aneurysms have been in the region of the thoracic outlet and have been complicated by features arising from pressure on neighbouring nerves and veins. Syphilitic aneurysms of the distal part of the axillary artery are extremely rare. The case described is thus of exceptional interest, particularly as the swelling was easily accessible for clinical examination, and disturbance of neighbouring structures that might play a part in the production of the marked unilateral clubbing can be excluded. In some of the older case reports the hand distal to an aneurysm has been described as cold, blue and swollen (Poland, 1870). These cases, as far as can be ascertained from the published records, have always been complicated by disuse of the limb resulting from brachial plexus lesions, by pressure on the subclavian vein, or by apparent complete obstruction of the main arterial supply to the limb. In such cases the mechanism of the production of the clubbing is obscure and it has been variously attributed to disturbance of the sympathetic innervation or to rise in venous pressure. Furthermore, in many of the older reports there is no clear distinction drawn between clubbing, hypertrophy and oedema.

The results of the present investigation have all consistently shown that the circulation through the right hand was considerably increased in comparison with the opposite side. This increase in blood flow on the right side was considerably greater than the variation observed in the comparison of the two sides in normal subjects by Cooper and others (1949). The instrumental readings have thus confirmed the clinical observation that the conspicuously clubbed hand was always the warmer.
It should be noted that the greater blood flow was associated with an increased oxygen tension in the venous blood on the right side. It was not possible to obtain the blood samples at the same time as the limb blood flow was being estimated and therefore results cannot be correlated with certainty. If, however, it is assumed that the arterial oxygen saturation on the two sides is equal; that the blood flow determinations quoted above afford a representative picture of the proportionate increase on the right side; and that blood taken from corresponding antecubital veins gives a reasonable mixed venous sample of forearm and hand blood; then it can be concluded that the blood flow on the right side is considerably increased above the metabolic requirements of the part.

Brachial artery blood pressure measurements on the two sides with the sphygmomanometer showed no significant differences. It was, however, realised that this method was not ideal, for when the cuff is inflated the flow through the artery is stopped, and if it is to be argued that the presence of an aneurysm in some way alters the brachial artery flow it would be highly desirable to obtain pressure measurements with the arterial flow unobstructed. Digital artery pressures by a cuff method were consistently higher on the right side. These results suggest that there was considerable peripheral arterial vasodilatation on the more conspicuously clubbed side.

Similar clinical observations regarding the increased temperature of a unilaterally clubbed hand developed in association with a pulsating syphilitic arterial aneurysm and unobstructed distal circulation have been made in the past by several
authors (Lewis, 1938; Rodgers, 1941). Richards & Learmonth (1942) recorded a similar finding of increased warmth in a foot distal to a syphilitic popliteal aneurysm, and confirmed their clinical observations by skin temperature readings. These authors made no mention of the condition of the toes of their patient but Sartor (1943) has reported a case of clubbing of the toes secondary to syphilitic aneurysm of the femoral artery. Brooks (1930) has described a case of unilateral finger clubbing in association with an aneurysm of the proximal part of the axillary artery. Estimations of the venous oxygen saturation were made in the two limbs and the venous blood on the clubbed side was found to have a higher oxygen content. In this respect his result was similar to that in this case. No other measurements of the circulation in a limb with an arterial aneurysm and clubbing have apparently been reported. Mendelowitz (1938) investigated the circulatory changes associated with bilateral clubbing of the fingers but his series did not include calorimetric observations on any case of unilateral clubbing secondary to a limb aneurysm. In comparison with the hands of normal subjects he described in bilaterally clubbed fingers an increased blood flow and a decreased pressure gradient from brachial to digital artery. His findings in bilateral clubbing arising from the commoner general causes were thus similar to those in this case when the markedly clubbed hand was compared with its relatively unaffected fellow.

The evidence obtained from the investigations on the case reported above and from a study of past records shows clearly that the change associated with a pulsating syphilitic aneurysm and unobstructed
distal arteries is an increase in the distal circulation. The temporal relationship between the development of the aneurysm, the increased peripheral blood flow and the clubbing of the fingers is of considerable interest. It is generally agreed that the aneurysm precedes and brings about the finger clubbing. The relationship between the increased peripheral circulation and the clubbing is more open to question as no measurements of the circulation have ever been made immediately after the formation of such an aneurysm. It is, however, highly significant that an event which reduces the peripheral arterial flow such as spontaneous clotting and subsidence of the aneurysm leads to the disappearance of the clubbing (Hogler, 1920; Hatzieganu, 1923). Surgical excision leads to a similar result (Smith, 1871).

In this case the only abnormality responsible for the development of the marked clubbing on the right side was the presence of the axillary aneurysm. This was associated with an increase in the arterial blood flow beyond it. There was no evidence that the aneurysm had caused any venous obstruction or any other disturbance.

The physical mechanism whereby such an aneurysm produces an increased distal circulation is difficult to elucidate. A crude model of the arterial circulation was constructed in which it was possible to show that the flow on the side containing a distensible sac was increased only if a valvular mechanism was present at the proximal entry to the sac, so that the added fluid from the elastic recoil of the sac was directed distally. With such a valvular action at the entry of the artery possibly due to increased angulation during diastole the
pulsating aneurysmal sac would greatly augment the distal blood flow. In this connexion it has been noted that popliteal aneurysms of arteriosclerotic origin are not associated with an increased distal circulation. These aneurysms are usually elongated fusiform dilatations while those of syphilitic origin tend to be more spherical and saccular and thus more likely to produce a valvular angulation at the point of entry of the artery. In the past, attention has been chiefly directed towards the more spectacular and dangerous complications of syphilitic aneurysms such as rupture, distal embolism, and pressure effects. It has not been fully realised that uncomplicated they may be associated with a distal hyperaemia. It is tentatively suggested that this physical augmentation of distal arterial flow, resulting in the fingers receiving more blood than is required for either heat elimination or nutrition of the tissues, leads to the development of the anatomical changes associated with clubbing of the fingers.

**Summary.**

Two cases of popliteal aneurysm and one of axillary aneurysm are described. Popliteal aneurysms were shown to be associated with widespread atherosclerotic disease and frequently aneurysms in the other large arteries of the lower extremity. The principal factors responsible for their development were destruction of the media by the disease process, obstruction of the artery immediately distal to the site of development of the aneurysm, and local trauma. Ischaemia of the limb distal to the aneurysm, owing to thrombosis, was the chief danger of the condition.
Blood flow measurements in one case demonstrated the extent to which this obstruction could be overcome by the collateral circulation.

The axillary aneurysm was pulsating freely and the peripheral circulation was unobstructed. It was associated with ipsilateral clubbing of the fingers. The circulatory changes distal to the aneurysm consisted of an increased blood flow through the hand and a decreased pressure gradient in the arterial tree as compared with the unaffected side. This increased blood flow was associated with a decreased oxygen consumption per unit volume of blood. The marked clubbing of the fingers of the right hand appeared to be associated only with these arterial circulatory changes.
Fig. 56. Foot blood flow in the case of popliteal aneurysm. Plethysmograph temperature 54°C. Time marker 1.5 sec. Blood flow 3.3 ml./min./100 ml. Pulsations were present in the plethysmogram though absent in the aneurysm. A pulsating collateral artery was felt on the medial side of the knee.
Fig. 57. Aneurysm of the popliteal artery. The aneurysm was filled with recent thrombus and the bifurcation of the artery was obstructed with old atherosclerotic lesions.
Fig. 58. Section of the wall of the popliteal aneurysm. On the left is the recent thrombus in the lumen. The arterial wall is greatly thinned and the musculature of the media has largely been destroyed. There is a considerable infiltration with lymphocytes. On the right is part of the wall of the popliteal vein. Stain haematoxylin and Van Giesen. X100.
Fig. 59. The heart and aorta of Case 6 showing the marked dilatation of the aorta and the gross degree of atherosclerosis which was responsible for the multiple peripheral aneurysms.
Fig. 60. The axillary aneurysm.

Fig. 61. Both hands showing conspicuous clubbing of the right fingers.
Fig. 62. Dorsal and lateral views of both index fingers shewing gross clubbing on the right side.
Fig. 63. Hand blood flows as recorded by venous occlusion plethysmograph. Right hand (clubbed) continuous line. Left hand dotted line.
Fig. 64. Heat elimination from both hands measured simultaneously. Right hand continuous line; left hand dotted line. Readings at minute intervals.

The foot bath temperature measured in degrees centigrade uses the same figures as the heat elimination scale.
SECTION VI

THE MECHANISM OF THE DEVELOPMENT OF CLUBBING OF THE FINGERS.

...
CLUBBING OF THE FINGERS.

The demonstration in the previous section that a physical disturbance leading to an increased arterial inflow into the hand was the apparent cause of the development of clubbing of the fingers naturally led on to an investigation as to whether this was the general mechanism of the development of the condition in all cases. As has been described above, Mendelowitz (1938) showed that in clubbing of the fingers due to disease there was usually an increased blood flow and a decreased pressure gradient in the arterial tree. He did not however postulate that this increased flow was the cause of the condition and subsequently it has been generally regarded rather as an associated feature. Clubbing of the fingers is one of the oldest clinical signs in medicine, having first been described by Hippocrates in about 400 B.C. Though many hypotheses have been put forward (Branwood 1949) no explanation has yet been generally accepted for all the bewildering and apparently unassociated conditions that may give rise to the condition. It is the purpose of this section to demonstrate that in all cases clubbing of the fingers is essentially a manifestation of a peripheral circulatory disorder and that the changes are the result of the fingers having to deal with an excessive volume of blood flow. The local circulatory changes will first be considered and then the mechanism that gives rise to these changes will be described.

The Local Circulatory Changes.

The anatomical changes in the vessels in clubbed fingers were studied by injection of radio-opaque material by Charr and Swenson (1946). They showed that there was a dilatation of the digital arteries and
and a greatly increased vascular bed in clubbed fingers. The vascular anatomical basis of clubbing of the fingers has recently been investigated in greater detail by Lovell (1950) who, using injection techniques, found that the calibre of the main nail bed arteries was larger in clubbed than in normal fingers. He also showed that an opaque injection mass (neoprene) passed readily through arteriovenous anastomoses underlying the nail bed in clubbed fingers; whereas in normal fingers arterial filling only was obtained. A complex reservoir of veins was found under the nail root and these, when distended with blood, endowed the clubbed finger with the peculiar sense of fluctuation in this region. The overgrowth of connective tissue in the distal segment of the finger was associated with a distension of this venous plexus.

Careful examination of patients with bilateral clubbing of the fingers has shown that this condition is always accompanied by a slight degree of clubbing of the toes and enlargement of the lobes of the ears. These latter areas are also the sites of arteriovenous anastomoses. They are, however, not so numerous as under the nail bed, the earliest region to be affected. Thus with gross clubbing the toes and lobes of the ears are always conspicuously affected; with lesser degrees of clubbing the changes in the fingers alone may be obvious. These investigations suggested to the writer that the arteriovenous anastomoses might serve to shunt the excess arterial blood reaching the fingers into the venous side of the circulation, and further evidence on this point was accordingly sought.

The presence of an arterio-venous fistula in a limb has been long recognised as a cause of hypertrophy of the tissues of the limb around and proximal to the
fistula (Horton, 1932). The hypertrophy is associated with an enormous increase in the blood flow through this part of the limb. (Lewis, 1940). The circulation to the distal part of the limb may be greatly reduced and occasionally even gangrene of the finger tips may develop. If however there are fistulae in the finger itself the local circulation is increased. The following case of clubbing of one finger is of interest in this respect.

A female, aged 28 years, was admitted to St. Mary's Hospital under the care of Mr. Handfield-Jones. She had noticed, for the first time at the age of 9 years, that her left arm was thicker and longer than her right and that her left upper limb was always the warmer. On examination the right upper limb was entirely normal. The blood pressure on this side was 130/70. The left upper limb was 4 cm. longer than the right and 3 cm. greater in girth in the mid-arm. The limb was considerably warmer than its fellow and the veins on the dorsum of the hand and up the forearm and arm were dilated and pulsating. Greatly increased local warmth and colour indicated the presence of arteriovenous fistulae in the antecubital and thenar regions. The left index finger was considerably warmer than the other fingers of the left and right hands which were of equal temperature. This increased warmth extended distally to the base of the nail. The digital arteries of this finger were pulsating freely while the arteries in the other fingers could not be felt. The left index finger-nail was distinctly curved and fluctuation was present at the base of the nail. The tip of the finger was not bulbous or swollen. All the other finger-nails were straight and entirely normal. The cause of the increased blood flow was thought to be an arteriovenous fistula in the terminal segment and this circulatory
disturbance was associated with distinct clubbing of the finger. This case of congenital arteriovenous fistulae was of two-fold interest. In the first place it illustrated clearly a fact already well recognised, that the increased arterial blood flow through the fistulae into the veins led to hypertrophy of the tissues. Secondly, the clubbing was restricted to the finger in which the arterial inflow was manifestly increased. The appearance of the clubbed finger was not entirely typical, but this was thought to be due to the fact that the excess blood was passing not through the normal nail bed arteriovenous anastomoses but through the congenital fistulae.

It is also possible to show that any development which leads to a reduction in the blood flow to a clubbed hand is associated with a regression of the clubbing. The following case illustrates this point:

F.C. a male aged 61 years had suffered from chronic bronchitis for many years and had a mild bilateral clubbing of the fingers. Following the development of a tuberculous axillary abscess he was admitted to St. Mary's Hospital under the care of Mr. C.P. Sames for excision of the right first rib in which the primary source of the infection was thought to lie. During operation the subclavian artery had to be ligated and the circulation to the limb was endangered. A collateral circulation developed only slowly. Three weeks after operation the right hand was colder than the left. After soaking the hands in warm water to remedy the temperature difference it was obvious that the clubbing on the right side had considerably diminished and it was no longer possible to elicit fluctuation of the nail bed as on the left side. The blood flow through the two hands at this time was measured simultaneously with two calorimeters.
(Greenfield and Scarborough 1949). At rest the heat elimination was: Right hand 74.0 cal/min and Left hand 230 cal/min. After placing the feet in water at 45°C to produce full reflex vasodilatation the maximal heat elimination was: Right hand 96.0 cal/min, Left hand 281.0 cal/min. (Fig.65).

In the case cited above the reduced blood flow after operation in the right hand was insufficient to maintain the clubbing of the fingers. This increased flow is thus apparently an essential factor, though the case obviously does not demonstrate that it is the only one. The view that the primary change in the development of finger clubbing is the local circulatory increase has been opposed on the grounds that clubbing is not seen in either sympathectomised hands or in hyperthyroidism (Branwood 1949). After sympathectomy there is no evidence that the blood flow in the hand is increased above the requirements of the part. In two cases of Raynaud's disease the blood flow through the hand was determined preoperatively at full vasodilatation. It was again determined as soon as possible after operation and then on successive days until a steady level was obtained (Figs.66 and 67). The blood flow rapidly declined from the high rate obtained soon after operation. Barcroft and Walker (1949) shortly afterwards reported similar results in their series of cases observed after sympathectomy. In these sympathectomised hands there is not a sustained increase in blood flow, and Freeman (1935) has shown that local metabolism is the chief factor that regulates their blood flow. There is no superfluous blood flow and clubbing does not develop.

In hyperthyroidism there is undoubtedly an increased blood flow into the hands, but this is purposeful. The increased metabolic rate requires an increased heat
elimination from the hands and the tissues of the fingers themselves under the influence of the thyroid hormone demand an augmented blood flow. Thus in severe hyperthyroidism there is considerable peripheral vasodilatation but no clubbing of the fingers. It has however occasionally been noticed that immediately after thyroidectomy in this type of case a transient clubbing of the fingers may appear (Mendelowitz 1942). It is suggested that in the postoperative period the dilated digital arteries deliver a volume of blood to the fingers which, with the hyperthyroidism cured, is excessive and is accordingly shunted through the arteriovenous anastomoses under the nail bed. The dilated arteries tend later to resume their normal calibre and the clubbing then subsides.

The local circulatory changes described above have all consisted in an augmentation of the blood flow. Clubbing of the fingers is, however, occasionally seen in association with an apparent reduction in the blood flow. These cases are usually associated with a nervous lesion and resultant disuse of the hand. It is known that in such circumstances the blood flow through the inactive tissues is greatly reduced (Lewis and Pickering (1936)). If a mild degree of bilateral clubbing is present the rapid onset of a nervous lesion leading to paresis on one side may be followed by the development of a pronounced degree of clubbing on that side. Such a feature was observed by the writer in a patient with bilateral clubbing probably due to cirrhosis of the liver associated with diabetes mellitus. A peripheral neuritis of relatively sudden onset led to weakness and disuse of the right hand which after half an hour's exposure was colder than the left. The right hand however soon showed a conspicuously greater degree of clubbing than the left.
In such circumstances it appears that, though the blood flow through the skin is apparently reduced, as judged by the relative warmth of the hand, that through the arteriovenous anastomoses deep to the nail bed is relatively increased. This mechanism serves to dispose of much of the blood reaching the finger, as the flow through the capillary channels is reduced to a level determined by the low metabolism of the inactive tissues. The circulatory disturbance is thus essentially similar to that in the commoner type of case in which the total blood flow is greater than normal.

In reviewing the local circulatory changes it is accordingly submitted that clubbing is essentially due to a relative excess volume of blood entering the fingers. The arteriovenous anastomoses situated principally under the nail bed are opened widely to shunt this excess into the venous system. The consequent filling of these blood vessels leads to a hypertrophy of the finger tip of a similar nature to that seen in a limb with congenital arteriovenous fistulae. It remains to describe the general circumstances that may give rise to these local circulatory changes.

The Central Mechanism.

Many different types of disease may lead to clubbing of the fingers but, with the development of more accurate methods of measuring cardiac output, a considerable amount of information has been acquired recently regarding the associated changes in haemodynamics. The different systems that may be involved will be considered from this point of view.

Pulmonary circulatory changes. Clubbing of the fingers is probably most frequently seen in association with pulmonary or pleural disease and it is obviously
essential to demonstrate the connexion between these conditions and the increased peripheral blood flow. In many cases of pulmonary disease with conspicuous clubbing the underlying condition is a septic infection of the lung or pleura. Clubbing, however, is frequently seen in bronchial carcinoma, and infection is obviously not a necessary condition. It will be apparent that any type of pulmonary disease which leads to an increased blood flow through the pulmonary arteries and their branches will necessarily lead also to an increased output by the left ventricle. The extent of this increase would not, however, be determined primarily by the requirements of the tissues supplied by the systemic blood stream. Such a mechanical disturbance is seen particularly in cases of arteriovenous aneurysms of the lung which are usually associated with a gross degree of clubbing both of the fingers and toes. (Barnes et al. (1948)). There is in addition an increased volume of circulating blood. If a large pulmonary shunt is present the cardiac output from the left ventricle will obviously rise considerably. In one case reported by Baker and Trounce (1949) the output of the left ventricle was calculated as 12 litres/min. It is thus apparent that an excessive volume of blood is being delivered to the periphery of the body. Some of this excess passes through regions provided with arteriovenous anastomoses such as the fingers, toes and lobes of the ears where clubbing typically develops. After excision of the aneurysm the blood volume returns to normal, an excess of peripheral blood flow is no longer brought about by the arterio-venous shunt in the lung and the clubbing disappears. In a case reported by Ettinger and others (1949) the blood
volume fell from 8.8 litres to 5.4 litres with the subsidence of the clubbing. They attempted no estimation of cardiac output.

A condition such as a rapidly developing lung abscess or empyema is obviously associated with a very considerable inflammatory hyperaemia and consequently an increased blood flow through that part of the lung. This increase may be partially supplied by the bronchial arteries but it would seem highly probable that the dilatation also affects the pulmonary arterioles. Here again this hyperaemia would primarily lead to an increased output from the right side of the heart and secondarily a corresponding increase in the output of the left ventricle. Thus blood in excess of the body's physiological requirements would be delivered into the systemic arterial system and, unrequired by the proximal tissues, would be carried to the periphery, leading to clubbing of the fingers and in the more extreme cases with the greatest excess to conspicuous clubbing of the toes and even of the ears. The fundamental local cause of the condition is however the same as in the simpler mechanical derangements of the circulation previously described in the limb or finger. In the pulmonary cases the rate of the development of the clubbing depends on the acuteness and duration of the inflammatory lesion. With lung abscess and empyema the inflammatory hyperaemia is most marked and clubbing appears within a few weeks. In cases of uninfected bronchiectasis the bronchial arteries probably carry an almost sufficient blood supply and clubbing is not marked. If infection develops and leads to an increased local vasodilatation affecting the pulmonary arterioles clubbing follows. In pulmonary tuberculosis clubbing is often
not present; the lesions are typically avascular but in the presence of secondary infection the blood supply is increased and clubbing may appear. In cases of bronchial carcinoma the development of clubbing is determined by the vascularity of the tumour, the presence of secondary infection and the origin of the blood supply. Bronchial carcinomata situated in the periphery of the lung are usually associated with finger clubbing; they are supplied mainly by pulmonary arterioles. A carcinoma situated at the hilum may be entirely supplied by the bronchial artery and clubbing is absent. It occasionally happens that a small hilar carcinoma is associated with the very rapid development of finger clubbing which may even be the first noticeable clinical feature. In this type of case it is suggested that the growth of the tumour has led to the formation of a small fistula between the branches of the pulmonary artery and vein so that the blood flow through the lung is considerably increased.

A septic lesion in the pleural cavity is usually associated with considerable clubbing of the fingers as previously described. The writer recently had the opportunity of seeing a patient who had an empyema persisting from a war wound received in 1917. Purulent fluid was still being withdrawn from the pleural cavity but no finger clubbing was present. Radiological examination however showed an extensive layer of calcification in the visceral pleura which would obviously completely shut off the pulmonary circulation. In this case the empyema cavity was obviously entirely supplied by the systemic circulation and there was presumably no increase in the pulmonary blood flow. Clubbing of the fingers was accordingly absent as it is in the case of any
abscess receiving its blood supply from systemic arteries.

**Cardiac circulatory changes.** Clubbing of the fingers is seen in two types of heart disease, namely congenital morbus coeruleus and bacterial endocarditis. In congenital heart disease associated with a shunt from right to left sides of the heart the position is very similar to that seen in arteriovenous aneurysm in the lung. Zak (1949) has measured the cardiac output in a group of such cases but has pointed out that his results are an approximation only. In his group the output of the left ventricle was 128% of average normal output. After the Blalock-Taussig operation whereby some of this excess output of the left ventricle is redirected into the pulmonary circulation clubbing of the fingers is noticeably reduced (Baker et al.1949). It is thus apparent that clubbing of the fingers in congenital heart disease with cyanosis may be due to an excess blood flow being directed to the periphery and it thus falls into line with the clubbing due to other causes previously mentioned.

Considerably less information is available regarding the circulatory disturbances associated with subacute bacterial endocarditis. No measurements of cardiac output before and after treatment with penicillin have been made. The writer has measured the maximal blood flow through the hand in two cases of subacute bacterial endocarditis before, during and after treatment and was able to demonstrate in each case a progressive reduction in the flow. This was followed by a regression in the degree of finger clubbing. The two factors that may play a part in reducing the maximal blood flow are a decrease in cardiac output and a reduction in the
total cross-sectional area of the arterioles at full vasodilatation. Obviously coincident measurements of cardiac output and peripheral blood flow are required to elucidate the mechanism. It does, however, seem possible that the presence of inflammatory lesions on the valves leads to an increased blood flow through the heart and thus to an excessive output to the periphery. Further investigations along these lines are being carried out by the writer. With regard to the above conditions it should be noted that the excess of cardiac output above the systemic circulation's requirement necessary to give rise to clubbing is small. Judging from the figures obtained in the case of unilateral clubbing an excess of about 10 per cent in the peripheral blood flow would be sufficient. By the method of cardiac catheterization it would be difficult to demonstrate such a relatively small increase in heart output.

**Hepatic and abdominal disease.** Clubbing of the fingers has been described in association with cirrhosis of the liver and with various intestinal disorders leading to diarrhoea. The writer has not had an opportunity to investigate the circulatory disturbances in these conditions and no other measurements have so far been reported. It is, however, well recognised that cirrhosis of the liver may lead to the development of cutaneous telangiectases and it is possible that the vessels of the finger tips may also be involved. Recent observations by Bull (personal communication) show that in advanced cirrhosis of the liver there is an as yet unexplained increased cardiac output. It thus seems probable that in liver disease the clubbed fingers are dealing with an excessive peripheral blood flow and that the mechanism is essentially similar to that previously described. The diarrhoeal conditions with
the associated malabsorption of essential amino acids also lead to considerable derangement of hepatic function and this may be the common factor in all types of abdominal disease associated with clubbing.

**Increased blood volume.** In the pulmonary and cardiac conditions associated with cyanosis there is also usually an increased blood volume and, where this is the case, the finger clubbing is gross. An increased blood volume alone may, however, give rise to finger clubbing. This was noticed by Barcroft (1925) in the natives living at high altitudes in the Andes. In such cases the venous plexuses beneath the nail beds are presumably distended to accommodate the increased volume of blood and the peripheral circulation is augmented owing to anoxaemia. Lovell (1950), in his studies of finger clubbing in association with cyanotic congenital heart disease, noted gross distension of the venous plexuses when the blood volume was large. Polycythaemia vera is but rarely associated with finger clubbing probably owing to the arterial thrombosis and the consequent peripheral circulatory stasis so frequently present in these cases.

**Summary and Conclusions.**

Evidence collected both from published reports and from personal observations show that clubbing of the fingers is associated with an increased peripheral blood flow and a dilatation of the digital arteries. Lovell (1950) has described arteriovenous anastomoses beneath the nail bed which are widely open in clubbed fingers. It is suggested that their function is to divert the excessive arterial inflow into the venous system. Further evidence from a case with congenital arteriovenous fistulae is also presented showing that an arterial inflow superfluous to the
requirements of the finger can cause the appearance of finger clubbing. A reduction in the blood flow through interference with the arterial circulation leads to regression of the clubbing. The manifestations of clubbing are seen only in areas where arteriovenous anastomoses abound, as in the fingers, toes and lobes of the ear. Distension of the venous plexuses associated with these anastomoses leads to hypertrophy similar to that seen in a limb with an arteriovenous fistula and to the characteristic tissue changes observed in a clubbed finger.

It was tentatively suggested that the general mechanism responsible for the development of the increased local circulation in clubbed fingers in pulmonary conditions was an increased blood flow through the pulmonary circulation. This necessitated an increased output into the systemic circulation, and the superfluous blood passing through regions provided with arteriovenous anastomoses was responsible for the development of clubbing. A similar mechanism accounts for the clubbing seen in congenital heart disease with a right to left shunt. Operative interference leading to diversion of the superfluous blood flow back into the lungs is followed by marked regression of the finger clubbing. In subacute bacterial endocarditis and hepatic disease further investigations are required, but such evidence as is available suggests that the finger clubbing associated with them is due to an excessive peripheral blood flow. Life at high altitudes which gives rise to an increased blood volume and a large peripheral blood flow is a further cause of clubbing of the fingers.

In this investigation it has accordingly been
possible to show that the circulatory abnormalities noted in the case of axillary aneurysm are probably of general application. The increase in arterial inflow leading to opening of the arteriovenous anastomoses under the nail bed is the common factor causing the development of finger clubbing in many different conditions. Further investigations are being planned to provide additional evidence on many points where information necessary for the elucidation of this hypothesis is lacking.

Postscript. It has been possible to include two further cases of clubbing of the fingers in which blood flow investigations have been made before and after treatment. The blood flows have been measured in a calorimeter over the range 31°-32° at full reflex vasodilatation obtained by immersing the opposite arm in water at 45° to produce sweating. The hand was inserted to the level of the knuckles and the position marked so that a similar volume was inserted on subsequent occasions. As a mild degree of fever was present in each case the maximal heat elimination has been corrected for changes in blood temperature by using the following formula:--

\[
\text{Corrected M.H.E.} = \frac{27-32°}{\text{MOUTH temp.}} \times \text{Observed M.H.E.}
\]

Case 1. A male age 48 years admitted with a lung abscess and conspicuous clubbing of the fingers. Blood flow determinations were carried out before and after treatment with penicillin which lead to disappearance of the clubbing. The results were:--

<table>
<thead>
<tr>
<th>Volume of fingers</th>
<th>B.P. M.T. Corrected M.H.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 300 ml.</td>
<td>112/76 37.6° 90 cal./min./100 ml.</td>
</tr>
<tr>
<td>After 300 ml.</td>
<td>110/74 37.0° 71 cal./min./100 ml.</td>
</tr>
</tbody>
</table>

Case 2. A female age 43 years admitted with subacute bacterial endocarditis and conspicuous finger clubbing. Blood flow measurements were made in duplicate before and after treatment with penicillin which abolished the clubbing. The results were:--

<table>
<thead>
<tr>
<th>Volume of fingers</th>
<th>B.P. M.T. Corrected M.H.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 180 ml.</td>
<td>135/70 37.8° 130 cal./min./100 ml.</td>
</tr>
<tr>
<td>190 ml.</td>
<td>130/70 37.6° 127 cal./min./100 ml.</td>
</tr>
<tr>
<td>After 180 ml.</td>
<td>126/70 37.3° 108 cal./min./100 ml.</td>
</tr>
<tr>
<td>180 ml.</td>
<td>120/70 37.3° 106 cal./min./100 ml.</td>
</tr>
</tbody>
</table>

In both cases recession of the clubbing was associated with a fall in the maximal blood flow. As the observations were made with sympathetic tone fully released the findings are consistent with the view expressed above that the clubbing is due to a slight excess of cardiac output and that the clubbing subsides when this superfluous flow ceases.

Further investigations are being carried out. It has been shown that after a Blalock operation there is a decrease in the maximal blood flow, especially on the side where the subclavian artery has been divided. The subsidence of the clubbing is earlier and more conspicuous on this side. The vascular anatomy of bronchial carcinomas with and without clubbing is being investigated by neoprene injections. Circulatory measurements in clubbing due to hepatic and intestinal disease are also being undertaken.
Fig. 65. Simultaneous records of blood flow in right (continuous line) and left (dotted line) hands. Ligation of the right subclavian artery had been carried out three weeks previously. Bilateral finger clubbing was originally present, but the clubbing disappeared in the right hand. Note that the initial response to placing the feet in water at 44°C is a vasoconstriction followed later by full reflex vasodilatation.
Fig. 66. The effect of sympathectomy on the hand blood flow. Before operation the hand blood flow was measured on two occasions after full reflex vasodilatation had been obtained by immersing the feet in water at 45°C. The blood flow as estimated by calorimetry steadily declined during the first 100 hours after operation. Right hand continuous line; left hand dotted line.
Fig. 67. The effect of sympathectomy on the hand blood flow. The results obtained with the plethysmograph were similar to those in the previous figure. Readings were not possible so soon after operation. Right hand continuous line; left hand dotted line. Plethysmograph bath temperature 34°C. Organic arterial lesions were present in the right hand and probably account for the lower blood flow at full vasodilatation.
SECTION VII

THE CIRCULATORY ACTION OF NORADRENALINE IN MAN AND ITS RELATION TO PHAEOCHROMOCYTOMA AND ARTERIAL HYPERTENSION.
NORADRENALINE AND ARTERIAL HYPERTENSION.

The investigations reported in the previous sections have all been primarily concerned with disturbances of blood flow resulting chiefly from localised structural changes in the artery. It has for long been recognised that essential hypertension is associated with an increase in the tonus of the peripheral arterioles. The effect of this generalised change in the calibre of the arterioles on the peripheral blood flow has been investigated by many workers using calorimeters or plethysmographs (Pickering (1936), Prinzmetal and Wilson (1936)). The general conclusion from these investigations has been that the increased tonus of the peripheral arterioles is not due to overactivity of the sympathetic nervous system. Abramson and Ferris (1942), however, found that the resting forearm blood flow in hypertensive subjects was slightly greater than in normal subjects and suggested accordingly that the increased peripheral resistance was not uniformly distributed over the body. The forearm, consisting largely of muscular tissue, has a relatively small sympathetic innervation and thus an increased forearm blood flow might be anticipated if essential hypertension were due to overactivity of the sympathetic nervous system. The effect of lumbodorsal sympathectomy on essential hypertension is difficult to assess at present but in the malignant form it is probable that the operation frequently prolongs life (Keith et al 1949). For long it was considered probable that the sympathetic nerves released as their humoral mediator either adrenaline or a closely related compound. Infusions of adrenaline, however, were shown to produce a type of hypertension and peripheral circulatory changes unlike those seen in essential hypertension. (Gordon and Levitt (1935), Pickering and Kissin (1936)). The chemical structure
and pharmacological activity of several catechol amines were investigated originally by Barger and Dale (1910) who pointed out that the actions of adrenaline and the effect of sympathetic nerve stimulation were not always similar and that the latter often resembled more closely the action of what was later called noradrenaline. Subsequently Cannon and Rosenblueth (1937) demonstrated excitatory and inhibitory actions following stimulation of sympathetic nerves and showed that these results could not be produced by adrenaline alone. This work revived interest in the subject of sympathetic mediators and culminated in the demonstration by Euler (1946) of a substance isolated from sympathetic nerves with actions closely resembling those of noradrenaline. More recently Gaddum and Goodwin (1947) found that the substance released on stimulation of the hepatic sympathetic nerves (liver sympathin) had similar properties to those of noradrenaline, and Peart (1949) reached similar conclusions for splenic sympathin. Bulbring and Burn (1949) have shown that noradrenaline is released from the normal adrenal gland.

The widespread existence of noradrenaline in the body and the demonstration of its presence in phaeochromocytomas of the adrenal gland removed from patients who came under the writer's observation led to the present examination of the circulatory actions of noradrenaline in human subjects and to a comparison with the changes seen in naturally occurring hypertension. The results observed during noradrenaline infusions into healthy subjects will first be described. Since this work was begun, investigations on noradrenaline have been reported by Goldenberg and others (1948), Barcroft and Konzett (1949) and Swan (1949). The peripheral circulatory changes observed...
in three patients with phaeochromocytoma will then be described. The nature of these changes will be discussed both in relation to noradrenaline and to essential hypertension.

Synthetic laevonoradrenaline, provided through the kindness of Dr. Tainter of the Winthrop Chemical Co., was used in most experiments. The racemic mixture \((d-1)\) was also used and had about half the activity of the pure laevor form. The pure substance was prepared in 1:1,000 solution according to the B.P. formula for adrenaline injection, and sterilized by autoclaving. Assays by Mr. J. J. Brown on the cat demonstrated that the solution kept in the refrigerator for three weeks, the longest period before use, showed no loss in activity. In each experiment an intravenous saline drip was given into the arm or leg. The noradrenaline solution was injected into the needle through a side-arm of the system by a mechanically-driven syringe delivering 1 ml. per min. During the observation the subject received saline, noradrenaline and saline in successive periods. Most of the subjects were healthy male students, but a few infusions were also given to some older patients free from circulatory disease. For comparison a few infusions of \(1\)-adrenaline were given. Some of the commercial adrenaline used was prepared from animal sources and probably contained a variable amount of noradrenaline (Auerbach and Angell (1949)). In other experiments synthetic adrenaline was used.

Results of Infusions.

Subjective Sensations. With the smaller doses of \(1\)-noradrenaline \((1-15 \mu g. \text{ per min})\) in the majority there were no abnormal sensations; some noted a sense of constriction behind the sternum associated with an
increased awareness of respiration. These feelings passed off in most subjects within a few minutes. A few complained of mild palpitations, but this was uncommon. With larger doses up to 30 μG/min these symptoms were more frequent. Only one subject complained of headache; his blood pressure at the time was 190/120. Others with a similar degree of hypertension were unaffected. It should be emphasised that all the above sensations were mild and in no way interfered with the performance of the experiments.

**General Appearances.** Within about 1½ minutes of beginning noradrenaline a definite blanching of the face, lips and mucous membranes of the mouth and a less obvious pallor of the limbs developed and persisted throughout the infusion. On stopping noradrenaline there was a feeling of warmth and a pronounced flushing of the face appeared and persisted for a few minutes.

The mucous membrane of the ileum seen in an ileostomy paled during an infusion of 25 μG per minute. The rectal mucosa seen through a proctoscope also paled slightly during an infusion of 25μG per minute.

*Intradermal injection of 0.1 ml of 1:1,000 toluidine dilution of 1-noradrenaline produced local intense pallor and gooseskin. Injection into the mucous membrane of the ileum also produced local pallor. The veins near the infusion needle constricted with noradrenaline, at times so intensely as to stop the infusion. In two subjects receiving 30 μG 1-noradrenaline per minute for 16 and 40 minutes respectively, a soft swelling in the region of the thyroid gland developed. In the subject receiving the shorter infusion the swelling subsided within an hour. In the other at the end of the infusion the neck measured 44 cms. in circumference and after six hours resumed
its normal measurement of 39 cms. (Fig. 68). In some subjects a similar but much less conspicuous swelling was observed. In none of the subjects receiving noradrenaline alone was any venous congestion noted in the neck.

Pupil. No changes in the size of the pupil were seen during the infusions, nor did local application of noradrenaline in a concentration of 1:1,000 to the conjunctival sac produce any alteration.

Pulse Rate and Blood Pressure. The results are summarised in Tables I, II, and V. In all subjects noradrenaline raised the systolic and diastolic arterial pressures and slowed the heart. The changes in experiment 3 (Table I) were slight but the dosage was low. Usually the pressure rose gradually during the first five minutes or so of the infusion and thereafter maintained a relatively steady level. Continuous intraarterial pressure tracings showed that the hypertension and bradycardia developed together and there was no evidence that the fall in pulse rate preceded the rise in pressure. No drop in pressure occurred at the onset of the infusion as is seen in the first minute of an adrenaline infusion (Figs. 69 and 72). A rise in the diastolic pressure was a constant feature of the noradrenaline infusions, but was less than that of the systolic so that the pulse pressure was usually increased. (Fig. 71). There was great individual variation, though the response of the same subject remained constant on different occasions. Thus some subjects showed a considerable bradycardia with relatively little rise in pressure, others a large increase in pressure with little slowing; and in some both features were marked.

In most of the subjects the rhythm during the noradrenaline infusions was slow but regular.
Electrocardiographs showed a sinus bradycardia with or without lengthening of the PR interval. Occasionally an irregular rhythm was observed and in two subjects this disturbance was conspicuous. In one the electrocardiogram showed the development of complete AV dissociation, but the previous control electrocardiograms showed bundle branch block presumably of congenital origin, though the heart was clinically normal (Fig. 73). In the second subject l-noradrenaline at the rate of 15µG per minute led to sinus bradycardia. At a rate of 30µG per minute there was complete suppression of normal sinus activity and the development of ventricular complexes of nodal origin. Coupling of the beats also occurred and in the second of the coupled beats abnormal P waves could often be detected. In this subject it was possible at a later date to reproduce these changes by digital compression of both carotid sinuses for 10 seconds (Fig. 74).

Heat Elimination from the hand. Table I summarises the observations. In 11 the heat elimination fell during noradrenaline to rise again after its termination. A representative result is shown in Fig. 75. In three there was a progressive rise or fall during the observations. The constrictor effect of noradrenaline was, as anticipated, most easily demonstrated when the subjects were warm and the hand vessels were dilated.

Forearm blood flow. Table II summarises the results in 10 observations. In all the subjects the blood flow was reduced (Fig. 77). In two cases the alteration was slight. When a marked depression of the blood flow developed there was a transient hyperaemia on stopping the noradrenaline (Fig. 76).

Effect of Atropine. In order to investigate more fully the nature of the bradycardia and its influence on the circulatory changes the response of five subjects to
noradrenaline was studied both before and after the intravenous administration of atropine in doses of 1.2 to 2.1 mgm. (Table 111). The pulse rate after atropine varied in different subjects from 84 to 108, so that the vagus was probably not completely paralysed. In all a slight transient reduction in heart rate was noted at the onset of the noradrenaline infusion but this was quickly followed by an increase in heart rate either up to or above the previous control level. After the transient bradycardia there was a great rise in arterial pressure. The dosage of 1-noradrenaline was restricted to 10µG/min, but even this amount, which only produced a slight rise before the administration of atropine, produced extremely high pressures in some atropinized subjects. (Fig.79). On stopping the noradrenaline the blood pressure fell rapidly but the heart rate fell more slowly to the previous control level with atropine. A rise in venous pressure in the neck was seen in one subject given noradrenaline after atropine. In this subject noradrenaline alone produced no recognisable change in the neck veins. The forearm blood flow was measured in three of these experiments. In one the results were inconclusive owing to a steady decrease in the control readings. In the other two noradrenaline after atropine led to an increase in the blood flow (Fig.80).

Comparison with Adrenaline. For purpose of comparison of the peripheral circulatory changes adrenaline and noradrenaline have been given to the same subject in equal dosage. In some respects their actions were similar. Both caused facial pallor and blanching of the mucous membranes and both were found to lead to a reduction of heat elimination from the hand in about equal degree. Intradermal injection of the two drugs
produced apparently identical local effects, and noradrenaline, as will be shown below, caused renal circulatory changes qualitatively similar to those described by other authors for adrenaline.

The differences between the two are of greater interest. Intravenous infusion of noradrenaline produced remarkably few subjective symptoms even when there was an extreme bradycardia and considerable hypertension. On the other hand infusion of small amounts of adrenaline led to palpitations and trembling. The effect of the two drugs on the heart rate was strikingly different. Noradrenaline, as previously explained, invariably induced marked slowing. Adrenaline, on the other hand, was extremely variable in its action. The most interesting differences were in the mode of onset of the circulatory effects of the two drugs. These were particularly well shown in the continuous intraarterial tracings. Shortly after the onset of an adrenaline infusion there was a marked fall in both the systolic and diastolic blood pressures and a considerable cardiac acceleration (Figs. 70 and 71). Such a response has previously been reported (Gordon and Levitt 1935, Pickering and Kissin 1936). This effect usually only lasted about 20-30 sec. and was followed by an invariable rise in systolic pressure. The diastolic also rose usually to or about the control level, so that the pulse pressure was increased. The heart rate fell, but usually not to the control level.

In three subjects the effects of adrenaline and noradrenaline on forearm blood flow were compared. The intravenous infusion of adrenaline increased (Fig. 88) and of noradrenaline decreased the forearm blood flow. These results agree with those of Allen, Barcroft and Edholm (1946) and Barcroft and Konzett (1949).

**Renal Blood Flow.** During six of the experiments the
renal clearances of inulin and diodone were determined. The chemical estimations were carried out by Drs. Depoorter and Sanderson. The results are shown in Table IV and the changes in one typical experiment are illustrated in Fig. 81. It will be seen that the usual changes in blood pressure and pulse rate occurred in each experiment. The inulin clearance showed little change except in experiment 31, in which it fell by 18% from the control value (average of periods 1, 2 and 4). In the remaining subjects it either fell very slightly or showed no significant change. On the other hand the diodone clearance was considerably depressed in all six experiments. The largest deviation from the control value was -31% and the smallest -12%, the mean deviation being -26%. It thus follows that the filtration fraction (C In/C.D) showed a consistent elevation with noradrenaline. The largest increment was 8.0, the smallest 2.9; the average in the six experiments was 5.4. The urine flow was recorded in two experiments; there was a suggestion of a fall during the noradrenaline infusions but the changes were slight and probably not significant.
Observations on Phaeochromocytomata.

Three cases of phaeochromocytoma have been studied; full clinical details are reported in the appendix (Cases 1, 2 and 3) but for convenience a short summary of the clinical features is also given here together with a full account of the peripheral circulatory changes. During recent years increasing attention has been paid to the diagnosis and treatment of tumours of the adrenal medulla and many reviews of the conditions have appeared (Mackeith (1944), Blacklock et al. (1947), Cahill and Aranow (1949)). Few investigations, however, have been made regarding the circulatory disturbances associated with the condition and the mechanism of the development of the paroxysmal and persistent forms of hypertension. The cases were accordingly studied chiefly from these points of view.

Case 1 a male aged 38 years in 1948 was in good health till May 1946 when he gradually developed lassitude and occasional attacks of dizziness and headache. The blood pressure at that time was 180/110. These attacks gradually became more severe and they were usually associated with epigastric discomfort, pallor, vomiting, shivering, shortness of breath, profuse sweating and the development of "goose-flesh" all over his arms. The pallor was particularly noticeable and was observed as a warning signal of the approach of an attack. He was admitted to hospital after a particularly severe attack.

There was no definite family history of hypertension but his sister died of eclampsia when aged 20 years. The blood pressure of his elder brother was 120/80 in 1948.
On examination he was a thin sallow individual with a moist pale skin. Venous congestion up to 2 cm. was present in the neck. The blood pressure was always about 170/115 and pulsus alternans and gallop rhythm were present. There was no cardiac enlargement. In the abdomen a mass with a firm rounded lower edge was felt deeply below the right costal margin. In both optic fundi there were papilloedema, haemorrhages, soft exudates, a distinct right macular fan of silvery exudate and a slight left fan. Perirenal insufflation of air and radiological examination showed clearly a right suprarenal tumour. Intravenous benzodioxane administered as described by Goldenberg et al. (1947) produced a rise in blood pressure (Fig. 83). There was no albuminuria and renal function was normal.

At operation a suprarenal tumour weighing 45 gm. was removed and was shown histologically to be a phaeochromocytoma. The opposite suprarenal was normal and no other tumour was found. A renal biopsy was also taken. Careful examination of serial sections of this specimen showed only slight hyaline changes in a few glomerular arterioles and occasional glomerular fibrosis.

After operation he had no further attacks and the abnormalities in the fundi gradually receded and finally entirely disappeared.

The circulatory disturbances before and after operation are shown in figure 82. The blood pressure remained elevated after operation and when he was last seen in December 1949 it was 170/122. There was no significant change in forearm blood flow. The changes in the maximal heat elimination were most striking. The noteworthy feature was the failure of the hand vessels to dilate while the tumour was
present and the heat elimination remained at an extremely low level although every effort was made to produce full reflex vasodilatation and the patient sweated profusely. After excision of the tumour the maximal heat elimination rose to a normal level. The actual readings illustrating these points were:

<table>
<thead>
<tr>
<th>Date</th>
<th>Maximal heat elimination in cal/min/100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9.48</td>
<td>34</td>
</tr>
<tr>
<td>14.9.48</td>
<td>35</td>
</tr>
<tr>
<td>21.9.48</td>
<td>39</td>
</tr>
<tr>
<td>23.9.48</td>
<td>Excision of phaeochromocytoma</td>
</tr>
<tr>
<td>30.9.48</td>
<td>55</td>
</tr>
<tr>
<td>5.10.48</td>
<td>87</td>
</tr>
<tr>
<td>7.10.48</td>
<td>75</td>
</tr>
<tr>
<td>30.10.48</td>
<td>89</td>
</tr>
<tr>
<td>27.11.48</td>
<td>76</td>
</tr>
<tr>
<td>2.7.49</td>
<td>93</td>
</tr>
</tbody>
</table>

As the hypertension persisted after operation and the benzodioxane test was obviously of no value in this case he was given histamine 0.05 mg. intravenously (Roth and Kvale (1945)). This produced no paroxysm of hypertension. At operation the opposite suprarenal gland had appeared normal. In spite of the sustained postoperative hypertension it was accordingly concluded that no further adrenal medullary tumour tissue was present on the evidence that the attacks had ceased, the fundi had returned to normal, the hand vessels dilated fully, the histamine test was negative and the patient felt entirely fit.

Case 2 a female aged 49 years in 1948 first complained of early morning headache in 1944 often associated with nausea, vomiting and profuse sweating. These symptoms gradually became more severe and she was sometimes awakened at night by
attacks of palpitations, thumping at the back of the head and profuse sweating. She is known to have had a persistent though variable hypertension since 1945 usually about 220/120.

Her mother died at 71 years from a cerebral thrombosis. Her father is alive at 74 years but is stated to have hypertension.

On admission to hospital the blood pressure was extremely labile but averaged about 200/130. The heart was normal. In the optic fundi were a few retinal haemorrhages, some soft exudates and early arteriovenous nipping. There was no papilloedema. The liver was enlarged to two fingers' breadth below the costal margin. A smooth tumour was present below the left costal margin. The renal function was normal.

At laparotomy on 21st October 1948 a tumour weighing 1100 gm. was removed from the region of the tail of the pancreas. Subsequent histological examination showed this to be a phaeochromocytoma. Pharmacological assay (Case 2 of Holton, 1949) showed it to contain the equivalent of 0.3 mg l-adrenaline and 10.0 mg dl-noradrenaline per gm. of tumour tissue.

There was a fall of blood pressure to normal after operation lasting about five weeks but subsequently it returned to the range 220-170/110-90. When last seen on 19th October 1949 the blood pressure was 230/120. The haemorrhages and exudates in the optic fundi had entirely disappeared. There was no recurrence of the palpitations and the nocturnal sweating attacks. A benzodioxane test did not produce a fall in blood pressure. As the diagnosis was not made before operation a full series of blood flow determinations was not possible.
Case 3 a male aged 31 years in 1949 was a highly intelligent patient who gave an extremely interesting history which should be read in full in the appendix. At the age of 11 years he was seen by Sir John Parkinson (Case 7 in Wolff, Parkinson and White (1930)). At that time he had had for years recurrent attacks in which he was pale and the pulse varied between 40 and 65. The attacks occurred about twice a week and each lasted 2-3 minutes. The blood pressure then was 110/75.

The present attacks began while serving as an officer in the army in 1941. They were characterised by pallor, epigastric discomfort and thumping of the heart. The pulse slowed, often dropping to 36, and he noticed that the beats then might come in pairs. In the more severe attacks there was shivering, headache, Dausea and vomiting. He was unable to micturate during an attack and if an attack came during the act the flow stopped. His wife noticed that his face paled before he had any symptoms. She might also be awakened at night by an attack because of the thumping of his heart beat. He was unaware of anything that would consistently produce an attack.

On examination he was a spare man with a pale skin. Physical examination apart from an attack was entirely negative. There were no changes in the optic fundi. The blood pressure ordinarily ran between 90/70 and 136/90. The heart was entirely normal. Radiological examination showed a soft tissue mass lying above the right kidney.

On 12th November 1949 a tumour weighing 200 gm. was removed. During the operation the pressure rose as high as 255/160. The patient sweated very copiously throughout the latter part of the
manipulation of the tumour. After removal the pressure fell to 115/85 at about which level it subsequently remained. Histological examination of the tumour showed it to be a typical phaeochromocytoma with many cells showing the chromaffin reaction. A renal biopsy showed entirely normal glomeruli and arterioles. Peripheral circulatory investigations were carried out before and after operation. The patient was seen in 20 attacks lasting up to about 15 minutes. During them the blood pressure was always above the normal range and was recorded as high as 254/154. The face was conspicuously pale. In one attack which developed during investigations in the laboratory the heat elimination from the hand fell and the face paled before the patient was aware of the onset. The blood pressure both systolic and diastolic rose and the pulse slowed. (Fig. 84). The maximal heat elimination of the left hand was determined as in Case 1 with the following results:

<table>
<thead>
<tr>
<th>Date</th>
<th>Maximal heat elimination</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.11.49</td>
<td>24</td>
<td>130/90</td>
</tr>
<tr>
<td>7.11.49</td>
<td>34</td>
<td>95/65</td>
</tr>
<tr>
<td>12.11.49</td>
<td>Excision of phaeochromocytoma.</td>
<td></td>
</tr>
<tr>
<td>23.11.49</td>
<td>72</td>
<td>126/74</td>
</tr>
<tr>
<td>22.12.49</td>
<td>76</td>
<td>122/82</td>
</tr>
</tbody>
</table>

A specimen of femoral arterial blood was withdrawn by the writer during an attack and heparin added. The plasma was separated by centrifuging in iced tubes and was sent packed in ice to Prof. J.H. Gaddum who received it about 12 hours later. It was not possible to detect any significant quantity of either noradrenaline or adrenaline in this specimen though it was thought that a slight trace of the
latter substance was present. The tumour is also being investigated in detail by Dr. Crawford in Prof. Gaddum's department but quantitative results of the assay are not yet available. It has been shown, however, to contain considerable amounts of both adrenaline and noradrenaline.

When last seen on 22nd December 1949 he felt entirely fit. He had had no attacks since operation and the blood pressure was 130/80.
The findings reported in the experimental infusions are in general in agreement with the results obtained by other workers. Goldenberg and others (1948) and Barcroft and Konzett (1949) have both reported the rise in systolic and diastolic arterial pressures and the bradycardia. The latter workers have also demonstrated decreases in calf blood flow on infusions of noradrenaline into the femoral artery. The conspicuous blanching from intravenous as well as intracutaneous injection showed that noradrenaline had a powerful constrictor action on the minute vessels of the skin and mucous membrane of the mouth and to a lesser extent on that of the ileum and rectum. The decrease in hand blood flow suggested but did not prove that the arterioles might also be affected. The decrease in forearm flow despite the rise in arterial pressure was evidence that the drug constricted muscle vessels, its action in this respect being in striking contrast to that of adrenaline. The action of the drug was thus vasoconstrictor in all the tissues studied.

The bradycardia was considered to be vagal in origin consequent on the rise in intravascular pressure, for the following reasons. The continuous intraarterial records showed that the slowing developed coincidentally with the rise in pressure and that in no case did the bradycardia precede the hypertension. The electrocardiographic changes were similar to those described by Lewis (1925) following excessive vagal activity, and their reproduction in one subject by carotid sinus pressure supported this view. The evidence obtained with atropine was not conclusive as it was not possible completely to
abolish the initial bradycardia on giving noradrenaline. The bradycardia was transient and was followed by cardiac acceleration which may be explained in at least two ways. First, noradrenaline is known to accelerate the isolated mammalian heart (Ahlquist (1948)). In normal human subjects acceleration is not seen, presumably on account of the reflex vagal inhibition. With partial paralysis of the vagus by atropine the direct action of noradrenaline on the heart may be more evident. Secondly, one of the subjects given atropine and noradrenaline showed a rise in venous pressure and although no direct measurements were made it is quite possible that an increase in right auricular pressure may occur and lead to cardiac acceleration. It is probable that a combination of the two drugs leads to a considerable increase in cardiac output accounting for the greater forearm blood flow and the enormous rise in arterial pressure. Noradrenaline alone has been shown either to decrease or leave unchanged the cardiac output (Goldenberg et al. (1948)).

The swelling in the neck has not previously been reported in experimental noradrenaline infusions. It appeared to be due to an increase in the size of the thyroid gland. A similar swelling was reported during the paroxysms of hypertension due to a phaeochromocytoma (Strombeck and Hedberg (1939)) but it was not apparent in the cases here reported. This effect of noradrenaline is of considerable interest and is being further investigated by the writer using radioactive iodine.

The purpose of these experiments was to compare the changes produced by noradrenaline with the circulatory disturbances existing in hypertensive states in man. In cases of phaeochromocytoma there
is strong evidence that both adrenaline and noradrenaline are present in the circulating blood and that these substances are released in excess by the tumour. In three such tumours Holton (1949) has demonstrated the presence of noradrenaline and adrenaline, the former in considerably larger amount. Few studies of the circulatory disturbances have been published but Evans and Stewart (1942) have shown in one case the presence of such a tumour to be associated with a considerable reduction in total cutaneous blood flow. The observations on the changes in Cases 1 and 3 are strongly suggestive of the presence of a circulating vasoconstrictor substance, even apart from the attacks. In both cases the hand blood vessels failed to dilate with heating of the body to a degree sufficient to produce copious sweating. It should be noted that during these investigations the patients were free from symptoms. This suggests that the vasoconstrictor substance present in the circulation on these occasions was noradrenaline. In Case 1 in whom the skin vessels were permanently constricted a small infusion of adrenaline produced the symptoms of an attack. Only after excision of the tumours was it possible to produce normal full reflex vasodilatation. In Case 3, observations during a spontaneously developing attack reproduced in a remarkable way the features recorded during an experimental noradrenaline infusion as is seen particularly in the comparison of figures 75 and 84. This patient stated that with the pronounced cardiac slowing during an attack the beats often came in pairs, a feature also previously noted in the experimental infusions (Fig. 74). Similar electrocardiographic changes have been reported during paroxysms of hypertension due to a
phaeochromocytoma by Burgess et al (1936), and by Hegglin and Holzman (1937). As the crises in this patient were of short duration and unpredictable it was not possible to make observations on forearm blood flow, renal clearances, or electrocardiograms during an attack. The records of forearm blood flow in Case 1 are not easy to interpret, but it does seem possible that a tumour secreting mainly noradrenaline with a trace of adrenaline could leave the blood flow relatively unaltered, especially as the changes in forearm blood flow in some of the experimental noradrenaline infusions were extremely slight. The changes noted during the attack in the third case are clearly compatible with the hypothesis that the tumour was secreting mainly noradrenaline. The clinical features in all the cases however suggest strongly that the tumours during the severe paroxysms secrete adrenaline as well as noradrenaline. It is the former drug that is chiefly responsible for the palpitations, nervousness and restlessness which constitute their main complaints. It is noticeable that in Cases 1 and 3 observers were always aware of the onset of an attack before the patient as the facial pallor developed before the symptoms. In Case 3 the heat elimination from the hand had decreased considerably before the patient realised that an attack was in progress. These features suggest that during an attack the tumour first secretes noradrenaline and that adrenaline is only released in appreciable amount at a later stage.

The assay in Case 2 carried out by Holton showed that this tumour contained over ten times as much pharmacologically active noradrenaline as adrenaline. The examination of the tumour in Case 3 was not complete at the time of writing but it is known to
have a content of noradrenaline, adrenaline and other as yet unidentified substances which may be precursors of the active agents. The investigation of the blood sample taken during an attack was disappointing, especially as Beer, King and Prinzmetal (1937) had been able to show the presence of a powerful circulating vasoconstrictor agent in such circumstances. This was later confirmed by Strombeck and Hedberg (1939) who, using a chemical method, demonstrated a 30-times normal adrenaline content in the blood between attacks and a 1000-times normal content in the attack. These estimations probably included noradrenaline. Recently Vogt (1949) has demonstrated the presence of noradrenaline in the blood during an attack. The unavoidable delay of twelve hours in the investigation of the plasma from Case 3 was not considered by Prof. Gaddum a possible explanation for the low levels of adrenaline and noradrenaline. Other workers have been unable to find any pressor substance in the blood (Biskind et al. (1941) ). It should be realised that an extremely small quantity of noradrenaline in the blood stream will produce profound disturbances. For example examination of the blood plasma in a subject receiving 30µG of 1-noradrenaline a minute (the largest dose given in the experiments) into a blood volume of five litres would be negative using the pharmacological methods at present available.

The evidence obtained from these personal studies and from past observations strongly suggests that these tumours are continually secreting an excess of noradrenaline. It has also been shown that a sudden outpouring of this substance with adrenaline is responsible for the paroxysmal attacks. It is,
however, important to consider the relation of the continued presence of excess of noradrenaline and adrenaline in the blood stream to the persistent hypertension. In cases 1 and 2, who both had a sustained hypertension before operation, the blood pressure did not return permanently to normal. This immediately raises the question as to whether the sustained hypertension present before operation was connected with the presence of the adrenal tumours. In Case 3 a tumour was also present, but here the blood pressure between the attacks was normal and it remained so after operation. In this case it is highly important to note that, during the laboratory investigations when the maximal heat elimination of the hand was found to be greatly reduced, presumably owing to circulating vasoconstrictor agents, no hypertension was present. Similarly in their case Strombeck and Hedberg (1939) found a greatly increased blood adrenaline (their estimation probably included noradrenaline) between the attacks while the blood pressure was normal. With a continuous infusion of adrenaline the blood pressure falls after an initial rise (Freeman et al (1941)). No infusions of noradrenaline of over 40 minutes duration have as yet been given to man but from evidence in animal experiments to be detailed later it is doubtful whether this substance would produce a sustained hypertension. It should also be noted that there was no fall in blood pressure in Case 1 after the administration of benzodioxane as described by Goldenberg et al (1947). The basis of this test is that benzodioxane, an adrenolytic substance, produces a fall in blood pressure if a phaeochromocytoma is present. The response of Case 1 however was that reported in subjects with essential hypertension.
Prunty and Swan (1949) have recently failed to confirm Goldenberg's claims with regard to the action of the drug in experimental short term infusions as they were unable to produce a fall in pressure by its administration. The mechanism of the response to this test is uncertain but it is probably connected with the hypotension resulting on cessation of a long-term infusion of adrenaline or noradrenaline. This will be described later and it will then become apparent that benzodioxane may in certain cases of phaeochromocytoma produce a fall of blood pressure by removing the influence of circulating adrenaline or noradrenaline even though these substances certainly are not responsible for the sustained hypertension.

In cases of phaeochromocytoma associated with chronic hypertension it has generally been claimed that the blood pressure returns to normal after excision of all the tumour tissue. Thus Green (1946) in a series of 19 patients followed up to three years after operation found that in all cases the blood pressure returned to normal. Cahill (1948) reported a case in which hypertension persisted but here the blood pressure fell after removal of a second tumour. These neoplasms are occasionally multiple (McKeith (1944)) and it was considered possible that adrenal medullary tumour tissue was still present in Cases 1 and 2. The exploration of the abdomen at the time of operation, the absence of postoperative paroxysmal attacks and the negative histamine and benzodioxane tests ruled out this explanation of the persistent postoperative hypertension. Moreover the return of the maximal blood flow through the hand to a normal level suggested that in Case 1 no excess circulating
vasoconstrictor substances were present after the operation. The recession of the retinal changes, the normal renal function tests in both cases and in Case 1 the presence of only slight abnormalities in the biopsy specimen make it unlikely that the chronic hypertension was due solely to renal vascular damage. The absence of any evidence of arteriolar damage either in the eye grounds or in the renal biopsy is remarkable in Case 3 as during the paroxysms the blood pressure rose as high as 254/154. Byrom and Dodson (1948) produced arteriolar lesions in animals by sudden short periods of severe hypertension and regarded these rises in pressure as the chief factor in the production of arteriolar necrosis. In Case 3 this experiment has been reproduced in man with a negative result. The kidneys in some cases with chronic hypertension and a phaeochromocytoma when examined at autopsy have been intact. (Mackeith (1944)) Nevertheless it is possibly significant that the pressure remained high in the two cases with vascular lesions but normal in the case with undamaged arterioles. The evidence for the presence of essential hypertension as an additional and unassociated condition in Cases 1 and 2 is difficult to assess. Essential hypertension is now recognised as an inherited familial disease. In Case 1 apart from a sister who died of eclampsia at the age of 20 years there was no significant family history and his brother, specially examined for the purpose, was found to have a normal blood pressure. In Case 2 the patient's father was stated to have hypertension but he was alive and active at the age of 74 years. The cause of the persistent hypertension thus remains obscure. In an attempt to exclude further any part played by noradrenaline in long sustained hypertension
as distinct from paroxysmal attacks, experiments on rabbits were carried out by the writer in conjunction with Professor Pickering. Through a catheter introduced into the jugular vein it was found possible to give continuous intravenous infusions for periods up to three weeks. Six rabbits were given continuous infusions of either noradrenaline or noradrenaline and adrenaline in the proportions found in the tumour of Case 2 for periods of a week or longer. The pressure remained elevated during the first two or three days of the infusion but thereafter returned to a normal level even though the dose of the drug was greatly increased. A typical result is shown in Fig. 85. In all the experiments it seemed that some defensive mechanism came into play after about two days and the blood pressure was consequently not sustained at an abnormally high level. However a large dose of noradrenaline rapidly injected from a syringe while the continuous infusion was running, but after the hypertension had subsided, produced a transient high rise in blood pressure. This was thought to reproduce the conditions seen in a paroxysm of hypertension due to a phaeochromocytoma. On stopping the continuous infusion the blood pressure fell to abnormally low levels, a feature previously described in man after prolonged adrenaline infusions (Koehler et al. (1937), Green et al. (1948)). By contrast in rabbits it was possible to produce a sustained hypertension of up to three weeks duration by the continuous intravenous infusion of renin.

In Cases 1 and 2 the chronic hypertension, on the evidence previously cited, was not due to the direct action of noradrenaline. In Case 3 it was shown that the presence of secretions from the tumour sufficient to produce persistent vasoconstriction in the hand
was not associated with hypertension. In the animal experiments it was impossible to produce a sustained hypertension with noradrenaline. It is difficult to reconcile these findings with the previous reports of chronic hypertension due to phaeochromocytoma being cured by operation. In many of the records the follow-up period has been too short as it is known that any surgical procedure may be associated with a temporary fall in blood pressure as was seen in Case 2. In one of the cases reported by Goldenberg (1947) a persistently elevated blood pressure did not return to normal after operation. Summarising the evidence obtained from a study of these three cases it may be said that the features of the paroxysms including the transient acute rises in blood pressure, and the greatly reduced maximal blood flow through the hand were due to circulating adrenaline and noradrenaline. On the other hand the chronic hypertension, which persisted after operation, was not directly related to the secretions of the adrenal medullary tumours.

Essential hypertension has recently been attributed to a disturbance in the amounts of noradrenaline and adrenaline produced at the sympathetic nerve endings, the rise in pressure being due to a relative excess of noradrenaline (Goldenberg et al. (1948) ). There are some similarities in essential and experimental noradrenaline hypertension. In both there is a rise in systolic and diastolic pressure with little subjective disturbance. The renal circulatory changes are also similar, for the characteristic picture of early essential hypertension is a lowered diodone clearance, normal inulin clearance and a rise in filtration fraction (Goldring and Chasis,(1944) ). However it is now clear that the same changes are
produced by many other pressor agents including adrenaline, ephedrine, paredrinol (Smith et al. (1940), Ranges and Bradley (1943), Barclay et al. (1947) ) and angiotonin (Bradley and Parker (1941) ). They cannot thus be regarded as specific.

On the other hand there are many differences between the two states. Essential hypertension is not associated with a reduction in hand and forearm blood flow or bradycardia. However, it is not known how long bradycardia would persist in man if noradrenaline were given indefinitely. More striking are the changes in facial complexion. Many hypertensives are highly-coloured, but with experimental noradrenaline hypertension the face is pale. If in essential hypertension noradrenaline is present in excessive amounts in the circulating blood it must be assumed that the facial vessels do not react to noradrenaline in the same way as in normal subjects. Accordingly intravenous 1-noradrenaline infusions were given at the rate of 10μG per minute to hypertensive patients; they developed facial pallor to the same extent as normotensive subjects. It is thus improbable that essential hypertension is associated with the presence of free circulating noradrenaline. The observation of Goldenberg and others (1948) that the absolute rise of blood pressure with noradrenaline is greater in hypertensive than in normotensive subjects was confirmed. However, it is probably not valid to assume on this evidence that hypertensives are unduly sensitive to noradrenaline, as the base lines are not comparable. It should be noted that noradrenaline is extremely rapidly eliminated from the general circulation, and these observations on hypertensive patients do not finally exclude the possibility that noradrenaline may be produced and
fixed locally in and around the arterioles. The evidence obtained from the infusions in healthy subjects, the observations on the hypertension associated with phaeochromocytomata, and the animal experiments shows that it is improbable that noradrenaline is the agent directly responsible for essential hypertension.

Summary.
1. L-noradrenaline when given by intravenous infusion to healthy young adults at a rate of 5 to 30μG per minute produced few or no sensations. The systolic, diastolic and mean arterial pressures rose, the heart slowed and there was a reduction in the blood flow through muscle, skin and mucous membranes.
2. The bradycardia was thought to be reflexly mediated through the vagus consequent on a rise of systemic arterial pressure for the following reasons:-
   (a) the slowing of the pulse appeared with or slightly after the hypertension and in no case preceded it.
   (b) the electrocardiogram showed depression of A-V conductivity of varying degrees.
   (c) in one subject the electrocardiographic changes with noradrenaline were reproduced by carotid sinus pressure.
   (d) it was largely abolished by atropine.
3. After intravenous atropine sulphate in doses of 1.2 to 2.1 mgm noradrenaline produced an initial slight bradycardia quickly followed by a considerable tachycardia and a marked rise in blood pressure and forearm blood flow. In one subject venous congestion in the neck was observed. On stopping noradrenaline the tachycardia gradually disappeared though the blood pressure fell promptly. These results may be
# TABLE I

## BLOOD PRESSURE, PULSE RATE AND HEAT ELIMINATION FROM THE HAND

**BEFORE, DURING AND AFTER NORADRENALINE INFUSIONS IN NORMAL SUBJECTS**

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Subject</th>
<th>Age</th>
<th>Weight Kg.</th>
<th>Dose μG/Min</th>
<th>First Control Period</th>
<th>Noradrenaline Infusion</th>
<th>Second Control Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B.P. Pulse H.E. Cal/min</td>
<td>B.P. Pulse H.E. Cal/min</td>
<td>B.P. Pulse H.E. Cal/min</td>
</tr>
<tr>
<td>1</td>
<td>C.B.</td>
<td>58</td>
<td>55</td>
<td>10 μG DL</td>
<td>114/77 75 217</td>
<td>134/85 65 152</td>
<td>110/78 78 224</td>
</tr>
<tr>
<td>2</td>
<td>G.K.</td>
<td>42</td>
<td>70</td>
<td>15 μG DL</td>
<td>112/62 69 320</td>
<td>112/68 61 299</td>
<td>110/68 70 294</td>
</tr>
<tr>
<td>3</td>
<td>J.O'C.</td>
<td>43</td>
<td>71</td>
<td>15 μG DL</td>
<td>116/78 76 312</td>
<td>139/100 57 242</td>
<td>115/76 78 330</td>
</tr>
<tr>
<td>4</td>
<td>A.S.</td>
<td>44</td>
<td>66</td>
<td>20 μG DL</td>
<td>145/85 75 167</td>
<td>205/115 58 114</td>
<td>147/86 75 213</td>
</tr>
<tr>
<td>5</td>
<td>A.S.</td>
<td>39</td>
<td>66</td>
<td>10 μG L</td>
<td>104/70 60 230</td>
<td>156/107 62 266</td>
<td>115/68 50 171</td>
</tr>
<tr>
<td>6</td>
<td>G.B.</td>
<td>52</td>
<td>58</td>
<td>15 μG L</td>
<td>135/79 97 330</td>
<td>143/105 62 175</td>
<td>135/71 54 312</td>
</tr>
<tr>
<td>7</td>
<td>A.H.</td>
<td>36</td>
<td>70</td>
<td>15 μG L</td>
<td>131/93 74 167</td>
<td>147/84 53 232</td>
<td>130/55 74 445</td>
</tr>
<tr>
<td>8</td>
<td>J.L.</td>
<td>22</td>
<td>59</td>
<td>20 μG L</td>
<td>106/58 82 270</td>
<td>157/112 53 232</td>
<td>135/79 73 354</td>
</tr>
<tr>
<td>9</td>
<td>A.B.</td>
<td>34</td>
<td>76</td>
<td>30 μG L</td>
<td>123/66 75 451</td>
<td>151/106 62 216</td>
<td>126/54 88 278</td>
</tr>
<tr>
<td>10</td>
<td>E.F.</td>
<td>38</td>
<td>63</td>
<td>30 μG L</td>
<td>132/80 60 410</td>
<td>201/112 42 152</td>
<td>135/80 73 289</td>
</tr>
<tr>
<td>11</td>
<td>G.S.</td>
<td>27</td>
<td>67</td>
<td>30 μG L</td>
<td>127/86 77 407</td>
<td>155/97 49 149</td>
<td>126/54 88 278</td>
</tr>
<tr>
<td>12</td>
<td>G.M.S.</td>
<td>22</td>
<td>61</td>
<td>30 μG L</td>
<td>116/54 69 285</td>
<td>201/112 42 152</td>
<td>135/80 73 289</td>
</tr>
<tr>
<td>13</td>
<td>H.P.</td>
<td>22</td>
<td>59</td>
<td>30 μG L</td>
<td>132/80 60 410</td>
<td>201/112 42 152</td>
<td>135/80 73 289</td>
</tr>
<tr>
<td>14</td>
<td>W.D.</td>
<td>21</td>
<td>80</td>
<td>30 μG L</td>
<td>132/80 60 410</td>
<td>201/112 42 152</td>
<td>135/80 73 289</td>
</tr>
</tbody>
</table>
TABLE II

BLOOD PRESSURE, PULSE RATE AND FOREARM BLOOD FLOW
BEFORE, DURING AND AFTER NORADRENALINE INFUSIONS IN NORMAL SUBJECTS

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Subject</th>
<th>Age</th>
<th>Weight Kg.</th>
<th>Dose</th>
<th>First Control Period</th>
<th>Noradrenaline Infusion</th>
<th>Second Control Period</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B.P.</td>
<td>Pulse</td>
<td>F.B.F. ml/100ml/min</td>
</tr>
<tr>
<td>15</td>
<td>G.P.</td>
<td>45</td>
<td>78</td>
<td>25 μG DL</td>
<td>108/68</td>
<td>65</td>
<td>3.4</td>
</tr>
<tr>
<td>16</td>
<td>B.B.</td>
<td>22</td>
<td>73</td>
<td>30 μG DL</td>
<td>120/53</td>
<td>65</td>
<td>4.5</td>
</tr>
<tr>
<td>17</td>
<td>O.B.</td>
<td>52</td>
<td>58</td>
<td>15 μG L</td>
<td>152/92</td>
<td>70</td>
<td>4.1</td>
</tr>
<tr>
<td>18</td>
<td>J.B.</td>
<td>27</td>
<td>63</td>
<td>20 μG L</td>
<td>146/90</td>
<td>61</td>
<td>3.6</td>
</tr>
<tr>
<td>19</td>
<td>A.D.</td>
<td>23</td>
<td>59</td>
<td>20 μG L</td>
<td>116/79</td>
<td>70</td>
<td>1.6</td>
</tr>
<tr>
<td>20</td>
<td>A.F.</td>
<td>31</td>
<td>57</td>
<td>20 μG L</td>
<td>126/76</td>
<td>81</td>
<td>3.7</td>
</tr>
<tr>
<td>21</td>
<td>H.P.</td>
<td>22</td>
<td>59</td>
<td>20 μG L</td>
<td>128/70</td>
<td>62</td>
<td>3.6</td>
</tr>
<tr>
<td>22</td>
<td>L.H.</td>
<td>81</td>
<td>70</td>
<td>30 μG L</td>
<td>120/75</td>
<td>80</td>
<td>3.5</td>
</tr>
<tr>
<td>23</td>
<td>J.G.</td>
<td>22</td>
<td>69</td>
<td>30 μG L</td>
<td>124/83</td>
<td>72</td>
<td>3.4</td>
</tr>
<tr>
<td>24</td>
<td>D.H.</td>
<td>21</td>
<td>67</td>
<td>30 μG L</td>
<td>115/65</td>
<td>69</td>
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TABLE III

BLOOD PRESSURE, PULSE RATE, AND FOREARM BLOOD FLOW DURING NORADRENALINE INFUSIONS BEFORE AND AFTER THE ADMINISTRATION OF ATROPINE IN NORMAL SUBJECTS

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Subject</th>
<th>Age</th>
<th>Weight Kg.</th>
<th>Noradrenaline Dose per min.</th>
<th>Atropine Dose</th>
<th>First Control Period</th>
<th>noradrenaline Infusion</th>
<th>Second Control Period</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>B.P.</td>
<td>Pulse</td>
<td>F.B.F. ml/100ml/min</td>
</tr>
<tr>
<td>25</td>
<td>D.S.</td>
<td>27</td>
<td>73</td>
<td>10 /G</td>
<td>1.2 mgm</td>
<td>115/76</td>
<td>48</td>
<td>148/100</td>
</tr>
<tr>
<td>26</td>
<td>T.H.</td>
<td>27</td>
<td>63</td>
<td>10 /G</td>
<td>1.2 mgm</td>
<td>110/76</td>
<td>60</td>
<td>118/86</td>
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<tr>
<td>27</td>
<td>W.P.</td>
<td>42</td>
<td>67</td>
<td>10 /G</td>
<td>2.1 mgm</td>
<td>108/65</td>
<td>64</td>
<td>114/70</td>
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<tr>
<td>28</td>
<td>D.B.</td>
<td>22</td>
<td>75</td>
<td>10 /G</td>
<td>1.2 mgm</td>
<td>130/68</td>
<td>62</td>
<td>142/88</td>
</tr>
<tr>
<td>29</td>
<td>A.P.</td>
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<td>78</td>
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<td>1.5 mgm</td>
<td>118/73</td>
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<td>134/94</td>
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<td>Experiment Number</td>
<td>Subject</td>
<td>Age</td>
<td>Weight Kg.</td>
<td>Period</td>
<td>L-Norepinephrine /µ G/min</td>
<td>Duration minutes</td>
<td>B.P.</td>
<td>Pulse</td>
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<td>5</td>
<td>-</td>
<td>30.5</td>
<td>134</td>
<td>74</td>
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</table>

* Done without using an indwelling catheter. To induce diuresis 1600 ml. water were drunk during the 90 minutes preceding the first period. A total of 1200 ml. were drunk during the five periods.
<table>
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<th>Experiment number</th>
<th>Subject</th>
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<th>Weight (Kg)</th>
<th>Drug and dose per minute</th>
<th>Control period</th>
<th>Infusion of drug</th>
<th>No Control period</th>
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<td>B.P. Pulse</td>
<td>B.P. Pulse</td>
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<td>After 45 sec</td>
<td>Rest of infusion</td>
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<td>31</td>
<td>60</td>
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<td>135/82 74</td>
<td>155/92 65</td>
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<td>L Adrenaline 30 µg</td>
<td>137/83 80</td>
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<td>L Adrenaline 30 µg</td>
<td>136/78 65</td>
<td>103/60 100</td>
<td>153/80 73</td>
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</table>
At conclusion of noradrenaline infusion.

(b) Subsequent control.

Fig. 63. Showing the swelling of the neck brought about by an infusion of 30 µG L-noradrenaline/min. for 40 minutes.
Fig. 69. Blood pressure and pulse rate changes during noradrenaline and adrenaline infusions as measured from continuous femoral arterial pressure tracings. The adrenaline was prepared synthetically.
Fig. 70. Blood pressure and pulse rate during noradrenaline and adrenaline infusions as measured by the capacitance manometer. Note the slowing of the pulse during the adrenaline infusion. Synthetic adrenaline was used.
Fig. 71. Femoral artery pressure tracings.

Upper tracing - Control.

Lower tracing - During noradrenaline infusion 
30 ug./min. Time interval 1 sec. Pressure scale in mm. of mercury. Note the bradycardia and pulse irregularity with noradrenaline.
Fig. 72. Femoral artery pressure tracings. Upper tracing control; middle tracing onset of adrenaline infusion 30 µg./min.; lower tracing after 3 min. of adrenaline infusion. Time interval 1 sec. Pressure scale in mm. of mercury. Note the tachycardia and hypotension at the commencement of the infusion followed later by bradycardia and hypertension.
Control. Lead 11. Though the heart was clinically normal and there was no history of disease development of the electrocardiograms after the experiment showed the presence of a congenital bundle branch block.

L-noradrenaline infusion 30 μg./min. Both records Lead 11. Complete auriculo-ventricular dissociation developed.

Fig. 73. The development of complete heart block in a subject with bundle branch block during a noradrenaline infusion.
Control.

15 µg. L-noradrenaline/min. Sinus bradycardia.


30 µg. L-noradrenaline/min. Nodal rhythm with occasional coupling of beats.

Carotid sinus pressure reproducing changes of last electrocardiogram.

Fig. 74. The changes in cardiac rhythm during noradrenaline infusions. Strong reflex vagal stimulation by carotid sinus pressure caused similar changes. All records are Lead II.
Fig. 75—Changes in pulse rate and heat elimination from the hand during noradrenaline infusion.
(a) During control period. 4.1 ml./100ml./min.

(b) During L-noradrenaline infusion 20 µG./min.
2.7 ml./100ml./min. Both time markers 1.5 sec.

Fig. 77. Forearm blood flows. Actual tracings as obtained by venous occlusion plethysmography showing the reduction in blood flow during noradrenaline infusion.
During control period, 4.0 ml./100ml./min.

During L-adrenaline infusion 20 μg./min. 6.6 ml./100ml./min. Both time markers 1.5 sec.

Fig. 78. Forearm blood flows. Actual tracings as obtained by venous occlusion plethysmography showing the increase in blood flow during adrenaline infusion.
Fig. 79. Changes in blood pressure and pulse rate during noradrenaline infusions before and after atropine. Note the excessively high rise in blood pressure during the second infusion.
**Fig. 80.** Changes in blood pressure, pulse rate and forearm blood flow during noradrenaline infusion before and after the administration of atropine.
Fig. 81. Changes in blood pressure, pulse rate and renal clearances during noradrenaline infusion. Note the fall in diodone clearance and the rise in filtration fraction during the infusion.
Fig. 82. Showing the changes in blood pressure, forearm blood flow and maximal heat elimination from the hand observed in the first case of phaeochromocytoma.
Fig. 83. The response of the blood pressure to benzodioxane in the first case of phaeochromocytoma.
Fig. 84. Observations on heat elimination from the hand, blood pressure and pulse rate during a spontaneously developing attack in Case 3. The subject was unaware of any abnormal sensations until the 23rd minute.
Fig. 85. The effect of a prolonged noradrenaline infusion in a rabbit. A persistent hypertension could not be obtained. A large additional dose of noradrenaline given intravenously by syringe on the 6th day produced a transient paroxysm of hypertension. Blood pressure continuous line. Heart rate dotted line.
GENERAL SUMMARY AND CONCLUSION
A summary has been included at the end of each section, but the scope of the thesis may be reviewed by way of conclusion. Attention has chiefly been directed to a study of anatomical and physiological abnormalities in the peripheral arterial circulation.

Methods of investigation were described in the first two sections. The pathological anatomy was studied by gross dissection of amputated limbs supplemented by histological and injection techniques. Physiological disturbances were observed by performing exercise tolerance tests and by measuring circulation times by the reactive hyperaemia and fluorescein methods. Particular attention was paid to the use of the Greenfield and Scarborough type of hand calorimeter and of plethysmographs for the upper and lower limbs. The majority of the observations have been made with these two instruments and the precautions necessary to obtain accurate readings were accordingly detailed. An electrical capacitance manometer designed for the direct recording of pressure in the peripheral arteries was described.

The pathological anatomy of peripheral vascular disease in the lower limbs was investigated and the changes found in younger subjects with thromboangiitis obliterans and in older subjects with atherosclerosis were described. Thromboangiitis involved chiefly the small distal arteries of the extremity while atherosclerosis
affected the larger more proximal arteries. In each disease the development of thromboses obstructing the arteries and spreading to occlude the origins of collateral vessels was responsible for the onset of ischaemic gangrene. The recanalization of obstructed arteries was studied in detail, particularly with regard to the development and function of the elastic-coated vessels seen penetrating the organized thrombus. The changes in blood flow and blood pressure resulting from these anatomical abnormalities were described. In diabetes mellitus of long standing it was shown not only that there was a premature atherosclerosis of the arteries in the limbs, but also that the smaller vessels were affected. Damage to the latter might, in many cases, be chiefly responsible for the development of symptoms of ischaemia.

The blood flow distal to a coarctation of the aorta was investigated and it was shown that the presence of this congenital abnormality did not reduce the maximal circulatory capacity of the limbs supplied by the collateral arteries.

Popliteal aneurysms of atherosclerotic origin were not associated with an unobstructed distal arterial pathway. Clotting within the aneurysm was a dangerous complication and the effect of such an aneurysm was to reduced the distal circulation. On the other hand, a pulsating syphilitic aneurysm on the axillary artery with the distal arteries
unobstructed augmented the peripheral blood flow. This increase beyond the requirements of the distal tissues led to the development of unilateral clubbing of the fingers.

The circulatory changes associated with clubbing were investigated in selected cases and it was shown that an increased peripheral circulation above the volume normally required by the tissues was essential for the development of clubbing. The excess blood was shunted through arteriovenous anastomoses situated in the finger and to a lesser degree in the toes and lobes of the ears. The central mechanisms that might give rise to this excessive peripheral blood flow were considered. In general they led either to an output of blood from the left ventricle greater in volume than the requirements of the tissues supplied by the systemic arterial circulation, or to an increase in blood volume. The grossest degrees of clubbing were seen when both factors together were operative.

The circulatory changes brought about by the infusion of noradrenaline into healthy subjects were described. Three cases of phaeochromocytoma were investigated particularly with regard to the associated abnormalities in the peripheral circulation. It was shown that persistent arterial hypertension was not due to the continuous release of noradrenaline into the circulation.

The investigations have thus been mainly concerned with the study of arterial disease and
hypertension, the two major problems confronting medicine today. They have been directed largely towards the mechanism of the development of these diseases and thus throw little light on their underlying aetiology. No apology is, however, required for this fact, for elucidation of the mechanism is the first logical step towards the investigation of the fundamental underlying cause.
APPENDIX OF CASE NOTES
CASE 1. Phaeochromocytoma. A report of a case with chronic hypertension and circulatory measurements before and after operation.

W.H. a male aged 38 years in 1948 was in good health until May 1946, when he gradually developed increasing anorexia, lassitude and a feeling of faintness. The blood pressure at that time was 180/110. Subsequently he noticed that he was sweating a great deal and had occasional attacks of dizziness and headaches. In January 1948 he began to lose weight and to develop attacks of epigastric discomfort followed by extreme pallor, vomiting, shivering, shortness of breath, profuse sweating and the development of "goose-flesh" all over his arms. The pallor was particularly noticeable and was observed as a warning signal of the approach of an attack. Since the onset of these attacks he noticed that he was unable to appreciate temperature differences with his right hand and he occasionally burnt his right fingers with cigarettes without noticing the heat. He developed a particularly severe attack on the 20th July 1948. That morning he went to work feeling rather dull and a bit hazy in his eyes and could not see well. He began to feel weak, nervous and irritable. He was extremely pale. He went home to bed and had severe continuous pain in the epigastrium and in the loins. He was admitted later in the day to Chase Farm Hospital and on examination there his hands and face were cold and clammy, the fingers cyanosed and the face very pale. There was profuse sweating over the whole of the body and his pyjamas were changed six times during the night. He was very anxious, there was goosesskin flesh over the extremities and his hair was standing on end. He was restless and shivering, his teeth were chattering and he thought he was going to die. The blood pressure was 200/140 and
there was obvious papilloedema with haemorrhages and exudates in both fundi. His symptoms gradually subsided and subsequently after a mass had been felt below the right costal margin a diagnosis of phaeochromocytoma was made and he was transferred to St. Mary's Hospital on 28th August 1948 under the care of Prof. G. W. Pickering.

Except for rheumatic fever when 10 years old the patient had previously been healthy. His father died aged 45 years after an operation for appendicitis. His mother died aged 60 years, cause not known. One sister died of high blood pressure in childbirth aged 20 years. One brother aged 42 years has a peptic ulcer. His blood pressure was 120/80 in November 1948.

On examination he was a thin sallow nervous individual with a moist skin and a coarse tremor of the hands. 2cm. venous congestion present in neck. Pulse regular usually about 100. Blood pressure 170/115 with alternans and irregular beats in the range 170-160. Cardiac apex was visible over a large area moving the ribs and palpable 12 cm. from mid-line in the 5th space. Gallop rhythm was present but no murmurs were heard. In the abdomen a mass with a firm rounded lower edge was felt deeply below the right costal margin moving with respiration. In the right hand he was unable to discriminate hot and cold up to the level of the wrist joint. The nervous system was otherwise normal but for bilateral papilloedema, small haemorrhages and soft white exudates. There was a distinct right macular fan of silvery exudate and a slight left fan.

Eosinophils: 1%. Lymphocytes: 36%. Monocytes: 1%.
Serum potassium 19.2 mg./100 ml. Serum cholesterol: 210 mgm.
Normal glucose tolerance curve. B.M.R. + 20%
E.C.G.: Left axis deviation with slight ST depression and inversion of T in all leads.

Intravenous benzodioxane test (Goldenberg and others, (1947)) produced a rise in blood pressure from 185/125 to 225/130.

Perirenal insufflation of air and radiological examination showed clearly a right suprarenal tumour.

At operation on 23.9.49, Mr. A. Dickson Wright removed a tumour of the right suprarenal gland measuring 5 cm. in diameter and weighing 45 gms. The opposite suprarenal gland was normal and no tumours were found elsewhere. The tumour was soft, lobulated, pinkish-grey in colour with areas of old and recent haemorrhage. Microscopically it was composed of irregular polygonal cells of varying size and shape, with frequent mitotic figures. The nuclei were vesicular and the cytoplasm granular (granules staining brown with chrome salts). The tumour was considered to be a phaeochromocytoma of the adrenal gland. A renal biopsy was also taken.

Many glomerular afferent arterioles showed irregular and scattered areas of hyaline change in their walls but no fibrinoid degeneration was seen. An occasional glomerulus showed ischaemic changes as evidenced by thickening of the capsule or hyalinization of the tuft; the majority of the glomeruli were of normal appearance.

The circulatory changes have been described in full in the text of the thesis.

After operation he has had no further attacks. The papilloedema rapidly subsided and the other abnormalities in the fundus gradually disappeared. Normal sensation returned to the right hand after four weeks. The blood pressure has remained persistently elevated. In
the electrocardiogram the left axis deviation persisted but T1, T2 and T4 are now upright and the ST depression has disappeared.

When last seen in December 1949 he felt entirely fit and had been regularly at work. He still complained of slightly defective vision in the right eye especially noticeable when reading. The fundus appeared entirely normal. The blood pressure was 170/122. In view of the persistent hypertension and the previous negative benzodioxane test the histamine test described by Roth and Kvale (1945) was carried out. This produced no rise in blood pressure.

Her memory had always been good but she had lost 25 lb in the last two years. She had occasional epigastric pain one hour after food relieved by small or nothing, but was little troubled by this and was otherwise regular. She had no symptoms referable to the genito-urinary system. She noticed that she was becoming increasingly nervous.

In November 1945 she attended the Royal Betham Hospital on account of headache, shortness of breath and swelling of the ankles. At that time her blood pressure was 230/130, the heart was stated to be moderately enlarged, the lungs were clear, the urine contained no albumen and the blood urea was 20 mg per 100 ml.

In November 1947 she again visited the Royal Betham Hospital. Her blood pressure was 175/80 and two irregular seatings sound under the costal margin were brought to be the liver and spleen. A varicis vein showed on inspection 10 cm from the stellate, skin appeared to be dilated posterior and 59 on the right by a greatly enlarged spleen. The urine contained a trace of albumen and a few colin erratic cells. A blood count was therefore

Mrs. R. B., aged 49 years in 1948, first complained of early morning headache in 1944 which lasted from a few hours to the whole day and was sometimes accompanied by nausea, vomiting and profuse sweating. These symptoms gradually became worse and since 1946 breathlessness on hurrying and swelling of the ankles in the evening were also noted. She had no nocturnal dyspnoea but sometimes woke at night with palpitations, thumping at the back of the head and profuse sweating. Her appetite had always been good but she had lost 28 lbs in the last two years. She had occasional epigastric pain one hour after food relieved by alkali or vomiting, but was little troubled by this. Her bowels were regular and she had no symptoms referable to the genito-urinary system. She noticed that she was becoming increasingly nervous.

In November 1945 she attended the Royal Bath Hospital on account of headache, shortness of breath and swelling of the ankles. At that time her blood pressure was 220/130, the heart was stated to be moderately enlarged, the fundi were normal, the urine contained no albumen and the blood urea was 30 mgm. per 100 ml.

In November 1947 she again visited the Royal Bath Hospital. Her blood pressure was 220/98 and two smooth swellings found under the costal margin were thought to be the liver and spleen. A barium meal showed no intrinsic lesion of the stomach, which appeared to be displaced forward and to the right by a grossly enlarged spleen. The urine contained a trace of albumin and a few epithelial cells. A blood count was normal.
Her mother died at 71 years from cerebral thrombosis. Her father is alive at 74 years and is stated to have high blood pressure which does not disable him. She has three brothers, two sisters and one son all alive and well.

She was admitted to St. Mary's Hospital under the care of Dr. W. D. W. Brooks on 20th September 1948. She was a ruddy complexioned middle aged woman of average build. Pulse 120, regular; vessel wall normal. Blood pressure 200/130. There was a dorsal scoliosis concave to the left. The apex beat was in the fifth left intercostal space 10 cm. from the midline and the sounds were normal. In the fundi were a few retinal haemorrhages, some soft exudates and early arteriovenous nipping. There was no papilloedema. The liver was enlarged two fingers' breadths below the right costal margin and its edge was firm. There was a smooth tumour moving with respiration below the left costal margin. The nervous system was normal.

Radiological Examination (Dr. E. Rohan Williams): Chest showed no pulmonary lesion. The transverse diameter of the heart was 119 mm. Excretion urography showed normal kidneys. A large mass was present lying in front of the left kidney but not of true renal origin.

Blood urea was 40 mgm per 100 ml. Urea concentration test maximum 2.3 gms urea per 100 ml. urine. Blood Wassermann and Kahn reactions negative. Blood haemoglobin 12 gms%, r.b.c. 4.75 m. per cmm., w.b.c. 7,500 per cmm. Polymorphs 67%, lymphocytes 29%, monocytes 4%. Electrocardiographs showed left axis deviation with low voltage T waves in all leads. Sodium amytal narcosis reduced the blood pressure from 240/125 to 130/80.

On 21st October 1948 Mr. A. Dickson Wright removed a large tumour from the region of the tail of the
pancreas together with the spleen. The tumour weighed 1,100 gms and was apparently encapsulated, with adherent pancreas and a piece of normal adrenal gland. The tumour was a phaeochromocytoma composed of very varied cells, some multinucleated. There were frequent mitotic figures and numerous large blood spaces. A portion of the tumour was placed in N/10 hydrochloric acid and sent to the Department of Pharmacology at the University of Oxford. Assay (Case 2 of Holton (1949)) showed it to contain 0.3 mg. L adrenaline and 10.0 mg. DL noradrenaline per gm. of tumour tissue.

After operation the blood pressure slowly rose from 120/80 on 22nd October to 142/88 on discharge from hospital on 25th November 1948. Thereafter she remained well till February 1949 when the headaches returned. There was no recurrence of the nocturnal sweating attacks and palpitations. The blood pressure has continued to rise but was extremely labile in the range 220-170/110-90. When last seen on 19th October 1949 the blood pressure was 230/120 and ankle oedema was present. The fundi showed only slight silver wiring of the arteries. The exudates and haemorrhages seen previously had entirely disappeared. A benzodioxane test (Goldenberg et al. (1947)) did not produce a fall in blood pressure.
CASE 3. Phaeochromocytoma. A report of a case with paroxysmal hypertension, biological assay of the tumour and circulatory measurements before and after operation and during an attack of hypertension.

B.H., a male, now a technical adviser in industry, was first seen by Sir John Parkinson when aged 11 years in 1929 (Case 7 in Wolff, Parkinson and White, 1930). There was then a history of exhaustion, occasional pallor and a varying pulse rate, often slow. He was always easily tired and for years had had recurrent attacks in which he was pale and the pulse rate varied between 40 and 65 over a period of a few days. His mother stated that the attacks when he was a child occurred about twice a week and each lasted 2-3 minutes. He became pale, sat or lay down and then used to return to play. At this distance it is impossible to say whether these attacks were similar to those occurring in adult life. Otherwise he was entirely well and fond of games including football. On examination he was a small child, but looked well. The pulse rate was from 50 to 60 and sinus arrhythmia was noted. The blood pressure was 110/75. The heart was of normal size and shape. Electrocardiograms in April 1929 showed small upright P waves in all leads. The PR interval was well under 0.1 second. The ventricular complexes had the form of left bundle branch block.

The present attacks began while serving in the army in June 1941. Since then they have continued, varying in severity and frequency, but on the whole getting worse. The frequency was from one to four a day in good periods to ten to twelve in bad periods. The attacks were always the same and varied only in duration and severity. They began with a sort of weak
feeling behind the lower sternum and in the epigastrium; then he felt his heart thumping and the pulse slowed; thus in 1943 his normal pulse was 52 dropping to 36 in a bad attack. He noticed that the pulse not only slowed but that the beats often came in pairs. His face went very pale and his hands, feet, nose and ears were pale and cool. In the more severe attacks he noticed a throbbing headache, shivering and epigastric pain, felt sick and vomited. In the worst attacks the headache was very severe, pins and needles developed in the feet and hands and in two very bad attacks he became short of breath. He was unable to micturate during an attack and if an attack came during the act the flow stopped. His wife noticed that his face paled before he had any symptoms. She might also be awakened at night by an attack because of the noise made by the thumping of his heart beat. He only sweated in those attacks that were accompanied by a very intense headache and thought this might be due to the pain. He never noticed tremors of the limbs and his mind remained clear. Characteristic of an attack was that it came, then receded, and came again, there being perhaps two to ten waves in all, four or five being the usual number. During the last year there has rarely been a day without an attack, and before admission he was averaging about six a day. The attacks were most likely to come on with exertion or opening the bowels but he knew of nothing which would always precipitate an attack. During the three months before admission and especially during the last six weeks after mumps he always felt jaded and extremely tired.

He was admitted to St. Mary's Hospital on 25th October 1949 under the care of Dr. J. W. Litchfield. The patient was a spare man whose skin and mucous membranes were well coloured. Physical examination was entirely
negative. In particular the fundi showed normal vessels and no papilloedema. The heart was not enlarged. No mass was felt in the abdomen and firm pressure from costal margin to pubes produced no attack. The blood pressure ordinarily ran between 90/70 and 136/90. He was seen in 20 attacks lasting a few to about 15 minutes. During them the blood pressure was above the normal range and was recorded as high as 254/154. The face was always conspicuously pale and this constituted the first sign of an impending attack. Breathlessness was not observed. In one attack which developed in the laboratory during circulatory measurements the heat elimination from the hand fell and the face paled before the patient was aware of the onset. The blood pressure both systolic and diastolic rose and the heart rate slowed (Fig 84). The urine, examined on several occasions, sometimes showed a trace of albumin but no deposit.

Radiological examination (Dr. E. Rohan Williams).
Chest: this revealed no pulmonary lesion. The size and shape of the heart and aorta were within normal limits. Excretion urography: both kidneys showed a normal excretion rate and there was no deflection of the calycine pattern on either side. There was, however, a faint suggestion of a rounded soft tissue mass, about 4 - 5 cm in diameter, above the upper pole of the right kidney.

On 12th November 1949 Mr. A. Dickson Wright removed a suprarenal tumour which was situated above the right kidney enveloped in very vascular perinephric fat. The tumour weighed 200 gm., was encapsulated and contained a tag of what appeared to be suprarenal cortex on one edge. During the operation the pressure rose as high as 255/160. The patient sweated very copiously during the later part of the manipulation of the tumour and after the suprarenal vein was tied. On
clamping the suprarenal vein at 10.29 a.m., the pressure was 230/140. The tumour was removed at 10.34 a.m., the blood pressure being 160/100. By 10.53 a.m. the blood pressure had fallen to 115/85 at about which level it subsequently remained.

Histological examination of the tumour showed that it was composed of large polygonal cells, with vesicular nuclei, arranged in diffuse sheets. Numerous thin-walled vascular channels were present, in addition to numerous empty spaces with no definite lining. In bichromate-fixed material brownish granules were present in the cytoplasm of the cells, whilst olive-green granules were demonstrated by Schmorl's method. The tumour was considered to be a phaeochromocytoma of the adrenal medulla. A renal biopsy showed no abnormalities in either arterioles or glomeruli.

The circulatory investigations and the pharmacological assay have been reported in the text of the thesis.

When last seen on 22nd December 1949 the patient felt entirely fit. He had had no further attacks since operation. The blood pressure was 130/80.
CASE 4. Atherosclerotic popliteal aneurysm with cerebral and coronary arterial thromboses and multiple cholesteatomata.

A.V.H. a male company secretary, aged 55 years, was first seen by the writer in October 1947. His history was that in 1926, while convalescing from influenza, he was sitting at breakfast when he suddenly found himself unable to grasp with his right hand. A few moments later pins and needles appeared in his right hand and spread up his arm, then through the whole of his right side including the leg and face. He found himself unable to speak. During the attack he had no impairment of consciousness and no loss of vision and he remembers clearly the events as they occurred. The trouble began to clear up in a few hours and had recovered completely in a few days. He has had no recurrence.

In 1935 while walking downstairs he had a sudden acute pain over the xiphisternum. The pain lasted about one hour and made him sweat. He did not vomit. Subsequently he noticed that a similar pain came on when he walked; he had to stop, when the pain would disappear. He has not had this pain since 1942.

In June 1942 he noticed shooting pains in his right foot coming whenever he tried to stand. He went to bed and the foot became mottled as far as the ankle. He was treated for sciatica. In January 1943, while driving a car, he suddenly experienced some pain in his right foot as though he had been struck. He got home with difficulty. His foot was very cold. The pain in his right foot remained severe and his foot felt dead. Ten days later the leg was amputated below the knee.

In November 1943 after walking a little he developed pain in his left calf which continued till the next day. That night he noticed his foot was
discoloured and this became more noticeable the following day. He was admitted to hospital and after sixteen days in bed his foot recovered.

The family history was that his father died at 75 years after an accident. His mother died at 60 years following a stroke. He has five brothers all alive and well, the eldest being nine years his senior; and five sisters, of whom one died at the age of 42 years with cerebral thrombosis.

He was admitted to Harefield Hospital in May 1944. Examination revealed a very slightly obese man with a bald head and a rather red face. The central nervous system, respiratory system and abdomen revealed no abnormalities. The heart showed no clinical enlargement, the sounds were normal, the rhythm regular with occasional extrasystoles, the pulse rate was 76, the blood pressure 145/110. The femoral arteries were both palpable. The right popliteal was not felt and the right leg was amputated at the junction of the upper and middle thirds of the tibia. The left foot was of normal appearance. The posterior tibial and dorsalis pedis arteries were not palpable, the left popliteal artery was palpable easily as far as the level of the tibial tuberosity. At the level of the knee joint expansile pulsation was obtained easily with the thumbs separated by 5 cms. An artery was visible and palpable on the antero-medial aspect of the right knee joint. The femoral artery pulsation was palpable along the course of the vessel in the thigh to about the junction of the middle and lower thirds of the femur.

On the extensor aspects of each elbow in the position of the olecranon bursa there was a tumour about the size of a walnut, 2.5 cm. in its long diameter. It was pedunculated and composed of yellow masses under a pink skin. The tumours were
freely mobile and rubbery in consistence. On each elbow there were a few small isolated tumours of similar appearance spreading along the olecranon border of the ulna. Over each patella was a similar tumour which was flat and covered with a thicker skin. The patient stated that these tumours appeared first in 1920 over his back at about the trouser level top. They subsequently disappeared from there and appeared on his elbows and knees. A few years ago he had one on his wrist which subsequently disappeared.

A biopsy of one of these tumours showed a cholesteatoma. The blood cholesterol in May 1944 was 310 mg. per 100 ml serum. The glucose tolerance test was normal. The electrocardiogram showed evidence of an old posterior infarction.

He was subsequently kept under observation at St. Mary's Hospital and was put on a low cholesterol diet. He remained well until January 1946, when, while resting after lunch, the pulse suddenly disappeared from his aneurysm. He was admitted to hospital on the same day and at 4 p.m. a faint pulse was still palpable in the aneurysm. It disappeared finally about 9 p.m. that night. The next day the foot was quite warm; there was no sensory loss and the medial geniculate artery was pulsating freely. Subsequently the foot has always tended to be slightly cool and when the body was warmed the exposed left foot became moderately warm, though not as hot as a normal foot. He has noticed that on walking up a slight incline he experiences a tight sensation in the left calf which is promptly relieved by resting.

During the period from 1947 to October 1949 the cholesteatomata have shrunk considerably and the overlying skin is much laxer and thicker. The blood
cholesterol has varied from 268 mg. to 223 mg. The blood pressure has been between 160/100 and 110/66. Extrasystoles have been fairly constantly present and a loud apical systolic murmur has developed. A strong accessory pulse on the medial side of the left knee has persisted but no pulses have been felt in this foot.

Blood flow determinations were carried out on the left foot on 28th July 1948. The resting blood flow in the foot with the plethysmograph water bath at 34°C was 3.5 ml/min/100 ml of foot tissue. It was not considered advisable to raise the bath temperature in view of the precarious condition of the circulation. After five minutes arterial occlusion at the mid-thigh the maximal flow attained during the reactive hyperaemia was 6.9 ml/min/100 ml, which is about one third of the normal value.
CASE 5. Multiple atherosclerotic aneurysms including a popliteal aneurysm and myocardial infarction. The record includes an autopsy report.

J.A., a male retired gamekeeper, aged 75 years in 1947 was admitted to the R.I.E. under the care of Prof. J.R. Learmonth in July 1945 with a history of several years intermittent claudication in both legs. For the last two months this had become so bad that he could only walk 50 yds. at the most. Suddenly 10 days before admission his left leg became cold and blue, he was unable to feel pin pricks and observed that there was no bleeding at the site of the pricks.

On examination at this stage he was a small wizened old man. The left foot and leg were cold blue and swollen as far as the middle third with a slight extension further up on the medial side of the leg. The dorsalis pedis, posterior tibial and popliteal pulses were not palpable on the left side but the femoral pulse was present. No record was available regarding the right lower limb pulses.

A left mid-thigh amputation was carried out on 9.7.45 (See subsequent biopsy report). The wound healed satisfactorily and an artificial limb was subsequently fitted.

Since discharge in 1945 he managed to get about fairly well with his prosthesis and he remained fit until 2.3.47. On that date when rising to get out of a chair he suddenly developed a sharp pain in the right leg extending up as far as the back of the knee. The foot and leg became numb and he was unable to stand and had to be assisted to bed. The pain ascended the thigh and went as high as the buttock. The pain has persisted and has rendered him restless and sleepless.

Appetite has been poor for the last week. He had a slight attack of urinary incontinence during January.
1947 but this is now better. General health has otherwise been reasonably sound.

On examination: the heart was found to be slightly enlarged with the apex 2 cm outside the midclavicular line. B.P. 190/120. Blood W.R. negative.

Left leg. Midthigh amputation well healed.

Right leg: showed mixed areas of cyanosis and pallor affecting the foot and lower part of leg. Over the mid-region of the leg on the lateral aspect there was an area of parchment-like skin brownish-red in colour. The foot and lower half of the leg were completely cold and sensation was absent up to the junction of the lower and middle two-thirds of the leg. Movements of the limb were completely restricted by pain. The dorsalis pedis, posterior tibial and popliteal pulses were absent, but the femoral pulse was palpable.

Amputation of the right lower limb was carried out at the mid-thigh on 6.3.47. (See biopsy report). He recovered from the operation at first but gradually became weaker. Two days after operation he began to have generalised epileptiform fits and was very collapsed after each. Two days before death the urine contained a little sugar. His condition rapidly deteriorated and he died on 12.3.47. Autopsy was carried out six hours after death.

Biopsy report. 9.7.45.

The dissection of the left lower limb was carried out by Dr. R. F. Ogilvie and I am indebted to him for the macroscopic report. The paraffin blocks were still available and fresh sections have been personally prepared and reported.

Macroscopical Appearance (R.F.O.) The skin covering the lower third of the leg and the entire foot is a distinct reddish-purple colour and the skin
over the distal part of the under surface of the foot shows in addition areas of greenish black discolouration. The popliteal artery, posterior tibial artery, anterior tibial artery and dorsalis pedis artery show considerable atheromatous change. Recent thrombosis extends from the popliteal artery far down into the posterior tibial artery.

Microscopical Report (G.M.W.).

Popliteal Artery: The lumen is occluded with recent ante mortem thrombus which is continuous with a small intimal haemorrhage through a rupture in the endothelial lining. The intima is grossly thickened with groups of cholesterol clefts and focal collections of foam cells in the deeper parts. Small vascular channels are apparent throughout the intimal coat. The internal elastic lamina is frayed and disrupted at many points. The musculature of the media is atrophic and thinned, especially opposite the more pronounced areas of intimal thickening. The adventitia is deeply infiltrated with small round cells and there is considerable congestion of the small periadventitial vessels.

Popliteal Vein: A slight degree of intimal thickening is present but otherwise the vein shows no definite abnormality.

Posterior Tibial Artery: The lumen is occluded with ante mortem thrombus of older standing than that in the popliteal. Organization has commenced and there are several patent channels in the thrombus. The intima is greatly thickened and contains numerous small capillaries. A haemorrhage is apparent in the deeper part and there are several localised collections of foamy cells. The internal elastic lamina is preserved intact for the most part, but at points is frayed and disrupted. The media is greatly thinned and
atrophic and in places the foamy atheromatous change has spread through the ruptured internal elastic layer to involve the muscular coat. A moderate infiltration with small round cells is present in the adventitial coat.

**Posterior Tibial Vein:** The lumen contains recent ante mortem thrombus with a high content of polymorphs. The vessel wall shows no definite abnormality.

**Anterior Tibial Artery:** The lumen contains only post mortem thrombus. The intima shows a mild degree of thickening but there are no collections of foamy cells or indications of definite atheromatous degeneration. No capillaries are visible in the intima and there are no haemorrhages. The venae comitantes show no abnormality.

**Dorsalis Pedis Artery:** The lumen is patent. The intima is slightly thickened but otherwise no abnormality is present. The condition of the vessel is essentially similar to that of the anterior tibial.

**Summary.** The changes found in the left lower limb arteries are those of advanced atherosclerosis. There was no evidence of aneurysm formation, though secondary degenerative changes were present in the musculature of the media. The gangrene of the limb was precipitated by recent thrombosis in the popliteal artery.

**Biopsy Report.** 6.3.47. (Dr. G. M. Wilson).

**Macroscopic Appearance.** The right lower limb has been amputated at the midthigh. The whole limb, but especially the distal part, was cyanosed.

On the anterolateral aspect of the leg was situated an area of dusky dark reddish purple discolouration measuring 20 cm x 9 cm. The skin here was thin and glazed but intact. The pattern of distended thrombosed
superficial veins was clearly delineated through the atrophic skin. Surrounding the oval area of dark discolouration was a zone of reddish purple erythema varying in depth from 2 - 6 cm and wider on the lateral aspect.

The skin of the toes and foot was healthy. There was some atrophy of the muscles of the foot and the subcutaneous fat of this region was considerably reduced in amount.

The femoral artery at the point of section was patent but the vessel wall showed marked atheromatous thickening of the intima and thinning of the muscular coat. The complete vascular tree was dissected out. The arteries throughout were hardened, thickened, and sclerotic. An aneurysmal dilatation was present in the popliteal artery immediately above its bifurcation (Fig 57). It measured 8 cm x 2 cm and was completely filled with thrombus. The distal exit was grossly narrowed by old atherosclerotic thickening.

Microscopical Reports. (Dr. G. M. Wilson).

Popliteal Aneurysm: In the wall the normal coats of the artery can be distinguished but are considerably modified in form. The intima is greatly thickened with a dense hyaline connective tissue stroma containing a few small vascular channels surrounded by an infiltration of round cells, polymorphs, and active fibroblasts. In the deeper layers of the intima the tissue is in parts structureless and necrotic with lipoidal deposits and in some areas the appearances are suggestive of old intimal haemorrhages. Recent ante-mortem thrombus is present on the inner aspect and commencing organization can be seen spreading from the intimal vascular channels. The internal elastic lamina cannot be distinguished. The media is thin and in parts consists only of a few
strands of tissue separating the intima and adventitia. The muscle fibres are atrophic and partially separated by fibrous tissue. Numerous vascular channels and pigment-laden macrophages are present in the media. The adventitia shows a slight increase in fibrous tissue. The vasa vasorum are prominent and numerous but the smaller accompanying arterioles show considerable intimal hyperplasia and reduction in the size of the lumen.

The popliteal vein at this level is thickened and the intima shows an increased cellular content of fibroblasts and occasional round cells.

**Femoral Vessels:** In the artery the intima shows considerable eccentric thickening. At one point a haemorrhage has occurred into the superficial layers of the intima. At another point haemorrhage into a similar position has been followed by ulceration into the lumen. Thrombus is adherent to the intima and organization is proceeding. Patchy calcification is present in the deepest part of the intima. Numerous vascular channels are present in this layer and are accompanied by fibroblasts, polymorphs and round cells in considerable numbers. The internal elastic lamina is largely fragmented. The media is greatly thinned and the muscle is to a large extent replaced by hyaline fibrous tissue in which a small patch of calcification is present. There are numerous vascular channels in the media and the perivascular spaces are infiltrated with polymorphs and round cells. The adventitia contains numerous congested vasa vasorum which show some intimal thickening.

The femoral vein presents a slightly thickened intimal coat which is diffusely infiltrated with chronic inflammatory cells. The lumen is patent and there is no recent thrombosis.
Posterior Tibial Vessels: The artery is occluded with organised thrombus in which are numerous new vascular channels and extensive deposits of haemosiderin. In one corner of the thrombus is a new vessel with a definitely arterial structure possessing an internal elastic lamina and a rudimentary muscular coat. There is a considerable cellular infiltration of the thrombus with fibroblasts, small round cells and a few polymorphs. Patchy calcification is present in the deeper layers of the intima and there is a small area of bone formation. The internal elastic lamina is relatively intact. The media is thin and the muscle has been largely replaced by fibrous tissue. The external elastic lamina is intact. The adventitia shows a slight infiltration with small round cells.

The posterior tibial vein is occluded with organised thrombus in which extensive recanalization has occurred. There are numerous deposits of haemosiderin.

Sections taken from the distal end of the vessels show essentially similar changes. The artery is occluded with thrombus and the wall presents extensive atherosclerotic changes. The venae comitantes are thickened particularly with respect to the intimal coat but they are not occluded.

Peroneal Vessels: The artery is completely blocked with organized thrombus with contains several thin-walled channels at one side surrounded by fibroblasts and round cells. The central portion of the thrombus is largely acellular. Some of the walls of the vascular channels are thickened but have no definite arterial structure and no elastic layer. Numerous deposits of haemosiderin are present within the thrombus. The intima appears thickened but no definite line of demarcation is distinguishable.
between this layer and the thrombus. The internal elastic lamina is disrupted in parts and the appearances suggest old intimal haemorrhage spreading into and disorganizing the media which is thin with the greater part of the muscle replaced by fibrous tissue. The adventitia is slightly thickened by increase of fibrous tissue. The vasa vasorum show intimal hyperplasia and narrowing of the lumen with some perivascular infiltration of small round cells.

The venae comitantes are occluded with thrombus which is being recanalized, the process being considerably more advanced in one vein.

**Anterior Tibial Vessels:** The arterial lumen contains recent thrombus with organization commencing at the margin. The intima shows some irregular thickening due to loose connective tissue proliferation. A slight infiltration with small round cells is present in the subendothelial tissue where organization is commencing. The internal elastic lamina shows some splitting but is preserved relatively intact. The muscular fibres of the media are degenerate and are being replaced by fibrous tissue. At some points the media shows irregular hyaline thickening and degeneration due to spread of the atheromatous process from the intima. The adventitia shows no definite abnormality.

The venae comitantes are partially occluded by organizing thrombus infiltrated with round cells and polymorphs. The intimal coat of the vein is slightly thickened and shows a similar cellular infiltration.

**Dorsalis Pedis Vessels:** The lumen contains very recent thrombus in which no organization has commenced. The endothelial lining appears intact and there is no definite intimal thickening. The media appears slightly thickened and shows an increased content of fibrous tissue.
The venae comitantes show some irregular thickening particularly of the subendothelial tissue.

Summary of Report on Left Lower Limb.

Atherosclerosis of Femoral, Popliteal, Posterior Tibial, Peroneal and upper part of Anterior Tibial Arteries.

Aneurysm of Popliteal Artery with obliteration of lumen by thrombosis.

Diffuse hyperplastic sclerosis largely obscured by atherosclerosis except in the dorsalis pedis artery.

Thrombophlebitis of Anterior and Posterior Tibial and Peroneal venae comitantes and earlier similar inflammatory changes in Popliteal and Femoral Veins.

Early medial calcification of Femoral Artery.

AUTOPSY REPORT. 12.3.47. (Dr. G. M. Wilson).

The body was that of an elderly well-nourished male. Both the lower limbs had been amputated at the mid-thigh. The scar of the left stump was soundly healed, but the remaining part of the thigh was considerably reduced in girth owing to muscular atrophy. The wound in the right stump showed no macroscopic evidence of healing and the sutures were still in position. There was no naked eye evidence of infection. A lipoma 3 cm in diameter was situated subcutaneously in the right infraclavicular region. Post mortem lividity and rigidity were established.

Peritoneal Sac: healthy, containing an average quantity of clear serous fluid.

Pleural Sacs: a few light band adhesions were present in the upper part of the left sac. An average quantity of clear serous fluid was present in each sac.

Pericardial Sac: contained a small quantity of
clear serous transudate. A circumscribed thickened fibrous patch about 2 cm in diameter and indicative of healed pericarditis was present in the epicardium over the anterior aspect of the apical region of the left ventricle. Similar rather thinner patches about 3 cm in diameter were present on the anterior and posterior surfaces of the right ventricle.

**Heart**, weight with thoracic aorta attached 560 gms: was considerably enlarged particularly in relation to the left ventricle. The subepicardial fat was of average amount and the superficial coronary arteries were thickened, tortuous, and partially calcified. The right atrium was dilated and the tricuspid orifice admitted four fingers; the valve cusps were healthy. The right ventricle was dilated and the trabeculae were prominent suggesting a slight degree of hypertrophy, though the muscular wall was not in general thickened. The pulmonary valves and trunk were healthy. The left atrium was moderately dilated. The mitral orifice admitted three fingers with ease; the cusps were thickened containing several atherosclerotic plaques. The chordae tendineae were healthy. The left ventricle was considerably dilated and hypertrophied. The myocardium was of a dark reddish-brown hue and towards the apex it was considerably congested. Patchy grey glistening areas of paler tissue indicative of fibrosis were present in the muscle of the left ventricle particularly in the septum. The papillary muscles showed an undue amount of fibrosis at their apices. The aortic valve cusps were thickened towards the bases with atherosclerosis. Both coronary arteries showed atheromatous changes with narrowing of the lumen which at one point in the descending branch was almost completely occluded. No recent thrombosis was detected in the arteries.
Aorta: showed marked atheroma in the ascending and transverse portions of the arch and in this region it showed a generalised dilatation (Fig 59). There was no evidence of any syphilitic changes. The descending thoracic and abdominal parts showed very advanced atheromatous degeneration with ulceration and haemorrhage into the grossly thickened plaques which in places were up to 2 cm in thickness.

Common Iliac Arteries: showed advanced atherosclerotic changes and were markedly tortuous.

Left Internal Iliac Artery: immediately distal to its origin it was dilated to form an aneurysm about 2 cm in diameter which was partially filled with firm concentric layers of ante mortem thrombus. The exit of the aneurysm was grossly narrowed by old atherosclerotic thickening.

Right Internal Iliac Artery: presented a very similar slightly larger aneurysm at its origin with a content of ante mortem thrombus. The exit was similarly partially occluded.

Left External Iliac Artery: about 5 cm below its origin was entirely occluded by firm organized thrombus. Distal to this obstruction the arterial trunk in the limb stump was largely atrophied and the lumen obliterated.

Right External Iliac Artery: was dilated to about twice its normal diameter and contained recent thrombus, possibly ante mortem as it appeared slightly adherent to the endothelium. The arterial wall showed considerable atheromatous change with intimal thickening and degeneration and atrophy of the medial coat.

Right Femoral Artery: was not dilated to such an extent but showed similar atheromatous changes and was obstructed with recent ante mortem thrombus. The ligature was secure at the distal end.
Brachial Arteries: showed widespread marked atheromatous changes. No evidence of aneurysmal dilatation was found.

Veins: no macroscopic abnormalities were apparent in the veins accompanying the above arteries.

Kidneys: weight R 140 gms, L 100 gms: were of slightly reduced size and contained numerous cysts varying up to about 1 cm in diameter. The capsule was adherent to the underlying kidney substance and stripped with difficulty revealing a coarsely granular mottled surface. On section the cortex and medulla were poorly differentiated and there was a decrease in both the depth of the cortex and in the total amount of renal parenchyma. The peripelvic fat was unduly abundant. The renal arteries were markedly atherosclerotic at their origins from the aorta and in the kidney substance the interlobular vessels were thickened and prominent.

Renal Pelves, Ureters, and Bladder: were normal.

Prostate: was of average size and appearance and showed no evidence of nodular hypertrophy.

Larynx and Trachea: were normal.

Bronchi: contained scanty mucopurulent exudate and showed a mild congestion of the mucous membrane.

Lungs: weight R 400 gms, L 300 gms: were completely collapsed and appeared small showing widespread senile atrophic emphysema. No localized abnormality was detected in the left apical region.

Mouth, Tongue, Pharynx and Oesophagus: were normal.

Stomach, Duodenum and Intestines: were normal.

Liver: weight 1300 gms was of average size and shape and of an unduly dark brownish colour. The cut surface showed the characteristic mottling of chronic
venous congestion.

Gallbladder, Biliary Passages and Pancreas: normal.
Spleen: weight 70 gms was of small size and firm consistence and showed changes typical of chronic venous congestion.

Thyroid, Suprarenals, and Pituitary: were normal.

Skull, Meninges, and Venous Sinuses: were normal.
Brain: showed no abnormality.
Cerebral Arteries, Arterial Circle, Basilar and Vertebral Arteries showed advanced atherosclerotic changes.

Microscopic Reports.

Heart: section from the apical region shows a marked patchy fibrosis with atrophy and replacement of the muscle fibres. There are several small areas of recent necrosis of the myocardium as revealed by the hyaline deeply acidophilic condition of the muscle fibres. Polymorph infiltration has commenced in the interstitial tissue but has not spread in between the individual necrotic muscle fibres. The vessels are considerably congested and small haemorrhages have occurred at several points. The appearances are those of a recent myocardial infarction of about three to five days duration superimposed on an old-standing fibrosis of the myocardium.

Kidney: a widespread fibrosis of the glomeruli is present, but in some parts the changes are more advanced than others. Many of the glomeruli are entirely replaced by hyaline fibrous tissue. There are considerable areas of interstitial infiltration with small round cells and the tubules show areas of atrophy and dilatation A few small cysts are present lined by a single layer of cuboidal cells. The
Afferent arterioles are slightly thickened but not grossly abnormal. The interlobular arteries show marked eccentric intimal thickening with reduction in the calibre of the lumen. The changes are those typical of renal atherosclerosis.

Pancreas: slight intimal thickening is present in the arteries which, however, show relatively little abnormality in comparison with the other vessels examined.

Abdominal Aorta: the whole wall is greatly thickened by gross atheromatous change. Ante mortem thrombus is present on the ulcerated endothelial surface. The intima is enormously thickened and contains numerous small haemorrhages and cholesterol clefts in the deeper parts. The media is thinned and atrophic.

Right Internal Iliac Arterial Aneurysm: laminated ante mortem thrombus is present within the lumen. The intima is thickened with characteristic atheromatous changes and small haemorrhages. The media is greatly thinned with marked atrophy of the muscular tissue.

Left Internal Iliac Arterial Aneurysm: the microscopic appearances are essentially similar to the preceding, but the intimal lesions are even more severe, the muscular coat having been almost entirely replaced by invasion of degenerate atheromatous material.

Right External Iliac Artery: the lumen is occluded with recent ante mortem thrombus around which organization is just commencing. There is marked atheromatous thickening of the intima and considerable
atrophy and destruction of the media.

**Left Internal Carotid Artery:** a mild degree of atheromatous thickening is present in the intima. The other coats are intact.

**Right Ophthalmic Artery:** slight intimal thickening is present but there are no definite atheromatous lesions.

**Summary**

Advanced Atherosclerosis of Aorta and Peripheral Arteries.

Aneurysmal Dilatation and Thrombosis of both Internal Iliac and Right External Iliac and Right Popliteal Arteries.

Bilateral Midthigh Amputations of both Lower Limbs.


Fibrosis of Myocardium and recent Myocardial Infarction.

Atherosclerotic Kidneys.
Obliterative Vascular Disease Case Reports.
Owing to the length full details of all the 78 cases studied are not given. A few have been reported briefly in the text. Short notes on the other cases are appended below.

Group 1. Thromboangiitis obliterans.

Case 6. G.H. male 28 years. Onset three years previously of pain in right foot and in right wrist. Later intermittent claudication in right calf and gangrene of right fingers. Amputation of right hand and ceased smoking. Claudication became less marked in right calf. Right lower limb pulses absent below femoral, but two accessory pulses on medial side of knee. Left lower limb pulses all present. Delay in reactive hyperaemia in right foot and toes. Maximal circulatory capacity right foot 12.0ml./min./100 ml., left foot 21.6ml./min./100 ml. No deterioration since ceased smoking two years previously.

Case 7. W.W. male 38 years. Onset four years previously of pain in right foot on exertion. Later ulceration of right toes and claudication in right calf. Onset of claudication in left foot two years previously. Right lower limb pulses absent below femoral; left absent below popliteal. No accessory pulses. Developed massive gangrene of right foot spreading up leg. Histamine and saline wheal tests showed gross tissue dehydration. Right mid thigh amputation: recent thrombosis in popliteal artery and old thrombotic lesions in tibial, pedal and plantar arteries. Maximal circulatory capacity left foot 8.8ml./min./100 ml; elevated 19 cm. 6.0ml./min./100 ml. Continued smoking and condition of left foot deteriorating.

Case 8. J.T. male 33 years. Onset two years
previously of pain in both feet. Subsequent ulceration of toes and amputation of first and second left toes with satisfactory healing. Arteries showed old and recent thromboses with recanalization. Maximal circulatory capacity right foot 9.5ml/min/100 ml; left foot not suitable for investigation. Smoking intermittently and condition of feet deteriorating.

Case 9. P.S. male 49 years. Onset 22 years previously with intermittent claudication in calves. Subsequent recurrent ulceration of toes and right finger tips. Bilateral lumbar sympathectomies. Amputation left second toe healed satisfactorily but subsequent intermittent infected lesions of other toes. Both popliteal pulses present but all more distal pulses absent except right posterior tibial. Maximal circulatory capacity right foot by heating 6.0ml/min/100 ml. (fig.47); by reactive hyperaemia 6.5ml/min/100 ml. Left foot not suitable for measuring but showed greatly delayed reactive hyperaemia time and considerable tissue dehydration by saline wheal test.

Case 10. J.W. male 38 years. Onset 5 years previously with claudication in both calves. Claudication persisted but skin of feet not affected except right great toe which was cold and cyanotic. Maximal circulatory capacity right foot 12.2ml/min/100 ml. Saline wheal, postural blood flow changes and effect of tourniquet on claudication investigated.

Case 11. K.P. male, 40 years. Onset of claudication in right calf six years previously. No cutaneous lesions. Left calf not affected. Both popliteal pulses present but none more distal on either side. Marked improvement in exercise tolerance on stopping smoking. Maximal circulatory capacity of right foot 9.8ml/min/100 ml.

Case 12. A.H. male, 43 years. Onset 20 years
previously with pain in right hand and right foot. Steady progress of disease leading to amputations of both lower limbs at midthigh. Popliteal arteries on both sides patent (fig.34). Limb injected and dissected. Serial sections cut (figs.25-27). Plantar and digital arteries obstructed.

**Case 13.** J.F. male, 42 years. Onset 19 years previously with pain in left foot on exertion and later gangrene in the right foot. Below knee amputation. Dissection of limb and serial sections of thrombosed vessels.

**Case 14.** H.S. male 27 years. Onset three years previously of pain in left foot and intermittent claudication in left leg. Gangrene of foot and below knee amputation. Dissection of limb and serial section of vessels (figs.22-24).

**Case 15.** J.S. male, 35 years. Onset five years previously of intermittent claudication in left calf, pain in right foot and phlebitis of right foot and leg. Biopsy of saphenous vein and serial sections cut. (fig.15).

**Cases 16, 17 and 18.** M.M., H.E. and A.W. reported in text.

**Group 2. Atherosclerosis.**

**Case 19.** A.B. male 59 years. Right popliteal thrombosis 18 months previously followed by intermittent claudication in calf. Left lower limb pulses all present. Maximal circulatory capacity right foot 5.9 ml/min/100 ml; left foot 27.0 ml/min/100 ml. (Fig.43).

**Case 20.** R.P. male, 51 years. Left popliteal thrombosis 14 months previously followed by intermittent claudication in calf. Right lower limb pulses all present. Maximal circulatory capacity
right foot 26.4ml/min/100 ml; left foot 8.6ml/min/100 ml. (Figs. 43 and 45).

Case 21. G.J. male 41 years. Intermittent claudication for four years. Absent popliteal and posterior tibial pulses. Symptoms worse on left side. Maximal circulatory capacity right foot 15.9ml/min/100 ml; left foot 12.4ml/min/100 ml. Postural changes and exercise tolerance studied.

Case 22. R.J. male, 49 years. Bilateral intermittent claudication for three years. Maximal circulatory capacity right foot 11.0ml/min/100 ml. No pulses below femoral.

Case 23. J.P. male 51 years. Left intermittent claudication. All pulses below femoral absent. Exercise tolerance tests. Maximal circulatory capacity right foot 8.4ml/min/100 ml.

Case 24. J.W. male 59 years. Bilateral intermittent claudication. All pulses below femoral absent. Exercise tolerance tests. Maximal circulatory capacity right foot 6.8ml/min/100 ml.

Case 25. W.V. male 62 years. Bilateral intermittent claudication. Maximal circulatory capacity right foot 9.0ml/min/100 ml. left foot 12.2ml/min/100 ml.

Case 26. F.W. male 63 years. Left intermittent claudication. Maximal circulatory capacity left foot 12.8ml/min/100 ml. Exercise tolerance tests.

Case 27. G.M. male, 67 years. Bilateral intermittent claudication. Maximal circulatory capacity right foot 9.2ml/min/100 ml. Exercise tolerance tests.

Case 28. F.J. male, 68 years. Left intermittent claudication. Maximal circulatory capacity left foot 13.0ml/min/100 ml. Exercise tolerance tests.

Case 29. P.G. male, 51 years. Right intermittent
claudication. Faint pulses felt in both feet. Calf blood flow during reactive hyperaemia right 23.1ml/min/100 ml; left 34.5ml/min/100 ml.

**Case 30.** G.S. male, 49 years. Left intermittent claudication. Both dorsalis pedis pulses present; posterior tibials absent. Calf blood flow during reactive hyperaemia right 36.0ml/min/100 ml; left 19.8ml/min/100 ml.

**Case 31.** R.J. male, 53 years. Incipient gangrene of right toe and intermittent claudication right calf. Maximal circulatory capacity right foot approximately 4.0ml/min/100 ml, but patient unable to lie still for sufficient records.

**Case 32.** M.S. female, 48 years. Intermittent claudication in calves for five years. Recurrent cutaneous lesions about toes which are always abnormally cold and blue. Blood pressure 270/150. No diabetes mellitus. All pulses absent below femorals. Maximal circulatory capacity right foot 14.0ml/min/100 ml; left foot 13.5ml/min/100 ml.

**Cases 33 and 34.** J.G. and C.P. reported in text.

**Case 35.** C.P. male 56 years. Bilateral intermittent claudication. Maximal circulatory capacity right foot 12.6ml/min/100 ml. (fig.44). Exercise tolerance and postural blood flow changes.

**Case 36.** F.B. male 44 years. Multiple cholesterol deposits on elbows and knees. Blood cholesterol 408 mgm.%. Absent posterior tibial pulses. Slight claudication in calves on hurrying uphill. Maximal circulatory capacity right foot 14.8ml/min/100 ml.

**Case 37.** W.R. male 63 years. Claudication in right calf. Absent posterior tibial and dorsalis pedis pulses. Right foot maximal circulatory capacity 12.9ml/min/100 ml.

**Case 38.** W.H. male 64 years. Claudication in
right calf for many years. Recent onset of pain in foot at rest. Plethysmography at 34° C attempted and blood flow appeared less than 3.0 ml/min/100 ml, but readings not satisfactory. Subsequent midthigh amputation. Old atherosclerotic occlusion at popliteal bifurcation and more recent thrombosis higher up popliteal artery.

Case 39. E.F. male 60 years. Intermittent claudication in both legs for ten years. Three weeks previous to operation sudden onset of severe continuous pain in left leg. Left midthigh amputation. Dissecting aneurysm found in wall of popliteal artery completely obliterating the lumen. Advanced atherosclerosis of posterior tibial artery; serial sections cut of recanalized portion (figs. 28 and 29). Similar advanced atherosclerosis of peroneal artery. Other arteries not conspicuously involved. Plantar arteries showed only slight intimal thickening.

Case 40. J.B. male 59 years. Pain in right great toe for 10 years. Abscess on right foot three months previously which failed to heal and was followed by gangrene of foot of rapid and sudden onset. Right midthigh amputation. Femoral and upper popliteal artery occluded by recent thrombosis. Old atherosclerotic lesions immediately above popliteal bifurcation. Gross old atherosclerotic lesions of anterior and posterior tibial and dorsalis pedis arteries. Plantar arteries showed only slight intimal thickening but considerable perivascular infiltration of leucocytes. Extensor digitorum brevis muscle showed no conspicuous abnormality.

Case 41. W.S. male 43 years. Intermittent claudication in right leg for three years followed by gangrene of foot and amputation at midthigh. Subsequent pain in left foot followed by gangrene of
gradual onset and left midthigh amputation. Left limb dissected. Femoral artery occluded by fairly recent thrombus. Popliteal artery grossly narrowed by old atherosclerotic changes and almost complete occlusion present immediately above bifurcation. Posterior tibial artery patent in upper half but occluded in lower part by old atheromatous thickening. Dorsalis pedis and plantar arteries patent and only showed slight intimal thickening. Microscopically the occluded arteries showed typical atheromatous degeneration without any definite cellular reaction.

**Case 42.** G.P. male 71 years. Sudden onset of pain in left leg a week before operation. Rapid onset of gangrene of left foot. Left midthigh amputation. The femoral artery immediately below section was occluded by recent thrombus which extended down into popliteal artery to its point of division. Posterior tibial artery occluded by old thrombus down to origin of peroneal branch which was also largely occluded. The first two centimetres of anterior tibial artery were occluded by old thrombosis. Other arteries patent. Dorsalis pedis and plantar arteries not affected. After operation rapid onset of gangrene in right foot and right midthigh amputation carried out. Recent thrombosis in popliteal artery found in relation to old atheromatous plaque (fig. 21). Old atherosclerotic lesions in anterior and posterior tibial arteries. Dorsalis pedis and plantar arteries not affected.

**Case 43.** W.M. male 59 years. Intermittent claudication for ten years. Gangrene of right foot of sudden onset 10 days before operation. On dissection recent thrombosis of popliteal artery and old atherosclerotic lesions at bifurcation. Anterior
and posterior tibial arteries moderately atherosclerotic but patent. Dorsalis pedis and plantar arteries not affected. Conspicuous inflammatory reaction in media of popliteal artery (fig.17).

Case 44. C. Mc C. male, 72 years. Sudden onset of pain in left leg a fortnight before operation. Rapid development of gangrene of foot. Midthigh amputation. Popliteal artery occluded by recent thrombosis. Tibial arteries grossly atherosclerotic. Dorsalis pedis moderately atherosclerotic. Plantar arteries patent and showed only slight intimal thickening. Serial sections of posterior tibial artery to show recanalization. Conspicuously cellular reaction in organization of thrombus in some vessels (fig.20).

Case 45. W. H. male, 57 years. Pain in left foot for one year at first on exertion, later while at rest. Intermittent claudication both legs. Gradual onset of gangrene of left foot. Left midthigh amputation. Femoral artery patent at point of section. Injection of limb attempted but unsuccessful as popliteal artery found obstructed by old and recent thrombosis. The anterior and posterior tibial arteries were obstructed intermittently by old atherosclerotic tissue but were successfully cannulated in patent portions and injected with India ink suspension in celloidin (fig.30). The plantar arteries were patent.

Case 46. R. R. male, 71 years. Sudden onset of pain in left foot four weeks before amputation at left midthigh on account of gangrene of foot. Recent thrombosis of femoral and upper part of popliteal artery. Old atherosclerotic lesions in lower part of popliteal artery which was cannulated and injected with lead phosphate suspension. Old atherosclerotic lesions of tibial arteries (fig.35). Plantar arteries patent.
Case 47. P.N. male 59 years. Intermittent claudication for six years. Sudden onset of pain in left foot four weeks before amputation at left midthigh. Femoral artery patent. Recent thrombosis of popliteal artery accounting for unsuccessful attempt at injection. Old atherosclerotic lesions at popliteal bifurcation and in upper parts of tibial arteries. Plantar arteries patent but showed intimal hyperplasia.

Case 48. T.F. male 58 years. Intermittent claudication left leg one year. Sudden pain followed by gangrene in left foot six weeks before midthigh amputation. Recent popliteal thrombosis and old atherosclerotic lesions at bifurcation of artery. Mild inflammatory reaction and dilatation of vasa in media (fig.18). Old atherosclerotic lesions in upper parts of tibial arteries; distal parts and dorsalis pedis artery only moderately affected. Plantar arteries patent.


Case 51. J.F. male 63 years. Gangrene of left

Case 52. A.B. male 54 years. Cold feet for many years. Discolouration and pain in right middle toe for six weeks. All peripheral pulses present. Calcification in posterior tibial arteries. Amputation of toe with satisfactory healing. The digital arteries were blocked with organized thrombus. No recanalization had occurred. The arterial wall appeared healthy but there was some perivascular fibrosis and infiltration of leucocytes. The changes were not specific and the nature of the thrombosis could not be ascertained.

Case 53. A.H. male 56 years. Intermittent claudication in both calves for several years. Onset of gangrene in right foot. Mid thigh amputation. Injection of lead phosphate unsuccessful as artery obstructed by recent thrombosis high in popliteal artery blocking the collateral channels. Old atherosclerotic lesions entirely blocked the artery immediately above its bifurcation.

Case 54. B.C. male, 53 years. Undue coldness of feet for several years, followed by pain at rest. Gangrene of right great toe. Mid thigh amputation. Injection of lead phosphate only partially successful, incomplete filling of the leg being obtained. Popliteal artery obstructed by old atherosclerotic lesions at bifurcation and more recent thrombosis higher up.

Case 55. J.D. male 59 years. Intermittent claudication in both calves, right more severely than
Developed gangrene of right toes with blistering and infection of the dorsum of foot. Right midthigh amputation. Injection unsuccessful. Recent thrombosis at site of amputation and old atherosclerotic lesions completely obstructing lower part of popliteal artery. Diffuse atherosclerotic lesions throughout the tibial arteries.

**Case 56.** P.F. male 64 years. Gangrene of right foot following acute pain developing while driving car. Foot burnt by bottle. Midthigh amputation. Recent thrombosis in popliteal artery which also showed old lesions at its bifurcation.

**Case 57.** J.P. male 69 years. Midthigh amputation on account of septic infection of foot probably secondary to ischaemia. Injection of limb with India ink suspension incelloidin. Dissection and clearing of arteries.

**Case 58.** male 59 years. Burn on foot healed slowly. Intermittent claudication in calves. Histamine and saline wheal tests. Plethysmography attempted but unsatisfactory as unable to keep still.

**Cases 59 - 63.** Investigated while developing foot plethysmograph but results not satisfactory owing to technical faults. All were cases of intermittent claudication but owing to temporary closing of the laboratory the observations could not be repeated.

**Group 3. Atherosclerosis and Diabetes Mellitus**

**Case 64.** A.P. male 67 years. Diabetes for two years; intermittent claudication both legs for one year. Maximal circulatory capacity right foot horizontal 13.2ml/min/100 ml. elevated 19 cm. 8.9ml/min/100 ml. Both popliteal pulses present but no distal pulses felt. No pulsations in plethysmograms.

**Case 65.** P.F. male 62 years. Diabetes for 12
years. Minor cutaneous lesions of toes of both feet intermittently during last 10 years. No pulses beyond femoral. Decalcification of bones of feet. Maximal circulatory capacity right foot 5.3ml/min/100 ml.

**Case 66.** S.S. male 38 years. Diabetes for three years. Intermittent claudication both calves for one year. All peripheral pulses present. Maximal circulatory capacity right foot 15.3ml/min/100 ml.

**Case 67.** P.J. male, 42 years. Diabetes for four years. Intermittent claudication right calf. All peripheral pulses present. Reactive hyperaemia blood flows right calf 21.7ml/min/100 ml. left calf 29.1ml/min/100 ml.

**Case 68.** E.F. female, 48 years. Diabetes for nine years. Recurrent infected cutaneous lesions on toes. Intermittent claudication both calves on hurrying uphill. All peripheral pulses present. Maximal circulatory capacity right foot 14.7ml/min/100 ml; elevated 19 cm. 10.7ml/min/100 ml.

**Case 69.** E.S. male, 60 years. Diabetes for two years and intermittent claudication in both calves for same period. No pulses felt beyond femorals. Maximal circulatory capacity right foot horizontal 13.3ml/min/100 ml.; elevated 19 cm. 9.3ml/min/100 ml. B.P. 140/95.

**Case 70.** J.R. male, 38 years. Diabetes for 15 years. Intermittent claudication on hurrying uphill. All peripheral pulses present. Retinal haemorrhages. Maximal circulatory capacity right foot horizontal 14.5ml/min/100 ml. elevated 19 cm. 9.8ml/min/100 ml. B.P. 105/75.

**Case 71.** K.M. male 39 years. Diabetes for 10 years. Intermittent claudication in both calves. Posterior tibial pulses only absent. Maximal
circulatory capacity right foot 10.0 ml/min/100 ml.

Case 72. J.S. male 65 years. Admitted with gangrene of right foot apparently of recent onset but no clear history was obtained. Heavy glycosuria discovered. Amputation at midthigh. Old atherosclerotic lesions at popliteal bifurcation and recent thrombosis higher in artery. Death four days after operation. Severe widespread atherosclerosis at autopsy.

Case 73. G.J. male 56 years. Diabetes for four years. Recurrent ulceration of toes of both feet and finally spreading septic infection around right great toe. Below knee amputation. Atherosclerotic obstructive lesions in tibial arteries and oblitative endarteritis in small arteries of foot.

Case 74. S.P. male 70 years. Diabetes for at least ten years. Two months previously injured right foot and abrasion failed to heal. Developed spreading cellulitis of foot. Right midthigh amputation. Popliteal artery showed old atherosclerotic lesions but no recent thrombosis. Cannulated and injected with lead phosphate (fig. 33). Old atherosclerotic lesions in tibial arteries and gross sepsis in foot. Conspicuous perivascular infiltrations of leucocytes and fibrosis.


Case 78. E.M. female, 74 years. Diabetes for ten years. Developed gangrene of right foot. Right midthigh amputation. Femoral artery patent and injected with lead phosphate. Irregular filling of tibial and pedal arteries with numerous well filled collateral branches. On dissection popliteal artery only had extremely narrow and irregular lumen with old atherosclerotic lesions; no recent thrombosis. Old thromboses in tibial arteries with partial recanalization. Marked intimal hyperplasia in digital arteries.


Case 80. male, 60 years. Diabetes for two years. Superficial burn of left foot which failed to heal. Below knee amputation. Severe atherosclerotic lesions in tibial arteries. Injection of limb through partially patent anterior tibial artery and study of collateral arteries around obstructions.
Case 81. male 58 years. Diabetes for three years. Gangrene of right foot following injury to toe. Below knee amputation. Injection through anterior and posterior tibial arteries attempted but unsuccessful. Widespread obstructive atherosclerotic lesions found at upper ends of tibial arteries.

Case 82. male, 48 years. Diabetes for five years. Gangrene tip of right great toe with sharp line of demarcation. All tibial pulses present. Amputation of toe with satisfactory healing. Digital arteries narrowed by intimal thickening but not entirely obstructed.

Case 83. male, 53 years. Diabetes for at least two years. Recurrent septic lesions around left third toe followed by gangrene of tip. Posterior tibial pulse present, dorsalis pedis absent. Amputation of toe. Digital arteries largely obliterated by fibrous thickening of intima.
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