OBSERVATIONS ON THE PATHOLOGY OF PERIPHERAL VASCULAR DISEASE

(Exclusive of congenital malformations and neoplasms)

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Introduction

Although the circulatory system cannot properly be considered except as a whole, there is such an abundance of pathological conditions to which it is subject, in whole or in part, that limitations of space alone demand that it be divided into parts and that only a part be considered here. This paper will therefore be confined to the peripheral vascular system, which is arbitrarily defined as all the circulatory system exclusive of the heart, aorta and pulmonary system. For a similar reason it is proposed to omit the consideration of vascular malformations and neoplasms.

Anatomical, Physiological and General Considerations

The purpose of the blood vessels is to conduct blood in the right quantity to the right place at the right time and it is at the capillary level that the metabolic interchanges occur. The demands of the tissues vary greatly from time to time, e.g. muscles in action require a greater blood flow than those at rest. Such intermittent demands for large quantities of blood are met by means of a capillary bed of variable size. Economy of work and conservation of heat are effected by diminishing the blood flow by vascular constriction, predominantly at the arteriolar level.

These functions of the vascular system are associated with appropriate anatomical structure.

(1) *The arteries of large calibre* (e.g. aorta, innominate, subclavian) which convey blood easily to all parts of the body, have a smooth endothelial lined intima which confines but does not appreciably impede the flow of blood: a thick media composed of fibrous and elastic tissue, fibrous tissue for strength and elastica for storing the dynamic energy of each cardiac systole and for releasing it during diastole, and so prolonging the forward impulse to the blood: and a connective tissue adventitia. Their structure does not allow them to vary much in calibre and serious interference with their integrity has very dangerous consequences for the individual. Syphilis (producing aneurysms), atheromatous degeneration (not usually to a degree to cause serious obstruction) and mechanical trauma (producing dissecting aneurysm, traumatic aneurysm, haemorrhage, etc.) are the commonest agents in diseases of these vessels.

The large arteries merge into (2) *The arteries of mixed type* (e.g. common iliacs) which are inter-

mediate between those of large calibre and (3) *The arteries of medium calibre* (e.g. radial) (Fig. 1) which comprise the majority of the macroscopically visible arteries in the body. They regulate the flow to the major and minor regions of the body. In their media the elastica is less, being generally limited to an internal and external elastic lamina. (In the cerebral vessels the external elastic lamina is absent.) Unstriated muscle is however present in large amount and, by response to autonomic nervous impulses, can produce wide variations in calibre. As in the large arteries the fibrous adventitia contains the small vasa vasorum through which blood is conveyed to most of the media. The intima and inner layers of the media are nourished by the blood in the lumen of the vessel itself, either directly or possibly through internal vasa vasorum. Serious local disease of these vessels and the resultant ischaemia can often be overcome by means of collateral circulation through unaffected portions of the vascular tree.

(4) *The arterioles* (e.g. afferent renal glomerular arterioles) (Fig. 2), which are chiefly muscular in construction and have but little elastica. The calibre of the arterioles is an extremely important factor in the general arterial blood pressure. In the voluntary muscles the calibre of the vessels (possibly of all sizes) is controlled largely by local metabolites. (Barcroft *et al.*, 1943.) Elsewhere it is controlled by the autonomic nervous system. A "pressor" substance, hypertensin (angiotonin) is now known to influence the calibre of the arterioles and its action is thought to be directly upon the muscle of the vessel wall.

(5) *The capillaries* have walls consisting only of endothelial cells and an outer fibrous perithelium. It is at this level that metabolic exchange occurs. They are liable to damage from circulating toxins and when pre-stasis or stasis of blood occurs they are the point at which plasma and erythrocytes may leak out of the circulatory system (Fig. 3).

In the acral subcutaneous parts of the body provision is made for by-passing the capillaries by means of (6) *Arteriovenous anastomoses*. These are richly innervated vessels with thick walls composed chiefly of modified muscle cells. Amongst the functions ascribed to these shunts is that of thermo-regulation. They do not suffer from any as yet known, specific disease processes, apart from neoplasia.

(7) *Venules and veins* (Fig. 1). These vessels convey the blood back to the heart. Lined by

endothelium, the wall is composed of elastica and plain muscle and of relatively more connective tissue than in an artery. The distinction between the media and the adventitia and between veins of various sizes is not sharp. They are controlled by the autonomic nervous system. Disease of the veins does not usually have such severe consequences as that of the arteries, with the possible exception of pulmonary embolism. Two distinct systems of veins, the systemic and portal systems are known. These systems communicate at certain well-known regions, at which the veins may become engorged in portal obstruction. Recently the importance of the paravertebral and spinal veins has become recognised in the explanation of the spread of emboli to the spine from the viscera without involvement of the lungs, e.g. bony metastases from prostatic carcinoma. (Batson, 1940).

The Effects of Vascular Disease

The effect of vascular disease is frequently to produce some degree of ischaemia in the field of distribution of the diseased vessels. The degree of ischaemia will depend upon the degree of narrowing of the arterial lumen, upon the site or sites of narrowing, upon the degree of collateral circulation, the degree of associated vasospasm, upon the way in which the available blood is shared out amongst the different tissues, upon the metabolic demands of the tissues, upon the rate at which the ischaemia develops and upon its duration. In the limbs the effect of vascular obstruction are generally:—(1) diminution of the pulse, (2) lowering of the skin temperature, (3) a pale or cyanotic skin colour, (4) pain, (5) glove or stocking anaesthesia. Structurally there may be: (1) generalised atrophy or necrosis, (2) nerve degeneration. In muscle ischaemia necrotic muscle may be replaced by fibrous tissue, Volkmann's Ischaemic Contracture (Griffiths, 1940).

Classification

Medical nomenclature and classification being still debatable subjects the opportunity is taken of classifying upon an aetiological basis. The word arteriosclerosis, unqualified, is deliberately excluded, for it is too general, and too comprehensive in meaning.

Diseases of the Systemic Peripheral Vascular System

<i>Arterial, Arteriolar and Capillary</i>	<i>Venous</i>
A. Due to Bacterial Infection.	
Acute bacterial arteritis. Tuberculous arteritis. Syphilitic arteritis.	Thrombophlebitis. Pylephlebitis.

B. Due to Chemical Trauma or Circulating Toxins.

Ergotism.
Glomerulo-nephritis.

C. Due to Mechanical Trauma.

Arterial concussion, contusion and laceration. Periarterial haematoma and false aneurysm. Traumatic arteriovenous communication. Bland embolism.	Venous contusion and laceration. Spontaneous venous thrombosis (of the axillary vein). Femoral venous thrombosis.
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D. Due to Thermal Trauma (cold).

Raynaud's disease and the Raynaud Phenomenon.
Immersion foot or Trench foot.
Frostbite.

E. Due to, or Associated with, Increased Intra-vascular Pressure.

Diffuse hyperplastic sclerosis: (a) of arteries, (b) of arterioles (fibrous, hyaline and necrotic). Massive cerebral haemorrhage.	Varicose veins. Haemorrhoids.
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F. Of Uncertain or Unknown Aetiology.

Chronic arterial disease: (a) Mönckeberg's medial sclerosis, (b) Atherosclerosis. Thrombo-angiitis obliterans (Buerger's disease). Rheumatic arteritis. Periarteritis nodosa.	Thrombo-phlebitis migrans.
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A. Diseases Due to Bacterial Infection

Pyogenic organisms.—Vessels passing through or adjacent to a focus of pyogenic infection may show acute inflammation of the wall—an acute bacterial arteritis or thrombophlebitis. Thrombosis is the usual sequel, especially in veins. Septic emboli may arise from the heart (e.g. ulcerative endocarditis) and become impacted in a small artery, cause secondary infection and weakening of the wall with the formation of a *mycotic aneurysm* (Figs. 4 and 5).

Syphilis.—In the aorta syphilitic disease of the vasa vasorum and damage to the elastica are the main features. In the arteries of medium calibre, especially in the brain, the condition is a pan-arteritis. The organism is present in the vessel wall and the severity or tempo of the reaction varies. Sometimes the condition is associated with much necrosis, a gummatous arteritis, sometimes necrosis is slight or absent and there is well marked concentric intimal fibrosis, minimal damage to the internal elastic lamina, slight medial replacement fibrosis, adventitial fibrosis and infiltration of all coats by lymphocytes and plasma cells (Fig. 6).

Illustrations

- FIG. 1.—Control posterior tibial vessels from a case without vascular disease. The artery (larger vessel) shows the internal elastic lamina, the muscular media and the narrow adventitia with contained external elastic lamina. The vein (smaller vessel) contains less elastic, less plain muscle, more fibrous tissue. Elastic van Gieson stain x 23 (N.P. 2100).
- FIG. 2.—Glomerulus and afferent glomerular arteriole (→) from a case without renal disease. H. & E. x 250. (N.P. 2890.)
- FIG. 3.—Fat embolism. Cerebral capillary haemorrhages in a patient who was knocked down by a bus four days before death. Thick frozen section in which blood is stained by Pickworth's method. x 30. (N.P. 2574.)
- FIG. 4.—Mycotic aneurysm. Intracerebral haemorrhage from middle cerebral artery (→) in which septic embolus from subacute bacterial endocarditis of aortic valve had impacted. (N.P. 1257.)
- FIG. 5.—Mycotic aneurysm. Cerebral artery with impacted infected embolus from a case similar to that in Fig. 4. At one point (↑) the arterial wall is giving way. H. & E. x 80. (N.P. 370.) Courtesy of Prof. J. R. Biggart.
- FIG. 6.—Syphilitic arteritis (cerebral vessels). There is well marked concentric intimal fibrosis, minimal damage to the internal elastic lamina, slight medial replacement fibrosis and infiltration of all regions, but especially the adventitia, by lymphocytes and plasma cells. H. & E. x 40. (N.P. 1184.) Courtesy of Dr. A. C. P. Campbell.
- FIGS. 7 and 8.—Tuberculous arteritis in tuberculous leptomeningitis showing predominantly mononuclear infiltration of all coats. Subendothelial infiltration (E) is a characteristic feature. H. & E. x 60 & x 350. (N.P. 1285.)
- FIG. 9.—Acute glomerulo-nephritis. The glomerulus shows proliferation and swelling of the capillary endothelial cells and there is an infiltration with polymorphonuclear leucocytes (compare Fig. 2). H. & E. x 250. (C.B. 111.)
- FIG. 10.—Subacute glomerulonephritis. Reticulin and collagen have been laid down between cells and loops of the now lobulated glomerulus, whilst proliferation of cells lining Bowman's capsule has produced a characteristic "crescent." H. & E. x 250. (D.B. 4789.)
- FIG. 11.—Chronic glomerulo-nephritis. Fibrous replacement and atrophy of the glomerular unit are occurring. H. & E. x 250. (D.B. 3012.)
- FIG. 12.—Arterial contusion. Mortar bomb injury to axillary artery 24 hours previously. The lumen is distended with recent thrombus. The wall shows (↓) severe damage to intima and media. H. & E. x 12. (N.P. 2075.)
- FIG. 13.—Arterial contusion. Section of arterial wall from region ↓ in Fig. 12, showing severe damage to media and intima. The adventitia is relatively intact. Elastic van Gieson stain. x 80.
- FIG. 14.—Arterial contusion. Section of arterial wall from region ↑ in Fig. 12, showing media and intima infiltrated by red blood cells and polymorph leucocytes. A portion of the internal elastica has become separated and lies in the luminal thrombus. H. & E. x 80.
- FIG. 15.—Arterial laceration. One month ago lateral wound of brachial artery. Now organised partly recanalised thrombus fills both the aperture (A A') and the lumen (L) of the vessel. H. & E. x 15. (N.P. 2298.)
- FIG. 16.—Post-traumatic aneurysm. Bisected sac of aneurysm of acromio-thoracic axis, five months after shell wound. The white rod passes along the lumen of the artery and can be seen through the wound in the wall. The sac consists of the organised periphery of the haematoma. Courtesy of Prof. J. R. Learmonth.
- FIG. 17.—Traumatic arterio-venous communication, eight months after a shell wound of the popliteal vessels. A small aneurysmal sac (S) forms part of the communication. Courtesy of Prof. J. R. Learmonth.
- FIG. 18.—Traumatic arteriovenous communication, of four months' duration. Shell wound of occipital artery and internal jugular vein. The section has been made in the plane of the fibrous communication (C) uniting artery (A) and vein (V), after the vessels have been opened up. H. & E. x 4. (N.P. 2334.)
- FIG. 19.—Higher power view of part of Fig. 18. The normal muscularis and elastica of the vessels come abruptly to an end, the artery and vein being united by well vascularised cellular fibrous tissue, the surface layers of which form an intact endothelial lining to the communication. Upon the arterial side fibrous tissue has grown over the surface of the arterial intima for a short distance. Elastic van Gieson-stain. x 20.
- FIG. 20.—Traumatic arterio-venous communication. Median cubital vein on proximal side of brachial arterio-venous fistula of two years' duration, showing hypertrophy of all mural elements (compare Fig. 1). Elastic van Gieson stain. x 24. (N.P. 2074.)
- FIG. 21.—Traumatic arterio-venous communication. Hypertrophied and dilated heart in the case of a 22-year-old traumatic fistula between profunda femoris artery and femoral vein. Courtesy of Dr. A. R. Gilchrist.
- FIG. 22.—Raynaud's disease. Secondary organic fibrous narrowing of the digital artery in a woman, aet. 32, with a nine years' history. Elastic van Gieson stain. x 75. Courtesy of Prof. J. R. Learmonth.
- FIG. 23.—Diffuse hyperplastic arteriosclerosis (renal interlobular artery). There is concentric intimal fibrosis, concentric reduplication of the internal elastic lamina and fibrous replacement of the media. Elastic van Gieson stain x 250. (R.I.E. 557/39.)
- FIG. 24.—Diffuse hyperplastic arteriolosclerosis (renal afferent glomerular arteriole), showing fibrous mural thickening. Compare Fig. 2. H. & E. x 250. (R.I.E. 557/39.)
- FIG. 25.—Hyaline change in renal afferent glomerular arterioles in a case of arterial hypertension. H. & E. x 250.
- FIG. 26.—Arteriolonecrosis (renal afferent glomerular arteriole) showing the necrotic change characteristic of malignant hypertension. H. & E. x 250.
- FIG. 27.—Chronic arterial disease (posterior tibial vessels). The artery (larger vessel) shows intimal fibrosis with recanalised mural thrombus, eccentric splitting of the internal elastic lamina, medial degeneration with calcification (black) and minimal adventitial and venous change. Elastic van Gieson stain. x 22.
- FIG. 28.—Atherosclerosis (basilar artery) showing eccentric sub-endothelial fibrous thickening with fatty change in the deeper part, eccentric splitting of the internal elastic lamina and fibrous replacement of medial muscle. Masson's trichrome stain. x 30. (N.P. 1084.)
- FIG. 29.—Thromboangiitis obliterans (posterior tibial vessels). The artery (larger vessel) shows recanalised intimal thrombus, little damage to internal elastic lamina, slight medial fibrosis and much adventitial fibrous tissue increase, binding together the artery and the similarly affected vein. Many of the clear apertures in the media are dilated vasa-vasorum. Elastic van Gieson stain, x 22. (E. H. 600 B.)
- FIG. 30.—Polyarteritis nodosa. Renal interlobular arteriole, from a case following sulphonamide therapy, showing acute degenerative or necrotic change in the vessel wall and predominantly polymorphonuclear (often eosinophile) leucocytic intramural and peri-vascular infiltration. H. & E. x 250. (E.H. 498 A.)
- FIG. 31.—Polyarteritis nodosa in stage of healing (vessels in epineurium of median nerve). The artery shows marked intimal and slight adventitial fibrosis: the vein is healthy. H. & E. x 85. (N.P. 2553.)
- FIGS. 1, 27 and 29 are reproduced by permission of the author and of the Editor of the *Edinburgh Medical Journal*.

Tuberculosis.—Arteries in the neighbourhood of a tuberculous focus may become involved. The process is most clearly seen in the leptomeninges where characteristic changes occur in tuberculous leptomeningitis. There is a mononuclear infiltration of all coats, especially below the endothelium and there is sub-endothelial connective tissue proliferation (Figs. 7 and 8).

B. Diseases Due to Chemical Trauma or Circulating Toxins

Ergot, a fungus which grows on rye, has long been infamous for its effect upon the plain muscle of the arteries and its ability to produce ischaemic necrosis. Lewis (1935) has shown that, in the cock's comb, the reduced blood flow through the peripheral capillaries produces severe nutritional disease of the wall. Plasma leaks out in association with stasis and necrosis in the tissues with retrograde thrombosis of larger vessels complete the picture.

Acute *glomerulo-nephritis*, from which the sub-acute and chronic phases may develop, is a disease which may follow bacterial infection (scarlet fever) and it is now thought to be an allergic response. This allergic response may be considered as manifesting itself throughout the body, but it is most conspicuous in the capillaries of the glomerular tuft, where slowing of the blood stream is associated with endothelial hyperplasia, sometimes with polymorphonuclear leucocyte infiltration and loss of albumin and red cells into the periglomerular space (Fig. 9). In the subacute stage the proliferative phases of the inflammation are present. Reticulin and collagen are laid down between cells and loops, respectively, of the glomerular capillaries, whilst the lining cells of Bowman's capsule proliferate to form the characteristic "crescent" (Fig. 10). In chronic glomerulo-nephritis replacement fibrosis of damaged tissue is the chief feature (Fig. 11).

The above are but examples of the many conditions in which blood vessels show a greater or lesser degree of reaction to the presence of circulating toxins, foreign proteins and abnormal chemical substances.

C. Disease Due to Mechanical Trauma

Blood vessels may suffer direct severe trauma from a penetrating wound by a bullet, with the risk of the introduction of foreign bodies or bacteria: from crushing; from stretching or tearing in association with the fracture of adjacent bones. They may suffer repeated minor traumata, e.g. at the hiatus tendineus in adductor magnus, or in the case of the classical popliteal aneurysm of postboys. The structures primarily involved may be either artery, vein or nerve, or any combination of these.

Arterial injury may be classified as (a) *Concussion* or arterial stupor, where there is no primary histological evidence of damage. (b) *Contusion* where the damage is often more severe in the inner coats of the vessel than is apparent from without. The damage may extend widely within the vessel from the point where the surface indication is most obvious (Figs. 12, 13 and 14). (c) *Laceration* including complete division. All these conditions may be associated with peripheral vasospasm, which may be relaxed if the damaged segment is removed.

Thrombosis is a common sequel of arterial injury and is even more marked in damaged veins. It may spread distally, it may wholly or partly obstruct the lumen, it may seal off a hole in the vessel wall (Fig. 15). Later the clot may contract rendering the lumen once more patent or allowing blood to leak out of a lateral wound. Thrombosis is followed by organisation and possible recanalisation.

When an artery is completely divided, if it is not a large one, then it is usually sealed off by prompt contraction and retraction of the inner coats. Thrombosis occurs and there is endothelial and subendothelial proliferation at the injured site and finally organisation.

It is lateral wounds, or wounds involving almost the whole of the arterial circumference, which give rise to most complications. In these wounds there is much haemorrhage into the peri-arterial tissues producing a *peri-arterial haematoma*. This is followed by a marked inflammatory reaction in both the damaged arterial wall and the surrounding tissues. The associated oedema accounts for much of the swelling at this time. It helps to limit the haematoma, but it would hinder exploration by the surgeon. The peri-arterial haematoma first coagulates peripherally, limiting the spread of haemorrhage. It may press upon the main or collateral vessels. The haematoma may develop into a *false aneurysm*, the aneurysmal sac being excavated in the haematoma by the pulse wave. Ultimately the sac has a wall of laminated clot lined internally by endothelium and with an outer fibrous wall (Fig. 16). The wall of the sac is thickest at the point most distant from the arterial wound, thinnest close to the wound; indeed, shortly after injury, the wall nearest to the wound is so thin and lightly adherent, that the whole aneurysm may easily be swept off the adventitia. Surrounding structures, especially nerves, may be included in the wall of the sac. These aneurysms may undergo spontaneous cure, though usually they tend to enlarge. They usually develop soon after the injury but development can be delayed. When this occurs it is probably due to the spontaneous yielding of a partly healed arterial wound.

Secondary haemorrhage usually occurs in the first two or three days or again seven to ten days after injury. The latter is the more serious. It is due to a defect in the localisation of the haematoma, some part of the limiting boundary of the clot giving way. This may be due to infection of surrounding tissues, to a rise of blood pressure consequent upon increased general activity, to movement, or sometimes to the giving way of the thin line of union between the small aneurysmal sac and the wall of the arterial wound. Infection of the haematoma itself is rare.

Traumatic Arteriovenous Communications. When, as the result of mechanical trauma, there is a communication between the blood flow in an artery and the blood flow in a vein, the condition is either one of aneurysmal varix, where there is direct communication between artery and vein: or varicose aneurysm, where the communication includes a false sac (Fig. 17).

Such lesions are often produced by an object passing either between the artery and vein, or going right through them from side to side. In the second type of injury the perforation in the vein, on the side remote from the artery, readily heals. A varicose aneurysm may not show for days or weeks. This gradual formation may be due to delay in the canalisation of the initial periarterial haematoma or because thrombus was present in the vein and blocked the wound.

The sequelae of a traumatic arteriovenous communication are both local and systemic. The sac of the aneurysm does not tend to increase in size, because the vein acts as a safety valve for the arterial pressure. An endothelial lining grows over the connecting passage (Figs. 18 and 19). There is proximal dilatation and distal narrowing of the artery, whilst the vein dilates, becomes tortuous and its wall becomes hypertrophied and arterialisised (Fig. 20). Centrally, as a result of the constant leak of blood out of the arterial tree there is enlargement and hypertrophy of the heart (Fig. 21). There is a normal systolic but a reduced diastolic blood pressure. If the fistula is occluded the diastolic blood pressure rises and the pulse rate slows. There is an increase of blood volume. Nutritional changes, distal to the communication, are minimal.

A condition of some rarity is *spontaneous thrombosis of the axillary vein*. French (1944) has suggested that this aseptic thrombotic process is due to exercise, which produces a sudden rupture of small tributaries draining into the axillary vein and that this rupture leads to thrombosis, which spreads to the axillary vein itself.

A more common condition is *thrombosis in the ilio-femoral veins*. A period of forced recumbency, with angulation of the femoral vein over the pubis,

with slowing of the blood stream and a rubbing together of the devitalised intima in the collapsed veins of the calf (Boyd, 1942) leads to thrombosis. The thrombus is not in itself so serious, but a large portion is apt to become detached and give rise to a massive pulmonary embolism. After pregnancy and abdominal operations, when there has been some element of sepsis and when the thrombosis is widespread in pelvic and femoral regions, the condition of *phlegmasia alba dolens*, "whiteleg" may occur.

D. Disease Due to Thermal Trauma (Cold)

Physiological mechanisms are present in our bodies which enable us to withstand reasonable and individually variable degrees of chilling. The chief physiological mechanism is that of vasoconstriction of peripheral vessels, especially arterioles. In some people there may be an exaggeration of this response and they then exhibit the *Raynaud phenomenon*, or, if in women, in the hands and bilaterally symmetrical, Raynaud's disease. It is a condition of intermittent abnormal spasm of the digital arterioles in response to cold. In its early stages it is not associated with any particular structural change but later there may be secondary organic intimal fibrosis (Fig. 22).

If loss of heat from the extremities is accelerated by prolonged exposure to a moist cold atmosphere then the condition of *immersion foot* or *trench foot* occurs. With long continued arterial and arteriolar spasm there is ischaemia and dilatation of the capillary bed: plasma escapes through the damaged capillary walls leading to oedema of the extravascular tissues and to a consequent "conglutination" or increased concentration of red blood cells within the capillaries (Kreyberg, 1945). Some damage, partly from ischaemia, partly from cold, occurs in the surrounding tissues. When the patient reaches a warmer environment the arteries and arterioles relax, blood returns to the part and the local temperature rises. More plasma may leak out of damaged vessels. In capillaries where the red blood cells are "conglutinated" it may be difficult for blood flow to recommence and pre-stasis or stasis may develop. Such stasis and consequent ischaemia will, in a warm environment, rapidly cause much more tissue damage and necrosis. This is the danger point in immersion foot and is thought by Kreyberg to be the mechanism of the greater part of the tissue damage. The vessels in immersion foot show but little change and thrombosis is not a feature except in regions of necrosis or secondary infection (Blackwood, 1944).

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If the part is chilled to below -5°C . then *frostbite* develops. Here, again, stasis of blood occurs. With return to a warmer environment an inflammatory response appears, with blistering and sloughing of dead tissues. Thrombi are now found in the arteries and veins of the skin and subcutaneous tissues, both in the necrotic regions and in those adjacent (Lewis, 1941). Obliterative endarteritis is reported to occur proximal to the necrotic region (Ducuing, d'Harcourt, Folch and Bofill, 1940, quoted by Bigelow, 1942). In frostbite as in immersion foot a state of vaso-neuropathy and cold sensitivity may develop and last for a long time.

In *high altitude frostbite* where the temperatures are very low, Davis, Scarff, Rogers and Dickinson (1943) found that, in the hands, the initial immediate response is constriction of the terminal portions of the superficial arterioles. Damage to the endothelium of the terminal cutaneous capillary loops results, after exposure, in transudation of fluid or there may be thrombosis at the arteriolo-capillary junction. These changes produce large blisters. When the exposure is more severe and the deeper arterioles are damaged, then dry gangrene results. Concentric intimal fibrosis of the digital arteries proximal to severe cutaneous lesions is reported as a sequel.

E. Diseases Due to or Associated with Increased Intravascular Pressure

Primary or essential hypertension, the commonest type of hypertension, is now thought to be due to the production, by the kidney, of a pressor substance called renin, which unites with hypertensinogen in the blood plasma to form hypertensin. This reaction is subject to the presence of an antipressor substance hypertensinase, also elaborated by the kidney.

Hypertension is associated with contraction of the muscle of small arteries and arterioles. It is not yet certain which is the primary factor in essential hypertension—the production of a pressor substance or some degree of vascular abnormality or disease.

In benign hypertension of some duration and in malignant hypertension, structural changes are found in the small arteries and arterioles of the kidneys and often of liver, pancreas, suprarenals, gastro-intestinal tract, spleen, muscle, retina and, to a lesser extent, in the brain. If the hypertension is benign and of some duration, then the vascular changes are partly hyperplastic and partly degenerative. If malignant the changes are degenerative and may be necrotic in character.

The changes are those of *diffuse hyperplastic sclerosis*. After hypertension of some duration,

the renal interlobular *arteries* show concentric subintimal fibrosis, roughly concentric splitting of the internal elastic lamina, well marked medial thickening partly due to muscular hypertrophy but chiefly to fibrosis (Fig. 23). The picture is one of work hypertrophy with subsequent failure and replacement fibrosis. In the *arterioles* the change, first seen in the afferent glomerular arterioles of the kidney, consists of fibrous thickening with narrowing of the lumen (Fig. 24). Fibrinoid degeneration often occurs, the arteriolar wall becoming much thickened and having a structureless hyaline eosinophilic appearance (Fig. 25). The characteristic lesion of malignant hypertension is that of arteriolo-necrosis, where the vessel wall shows necrotic changes with consequent haemorrhage, superimposed upon the lesion of fibrinoid degeneration (Fig. 26). Fibrous thickening will be visible if the "malignant" hypertension was preceded by a period of "benign" hypertension.

Massive Cerebral Haemorrhage.—A common cause of death, in arterial hypertension, is massive cerebral haemorrhage. It occurs generally in the basal ganglia or pons, where the blood supply is from short rather large arteries, which come off at right angles from their large parent trunks. The pathogenesis is in dispute, but it is probably not due to the rupture of an atheromatous vessel under a high pressure, nor to the rupture of Charcot miliary aneurysms (really adventitial haemorrhages). It may be due to the rupture of a vessel whose supporting tissues have died from the ischaemia of intermittent vasospasm (Globus, 1938) or it may be due to the confluence of haemorrhages from capillaries, whose walls, damaged by anoxaemia during vasospasm of the feeding arteriole, cannot contain the blood which rushes into them when the arteriolar spasm relaxes.

Hypertension in veins of the portal system produces *haemorrhoids*. In the systemic system it is usually seen in the lower limbs in the form of *varicose veins*. Here there is a strong element of hereditary weakness of the veins. The venous walls lack elastic tissue, they stretch easily, and when the valves are thus rendered incompetent the whole long column of blood can exert its pressure. The veins become varicose and considerable perivascular fibrosis occurs. Thrombosis is common, calcification may occur.

F. Diseases of Uncertain or Unknown Aetiology

Chronic Arterial Disease.—This is a disease usually occurring in the elderly of both sexes and in diabetics. In the extremities, especially the

lower extremities, the change is usually that of *Monckeberg's medial sclerosis*, where the vessels show focal regions, often rings, of medial calcification (sometimes even of ossification), and slight intimal fibrosis (Fig. 27). Often superimposed upon this is *atherosclerosis* which, by itself, is a disease both of the aorta and larger limb vessels, but also of the cerebral, coronary and intestinal vessels. It consists primarily of a fibrous sub-endothelial thickening of the intima. Fatty change is common in the deeper part of the plaque, calcification may occur and haemorrhage here may suddenly occlude the vessel. Thrombosis may occur upon the damaged intima. The internal elastic lamina usually shows eccentric splitting and may be increased in amount. Fibrous replacement of the medial muscle may occur. The adventitia is usually unaffected (Fig. 28).

The aetiology of these conditions is still in doubt. They occur in regions of pressure or strain. Loss of elasticity of the muscularis and degenerative changes in the elastica are both changes occurring normally with increasing age. Winternitz (1938) demonstrated the presence of vasa vasorum, especially those given off from the lumen and suggested that, in response to unknown toxic or bacterial agents, these vessels might show exudative changes (including haemorrhage) or proliferative changes and that upon this basis of tissue reaction rests the aetiology of atherosclerosis.

Thromboangiitis obliterans (Buerger's disease) is a disease of young male adults, affecting one or more segments of the vascular tree, occurring most frequently in the lower limbs. In the early stages there is acute inflammation of the wall and perivascular tissues of both artery and vein with polymorphonuclear leucocytic infiltration. Thrombosis occurs within the vessel and is subsequently organised and recanalised. At the edge of the thrombus Buerger (1924) saw miliary foci not unlike "tubercles."

At the stage when it is usually seen there is medial and adventitial fibrosis, involving and binding together both artery and its accompanying vein. The internal elastic lamina is not particularly damaged. The lumen of both artery and vein contains organising thrombus which may be extensively recanalised. The vasa vasorum are prominent and may afford a local collateral pathway (Fig. 29). There is sometimes an associated element of spasm. The aetiology is unknown.

In its early stages the condition is either associated with or may be preceded by *thrombophlebitis migrans*, a migrating superficial phlebitis of the extremities. A short portion of a vein becomes tender, swollen and reddened; in a few weeks the inflammation subsides and then migrates to another part of the same or a different vein. The histolo-

gical findings during the acute stage are similar to those seen in the acute stage of thromboangiitis obliterans.

Rheumatic Arteritis.—Von Glahn and Pappenheimer (1926) described a focal disease of peripheral arterioles and capillaries which was present in association with rheumatic heart disease. The active lesions were characterised by necrotic changes in all layers of the vessel wall and an infiltration of fibrin, polymorphonuclear leucocytes (occasionally eosinophile) and large mononuclears into the vessel wall and surrounding tissue. Vessels were also seen undergoing healing with recanalised connective tissue obstruction of the lumen. They considered it to be distinct from periarteritis nodosa, which it closely resembles except for the absence of thrombosis, but it is doubtful if this opinion can now be upheld.

Periarteritis nodosa is an acute or subacute focal inflammatory disease of medium and small arteries. It affects vessels in all parts of the body so that biopsy of muscle may be used as a diagnostic procedure. Macroscopically the vessels show nodular swellings up to pea size, those of very small size being the commonest. Histologically, in a flamboyant case, there is necrosis of the media and intima, including the intimal elastic lamina; there is infiltration of all coats and especially the perivascular region by neutrophile and eosinophile polymorphonuclear leucocytes (Fig. 30). Thrombosis and aneurysmal formation occur. Though generally progressive, local healing may occur with fibrous replacement of the damaged vessel wall (Fig. 31). It is a disease of all ages but more common in early or middle age. The presence of eosinophile leucocytes in the exudate has always suggested an allergic aetiology. Rich (1942) noticed the occurrence of the condition following therapeutic administration of serum and of sulphonamides. He has been able to produce the condition in rabbits by injection of horse serum and considers the disease to be a manifestation of anaphylactic type hypersensitivity.

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A NEW TEST FOR PREGNANCY

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History

It is now fifteen years since Hogben published a little note in the *Proceedings of the Royal Society of South Africa* on the relation of the Pituitary Gland to Ovulation and Skin Secretion in *Xenopus laevis*. Since that time, this toad, so far only known to a few zoologists, has been introduced, first hesitantly and then with enthusiasm, into the physiological laboratories of many countries. Its natural habits and its behaviour in the laboratory—so different from that of other amphibians—have been studied by many authors; it has been bred in large numbers, in London, New York, Basle, Berlin, and elsewhere, and even during the war there has been such a demand for these toads in Cape Town that it is often impossible to obtain supplies. It is fortunate that lately the South African Department for Inland Fisheries has taken an interest in the supply of *xenopus*. In their country of origin there should be no difficulty of breeding them in large numbers, and experience has shown that, if proper precautions are taken, the transport to London or elsewhere presents no great difficulties either.

Biology

Xenopus (Fig. 1) is classified as a toad of the genus *aglossa* by the zoologists, but it neither looks even remotely like the toads we know in Europe, nor are his habits similar to theirs. From the laboratory worker's point of view the arrangements that must be made to keep *xenopus* are

more like those required for keeping fish for, like them, these toads spend all their life in the water. This habit makes *xenopus* even more suitable as a laboratory animal because they can be kept fairly crowded, in simply constructed tanks and if they are only well fed and supplied with plenty of fresh water they survive, even under laboratory conditions, very well. Indeed, if some of them did not occasionally die through being used for tests or from infestation with fluke larvae their life in captivity might be 15–20 years.

Many observations have been published on the breeding of *xenopus* in captivity. Aquarists, tired of this "uninspiring" toad that would not breed in their aquaria, exiled it to a disused tank in the back garden, and after a few weeks found there hundreds of tadpoles. Imitation rain and change of the pH have sometimes been successful, sometimes not, and it must be said that without the use of the syringe *xenopus* is a most capricious breeder in captivity. Under artificial hormonal stimulation, however, it is not difficult to obtain fertilised eggs and the tadpoles grow up into small frogs during the summer season (Fig. 6). During that time they can be fed with infusoria, liver emulsion, dried egg emulsion or blood. In a well stocked aquarium, and if not too numerous, they need not be fed at all and can be seen to feed partly after the manner of whales, straining the water through their gill slits, partly nibbling at the infusorial growth which covers the water plants. Their gills are just visible, for a day or two after hatching. After that they undergo retrogression and the tadpole has to come to the surface every few minutes for a breath