

ISCHAEMIC LESIONS OF PERIPHERAL NERVES : A REVIEW

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For more than 50 years French and German authors have written about ischaemia as a cause of peripheral neuritis. Joffroy and Achard (1889) and Dutil and Lamy (1893) were among the first to describe ischaemic neuritis occurring in cases of peripheral vascular disease. Lapinsky (1899) drew attention to nerve lesions which were the result of acute arterial occlusions. In a lengthy article he discusses in great detail the sensory disturbances and paralyses which follow arterial thrombosis and embolism, and attributes them to lesions of ischaemic origin of the peripheral nerves. Desplats and Baillet (1911) described further cases in which they believed that nerve lesions had developed as a result of ischaemia, but the evidence which they put forward in support of their opinion is far from convincing. Foerster (1912, 1913) wrote extensively on the subject of arteriosclerotic neuritis. More recently Gallavardin, Laroyenne, and Ravault (1925), Coste, Bolgert, and Debray (1933) and Schlesinger (1933) have all reported cases in which there was a clear connexion between the presence of ischaemia and a peripheral neuropathy.

In America "neuritis of vascular origin" has long been recognized as a clinical entity. Under this heading, Woltman (1938) discusses tourniquet paralysis, Volkmann's ischaemic neuritis, neuritis associated with infarction of larger vessels, arteriosclerotic and senile polyneuritis, and neuritis associated with periarteritis nodosa. Fetterman and Spittler (1940) refer to trauma, embolism, arteriosclerosis, thromboangiitis obliterans, syphilis, periarteritis nodosa, and polycythaemia vera as causes of vascular disorders of the peripheral nerves.

Although British authors appear to have been familiar with the concept that vascular disturbances could result in lesions of the peripheral nerves, little was written on the subject until the outbreak of the recent war. Collier (1932), for example,

in his Morrison lectures on "Peripheral Neuritis" refers to the possibility that vascular lesions may be responsible for certain types of diabetic neuritis, but makes no other mention of the subject. A similar lack of reference to ischaemic neuropathies is found in other articles on neuritis and in the standard neurological textbooks.

In 1942 Adams reviewed the literature on the blood supply of nerves and included in his review a summary of the clinical evidence that lesions of nerves could be due to interference with their blood supply. Since then the papers of Seddon and his colleagues (Holmes, Highet, and Seddon, 1944; Seddon and Holmes, 1945) and Parkes (1945) on traumatic ischaemia of peripheral nerves have stimulated further interest in all aspects of the problem of nerve ischaemia.

The proper approach to any clinical problem is from an understanding of its anatomical and physiological background. Before discussion of the clinical aspects of nerve ischaemia it is therefore important to consider what is known of the blood supply to nerves, and what has been observed by physiologists and others in experiments on both animals and man in which the circulation to peripheral nerves has been disturbed.

Anatomy and Physiology

Blood Supply of Nerve.—Recent authoritative reviews of this subject have been published by Adams (1942) and Sunderland (1945).

All nerves receive a good blood supply through their vasa nervorum. As the main nerves of a limb pass distally they are supplied with nutrient arteries by adjacent vessels. The majority of nutrient arteries are either direct branches of the main arteries of the limb or subsidiary branches of arteries which, on their way to supply muscles, cross or run close to a nerve. The origin and number of the nutrient arteries supplying any given nerve are variable and there are long segments of

nerve which do not receive a nutrient artery. When the artery approaches the nerve it may behave in a number of ways, but usually, either before or after it enters the epineurium, it divides into two branches each of which, after pursuing a tortuous course, either proximally or distally, anastomoses with similar branches from adjacent nutrient arteries. Thus a continuous anastomosis is formed within the nerve trunk. When a nerve divides or gives off a branch, an anastomosis continuous with that on the parent trunk accompanies each division or branch. Arteriolar branches from the primary divisions of the nutrient arteries form an interfascicular network from which arises the capillary plexus supplying the nerve tissues.

The blood supply of a nerve is thus fundamentally segmental, but a feature of the arrangement of the intraneural vessels is the considerable overlap of supply between nutrient arteries entering the nerve at different levels. This means that in any given segment of nerve it is improbable that a single vessel will dominate the circulation, and in the event of one of the regional nutrient arteries being occluded, a preformed collateral pathway is at once available.

Effects of Ischaemia upon Nerves.—Three types of experiment illustrating the effects of ischaemia upon nerve must be considered :—

Anatomical Studies.—A number of workers have tried to produce ischaemia of peripheral nerves by interfering with their blood supply. As typical examples of such attempts the recent experiments of Adams (1943) and Roberts (1948) may be cited. In the rabbit, Adams ligated the inferior gluteal artery and all other nutrient arteries supplying the sciatic nerve between the hip and knee, but was unable to find histological evidence of nerve ischaemia except in two cases in which considerable mobilization of the nerve was necessary. Roberts attempted to produce ischaemia of the sciatic nerves of dogs by a variety of procedures. In acute experiments, after he had interfered with the blood supply to one sciatic nerve, he outlined the blood vessels of the nerves by injecting a dye into the aorta. Ligation of a single nutrient artery produced only a relative ischaemia of a short segment of nerve. A length of nerve could be made almost completely bloodless either by stripping its epineurium or by stretching it. Embolism of the nutrient arteries was produced by injecting into them either lycopodium spores or sterile powdered graphite. When this was done, patchy areas of ischaemia were produced throughout the nerve. A segment of nerve constricted by a tourniquet or isolated between two ligatures

remained ischaemic when the constriction was removed. In long term survival experiments ligation of several nutrient arteries, or stripping of the epineurium from a long length of nerve caused only slight and transient interference with function. Experimental embolism produced marked neurological and nutritional disturbances in the foot, but some of these changes might have been due to the lodgement of emboli in small peripheral arteries supplying tissues other than the nerve.

Physiological Studies on Animals.—If a nerve is to function properly it requires an adequate supply of oxygen which *in vivo* it receives through the blood supply. Gerard (1930) studied the effects of anoxia upon isolated nerve and showed that mammalian (dog) nerve was more susceptible to the effects of oxygen lack than nerve from lower vertebrates (frogs), thus indicating the greater dependence of the former upon its blood supply. Earlier Koch (1926) had studied the "current of injury" in the sciatic nerve of the rabbit before and after occlusion of the aorta. He found that the onset of ischaemia was associated with an increase in a previously subsiding injury current. In more recent years important experimental studies of the effects of ischaemia on nerve have been made by Bentley and Schlapp (1943) and Porter and Wharton (1949). A small but definite circulation is essential for the conduction of impulses along a nerve. In normal circumstances the blood supply provides an ample margin of safety. If a nerve alone is made completely ischaemic by interruption of its blood supply, it may receive enough oxygen by diffusion from adjacent vascularized tissues to enable it to continue to function for some time. If a limb is rendered completely ischaemic, conduction fails first in the distal segments of the nerves. Thus in one experiment in which the hind limb of a cat was made ischaemic by a tourniquet applied to the root of the limb, the nerve in the leg became inactive in 30 minutes, whereas that in the thigh continued to conduct up to two hours (Bentley and Schlapp, 1943).

The immediate effect of ischaemia upon nerve, however, is not a depression of conduction but an increase in irritability as Koch's (1926) experiments suggest. Porter and Wharton (1949), working with the cat's peroneal nerve, showed that cessation of the circulation was followed, after a latent period which varied from 15 seconds to seven minutes, by an increase in irritability which reached its maximum in about six minutes and was followed by a rapid loss of irritability so that the nerve became inexcitable in from 10 to 26 minutes from the onset of ischaemia.

Physiological Studies on Man—A number of observations have been made upon human limbs in which the blood supply has been temporarily interrupted by the application of a sphygmomanometer cuff inflated to a pressure greater than systolic blood pressure. The results of such experiments are complicated by the fact that two different factors, ischaemia and direct pressure upon nerves, may be operative. While some authorities (e.g. Denny-Brown and Brenner, 1944) believe that pressure upon a nerve exerts its effect mainly by causing a local area of ischaemia, others (e.g. Bentley and Schlapp, 1943) think that a nerve block produced by ischaemia has different characteristics from one caused by pressure. Nevertheless the results of these physiological studies on human limbs can be applied to clinical problems in many of which both ischaemia and pressure are encountered as possible aetiological factors.

Lewis, Pickering, and Rothschild (1931) described a centripetal paralysis of both motor and sensory functions which began in the finger tips about 15 minutes after the onset of ischaemia produced by suprasystolic compression of the arm. They attributed this paralysis to the effect of ischaemia upon the nerves rather than the nerve endings, and brought forward evidence which suggested that nerves in the proximal portions of the limbs were more sensitive to ischaemia. They contrasted the centripetal paralysis due to ischaemia with the loss of function produced by local pressure with a clamp upon the ulnar nerve; in the latter case anaesthesia developed uniformly over the whole territory supplied by the nerve. Later Lewis and Pochin (1938) showed that ischaemia did not cause the different modalities of sensation to disappear in a definite order. Defects in the sensations of touch, appreciation of passive movement, heat and cold, and fast-conducted pain appeared almost simultaneously, but the time at which each of these sensations finally disappeared varied considerably; touch was lost early but the other modalities declined slowly and were lost within a short period of one another. The defect in slow-conducted pain developed later but was noted before the other forms of sensation were lost. The final phase of sensory loss due to ischaemia, however, was a period in which slow-conducted pain was the only sensation which could be elicited. They were unable to correlate the elimination of the different sensory functions with the size or conduction velocity of the nerve fibres thought to subservise these functions. Nevertheless their observations clearly prove that the nerve fibres which are most resistant to ischaemia are slow-conducting fibres

conveying the delayed, more intense portion of the double pain response (Lewis, 1942).

The views of Lewis and his colleagues that a paralysis induced by ischaemia begins peripherally and spreads centripetally and that nerve trunks are more susceptible to the effects of ischaemia in their proximal segments, were accepted and apparently confirmed in similar studies by Zotterman (1933) and Kugelberg (1944). Sinclair (1948), however, has recently repeated Lewis's experiments and has questioned some of his observations and interpretations. He found that the sensory paralysis induced by compression of the arm with a sphygmomanometer cuff inflated to above systolic pressure does not show a regular centripetal spread, but that the territories supplied by the major nerves are successively involved, usually in the sequence median, ulnar, medial, and lateral cutaneous of the forearm. He has further suggested that the differences noted by Lewis and his colleagues between the effects of compression of the arm and the forearm and interpreted by them as indicating that nerve fibres become more sensitive to ischaemia as they are traced back from their endings towards the central nervous system, are due rather to anatomical differences between the contours of the arm and forearm and the ease with which the nerve trunks themselves can be compressed in these segments. When the cuff is applied to the arm, complete ischaemia of the hand and forearm is produced, and the main nerve trunks, poorly protected by muscle, are easily compressed against the humerus, whereas compression of the forearm seldom causes complete ischaemia of the hand and the main nerve trunks are well protected from pressure by muscles.

The experiments of Bourguignon and Laugier (1923), Thompson and Kimball (1936) and Kugelberg (1944, 1946) are of a rather different nature. These workers studied the electrical excitability of nerves in the limbs of man during a period of ischaemia produced by the method discussed above. Their results, which are similar to those obtained by Porter and Wharton (1949) on the cat's nerve (see above), may be summarized by saying that a period of increased excitability of the nerves is followed by a decreasing response to electrical stimuli until they become inexcitable approximately 30 minutes after the onset of ischaemia.

The neurological disturbances which occur when the blood supply is restored to an ischaemic limb are also pertinent to a clinical study of nerve ischaemia. When the circulation returns after an occlusion lasting approximately 30 minutes, muscle power and sensation, as judged by clinical

examination, are approximately normal in less than one minute. Barlow and Pochin (1948), however, have shown that complete recovery of the nerves takes considerably longer. By studying the susceptibility of the nerves to a further period of ischaemia, they have shown that after an occlusion of 25 minutes, at least six hours elapse before the nerves return to complete normality. Within a matter of seconds after the return of blood, intense paraesthesiae are felt in the extremity and fasciculation of muscles may be observed. During the last 20 years these phenomena have been extensively studied, and the relevant literature is well reviewed in recent papers by Weddell and Sinclair (1947) and Merrington and Nathan (1949). Different qualities of post-ischaemic paraesthesiae can be distinguished: thermal paraesthesiae, pricking, tingling, and pseudo-cramp. The last refers to a sensation of tension on the muscles and is felt only after long periods of ischaemia. There is a lack of unanimity regarding the site of origin of these paraesthesiae and the nerve fibres concerned in their conduction to the central nervous system. Weddell and Sinclair (1947) suggest that they are produced by stimulation of nerve endings during the removal of a chemical substance which accumulates during the period of ischaemia and that they are conveyed by pain fibres. Merrington and Nathan (1949), on the other hand, are of the opinion that the sensations arise in the nerves recovering from the effects of ischaemia and that the fibres concerned are those responsible for the sensations of touch, pressure, and movement. I consider that the latter hypothesis is the more probable, and it is strongly supported by some of Kugelberg's (1944, 1946) observations. He has demonstrated that nerve fibres recovering from ischaemia and particularly those directly beneath the cuff are hyper-excitable; bursts of spontaneous repetitive discharges can be recorded and any stimulus applied to the nerve instead of provoking a single response initiates a burst of impulses. Post-ischaemic paraesthesiae are the clinical manifestation of this abnormal activity in sensory nerve fibres. Similarly fasciculation can be attributed to spontaneous impulses arising in motor nerve fibres, and may also be favoured by an increased irritability of the muscles themselves due to a lowered concentration of ionized calcium as suggested by Reid (1931).

Clinical Observations

Arterial Embolism.—Ischaemia is seen in its purest form as a result of arterial embolism. Since the obstruction to the circulation is sudden and intravascular, the influence of such factors as

pressure, haemorrhage, and pre-existing disease in the limb can usually be confidently excluded. As Lewis (1936b) has pointed out, the moment of lodgement of an embolus is seldom, if ever, recognized. The initial symptoms of coldness, numbness, weakness or pain in the limb do not appear until the obstruction to the circulation has been present for some time. Pain in the early stages is due to muscle ischaemia, but numbness, sensory loss, and motor paralysis are the result of ischaemia of the peripheral nerves. If the blood flow is restored within a few hours either by embolectomy or by the establishment of an adequate collateral circulation, the motor and sensory manifestations will rapidly improve and the limb return to normal. On the other hand, if the ischaemia persists for some hours but is relieved in time to prevent loss of the limb from gangrene, persistent motor and sensory disturbances may be observed. Haimovici (1950) found that this was the course of events in 13.5% of 330 cases of peripheral arterial embolism.

In this state of chronic post-embolic ischaemia, lesions of the peripheral nerves are usually accompanied by muscle necrosis and nutritional disturbances of skin and subcutaneous tissue. However, there is reliable evidence that in some cases nerves alone are damaged by the ischaemia (Blackwood, 1944). When patients reach the chronic stage they may continue to complain of pain, but it is seldom severe and is usually of the nature of annoying and rather intense paraesthesiae which tend to subside spontaneously within two to three months. On examination of the affected limb the signs of a peripheral neuropathy may be complicated by the presence of infarcted muscle and contractures of the hand or foot. If the muscles have not been directly damaged by the ischaemia they may be wasted, show coarse fasciculation, and be tender on pressure. A flaccid paresis affecting the most distal muscles may be noted. In the lower limb the ankle jerk is absent. Examination of sensation reveals a distal segmental area of anaesthesia or hypaesthesia associated with a delayed and very unpleasant response to pinprick and pressure stimuli.

In cases in which an embolus has lodged at the aortic bifurcation and has been successfully removed, the residual neurological defect may suggest a spinal root or cord lesion rather than a peripheral neuropathy (Learmonth, 1948, Case 3).

Trauma.—Only recently has ischaemia been recognized as an important factor in the pathogenesis of some nerve lesions which follow gunshot wounds and other injuries of the limbs. In some

cases an association between injury and ischaemia may be obvious ; for example, it may be known that the main artery of the limb has been damaged, but in many cases the possibility that ischaemia is wholly or partly responsible for the nerve lesions may be overlooked unless the limb is carefully examined for evidence of a vascular lesion.

When the main artery of a limb is interrupted, the results are extremely variable. If an adequate collateral circulation is immediately available, the effects may be so minimal that it is difficult to detect any neurological disturbance. On the other hand, massive gangrene of the limb may develop. Between these two extremes there is a group of cases in which the nerves, muscles, skin, and subcutaneous tissues suffer severely from the effects of ischaemia, but the limb as a whole survives. The end-result in these cases is an ischaemic paralysis of the limb. In such cases the nerve lesions may be due entirely to ischaemia or there may have been concomitant injury to both nerves and blood vessels so that, although the nerves are damaged at the level of injury, the effects of ischaemia must be considered in assessing the clinical findings and the prospects of recovery.

In time of war cases of this nature are not uncommon, and an excellent description of the syndrome of ischaemic paralysis was given by Tinel (1917). During the recent war considerable attention was focused on such cases, and elsewhere I have reviewed the recent literature and given details of other cases observed at three of the British peripheral nerve injury centres (Richards, in M.R.C. Report in preparation).

If it is known that a main artery has been injured and there is clinical evidence of ischaemia (infarcted muscle, gangrene of digits), it is not difficult to surmise that the nerve lesion may also be due to ischaemia, but the problem is not always so simple. For many years it had been recognized that the complication of fractures in the region of the elbow known as Volkmann's contracture was commonly accompanied by serious peripheral nerve lesions which, despite encouraging findings when the nerves were explored at the level of the fracture, seldom recovered well. An explanation for these apparently anomalous findings has only recently been provided by the work of Griffiths (1940) and Seddon and his colleagues (Holmes and others, 1944). The former showed that the majority of cases of Volkmann's contracture, if not all, are due to an arterial injury complicating the fracture, and that the contracture is the result of ischaemic necrosis of the flexor muscles in the forearm. Holmes, and others (1944) made a detailed study of the nerve lesions in seven cases of Volkmann's

contracture. They found, as had others before them, that in the majority of cases the nerves were normal at the site of the fracture. When the nerves were dissected distally, a remarkable change was found where they entered that portion of the limb in which the muscles were necrotic ; they appeared shrunken and avascular and resembled strands of fibrous tissue rather than nerves. The inference from these findings was that the nerves, like the muscles, had been damaged by ischaemia, and the authors concluded that this was the aetiology of the majority of nerve lesions in cases of Volkmann's contracture. They also described histological changes in the nerves which they regarded as pathognomonic of severe nerve ischaemia ; a great increase in endoneurial collagen sometimes progressing to complete replacement of the nerve bundles by collagen.

A less severe degree of nerve ischaemia than that encountered in cases of classical Volkmann's contracture may be seen in association with fractures which are complicated by considerable swelling of the limb and pressure beneath the deep fascia which temporarily interrupts the peripheral circulation (Parkes, 1945).

Unfortunately there is no typical clinical picture which will enable a diagnosis of traumatic ischaemia of peripheral nerves to be made with certainty. If the main vessel of the limb has been injured either directly by a gunshot wound, or indirectly in association with a fracture, the nerve lesions may be single or multiple. There is a certain amount of evidence to suggest that the larger nerve trunks are more susceptible to ischaemia ; I have seen two cases in which the median nerve only was affected by a high lesion of the brachial artery. If more than one nerve is affected, it is usual for the distal branches to be affected most severely so that the area of sensory disturbance has a segmental ("glove", "sock", "carpet-slipper") pattern and does not correspond to the anatomical territory of one or more nerves. In cases where the nerve ischaemia is the result of pressure beneath the deep fascia, this segmental distribution is confused by the fact that nerves which lie outside the deep fascia, e.g., the saphenous nerve, escape damage.

The quality of the sensory disturbance may be of help in establishing a diagnosis. In some cases of suspected nerve ischaemia the only sensory response which is preserved is a delayed and very unpleasant response to deep pinprick or pressure and best elicited by "pinching" the fingers or toes. The studies of Lewis and Pochin (1938) showed that in experimental pressure ischaemia of a human limb a slow-conducted pain response of this type can be elicited after all other modalities

of sensation have been lost. Wortis, Stein, and Jolliffe (1942) and Parkes (1945) have drawn attention to the important significance which such a finding may have in a case in which a clinical diagnosis of nerve ischaemia is being considered. However, a slow-conducted pain response can be elicited as the only sensory response in a number of other clinical conditions, e.g., *tabes dorsalis*, peripheral neuritis, and incomplete or recovering nerve lesions due to any cause. The presence of this type of response indicates that the tissues from which it is elicited are supplied only by a few isolated pain fibres (Weddell, Sinclair, and Feindel 1948). Therefore, while a slow-conducted pain response is often a very striking feature in cases of nerve ischaemia, it cannot be regarded as a pathognomonic sign, nor does its absence in association with either complete or incomplete anaesthesia or analgesia exclude a diagnosis of nerve ischaemia.

Assessment of the degree of motor paralysis may be difficult; often it is hard to tell which muscles are paralysed because they are ischaemic and which are denervated. Thus before a clinical diagnosis of traumatic ischaemia of a peripheral nerve can be made, it is necessary that there should be evidence—absent or diminished pulsation in the peripheral arteries, ischaemic muscles, or areas of superficial gangrene—to indicate that the circulation of the limb is or has been inadequate.

In some cases in which, after careful clinical examination of the limb, the possibility that ischaemia is an aetiological factor has been confidently dismissed, histological examination of excised portions of nerve has revealed evidence of ischaemic damage. Seddon and Holmes (1945) have described a case in which the characteristic histological changes of nerve ischaemia were found only in the distal stump of a divided median nerve. The case was one in which the radial artery had been injured as well as the median nerve, and the authors put forward the following explanation for the ischaemia of the nerve. Division of the nerve had interrupted the longitudinal blood supply from above. This in itself would not be sufficient to cause serious ischaemia of the nerve, but the radial artery had also been interrupted and the median nerve in the lower forearm receives its blood supply from branches of this vessel so that the distal segment of the divided nerve was deprived of its entire blood supply. More recently Woodhall and Davis (1950) have reported that, on routine histological examination of the proximal and distal stumps of nerves removed at operations for nerve suture, they have found changes in the arteriae nervorum and varying degrees of ischaemic damage

of the nerve bundles to be not uncommon. Unfortunately they do not state in every case whether the specimens were obtained from patients who had sustained a concomitant vascular injury. They describe one case of thrombosis of the arteria comes nervi ischiadici and one of thrombosis of the artery accompanying the median nerve. In both cases the distal stumps showed an increase in the amount of endoneurial collagen. They emphasize that changes in the arteries and evidence of nerve ischaemia are always more pronounced in the distal segments, and therefore suggest that the interruption of the longitudinal blood supply of a nerve may not be as harmless an event as has been heretofore believed. They further advise that when the distal segment of a divided nerve has to be freed for some distance to enable suture to be performed, it is important to preserve carefully all vessels running to the nerve.

Despite these discouraging pathological findings, it has been my experience that injured nerves may regenerate well in an ischaemic limb. In one case of severe ischaemia of the upper limb the ulnar nerve, sutured in the axilla, regenerated sufficiently well to reinnervate the abductor minimi digiti muscle which had previously been found by biopsy to contain areas of infarction. The poor functional results in cases of ischaemic paralysis are due not so much to failure of nerve regeneration as to the effects of the ischaemia upon the muscles, joints, skin and subcutaneous tissue.

These observations suggest that the importance of ischaemia in the aetiology and prognosis of many cases of peripheral nerve injury has previously been much under-estimated.

Tourniquet Paralysis.—Fortunately it is a rare event for the use of a tourniquet to be followed by persistent paralysis of the limb. When tourniquet paralysees do occur, they are seldom reported, but Eckhoff (1931) and Speigel and Lewin (1945) have reviewed the available literature and described several cases. Elsewhere I have discussed the condition and reported two further cases (Richards, M.R.C. Report). Tourniquet paralysis occurs most often in the upper limb, and the radial nerve is always affected, in some cases alone, in others along with the median and ulnar nerves. Only three cases of the condition in the lower limb have been recorded. As a rule the nerve lesions are not serious and recover spontaneously in from three to six months, but there is evidence that sometimes the paralysis may be permanent. In the mildest cases the paralysis is purely motor and is the result of a non-degenerative lesion of the nerves—a neurapraxia (Seddon, 1943)—but all grades from this

to complete motor and sensory paralysis without recovery have been recorded.

It is apparent that there are two possible aetiological factors which, acting either alone or together, may produce the nerve lesions—*ischaemia* and *pressure*. An efficient tourniquet causes complete *ischaemia* of the limb distal to the site of application. Earlier in this paper the results of experiments in which the arm was compressed by a sphygmomanometer cuff were discussed. It was shown that *ischaemia* of a limb produced in this way results in a peripheral type of paralysis affecting both motor and sensory functions. On release of the pressure rapid recovery occurs and is accompanied by post-*ischaemic* paraesthesiae and fasciculation in the muscles. It is tempting to assume that if the circulation were cut off for a sufficiently long period, pathological changes would occur in the nerves and give rise to a persistent paralysis. There are reasons why this simple explanation for the occasional occurrence of tourniquet paralysis should be questioned.

First, in cases in which paralysis has followed, the length of time for which the tourniquet has been applied is often no longer than that in similar cases in which no untoward effects have been observed, and in some cases has been no longer than that (30–40 minutes) which is often employed in experiments on man. I have seen a case in which a very tight band on the arm for only 20 minutes caused paralysis of the median, ulnar, and radial nerves which, three weeks after the incident, was still clinically complete. Perhaps this is an exceptional instance, but all authors agree that tourniquet paralysis occurs after both short and long operations. This is in keeping with the experimental observations of Denny-Brown and Brenner (1944); in the cat they found that “the amount and duration of pressure (with a tourniquet) necessary to cause persisting paralysis are extremely variable”. It seems probable that individuals may vary considerably in regard to the susceptibility of their nerves to pressure, and that a degree and duration of compression which is harmless in one patient in another may produce either a transient or persistent paralysis. Even if one allows that there is a natural tendency to underestimate the time for which a tourniquet has been applied, especially in cases in which paralysis has followed, it is certain that nerves can recover from a period of pure *ischaemia* greater than the longest time for which a tourniquet is ever applied. Lewis (1936a), for example, states that nerves recover after being *ischaemic* for 12 or even 20 hours.

Secondly, the type of paralysis is not always similar to that observed in experiments on com-

pression paralysis. A peripheral segmental paralysis is the exception rather than the rule, and the radial nerve is always that most seriously affected in cases of tourniquet paralysis, whereas Sinclair (1948) found that the median nerve was the most susceptible to compression paralysis. In two of the cases recorded by Spiegel and Lewin (1945) irreparable damage was done to the radial nerve, yet the other nerves escaped completely.

There are several pieces of evidence which incriminate direct pressure upon the nerves as an important factor. In mid-arm, where a tourniquet is usually applied, the radial nerve is more easily compressed against the humerus than the other main nerves. The relative infrequency of tourniquet paralysis in the lower limb may be explained by the fact that the sciatic nerve in the thigh is well protected by muscles. Although details of the type of tourniquet used are not available in all the reported cases, in many either a narrow rubber tube or an elastic bandage, both of which can be applied to a limb with considerable force, were used and often applied directly to the limb. A case of tourniquet paralysis following the use of a sphygmomanometer cuff has yet to be reported. There is no difference between a mild case of tourniquet paralysis and a pressure palsy of the radial nerve due to sleeping on the arm (“Saturday night palsy”).

In summary, there is insufficient evidence for tourniquet paralysis to be regarded as a pure *ischaemic neuropathy*. It is probable that *ischaemia* is an aetiological factor, especially in cases which follow prolonged occlusion, but the injurious effects of direct pressure upon the segment of nerve beneath the tourniquet appear to be more important.

Occlusive Vascular Disease.—“*Ischaemic neuritis*” is recognized to be the cause of a type of rest pain in patients suffering from occlusive vascular disease (Slessor and Learmonth, 1949).

The importance of nerve lesions in such cases was recognized first by Joffroy and Achard (1889). They reported the case of a woman aged 63 who had occlusive vascular disease of the lower limbs with a marked degree of atrophy of the muscles of the legs and severe pain. At necropsy they found an extensive obliterating arteritis of the *vasa nervorum* and a patchy Wallerian degeneration of the nerve fibres. Four years later Dutil and Lamy (1893) described a similar condition in a man aged 40. This case is of interest as the pathological findings are given in great detail and are typical of those found by Buerger (1908) in the group of cases to which he gave the name *thromboangiitis obliterans*. Subsequently there have been several clinical and pathological studies on the state of the

nerves in cases of thromboangiitis obliterans (Meleney and Miller, 1925 ; Barker, 1938), arteriosclerosis obliterans (Gallavardin and others, 1925 ; Priestley, 1932), and "spontaneous gangrene" (Panchenko, 1938).

Although mild degrees of neuropathy are probably present in the majority of cases of occlusive vascular disease, severe neuropathy is not common ; Schlesinger (1933) reported an incidence of 4.7% in 470 patients of all ages suffering from intermittent claudication, and Goldsmith and Brown (1935) found it in only 7% of cases of thromboangiitis obliterans. It occurs in the lower limbs only and has certain very characteristic features.

"Ischaemic neuritis" is seldom encountered where there is a short history of vascular disease. The patient is nearly always a man who has a long history of claudication or other symptoms indicating a moderate degree of peripheral ischaemia followed by an episode which suggests occlusion of a major proximal vessel. Perhaps because the muscles and skin have already become adjusted to a relatively poor blood supply, the limb survives a major vascular catastrophe which, had it occurred in a previously normal limb, in all probability would have resulted in gangrene. The nerve trunks cannot accommodate themselves to a blood supply less than their basic needs and consequently the patient finds himself left with a useful but painful limb. Thus the presence of ischaemic neuritis indicates a severe degree of peripheral ischaemia. Although a patient who suffers from "ischaemic neuritis" nearly always has occlusive vascular disease of both lower limbs, the "neuritic" symptoms are frequently unilateral and indicate the limb most severely affected.

Pain is always the predominant symptom and is often severe and continuous. Superficial and deep-seated pains can be distinguished. The former is described as burning ; "red-hot", "on fire", "hyperaesthesia", "like a dentist's drill under the skin" are expressions used by patients to describe their sensations. The pain is felt over large areas of the limb which rarely correspond to the anatomical distribution of a nerve or nerves. The deep pains are more apt to be paroxysmal and resemble the lightning pains of tabes dorsalis ; patients describe bursts of pains which radiate from the base of the toes up the leg to the knee and even into the thigh. According to Goldsmith and Brown (1935) paroxysms of pain of this nature may be accompanied by attacks of discoloration of the foot. These pains are always worse at night, are aggravated by heat but may be relieved by moderate warmth. They are frequently eased when the feet are pendent

and supported, and for this reason patients with "ischaemic neuritis"* often sleep sitting in a chair with their feet on a low stool. In my experience, morphine is the only analgesic which has a uniformly satisfactory effect in relieving the pain. Codeine, pethidine, physeptone, and other analgesics may all give temporary relief, but soon lose their effect, and, as pain usually persists for months, surgical measures for its relief are frequently necessary. As the condition is encountered only in the lower limbs, cordotomy can be relied upon to give complete relief and often gives the patient a useful, pain-free limb.

In addition to these typical pains, patients may complain that their foot feels numb, is unduly sensitive to cold, and that the skin of the sole feels unduly thick or "cushioned".

Apart from gross muscle wasting, objective neurological disturbances are minimal ; absent or diminished ankle jerks, patches of hypaesthesia and hypalgesia, and on the sole the characteristic delayed, unpleasant and persisting response to pain and pressure stimuli are the features most commonly observed.

Diabetes Mellitus.—The importance of a vascular factor in the pathogenesis of diabetic neuropathy is a problem which has received considerable attention but cannot be said to be finally settled.

Collier (1932) described four types of diabetic "neuritis" : (1) an interstitial neuritis or fibrositis presenting as sciatica, lumbago, etc. ; (2) the rapid and painless onset of complete and irrecoverable paralysis of one or more large peripheral nerve trunks ; (3) paralyzes of oculomotor nerves ; and (4) a general peripheral neuritis. The second type he believed to be due to a thrombosis of the artery supplying the nerve trunk, and he suggested that similar vascular lesions might be one of the factors responsible for the fourth group.

The pathological studies of Woltman and Wilder (1929) on the peripheral nerves of diabetic patients revealed a high incidence of arteriosclerosis in the vasa nervorum.

Jordan (1936) found that 95.8% of 120 cases of diabetes with acute and severe neuropathy presented signs of peripheral vascular disease. While he suggested that the latter might be a causative factor in the production of the neuropathy, he was inclined to regard both conditions as the result of some common factor associated with the diabetes.

Randall (1938) studied the lipid composition of

* Throughout this review the term "ischaemic neuritis" is used to refer only to this painful type of neuropathy which occurs in occlusive vascular disease.

normal nerves and of nerves from cases of arteriosclerosis and diabetes mellitus. In the normal nerves the lipid constituents were the same in both proximal (femoral and sciatic) and distal (posterior tibial) nerves, but the nerves from both the arteriosclerotic and diabetic subjects were found to show a decrease in phospholipids, cholesterol, and cerebroside and an increase in neutral fat, and these chemical changes were more pronounced in the distal nerves. He attributed these changes to "an inadequate blood supply and the concomitant anoxaemia."

Kauvar (1941) reviewed the relation of arteriosclerosis to diabetic neuropathy of the lower extremities and divided his diabetic patients into three groups: (1) young, uncontrolled diabetics with peripheral neuritis but without evidence of vascular disease; (2) uncontrolled diabetics with neuritis and vascular disease; and (3) controlled diabetics with neuritis and generalized arteriosclerosis. The first group consisted of only two patients in whom the neuritis rapidly recovered when the diabetes was controlled. In the other two groups there was a definite correlation between the extent of the vascular disease and the neuropathy. In the discussion he pointed out that diabetic neuropathy seldom occurs in a patient below the age of 40 years, that it shows a marked predilection for the lower limbs, and that it is usually not related to the severity or degree of control of the diabetes. He therefore concluded that arteriosclerosis and the resultant ischaemia are major causes of diabetic neuropathy.

A similar view is expressed by Dry and Hines (1941) who postulate that a common mechanism, namely, involvement of the nutrient vessels, underlies the neuropathy, retinopathy, and intimal arteriosclerosis which occur in diabetes, and conclude that "diabetic neuritis is essentially an ischaemic neuritis and its genesis is dependent on interference with the vascular supply to the nerve bundles".

Rundles (1945), however, in a more extensive review in which the subject of diabetic neuropathy is considered from a more general viewpoint, does not agree that peripheral vascular disease and neuropathy are frequently associated; in 80% of his 125 cases of diabetic neuropathy there was no evidence of peripheral vascular disease. While he agrees that the two conditions may co-exist, he rejects the hypothesis that ischaemia is an important aetiological factor and ascribes the neuropathy to "the abnormal metabolism of chronically unregulated diabetes".

There is no doubt that a peripheral neuropathy can and does occur in diabetic patients who do

not have symptoms or signs of peripheral vascular disease. On the other hand, it is common for the elderly arteriosclerotic diabetic to develop a neuropathy which progresses with his vascular disease. This, however, as Treusch (1945) points out, is only one of several types of diabetic neuropathy. Even in cases where the presence of an ischaemic factor appears obvious, it is probably not the only one. Diabetics appear to develop neuropathy with less severe ischaemia than that necessary to cause nerve lesions in non-diabetics with either arteriosclerosis or thromboangiitis obliterans; ischaemic neuritis is seldom, if ever, seen in a woman who is not a diabetic.

Periarteritis Nodosa.—Considerable attention has recently been focused on this disease which is either becoming more common or is being diagnosed more frequently. Among the protean manifestations of periarteritis nodosa, peripheral neuritis is encountered with a frequency which is variously estimated to be between 12 and 52% of cases (Lovshin and Kernohan, 1948). The neuritis presents in one of two forms: either as a "mononeuritis multiplex", that is an involvement of several individual large nerve trunks either simultaneously or at varying intervals, or as a symmetrical peripheral neuritis.

When neuritis occurs it appears early in the course of the disease and often is the presenting complaint. The onset may be sudden or gradual; pain and paraesthesiae either alone or together are the most frequent initial symptoms and objectively muscular weakness is usually more pronounced than sensory changes.

Although clinical evidence of gross ischaemia of the limbs may be absent, histological studies of nerves from cases of periarteritis nodosa show clearly that the neuropathy is due to ischaemia (Kernohan and Woltman, 1938). Occlusion of nutrient arteries leads to focal areas of infarction in the nerves which result in degeneration of the nerve fibres in the more distal portions of the nerves. The alternative hypothesis that the neuropathy is due to the same mechanism, toxic or allergic, which causes the arterial lesions, is not supported by the histological findings.

Miscellaneous Causes.—There are a number of other conditions in which ischaemia may be partly responsible for the development of a peripheral neuropathy. In haemophilia lesions of the peripheral nerves are uncommon, and when they do occur are usually due to the direct pressure of a haematoma; the nerve most frequently affected appears to be the femoral (Aggeler and Lucia, 1944). Occasionally when haemorrhage beneath

the deep fascia occurs in a limb, there may be serious interference with the circulation and ischaemic lesions of the peripheral nerves may result; this was the sequence of events in the case reported by Lord (1926) and in the two cases observed by Seddon and quoted by Parkes (1945).

Fetterman and Spitler (1940) describe an ischaemic lesion of the sciatic nerve as the result of an accidental injection of bismuth into the inferior gluteal artery which was thought to have produced multiple emboli in the vasa nervorum. They also stress the role of vascular lesions in the pathogenesis of syphilitic neuritis and attribute to vascular changes in the nerves the pains and paraesthesiae which are experienced in the limbs by patients with poly-cythaemia vera.

Ischaemia is undoubtedly one of the factors responsible for the neuropathy observed in cases of trench foot, immersion foot, and allied syndromes, but the direct effect upon the nerves of the prolonged exposure to low temperature is equally important. Pressure upon nerves must be considered as a possible third factor in view of the gross swelling of affected extremities which occurs during the period of hyperaemia (Ungley, 1949).

In a recent article Bastos (1949) has suggested that in certain irritative nerve lesions, e.g., traumatic ulnar neuritis due to intermittent pressure upon the nerve in the ulnar groove, the nerve lesion may be responsible for initiating vasoconstrictor impulses which would affect the vasa nervorum distal to the site of the original lesion and thus cause a relative ischaemia of the nerve. He claims that in cases of this nature he has hastened recovery by adopting procedures which cause vasodilatation, e.g., sympathectomy.

Discussion

Peripheral nerves receive an abundant blood supply and the intraneural vascular anastomosis ensures that interference with any one source of supply is unlikely to cause serious interruption of the circulation to the nerve. This is confirmed by the difficulty which is encountered when any experimental attempt is made to produce histological evidence of ischaemic damage to nerve. On the other hand, physiological studies show that nerve fibres cease to conduct soon after their blood supply is cut off. From these observations, it may be concluded that nerves can survive with a blood supply which is much less than that which they require to function properly.

In man, when the circulation to a limb is arrested, a peripheral segmental motor and sensory paralysis develops. This can be shown to be due to ischaemia affecting the peripheral nerves. If the circulation

is restored within 30 to 40 minutes, rapid and complete recovery occurs and is followed by paraesthesiae and muscle fasciculation due to a temporary hyperexcitability of the previously ischaemic nerves.

It is not difficult to correlate the clinical findings with these anatomical and physiological observations. A sudden arterial occlusion in a previously healthy limb, as typified by arterial embolism, is associated with the onset of motor and sensory paralysis which begins distally and spreads up the limb but will recover rapidly if the circulation is restored within a few hours; moreover, patients invariably complain of intense paraesthesiae as "life" returns to the limb. On the other hand, if the blood supply to a limb is gradually reduced, evidence of interference with nerve function is seldom observed; the incidence of ischaemic neuritis in cases of occlusive vascular disease is low.

Pure ischaemia of this nature is apparently much less injurious to nerve than ischaemia produced by, or associated with, compression. Whereas nerves will recover rapidly after at least 12 hours of pure ischaemia, a persistent paralysis has resulted from as short a period as 20 minutes' ischaemia produced by constriction of a limb. It is difficult to account for this difference but two possibilities must be considered. (1) Pressure of itself is injurious to nerve fibres, and if sufficiently severe will produce a pressure necrosis of the nerve; this is the view of Allen (1938) and Spiegel and Lewin (1945). (2) Pressure damages the blood vessels in the constricted segment of nerve so that even when the pressure is relieved the circulation cannot be restored to that portion of nerve; this is supported by Roberts's experimental observation that a segment of nerve constricted by a tourniquet remained ischaemic after the pressure was released.

It seems to me that clinically it is possible to distinguish two types of "compression paralysis": (1) that due to constriction by a narrow band, e.g., a narrow rubber tourniquet in which direct pressure is the major factor and in which damage to nerve trunks depends upon the amount of pressure which each nerve receives, and (2) that due to compression over a considerable length of limb, e.g., pressure beneath the deep fascia following a fracture, in which ischaemia is the major factor and to which the nerves are susceptible in proportion to their dependence upon their blood supply so that the largest nerve trunks suffer most severely. Only the latter type is comparable to the experimental paralysis produced by compression of a limb with a sphygmomanometer cuff inflated to above systolic blood pressure.

The relationship between pain and ischaemic changes in the nerves is of interest. Pain is not an invariable accompaniment of acute arterial occlusion and when it occurs its quality and distribution do not suggest that it is neuritic in origin. Lewis (1936b) has clearly shown that the source of this pain is the ischaemic muscles of the limb. The pain is aggravated by activity of the muscles and is associated with acute tenderness of the muscles. The mechanism of production of the pain is assumed to be similar to that causing intermittent claudication—a pain-producing substance accumulating in the ischaemic muscle. The fibres which convey the sensation of pain must be amongst those most resistant to ischaemia for severe pain may be present, or can be produced by pressure, in the calf, in cases in which all modalities of cutaneous sensation are absent as high as the knee.

“In cases in which sudden arterial occlusion does not lead to gangrene, the symptoms due to sudden occlusion may merge imperceptibly into those of ischaemic neuritis, described by Goldsmith and Brown. The pains tend to be paroxysmal and severe and to cover large areas which do not correspond to any definite nerve distribution. They may persist for weeks or months” (McKechnie and Allen, 1936). This has not been my experience. If the limb has been previously healthy and survives the vascular catastrophe, even although there may be evidence of ischaemia of muscles, nerves, skin and subcutaneous tissue, pain is seldom a prominent feature. In a series of 34 patients with ischaemic paralysis following gunshot wounds of the arteries, only six complained of severe pain and the quality of the pain was unlike that of typical ischaemic neuritis (Richards, M.R.C. Report). In established cases of Volkmann's contracture with nerve lesions due to ischaemia pain is also rare (Holmes and others, 1944).

On the other hand, the most prominent feature of the ischaemic neuropathy which may occur in cases of occlusive vascular disease is severe pain, and objective evidence of loss of nerve function may be minimal. Furthermore, in such cases its onset is often related to an acute occlusion of a large proximal vessel in a limb in which mild symptoms of circulatory insufficiency have been present for some time.

The clinical evidence therefore seems to suggest that when a nerve is acutely deprived of its blood supply, even to the extent of causing infarction, pain may not be a prominent feature and seldom outlasts the acute stage, but, if the blood supply of a nerve is reduced either gradually or by a series of episodes none of which is sufficiently severe to

cause necrosis of the entire nerve, then the characteristic pains of ischaemic neuritis will appear.

The nature of the lesion in the nerve which is responsible for the pain is uncertain. Anyone who has seen many cases of causalgia and ischaemic neuritis must have been impressed by the similarity of the pain in the two conditions. The chief difference lies in the diffuse spread of the pain in ischaemic neuritis, but this may be explained by the fact that causalgia is essentially a mononeuritis whereas occlusive vascular disease affects all the nerves of the limb, often in a patchy manner, and causes multiple lesions. The mechanism of the artificial synapse has been invoked by Doupe, Cullen, and Chance (1944) to account for the pain of causalgia. Their view, which has met with considerable acceptance, is that as a result of either disease or injury, defective insulation occurs in the nerve trunk and thus impulses which are constantly passing down sympathetic fibres are able to stimulate afferent pain fibres. It seems not inconceivable that the pains of ischaemic neuritis are due to the presence of multiple artificial synapses in more than one nerve, which have been produced by the defective blood supply to the nerve trunks.

The diagnosis of ischaemic neuritis in cases of occlusive vascular disease is not difficult but the diagnosis of the other types of ischaemic neuropathy may be difficult. There is no typical clinical picture which can be relied upon so that, unless histological proof can be obtained, the diagnosis must be inferred from the presence of other signs suggesting a vascular disturbance in the limb. The difficulty is particularly great in cases of periarteritis nodosa which may present as a peripheral neuritis of either the multiple symmetrical or mononeuritic type. Therefore in neuritis of obscure origin, ischaemic neuropathy and periarteritis nodosa, especially, should be considered.

Summary

From the material presented in this review, it is apparent that there is ample physiological and clinical evidence to suggest the hypothesis that lesions of peripheral nerves can be due to vascular disorders. A short period of ischaemia produces a temporary disturbance of nerve function which, when the circulation is restored, recovers rapidly and completely. Severe or prolonged ischaemia causes structural changes in the nerves, and persistent or even permanent lesions result. In clinical practice ischaemic lesions of peripheral nerves are seen in cases of arterial embolism, after injuries to the limbs in which the peripheral circulation is interrupted either as a result of trauma to a main vessel or by pressure beneath the deep fascia

complicating a fracture, in tourniquet paralysis, in occlusive vascular disease, in diabetes mellitus, in periarteritis nodosa and, less commonly, in a few other diseases. In some of these conditions, e.g., arterial embolism or injury, the nerve lesions are due entirely to ischaemia; in others, e.g., tourniquet paralysis and diabetes mellitus, it is probable that other factors also play a part.

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