Biology and Disease of the Peripheral Nerves*

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When a physician makes a diagnosis of peripheral neuritis in a patient who has muscular paralysis associated with sensory loss he automatically thinks of the loss of function of peripheral axons, which are the long conducting processes of nerve cells situated in the spinal cord and dorsal root ganglia. He attempts to classify these on aetiological grounds. The pathologist, on the other hand, makes his report in terms of damage to axons and their myelin sheaths but can rarely comment on the causation. Ultimately both must appeal to the biochemist or the electrophysiologist for help. None of these scientists can give the whole answer, and our present ignorance about peripheral neuropathy is in some measure due to a failure to appreciate the fact that the peripheral axon is only one part of a complicated biological system.

It is not possible to do justice to all of these aspects in one lecture, but it is my purpose to draw attention to some neglected aspects of clinical biology and to signpost some of the roads ahead. More detailed accounts of some of the clinical and biochemical aspects of peripheral neuropathy have been published elsewhere (Simpson, 1962a, 1964).

Collation and classification of data have the pragmatic justification for the practising physician of providing associations of ideas which are helpful in sorting out a clinical problem. Classification by aetiology is the most obvious approach, but nobody will dispute that the thoughtful physician is also an experimental biologist. Though he may not design the experiment, by observing its course and influencing its outcome he may make valuable contributions to biological knowledge, and this is nowhere truer than in the "biochemical lesions."

Peripheral neuritis is badly named, since it is rarely inflammatory. "Neuropathy" is often a better term, and further clinical information is given by specifying it as polyneuropathy, mononeuropathy, mononeuritis multiplex, and so on. But we must not fall into the dermatological heresy of believing that a complicated descriptive terminology is sufficient for the classification of disease. The causes of neuropathy are legion and the diagnosis is not complete until the cause has been found. Unfortunately a first cause is determined in less than half the cases investigated by all modern means. This is a sad confession to make after a quarter of a century of effort by clinical biochemists in a field which illustrates the biochemical lesion *par excellence*.

Disorders of Carbohydrate Metabolism

It has been recognized for a long time that the nervous system depends almost entirely on carbohydrate for its source of energy and that it is very vulnerable to disturbances of its oxygen supply. It therefore seemed reasonable that disease would cause

neural failure by interference with its energy processes. An early success, based on a misinterpretation of experiments on the pigeon, appeared to confirm this when vitamin B₁ was shown to be an essential coenzyme for the oxidation of glucose beyond the pyruvate stage. The blood level of pyruvate is often raised in patients with neuropathy, especially while they are metabolizing a glucose load (Joiner *et al.*, 1950), yet this abnormality may be found in neuropathies of many types and a therapeutic reversal with thiamine is uncommon. Indeed, the practical value of vitamin B₁ in the treatment of neuropathy is questionable except where there is a clear dietary deficiency of it, and this is usually associated with deficiency of other food factors (Meiklejohn, 1940; Spillane, 1947). There can be few comparable examples of uncritical acceptance of the results of irrelevant animal experiments despite the cumulative experience of half a century of human therapeutics, yet vitamin B₁ is still a best seller.

Disorders of Protein Metabolism

There are many other enzyme systems in the intermediary metabolism of the neurone which can be affected by disease or poisoning (Simpson, 1964). The most neglected aspect concerns the metabolism of structural and enzyme proteins, and so I will use this to illustrate my theme, which is a consideration of the neuropathies as natural experiments on the biology of the peripheral nerves. Contrary to previous opinion, the nerve cell has a high turnover of protein and lipid, and it is probable that quantitative or qualitative differences in the composition of these reflect the existence of a biochemical specificity in the nerve cells (Hydén, 1960). The differential susceptibility of different types of peripheral nerve fibres to disease may very well depend on this.

Most of the active production of protein takes place in the cell body, and a stream of protoplasm is pumped centrifugally to the tip of the axon (Weiss and Hiscoe, 1948). For this reason the effects of metabolic failure are first seen at the end of the stream. This explains the "dying back" of the axon described by the pathologist and the peripheral weakness and "glove-and-stocking" anaesthesia familiar to the clinician. But it should be noted that the metabolic failure is in the cell body, so that a firm distinction between peripheral neuropathy and cellular atrophy cannot be made.

Some enzymatic processes are regulated by mitochondria throughout the neurone, but it is probable that the main protein metabolism is regulated in or near the nucleus. Since this mechanism is utilized by a virus proliferating at the expense of the cell, it follows that a virus infection of a peripheral neurone will be polioclastic even if the virus gains entry to the cell in some distant part. Poliomyelitis and herpes zoster are the type infections of the lower motor neurone and first-order sensory neurones respectively. There is no evidence that a virus peripheral neuritis can occur, though it is possible that Schwann cells could be infected.

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There is, however, a clear clinical association between many virus infections and polyneuritis, but the latter usually occurs with a characteristic delay, suggesting that it is due to an allergic reaction rather than to a direct attack by the virus (Haymaker and Kernohan, 1949 ; Miller *et al.*, 1956). The primary infection may even be in the nervous system as in post-herpetic paralysis (Knox *et al.*, 1961). These cases are indistinguishable from the apparently spontaneous cases of the Landry-Guillain-Barré syndrome. It seems undesirable to perpetuate the term "acute infective polyneuritis," since there is no evidence for an infective origin in the usual sense. On the other hand, there are close clinical and pathological resemblances with the more restricted neuropathies which usually involve the shoulder-girdle and which may follow serum therapy or inoculation of vaccines and other protein substances (Parsonage and Turner, 1948). These types may be associated with symptoms of anaphylaxis and support the hypothesis of an allergic causation. Very strong support comes from the experimental production by Waksman and Adams (1955, 1956) of peripheral neuropathy in rodents by injection of peripheral nerve tissue along with Freund's adjuvant.

Haymaker and Kernohan (1949) drew attention to the frequency of disorders of the reticulo-endothelial system in the Landry-Guillain-Barré syndrome. One disease which is particularly commonly associated with it is infectious mononucleosis. Sarcoidosis is another disorder of the reticulo-endothelial system with altered immunological reactions. It is usually associated with localized neuropathies of cranial or peripheral nerves, but peripheral neuropathy may occur (Jefferson, 1957). In the past five years there have been several reports of polyneuropathy complicating various reticuloses such as Hodgkin's disease, follicular reticulosis, reticulosarcoma, lymphosarcoma, and myelomatosis (Hutchinson *et al.*, 1958 ; Victor *et al.*, 1958). I have at present under my care a patient with Guillain-Barré syndrome complicating polycythaemia vera which appears to be of similar type.

In some cases the neuropathy of reticulosis may be explained by infiltration of nerve roots, but this is not always demonstrable and it may precede other manifestations of reticulosis. The common factor may be a disturbance of protein metabolism (Simpson, 1962a). Abnormal proteins are found in the blood, such as myeloma globulins, cryoglobulins, and macroglobulins. Some related proteins are normal blood constituents which play a part in immunity reactions. They are probably elaborated by lymphocytes and plasma cells. Similar "para-proteinaemia" (abnormal proteins) or "dysproteinaemia" (quantitative alteration in normal serum components) occurs in the neoplastic diseases, in the collagen group of disorders, in chronic infections, and in hepatic cirrhosis, all of which may be associated with polyneuropathy. At least two rare para-proteinaemias which may accompany polyneuropathy are probably inborn errors of protein metabolism. These are the primary macroglobulinaemia of Waldenström (Garcin *et al.*, 1958 ; Logothetis *et al.*, 1960) and primary amyloidosis (Andrade, 1952 ; Chambers *et al.*, 1958).

These examples make it quite clear that there is an intimate relation between disorders of plasma proteins and neuropathy (Table I), but the mechanisms involved are unknown. In the "allergic" group and in the reticuloses the characteristic pathological lesion is a patchy demyelination with less severe axonal damage, but these may be secondary to interstitial oedema (Haymaker and Kernohan, 1949). In amyloid neuropathy the nerve fibres appear to be kinked by nodules of amyloid material deposited irregularly in and around nerves, sympathetic ganglia, and posterior root ganglia. The deposit of amyloid may be sufficient to cause visible thickening of some of the affected nerves. Extrinsic nerve compression in the carpal tunnel and other sites is also found. Nevertheless the remarkably consistent development of the clinical syndrome of primary amyloidosis with selective involvement of small sensory fibres makes it unlikely that purely mechanical effects can account for the whole picture, and the possibility of a parenchymatous neuropathy is not excluded. The symmetrical peripheral type is certainly difficult to account for unless the axon is involved.

Similar changes found in other genetically determined neuropathies, peroneal muscular atrophy, and hypertrophic polyneuropathy suggest that there is an inborn error of protein metabolism in one or other part of the nerve complex. The most prominent pathological changes are also interstitial in these types, but the centripetal spread of paralysis or of glove-and-stocking anaesthesia suggests the dying-back of neurones owing to metabolic failure. In the peroneal muscular atrophy of Charcot-Marie-Tooth this is the most striking feature of the clinical picture, leading to the well-known hock- and champagne-bottle contours of the lower limbs as muscle fibres waste according to their distance from the spinal cord rather than in the distribution of any particular nerves. Atrophic changes are found in the ganglion cells of both the anterior horns and the dorsal roots, but the most constant pathological finding is an excess of interstitial connective tissue in medium and fine branches with some loss of the larger fibres (Greenfield *et al.*, 1958).

In hypertrophic interstitial neuropathy of Dejerine and Sottas, a closely related disorder, the interstitial tissue is so excessive that the nerves appear to be hypertrophied. The concentric "onion bulb" lamellae sometimes consist of a mucopolysaccharide substance with metachromatic staining reactions termed "mucoid" by Krücke (1939). He believed it to be due to serous permeation and oedema caused by an increased permeability of the vasa nervorum. Austin (1956), on the other hand, thought that the primary disorder is in the Schwann cells, which, according to his hypothesis, proliferate and produce the mucopolysaccharide interstitial tissue which causes further enlargement of nerves. If Krücke is right the relation with amyloidosis and other secondary types of nerve hypertrophy is obvious. Whatever the truth regarding this extraneuronal protein infiltration, it is clear that the neurological manifestations cannot be due to axonal compression alone, since the neuropathy is usually symmetrically distributed and

TABLE I.—Some Causes of Polyneuropathy. A common Factor May be a Disturbance of Protein Metabolism

Genetic	Reticulo-Endothelial	Collagenoses	Allergic
Peroneal muscular atrophy Sensory radicular neuropathy Hypertrophic interstitial neuropathy Reifsum's syndrome		Auto-immunity	
	Primary amyloidosis Primary macroglobulinaemia Cirrhosis hepatis Inf. mononucleosis Reticulosis Myelomatosis	Sarcoidosis	
	(Carcinoma)	Periarteritis nodosa Systemic lupus erythematosus Thrombotic microangiopathy Rheumatoid arthritis	
			Acute infective polyneuritis Serum neuritis Experimental neuritis
		Para and dysproteinaemias	

palpable enlargement of nerves may be a late development or may never occur.

Both of these congenital types of neuropathy may be associated with involvement of the central nervous system, and they are probably related to the hereditary ataxias and to neurofibromatosis. A particular variety of hypertrophic neuropathy termed "heredopathia atactica polyneuritiformis" by Refsum (1946) is associated with cerebellar signs, atypical retinitis pigmentosa, ichthyosis, and various congenital anomalies of the skeleton and heart. It is inherited as a Mendelian recessive, so it is very rare. Another rare familial neuropathy in which only sensory fibres are affected is hereditary sensory radicular neuropathy, which causes loss of pain and temperature sensation in the feet with consequent mutilating ulcers. Denny-Brown (1951) found that there was primary degeneration of dorsal root ganglia and their axons. The most severely affected ganglia had deposits of hyaline material which showed some of the staining reactions of amyloid, but this is not a constant finding. The disease appears to be related to peroneal muscular atrophy, and again there is the suggestion of an inborn error of metabolism involving axonal and perineurial proteins.

Now I would like to retrace my steps to the so-called "acute infective polyneuritis," which we have seen may be the result of an allergic reaction. In recent years there has been increasing recognition of the occurrence of peripheral neuropathy in disorders of connective tissue such as periarteritis nodosa and, less commonly, systemic lupus erythematosus, rheumatoid arthritis, and other so-called "collagen diseases." Hart and Golding (1960) drew attention to the fact that rheumatoid arthritis associated with neuropathy is usually of "complicated" type with a high level of abnormal globulins in the serum. The neuropathies are generally assumed to be due to arteritis of the vasa nervorum (Miller and Daley, 1946). This is certainly true in many instances, particularly in periarteritis nodosa, where mononeuritis or mononeuritis multiplex is characteristic, and I have seen two cases of rheumatoid neuropathy associated with erythema reticulata, which is believed to be due to arteritis. There may also be a parenchymatous factor, as symmetrical sensorimotor polyneuropathy is also encountered in rheumatoid disease, and it may be that a hypersensitivity mechanism involves the nerves as well as other tissues.

The fashionable interpretation of a hypersensitivity lesion is that the reticulo-endothelial system forms free or cell-borne proteins which attach themselves to tissues wrongly recognized as "foreign," leading to their destruction by some ill-understood inflammatory reaction. It is difficult to account for the change in the tissue which makes it assume antigenic properties and equally difficult to explain why it ever stops. An alternative hypothesis could be that the reticulo-endothelial system or mesenchymal cells produce abnormal proteins which may function as "antibodies" or be deposited as "fibrinoid," "haematotoxilin bodies," "amyloid," and so on (Teilum, 1948; Simpson, 1962a). Waldenström (1961) suggested that some people have a genetically determined ability to form certain gamma-globulins too easily, perhaps because they lack an inhibitor substance.

Disorders of Intermediary Metabolism

We must now take stock of the position we have reached. We have seen that many disturbances of protein metabolism may affect the complex of neurone, Schwann cells, and interstitial substance of peripheral nerves. Some of these changes are acquired as the result of a wide range of diseases. Others are genetically determined. The mode of inheritance may vary, and this may correlate with the rate of progression of the disorder. Central neurones may or may not be affected. These observations may serve as a warning that a common end-result does not necessarily indicate identity of metabolic defect. A metabolic chain may be abnormal at various places and similar

end-results will occur. It does not matter what causes the chain to be broken or diverted. An enzyme may be missing or defective because it is wrongly specified in the genes, or a coenzyme, or necessary substrate, may be missing from the diet. The chain may be arrested or diverted by a chemical substance which is then called toxic, or the unknown causes of "degeneration" may arrest it prematurely.

These are the elementary concepts of a "biochemical lesion" and they are well exemplified by peripheral neuropathy. I have spent some time exploring some aspects of protein metabolism, which I believe has been neglected in diseases of the peripheral nerves in favour of the more obviously vulnerable energy mechanisms. Time does not permit me to go into details of the many remaining causes of neuropathy, some of which I have discussed elsewhere (Simpson, 1962a, 1964), but a diagrammatic summary of some of these from the biochemical point of view may be helpful.

We know remarkably little about the neuropathies that are associated with metabolic disturbances in the body as a whole. These are often genetic in origin or associated with a disorder of the endocrine system (Table II). Our knowledge of the proximate biochemical disorders is too limited to make it profitable to break down the classification any further, especially since some enzymatic reactions are common to the metabolism of carbohydrate, protein, and fat. Pyridoxine, for instance, is involved in energy metabolism but is also an important catalyst of transamination in the formation of amino-acids. Pantothenic acid, as well as playing a part in glucose metabolism, is involved in the formation of acetylcholine. I have, however, picked out one aspect of intermediary metabolism, the pyrroles used in cytochrome systems.

TABLE II.—*Some Genetically Determined Neuropathies Involving Carbohydrate, Fat, or Intermediary Metabolism Directly or by Endocrine Disorder*

	Genetic or Endocrine
Carbohydrate	Diabetes mellitus, hyperinsulinism
Fat	Sulphatide lipidosis
Pyrrole	Acute intermittent porphyria
Other intermediary ..	Myxoedema

Acute intermittent porphyria is associated with a derangement of pyrrole metabolism in the liver (Goldberg, 1959). The monopyrrolic substances which are excreted in the urine are not toxic in themselves, and overproduction of them may be associated with failure to form a substance which is essential for the nutrition of myelin. Cyanocobalamin is a tetrapyrrole, and when it is lacking from the body demyelination of certain neurones occurs, including peripheral nerve fibres. The role of the liver in preparing substances for utilization by the nerve cells and satellite cells of the central and peripheral nervous system should be noted, and it has been suggested that liver function may be abnormal in diabetes. The liver doubtless plays an essential part in many aspects of the intermediary metabolism of the nervous system, and this point should be kept in mind when considering biochemical lesions.

Neuropathy as a Clue to the Metabolism of Peripheral Nerves

The exact defect may be difficult to isolate in the inborn errors of metabolism and still more in disorders such as diabetes mellitus, where many abnormalities are found. In fact, there may be different biochemical or vascular "causes" for the several different types of neuropathy which can be distinguished in diabetic patients (Simpson, 1962a). Valuable clues to the metabolism of peripheral neurones as a whole, and to the biochemical specificity of the different types of neurone, may be obtained from a study of neuropathies due to nutritional deficiency or to toxic causes. Neuropathy associated with malabsorption does not, in my experience, respond to parenteral administration of the known vitamins, and I feel that there may

be some essential food factors which remain to be identified. The relation of neuropathy with steatorrhoea without gross intestinal hurry and with hypocalcaemia suggests that a substance which is fat-soluble may be involved.

Some of the "toxic" neuropathies can already be explained in terms of competition with or destruction of known vitamins (Tables III and IV), and it is possible that others, such as alcohol and heavy metals, may act in this way in the citric-acid cycle (Peters *et al.*, 1946). Lead neuropathy resembles porphyria clinically and biochemically. It is for this reason that other toxic neuropathies require the most careful study because they provide the natural experiments which may map out the biochemical mechanisms of peripheral nerves, since the chemist can often define with some accuracy the locus of action of a pure toxic substance. Diphtheritic toxin, for instance, probably acts on the cytochrome system. Unfortunately the most obvious lesion is not necessarily responsible for the neuropathy. Tri-orthocresyl phosphate, the substance responsible for "jake paralysis" and the recent tragic outbreak of polyneuropathy in Morocco, is a powerful antagonist of some cholinesterases, but it seems probable that neuropathy is due to some other enzymatic disturbance (Cavanagh, 1954).

TABLE III.—*Neuropathies Associated with Lack of Vitamins from Dietary Deficiency, Malabsorption, Antivitamins, or Utilization by Organisms*

	Deficiency	Malabsorption	Competition
Carbohydrate	Thiamine	+	Bracken. ? Bush teas
	Pantothenic acid	+	
Pyrrole	Nicotinamide	+	Isoniazid
Other intermediary	Cyanocobalamin	+	Diphyllobothrium, etc.
	Pyridoxine	?	Isoniazid

TABLE IV.—*Some Toxic Neuropathies Not Associated With Conditioned Avitaminosis*

	Toxic
Carbohydrate	Alcohol, arsenic, mercury, thallium, etc.
Pyrrole	Lead
Other intermediary	Diphtheria and other bacterial toxins, aryl phosphates, Rentokil, carbon monoxide, carbon disulphide, thalidomide, Furadantin (nitrofurantoin), chronic uraemia

Clinical observation of toxic neuropathy may also throw some light on the kinetics of biochemical processes within the body. An obvious example is the long latent period of vitamin-B₁₂ neuropathy. In organophosphorus poisoning the latency is two weeks. Diphtheritic neuritis develops three to four weeks after the onset of the illness. Thalidomide may need several months of ingestion. The latter is particularly mysterious, since, in my experience, the sensory neuropathy may continue to progress at a very low rate for at least three years after the withdrawal of the drug, or the first evidence of neuropathy may appear after the drug has been stopped. This must surely be almost unique in toxicology. There may be an even longer latent period in the neuropathy which has recently been described in patients with chronic uraemia (Asbury *et al.*, 1963). The longer survival now common with the introduction of haemodialysis may make this more common. I have personally examined two cases in which the severe pain, restless legs, and minimal peripheral weakness suggested the possibility of a deficiency of pantothenic acid. Another possible mechanism in both of these patients was ischaemia, since there was gross calcification of arteries in the limbs. At this point I should discuss the role of ischaemia in neuropathy. It is undoubtedly important, though, I feel, too often accepted as an adequate explanation. I want instead to turn to another part of my theme.

Peripheral Nerve as a Biological Complex

The nerve cell and its axonal process is the most important part of the peripheral nerve, but it depends for its nutrition and normal function on satellite cells and on other organs.

Every peripheral axon is closely wrapped in a Schwann-cell layer. Around the larger fibres the Schwann cell is wrapped spirally and myelin is formed between its layers. Myelin forms an effective barrier to the passage of electrolytes and hence of electrical current out of the axon process except at the nodes of Ranvier. This has the purposes of insulation and of acceleration of conduction velocity by the mechanism of saltatory conduction, a device which is most economical of energy. The myelin is believed to be laid down by Schwann cells. Segmental demyelination, such as occurs in poisoning by lead and diphtheria toxin, is possibly due to a primary lesion of Schwann cells.

It is almost certain that the neurone also contributes to the maintenance of the myelin (Brante, 1952). This is well seen in Wallerian degeneration when the axon is severed or dies back. The myelin sheath degenerates despite active proliferation of Schwann cells. It is less well known that the Schwann cell, which is the site of a high energy turnover, probably contributes to the maintenance of the axon itself. The Schwann-cell layer is continuous over the nodes of Ranvier of myelinated fibres and infolds the whole length of the thin C fibres. What is its function? It has recently become increasingly apparent that the satellite cells of the central nervous system, the glia, play an important part in the metabolism of the neurone, possibly intermediate between the blood-stream and the nerve cells, and possibly constituting the blood-brain barrier. Echmitt (1958) suggests that satellite cells of peripheral nerves have been developed to maintain regions of the nerve cell remote from its metabolic centre in the nucleus, possibly a highly important step in evolution to allow rapid communication over relatively large distances in multicellular organisms. In addition to providing local metabolic energy they may provide the particular type of energy-coupling necessary for ion pumping.

It is interesting to note the recent suggestion that there is also a blood-nerve barrier which may determine the distribution of toxic neuropathies such as diphtheritic polyneuritis and even the Guillain-Barré syndrome (Fisher and Adams, 1956). There is therefore a mutual interdependence between axon and Schwann cells, and it may be that the ground-substance of the peripheral nerve is involved in the interchange of protein and fluid with the Schwann cell as intermediary. There is also an increasing amount of evidence that the peripheral neurone, in addition to having a trophic function on muscle (Miledi, 1960), may depend in some measure on a factor derived from muscle (Aitken, 1949). I have already drawn attention to the possible role of the liver and the reticulo-endothelial system.

Primary Axonal Failure

Because of this symbiosis it is not possible in the present state of knowledge to localize the various biochemical disorders, and I have not attempted to do so, but I hope that in time this will be possible. Meanwhile it is important to bear in mind the vital difference between primary axonal failure and primary demyelination. If neurone metabolism is not primarily disrupted a striking feature is the rapid and vigorous regeneration which occurs. Fine fibres sprout from the central end of a severed nerve fibre or from some of the nodes of the partially demyelinated nerve. The nerve-ending at the motor end-plate of skeletal muscle becomes bubble-shaped as an early response to neuronal damage, but within a few days it too gives rise to sprouts, which can be identified by supravital staining of biopsy specimens (Coërs and Woolf, 1959). It is possible that a chemotactic stimulus from denervated muscle or sensory endings is necessary for this branching.

Wohlfart (1958) showed that if some motor fibres are spared by peripheral nerve disease they tend to produce sprouts which reinnervate many of the denervated muscle fibres. This collateral sprouting gives rise to giant motor units which can be recognized functionally by their electromyographic picture.

Small polyphasic units on electromyographic examination probably indicate regenerating units from local or collateral sprouting. These appearances are common to the electromyographic picture of most cases of peripheral neuropathy. They are, however, much less frequent in the records of patients with Charcot-Marie-Tooth neuropathy (Amick and Lemmi, 1963). I have seen only two cases of hypertrophic neuropathy and three of a rare recurrent polyneuropathy of unknown cause which may be related to it (Nattrass, 1921; Austin, 1958). In each case the electromyograph of voluntary effort was characterized by a fall-out of motor units, with normal surviving units showing no evidence of regeneration. I do not have sufficient evidence to be certain, and particularly regret that I am unable to obtain nerve-ending biopsies for correlation, but it seems possible that this is electromyographic evidence of defective regeneration and hence of primary dystrophy of the axon.

Further evidence on the state of the axon process may be found by another electromyographic method. When a normal motor nerve is maximally stimulated at a rate of 30–60 stimuli per second, no evidence of transmission failure can be detected in the first half-minute. In occasional cases of lower-motor-neurone disease an early “myasthenic” decrement of the muscle response is seen, though the nerve action potential remains unchanged (Simpson, 1962b). The precursor of acetylcholine responsible for neuromuscular transmission is believed to be formed in the anterior horn cell and pumped peripherally with the axoplasmic stream, so it seems likely that this rare finding is evidence of incipient neuronal failure. A further interesting point is that there may be an absence of facilitated acetylcholine release such as often temporarily restores transmission in true myasthenia gravis. Absence of this feature is best seen in botulism and may be evidence of damage to the nerve terminals. The rarity of these signs of neuronal failure suggests that regeneration is the rule.

Primary Damage of Myelination

Where the primary lesion is in the Schwann cells and nerve sheaths there is often striking slowing of the conduction velocity of motor-nerve fibres. It might seem reasonable that this should be so, but, in fact, when I first reported the presence of slowing of peripheral nerve conduction it was in compressive lesions such as the carpal-tunnel syndrome (Simpson, 1956). At that time the few patients I was able to examine with polyneuropathy showed no abnormality of conduction. Henriksen (1956) independently confirmed the carpal-tunnel findings but also found slowing in late cases of polyneuritis, and this has been my subsequent experience. It seems to me that the important finding is the negative one. It is possible to have severe paralysis of voluntary movement, yet the conduction velocity of the fastest motor-nerve fibres may be within normal limits until there is more than 80% reduction in the number of muscle fibres innervated. I have investigated a number of neuropathies due to metabolic disorders and found that conduction velocity was slowed only if abnormality of myelin was likely to be present (Simpson, 1962c). Myxoedema, for instance, does not normally cause significant slowing of nerve conduction, though local median-nerve compression in the carpal tunnel is common (Murray and Simpson, 1958).

Rather surprisingly, conduction velocity may be normal in severe porphyric polyneuritis (Simpson, 1962c). It seems likely that the velocity of conduction is not affected until the myelin of many segments of nerve is damaged and the mechanism of saltatory conduction abolished. The converse is of course equally true. In neuropathies involving both myelin and axon, clinical recovery may be considerable while conduction velocity remains slow. I have seen a few patients who have presented clinically as cases of entrapment or compression mononeuropathy in whom electrical studies showed marked slowing of

other peripheral nerves, and this has also been the experience of Thage *et al.* (1962). It appears that muscle innervation remains effective until some secondary factor such as comparatively slight pressure is added. The “all or none” law of muscle innervation is not concerned with temporal factors. Power depends on the number of motor units available, with the modifying factor of active regeneration. Conduction velocity depends on whether these fibres are properly myelinated or not. Electromyography combined with new biopsy techniques has led us to the threshold of a possibility of differentiating the roles of the various elements of the biological complex which is a peripheral nerve. But the problem of peripheral neuropathy is fundamentally biochemical, and, alas, the promise of a quarter of a century still awaits fulfilment.

Summary

A peripheral nerve is a biological complex of nerve axons, myelin, Schwann cells, and interstitial fluid forming a micro-environment bounded by sheaths. Myelin plays an essential part in conduction in the larger fibres. It is laid down and maintained by Schwann cells with an essential contribution from the neurone. The axon is a tube of cytoplasm maintained mainly by the neurone, but the Schwann cells may contribute to its maintenance peripherally and act as a blood-nerve barrier determining the site of action of some toxic substances. Additional extraneural mechanisms for supplying protein are postulated.

The complex system makes it impossible at present to define the primary lesion in many neuropathies which may be regarded as biochemical disorders. Attention is drawn to some disturbances of protein metabolism as a possible factor common to many neuropathies. Toxic neuropathies are valuable clues to the biochemistry of the nerve.

Classification of neuropathies as being due to primary axonal failure or primary damage of myelin is tentatively suggested by electromyographic criteria.

REFERENCES

- Aitken, J. T. (1949). *J. Anat.*, **83**, 32.
- Amick, L. D., and Lemmi, H. (1963). *Arch. Neurol. (Chic.)*, **9**, 273.
- Andrade, C. (1952). *Brain*, **75**, 408.
- Asbury, A. K., Victor, M., and Adams, R. D. (1963). *Arch. Neurol. (Chic.)*, **8**, 413.
- Austin, J. H. (1956). *Medicine (Baltimore)*, **35**, 187.
- (1958). *Brain*, **81**, 157.
- Brante, G. (1952). *Proceedings 1st International Congress of Neuro-pathology*, **3**, 119.
- Cavanagh, J. B. (1954). *J. Neurol. Neurosurg. Psychiat.*, **17**, 163.
- Chambers, R. A., Medd, W. E., and Spencer, H. (1958). *Quart. J. Med.*, **27**, 207.
- Coërs, C., and Woolf, A. L. (1959). *The Innervation of Muscle: A Biopsy Study*. Blackwell, Oxford.
- Denny-Brown, D. (1951). *J. Neurol. Neurosurg. Psychiat.*, **14**, 237.
- Fisher, C. M., and Adams, R. D. (1956). *J. Neuropath. exp. Neurol.*, **15**, 243.
- Garcin, R., Mallarmé, J., and Rondot, P. (1958). *Bull. Soc. méd. Hôp. Paris*, **74**, 562.
- Goldberg, A. (1959). *Quart. J. Med.*, **28**, 183.
- Greenfield, J. G., *et al.* (1958). *Neuropathology*, Chapt. 12. Arnold, London.
- Hart, F. D., and Golding, J. R. (1960). *Brit. med. J.*, **1**, 1594.
- Haymaker, W., and Kernohan, J. W. (1949). *Medicine (Baltimore)*, **28**, 59.
- Henriksen, J. D. (1956). Thesis M.S., Univ. Minnesota, Minneapolis.
- Hutchinson, E. C., Leonard, B. J., Maudsley, C., and Yates, P. O. (1958). *Brain*, **81**, 75.
- Hydén, H. (1960). In *The Cell*, edited by J. Brachet and A. E. Mirsky. vol. IV, Chapt. 5. Academic Press, New York.
- Jefferson, M. (1957). In *Modern Trends in Neurology*, Chapt. 16, 2nd series. Butterworths, London.
- Joiner, C. L., McArdle, B., and Thompson, R. H. S. (1950). *Brain*, **73**, 431.
- Knox, J. D. E., Levy, R., and Simpson, J. A. (1961). *J. Neurol. Neurosurg. Psychiat.*, **24**, 167.
- Krücke, W. (1939). *Virchows Arch. path. Anat.*, **304**, 442.
- Logothetis, J., Silverstein, P., and Coe, J. (1960). *Arch. Neurol. (Chic.)*, **3**, 564.
- Meiklejohn, A. P. (1940). *New Engl. J. Med.*, **223**, 265.

- Miledi, R. (1960). *J. Physiol. (Lond.)*, **154**, 190.
 Miller, H. G., and Daley, R. (1946). *Quart. J. Med.*, **15**, 255.
 — Stanton, J. B., and Gibbons, J. L. (1956). *Ibid.*, **25**, 427.
 Murray, I. P. C., and Simpson, J. A. (1958). *Lancet*, **1**, 1360.
 Nattrass, F. J. (1921). *J. Neurol. Psychopath.*, **2**, 159.
 Parsonage, M. J., and Turner, J. W. A. (1948). *Lancet*, **1**, 973.
 Peters, R. A., Sinclair, H. M., and Thompson, R. H. S. (1946). *Biochem. J.*, **40**, 576.
 Refsum, S. (1946). *Heredopathia atactica polyneuritiformis*. Tanum, Oslo.
 Schmitt, F. O. (1958). *Exp. Cell Res.*, Suppl., **5**, 33.
 Simpson, J. A. (1956). *J. Neurol. Neurosurg. Psychiat.*, **19**, 275.
 — (1962a). In *Modern Trends in Neurology*, edited by D. Williams, Chapt. 14, 3rd series. Butterworths, London.
 — (1962b). *Dev. Med. Child Neurol.*, **4**, 55.
 — (1962c). In *Progress in Electromyography*, edited by P. Pinelli, p. 36. Elsevier, Amsterdam.
 — (1964). *Biochem. Clin.* In press.
 Spillane, J. D. (1947). *Nutritional Disorders of the Nervous System*. Livingstone, Edinburgh.
 Teilum, G. (1948). *Amer. J. Path.*, **24**, 389.
 Thage, O., Trojaborg, W., and Buchthal, F. (1962). *Dan. med. Bull.*, **9**, 26.
 Victor, M., Banker, B. Q., and Adams, R. D. (1958). *J. Neurol. Neurosurg. Psychiat.*, **21**, 73.
 Waksman, B. H., and Adams, R. D. (1955). *J. exp. Med.*, **102**, 213.
 — (1956). *J. Neuropath. exp. Neurol.*, **15**, 293.
 Waldenström, J. (1961). *Harvey Lect.*, **56**, 211.
 Weiss, P., and Hiscoe, H. B. (1948). *J. exp. Zool.*, **107**, 315.
 Wohlfart, G. (1958). *Neurology (Minneapolis)*, **8**, 175.

Clinical and Radiological Results of Repair of Hiatus Hernia

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There is a wide divergence of views among both surgeons and physicians about the indications for and the results of surgical repair of hiatus hernia. Some surgeons claim a high percentage of cures, while others have been so disappointed with a repair operation that they have given it up in favour of partial gastrectomy and vagotomy (Wells and Johnston, 1955). There are, too, a number of conflicting views about the best technique for the repair, each view based upon a different conception of what is the precise mechanism responsible for preventing gastro-oesophageal reflux. An additional complication is introduced by the concept that the corrosive quality of the refluxed material can be reduced by partial gastrectomy or by vagotomy, and its quantity reduced by drainage.

Some of the difficulties encountered in trying to compare the results in one series of patients with those in another can be resolved by defining more precisely the standard of reference. For example, the radiologist may feel that a particular method of repair of the hernia is a poor one because of the high incidence of radiologically demonstrable hernia or reflux after operation; and the incidence that he finds will depend very much on his particular examination technique. The surgeon, already discouraged by what his radiological colleague reports, may be further discouraged when his patient admits to persisting, if less severe, symptoms of reflux. In the surgeon's view the operation has been an anatomical and functional failure.

We therefore attempted to assess the results of surgical repair from three aspects: (1) what the patient thought of the overall result, and of the effect of the operation on each symptom; (2) what the radiological appearances were; and (3) how far the patient's opinion of the overall result correlated with the operative procedure.

All the patients were under the care of and referred for surgery by two physicians specializing in gastro-enterology (Drs. F. Avery Jones and T. D. Kellock), whose policy has been to persevere with medical treatment and the successive trial of a variety of therapeutic measures unless very strong indications for surgery have been present. The patients had been selected for surgery, therefore, according to clearly defined criteria. The

small number of patients in this series is merely a reflection of the reluctance to advise surgery except for patients with intractable symptoms. Out of a total of 894 new hiatus hernias diagnosed in the hospital's radiology department between January 1952 and January 1963 only 5–6% were operated upon. All the operations in this series were performed by one surgeon (Mr. J. W. P. Gummer), but the follow-up was carried out by three general physicians who had never seen the patients before.

The purpose of this paper is (1) to draw attention to those symptoms which are likely to be usefully reduced in severity by repair of a hiatus hernia, and to those which are not; and (2) to emphasize that a large proportion of the patients were pleased with both the immediate and the long-term results, despite the fact that the majority still had radiological evidence of hernia or reflux, or both, and many still had mild symptoms.

Patients and Methods

An attempt was made to interview and examine radiologically all patients operated upon by one surgeon (Mr. J. W. P. Gummer) between January 1952 and January 1963. Most of them came from the local community, but some had been referred from various parts of Britain and overseas and had been investigated radiologically elsewhere. Patients who had been operated on for strictures were not included in the present series.

There were 63 patients (17 males, 46 females) who had been operated on for 60 sliding and 3 para-oesophageal hernias (diagnosis made at operation). Five patients had been followed up in the department until death, nine had been lost to follow-up after a variable period, and 12 others were unable to attend for interview but answered a detailed questionnaire by post. The remaining 37 were interviewed and examined by us. Table I shows the age distribution at the time of operation of those interviewed and of the whole series. Table II shows the number of patients operated upon each year, and Table III the length

TABLE I.—Age at Operation of Patients Personally Examined and of Whole Series

Age:	20–	30–	40–	50–	60–	70–
Whole series	2	7	11	20	19	4
Personally examined ..	2	3	8	12	10	2

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