Section of Neurology

President—Professor P. C. P. CLOAKE, M.D., F.R.C.P.

[*April* 3, 1952]

DISCUSSION: RECENT WORK ON THE PERIPHERAL NEUROPATHIES

Dr. J. St.C. Elkington: The phrase "peripheral neuropathy" is a comparatively recent recruit to medical literature. It may be said to comprise that group of disorders previously referred to as "peripheral neuritis", "polyneuritis", "multiple neuritis", or "symmetrical peripheral neuritis" on the one hand and the different varieties of "neuritis" of individual peripheral nerves on the other. The phrase has certain advantages. In addition to providing a convenient common name for these two groups of conditions, it has the advantage of avoiding the suggestion that they are inflammatory in nature for we now know that the majority of them are not. To define the term "recent" is more difficult, particularly in a subject where the growth of knowledge has been continuous for many years but it has seemed to me that a period of thirty years would be a convenient one, as this covers the era of modern biochemistry as applied to clinical medicine and of the growth of our knowledge of vitamins.

Sir William Gowers (1892) was much in advance of his time. He drew a clear distinction between "multiple neuritis", or "polyneuritis" on the one hand and isolated "neuritis" of one or more peripheral nerves on the other. In the former, "multiplicity is its most obtrusive symptom"; "it is characterized by its symmetry and is due to a morbid blood state having a direct influence on the nerve tissues"; "its cause is the presence in the blood of some virus, often an organic, or inorganic chemical compound to which the nerve fibres are susceptible, just as they are susceptible to curara". In the latter, "the connective tissue and especially the sheath of the nerve is the part primarily affected, and the nerve fibres are damaged only in a secondary manner". This subdivision of peripheral neuropathies remains valid to-day and will be adhered to in this review. It is with the first group that I shall principally be concerned.

After reading Gowers' account of multiple neuritis, it is clear that it is not on the descriptive clinical aspect of the subject that advance is to be looked for. Few of us have seen as much polyneuritis as he and fewer still can rival his powers of description. The advance in our knowledge of this condition in the past thirty years is to be found rather in two different directions, namely:

(*a*) A change in our conception of the pathology of the condition and the substitution of a chemical and even a physical concept for a structural concept as to the essential cause of the condition. In other words a movement from a static to a dynamic viewpoint.

(*b*) A widening of our knowledge of its causes.

A Change in Outlook

Morbid anatomy and histology have given little help in solving the problems of polyneuritis. This statement implies no criticism of these methods in themselves, but they are not capable of solving the essential problem of why the nerve fibre ceases to function. Numerous examinations both during life and after death have demonstrated that in cases of chronic polyneuritis the nerves show degeneration of the axones, a breakdown in the myelin sheaths, changes in the neurilemma and proliferation of the interstitial fibrous tissue. In more acute cases the changes are confined to swelling of the axones together with chromatolysis and nuclear changes in the corresponding nerve cells. These changes are non-specific and can be seen in their full range in many different varieties of polyneuritis, the details depending upon the intensity and duration of the disease, rather than upon its cause. Such histological studies tell us no more about the true nature of the disorder than sections of the heart valves in mitral stenosis tell us about the nature of acute rheumatism. No one who has watched a case of "infective polyneuritis" varying in intensity from day to day and almost from hour to hour, or has seen a case of acute porphyria overwhelmed and dying of universal paralysis within a day or two of the first symptom can doubt that we are here dealing with a disorder of function whose explanation is to be sought in terms of biochemistry rather than of morbid anatomy.

A brief examination of the processes known to be involved in the activation of muscles and glands by impulses transmitted down the peripheral nerves may be of value in indicating some of the ways in which this process may break down.

The process whereby the nerve impulse is transmitted along a nerve fibre is now generally accepted as being electrical in nature. It depends upon the passage of a self-propagating wave of altered permeability down the nerve-fibre membrane which separates the axoplasm with its high concentration of potassium ions from the extracellular saline medium with its high concentration of sodium ions. This delicate system can only function if the concentrations of potassium ions in the axoplasm and of sodium ions in the extracellular fluid are maintained within certain limits. In extreme disorders of electrolyte metabolism nerve conduction is impaired or lost. This seems to provide a possible explanation of the cases of paralysis that may occur in the terminal stages of renal disease and Addison's disease.

It is known, too, that the maintenance of sodium and potassium equilibrium across the cell membrane involves the continuous expenditure of minute amounts of energy and that the passage of the nerve impulse is associated with the liberation of heat. As far as is known the only source of energy available to nerve tissue is the metabolism of carbohydrate. It might therefore be expected that some connexion would exist between nerve conduction and carbohydrate metabolism—an aspect of the subject which will be dealt with by Professor Thompson.

The transmission of the impulse from the nerve fibre to the effector organ—either muscle or gland—is brought about by the liberation of a pharmacologically active substance, acetylcholine, adrenaline, or some allied substance. This, in its turn, is immediately removed by the action of an appropriate enzyme. This complicated mechanism of transmission provides several opportunities for breakdown. The activating substance may be liberated in insufficient amounts; its action may be blocked by the presence of some chemically allied substance of greater stability or the enzyme system may be impaired or destroyed by some inimical chemical agent. Such processes are known to underlie examples of what we may call "acute experimental neuropathy" such as poisoning by curare, methonium compounds and fluorophosphate compounds. Not all of them have yet been proved to take place in naturally occurring polyneuritis.

So far my remarks on the transmission of the nervous impulse have been concerned with efferent impulses. There is every reason to suppose that the process of transmission of the impulse up an afferent nerve is essentially the same as that of transmission down an efferent one and is liable to the same disorders. But little is yet known as to what happens at the peripheral sensory end-organ whose function it is to lower the threshold of the nerve to a specific form of sensory stimulus. This will need to be unravelled before polyneuritis can be fully understood for one of its most puzzling features is the extent to which its effects may be selective, involving predominantly either motor or sensory functions, or picking out one aspect of sensation and sparing others. An equally puzzling feature is what may be referred to as "regional specificity" seen in many cases of peripheral neuropathy. We do not know why the nerve elements in the distal parts of the limbs are so commonly affected first in many varieties of peripheral neuritis. Their distance from their cell bodies seems an inadequate explanation. Indeed in many cases of so-called "infective polyneuritis" it is the proximal muscle groups that are first involved. Again, why should botulinus toxin absorbed from the intestine have a selective action on the nerve fibres or cells innervating the bulbar muscles. Why should Stilbamidine have a special affinity for the sensory fibres of the trigeminal nerves, or streptomycin for those of the vestibular and cochlear nerves?

Widening Knowledge of Ætiology

Our views on the ætiology of polyneuritis are changing. Gowers stated that all cases of multiple neuritis were due to the presence of some alteration in the circulating blood which had an adverse effect on the nerve elements. Even in his day, many toxic agents were recognized such as metallic poisons, diabetes and bacterial toxins, but in many cases the cause remained obscure. To-day it is still true that in many cases no exact cause can be determined. I have looked through the notes of 34 cases of multiple neuritis admitted to the National Hospital, Queen Square, in the past four years. Of these, the cause was considered to be established in 15 cases (i.e. 44%). In 6 cases (18%) it was considered doubtful and in 13 cases (38%) it remained unknown in spite of the most searching investigation. These figures serve to underline the fact that we are still very far from having solved the problem of the ætiology of polyneuritis.

Extrinsic Poisons

In Gowers' days the commonest causes of polyneuritis were extrinsic poisons of which the most important were alcohol and certain inorganic substances such as lead and arsenic. Nowadays these play a much less prominent role. But the advance of industry and of industrial chemistry has substituted in their place a long list of organic compounds which exert a toxic effect on the peripheral nervous system. To-day a large number of potentially toxic substances are used in flavouring, preserving, or processing foods and as pest destroyers, particularly as insecticides. Six months seldom pass without some new example being reported in the medical press of neuropathies resulting from poisoning by such agents. Poisoning by tri-ortho-cresyl phosphate is perhaps the best-known example of this group, but a series of cases caused by methyl mercury compounds reported by Hunter *et al.* (1940)

was equally dramatic and the same author (Bidstrup and Hunter, 1952) is about to publish some cases caused by a complex fluorophosphate compound. Other cases have resulted from the use of a variety of domestic insecticides. It seems reasonable to suppose that unrecognized examples of this kind account for some of the cases in which the ætiology remains unknown. In watching for them we should bear in mind not only the possibility of chemical agents being toxic to man, but also the fact that individuals in ignorance may employ these agents improperly, or may have an idiosyncrasy, either congenital or acquired, to their action.

Intrinsic Poisons

Of intrinsic, or metabolic poisons as causes of neuropathy, diabetes, the commonest and best-known member of this group remains as mysterious as it was in Gowers' day. He observes that diabetic peripheral neuritis is not related to the amount of sugar in the urine and suggests that it is the result of the perverted metabolism present in the diabetic state. The literature of recent years does not, I think, contain any real advance in our knowledge of its mechanism. This is surely a challenge to anyone looking for a subject for clinical investigation.

A more recently recognized member of this group is the neuropathy associated with acute porphyria. First recognized in connection with poisoning from the sulphonal group of drugs, a considerable number of cases have now been reported in cases of naturally occurring porphyria which depends upon a heredo-familial error of metabolism. Interesting in itself, it is perhaps more important as a possible prototype of other varieties of metabolic disturbance as yet unrecognized. In this connexion one is reminded of the points of close resemblance between acute porphyria and the most acute cases of dermatomyositis.

Another interesting example of neuropathy associated with a perversion of metabolism is that occurring with amyloidosis. It has long been known that the peripheral nervous system may be involved in classical amyloid disease. It is less well recognized that neuropathy may occur prematurely and before the classical manifestations of the disease are present. For several years past I have been watching with melancholy interest a patient whose peripheral nervous system is being progressively destroyed by amyloidosis—proved by biopsy—and there is still no evidence of any of the accepted causes of this condition or, apart from diarrhœa, of any involvement of the viscera.

Deficiency Neuropathies

An increasingly important place has been given of recent years to dietary deficiencies as causes of neuropathy. The prototype of this group is, of course, beri-beri, a condition whose clinical features have been well known since the seventeenth century, but whose precise cause has been established only in the last thirty years. It is now generally accepted as being due to a chronic deficiency in the tissues of thiamine (vitamin B_1). The other principal member of this group, pellagra, is less clearly defined both clinically and ætiologically and in the years between the wars much work was done—in this country notably by Stannus (1947) in an attempt to elucidate the various combinations of cutaneous and neuritic symptoms arising in different communities living on inadequate diets.

The circumstances of the late war provided further opportunity for studying and clarifying this complex subject and although no clinical syndromes were encountered that had not been described before, it was possible to define more clearly the different varieties of neuropathy and myelo-encephalopathy that might result from a deficient diet and to throw more light on the ways in which they were produced. The subject has been well reviewed by Denny-Brown (1947) and by Spillane (1947). It is clear that the nutritional neuropathies cannot be explained simply by the absence of adequate B_1, or even of the whole B complex from the diet. Among the additional facts that have to be taken into account are:

(*a*) The normal dietary habits of the individual. A diet capable of maintaining an Asiatic in good health may lead to a deficiency state in a Western European. It was noticeable in some P.O.W. camps that deficiency symptoms appeared first amongst those accustomed to eating a lot of meat.

(*b*) The deficiency disorders cannot be explained solely in terms of vitamins. Account needs to be taken of the total protein intake and of its quality, as well as of its relationship to the carbohydrate intake. The fat and mineral content of the diet and the presence of trace metals have also to be considered.

(*c*) Deficiency may arise in the presence of an adequate intake through defects of absorption. The parts played in this respect by dysentery, steatorrhœa and fistulæ are beginning to be understood. The importance of the intestinal flora and its modification by various therapeutic agents has also been recognized.

(*d*) The possibility of the presence in the tissue of an anti-enzyme has to be borne in mind. It has recently been shown that a form of neuropathy can be produced in horses by adding 20% or more of bracken to their hay. This has been shown to be due to the absorption of a thermolabile enzyme which destroys thiamine. A comparable situation exists in the so-called "Chastek" paralysis that occurs in foxes fed on raw fish which has also been shown to be due to the absorption of a thermolabile anti-thiamine enzyme present in certain fish and molluscs.

(*e*) It is necessary also to consider the possibility of "antimetabolites" rendering vitamins ineffective. These substances are closely akin to the vitamins in chemical structure but are more stable. They usurp the place of the vitamins in enzyme systems whose action is thereby brought to an end. Examples of such "structural analogues" are pyrithiamine and oxythiamine in respect of thiamine, sulphapyridine in respect of nicotinamide and mepacrine in respect of riboflavine.

Neuropathies Associated with Carcinoma

I turn now to the interesting group of neuropathies associated with the presence of a carcinoma in other parts of the body. The first group of this kind to be described was that of subacute cerebellar degeneration, first reported by Casper in 1929, by Parker and Kernohan in 1933 and by Greenfield in 1934. At first the association of the neuronic degeneration with a visceral carcinoma was thought to be a coincidence, but gradually the existence of a causal relationship between them has been accepted. Further description of this group is inappropriate to this contribution.

The second group was that first described by Denny-Brown in 1948 under the descriptive title of "Primary Sensory Neuropathy with Muscular Changes Associated with Carcinoma". His 2 cases, each of which had a bronchial carcinoma, presented the clinical picture of a purely sensory polyneuritis which was associated pathologically with a primary atrophic process in the nerve cells of the posterior root ganglia without either inflammatory, or vascular reaction. In addition, there was primary degeneration in the striated muscles which Denny-Brown refers to as a polymyositis. He points out the clinical and pathological resemblance of his cases to the neuropathy produced experimentally in pigs by Wintrobe by feeding the animals on a diet lacking in pantothenic acid.

The third group is that of a polyneuritis of the classical mixed type first described by Wyburn-Mason in 1948. This last group may well prove to be relatively common, as I have personally observed 3 cases in the last few years, a larger number has been collected by workers at the London Hospital and many of our colleagues have encountered a number of similar cases. The primary carcinoma is usually in a bronchus and is commonly so small as to give rise to few if any chest symptoms and may even evade the most careful X-ray examination.

The mechanism whereby a remote carcinoma may give rise not to one, but to at least three apparently distinct disorders of the nervous system is still a complete mystery. It is clear that these cases do not depend upon miliary secondaries, or upon diffuse carcinomatosis of the leptomeninges. The histological appearances are those of a selective degeneration. The multiplicity of the syndromes reminds one of the similar diversity of the clinical pictures seen in the mixed nutritional neuropathies met with during the war when polyneuritis, ataxia, with or without retrobulbar neuritis, and spastic paraplegia appeared under apparently identical circumstances.

Conclusion

Of the important group of peripheral neuropathies commonly referred to as acute infective polyneuritis, I will only say that the evidence that they are in fact "infective" is far from convincing and the nature of the hypothetical infecting agent quite unknown.

My review has, I fear, added nothing to our understanding of the peripheral neuropathies, but I hope that it may have demonstrated that we are at present only standing on the threshold of knowledge of this fascinating subject.

REFERENCES

BIDSTRUP, P. L., and HUNTER, D. (1952) *Brit. med. J.* (i), 277.
CASPER, J. (1929) *Zbl. ges. Neurol. Psychiat.*, **53**, 854.
DENNY-BROWN, D. (1947) *Medicine*, **26**, 41.
—— (1948) *J. Neurol. Psychiat.*, **11**, 73.
GOWERS, W. R. (1892) A Manual of Diseases of the Nervous System. London.
GREENFIELD, J. G. (1934) *Brain*, **57**, 161.
HUNTER, D., BOMFORD, R. R., and RUSSELL, D. S. (1940) *Quart. J. Med.*, **9**, 193.
PARKER, H. L., and KERNOHAN, J. W. (1933) *Brain*, **56**, 191.
SPILLANE, J. D. (1947) Nutritional Disorders of the Nervous System. Edinburgh.
STANNUS, H. S. (1947) Nutritional Eye Disease. Treacher Collins Prize, MS. in Bowman Library, Roy. Soc. Med.
WYBURN-MASON, J. (1948) *Lancet* (i), 203.

Professor R. H. S. Thompson (Department of Chemical Pathology, Guy's Hospital Medical School, London): *Some Biochemical Features of the Peripheral Neuropathies.*

It is widely recognized that disturbances of carbohydrate oxidation can profoundly upset the functions of the nervous system. In vitamin B_1 deficiency it now seems, mainly as a result of the work of Sir Rudolph Peters and his colleagues (Peters, 1936), that the chief biochemical abnormality within the nerve cells is a failure in the normal oxidative metabolism of the pyruvic acid formed during the breakdown of glucose. As is well known, vitamin B_1 pyrophosphate is a co-enzyme essential for pyruvate oxidation, and in its absence this oxidation cannot take place; pyruvate therefore accumulates in the tissue fluids and in the blood, and the nerve cells are deprived of their normal source of energy.

In experimental vitamin B_1 deficiency the rise in the level of pyruvic acid in the blood has been clearly demonstrated (Thompson and Johnson, 1935), and in beri-beri also Platt and Lu (1939) found increased amounts. Several groups of American workers have shown that even relatively mild degrees of vitamin B_1 deficiency in man can be detected by estimations of the blood pyruvate level after giving a "loading" dose of glucose to the patient, even though in these less severe states the fasting level may not be abnormal (Bueding, Wortis and Stern, 1942; Williams, Mason, Power and Wilder, 1943).

A deficiency of vitamin B_1, however, is not the only way in which pyruvate oxidation in nerve cells can be inhibited. Quite apart from a failure of the co-enzyme, due to thiamine deficiency, the protein component of the enzyme system may be damaged by some blood-borne toxic substance. Arsenic is an example of such an agent which is particularly relevant to a discussion on peripheral neuritis. Trivalent arsenicals react with the protein of the pyruvate oxidase enzyme by combining chemically with essential sulphur groupings, $-SH$ groups, in the molecule, and as a result the enzymic activity of the protein is lost. Although in this case there is no deficiency of the vitamin-containing co-enzyme the end-result is the same—an inactivation of the pyruvate oxidase system leading to raised levels of blood pyruvate, to a block in the continuous supply of energy to the cell and, in some cases, leading also to a peripheral neuritis resembling that associated with vitamin B_1 deficiency.

Arsenicals are not the only substances that can inactivate this enzyme protein. Certain other heavy metals such as mercury or copper, and metalloids such as antimony, together with certain non-metallic organic compounds, are also toxic to this enzyme. As an example of the latter, the ingestion of sanguinarine, an alkaloid, has been shown to block pyruvate oxidation in this way (Sarkar, 1948), and it seems likely that this is largely responsible for the epidemic dropsy that occurs in parts of India, and which was formerly thought to be a type of wet beri-beri.

It is clear, therefore, that although in a case of polyneuritis due to vitamin B_1 deficiency the blood pyruvate level may be abnormally raised after the ingestion of a dose of glucose, raised values might also be found in other cases due not to a thiamine deficiency, but to the presence of some toxic factor such as I have just mentioned. In view of this it seemed of interest to study blood pyruvate levels not only in cases of polyneuritis in whom there was some reason to suspect a thiamine deficiency, but in an unselected series of cases in order to discover whether any evidence could be obtained of impairment of pyruvate metabolism due to one of these other causes. Through the kindness of clinical colleagues both at Guy's and at Queen Square and elsewhere nearly 90 cases of peripheral neuritis have now been examined from this biochemical point of view (Joiner, McArdle and Thompson, 1950).

It was found that when compared with the normal values, a considerable number of the cases of peripheral neuritis showed abnormally high levels of pyruvic acid, 16 out of the first 40 cases being above the normal range. It cannot, however, be concluded from these results that all these cases showing high blood pyruvate levels are necessarily suffering from vitamin B_1 deficiency. In the hope of separating those due to a thiamine deficiency from those due to some other cause large daily doses of the vitamin were given parenterally (100 mg. daily by intramuscular injection) and after fourteen days of such therapy the test was repeated. Although it would be unlikely that any decisive clinical change would be brought about in so short a time, we had reason for thinking that the biochemical lesion, and also the blood pyruvate level, should be restored to normal after fourteen days of treatment with this large parenteral dose. 7 of the 14 cases which were studied in this way showed normal blood pyruvate levels after the fourteen days' treatment, but the remaining 7 cases showed no significant change in the blood levels. In 2 cases intensive thiamine therapy was continued for longer periods and the blood tested again later, but again no change in the pyruvate level was observed.

From the point of view of the changes in carbohydrate metabolism that can be detected by these tests it would seem that peripheral neuropathies fall into three main groups:

(1) A type in which no impairment of pyruvate metabolism can be detected. In this group vitamin B_1 deficiency is presumably not playing any important part in the production of the disease.

(2) A type in which there is some block in the path of pyruvate oxidation; raised blood pyruvate levels are found, but can be rapidly restored to normal values by treatment with vitamin B_1.

In this type it would seem fair to conclude that there is a deficiency of vitamin B_1; the deficiency may not necessarily be dietary in origin, but might be due to a failure in absorption or in the proper utilization of the vitamin.

(3) A type, also showing impaired pyruvate metabolism with raised pyruvate levels in the blood, but in whom prolonged and massive therapy with thiamine produces no effect either clinically or on the blood pyruvate levels.

This last type of case might therefore be associated causally with the presence of some circulating substance which combines with and inactivates the protein of the pyruvate oxidase. If arsenic or some other heavy metal were the toxic agent it would be reasonable to attempt therapy with Dimercaprol.

The chemical method which is in general use for the estimation of pyruvic acid is, unfortunately, not completely specific. It is essentially a method for the estimation of keto-acids which has been

elaborated in such a way as to make it particularly suitable for the determination of pyruvic acid. It will however, to a certain extent, estimate also other closely related keto-acids.

Consequently, it is important in the first instance to identify more exactly any keto-acid which we estimate by this method. It has already been established from experimental work with animals that the keto-acid which accumulates in the blood in thiamine deficiency is pyruvic acid. It has in fact been isolated in the form of a crystalline derivative from the blood of animals deficient in vitamin B_1.

But with polyneuritis of the third type that I have mentioned above, i.e. associated with raised levels of pyruvic acid in the blood which are not restored to normal by treatment with thiamine, we felt that it was necessary to determine whether this excess keto-acid which we are calling pyruvic acid is really pyruvic acid itself, or some closely related keto-acid resulting from some similar but distinct metabolic disturbance.

We are therefore now attempting to identify more precisely the keto-acid accumulating in the blood of patients whose peripheral neuropathy does not appear to be associated with any simple deficiency of thiamine. For this purpose we have used the technique of paper chromatography which was first applied to the separation and identification of the coloured 2:4-dinitrophenylhydrazones of keto-acids by Cavallini, Frontali and Toschi (1949). By this technique it is possible to separate out the different keto-acids present in blood on a strip of filter-paper, and to identify them by comparing their positions with those taken up by the hydrazones of pure keto-acids, under the same conditions.

In blood from healthy subjects only 3 keto-acids are present in detectable amounts—aceto-acetic acid, α-ketoglutaric acid and pyruvic acid, and of these pyruvic acid is present in greatest amount.

Having separated and identified the pyruvic acid by this means it is then possible to cut out the piece of paper carrying the coloured spot, and to extract and estimate quantitatively the amount of pyruvic acid or other keto-acid present.

So far we have only investigated one case of peripheral neuritis by this technique, but in this patient we were able to show that the large increase in keto-acids occurring after the ingestion of glucose was mainly due to pyruvic acid, although some increase in aceto-acetic acid was also present; the level of α-ketoglutaric acid was within the normal range.

We are left with the problem of those cases in which no abnormality of pyruvate metabolism can be demonstrated, and here it would seem that if we are to look for any underlying metabolic abnormality, we must consider the possibility of disturbances of other biochemical systems. A clue to another possible type of causative lesion is provided in the case of the syndrome produced by poisoning by tri-ortho-cresyl phosphate or by certain of the organo-phosphorus compounds that are now coming into use as insecticides.

It has been known for many years that tri-ortho-cresyl phosphate can produce a flaccid paralysis and demyelination of peripheral nerves and of tracts in the cord in man. But the mechanism by which it produces these changes is obscure. Bloch in 1941 first reported that tri-ortho-cresyl phosphate is an inhibitor of cholinesterase, and he suggested that the motor paralysis might be due to inactivation of the cholinesterase at the motor end-plates, in the affected muscles. There are, however, a number of aspects of the problem which would be hard to reconcile with this view, and when we put it to the test we found that the cholinesterase present at the motor end-plates and at synapses is not inhibited by this compound, whereas the so-called "pseudo-cholinesterase" (a closely related enzyme) present in the plasma is highly sensitive to it (Earl and Thompson, 1952). This pseudo-cholinesterase is also present in the peripheral nerves and in the central nervous system, where it appears to be particularly associated with the white fibre tracts. And although the true cholinesterase of the C.N.S., located chiefly in association with the synapses, is insensitive to tri-ortho-cresyl phosphate the pseudo-cholinesterase of nerve tissue is markedly inhibited by relatively low concentrations of this substance.

Further, if animals (chickens) are poisoned by oral administration of a single dose of this compound, and if the brain or spinal cord is examined at intervals after poisoning, it is found that while the level of true cholinesterase is within the normal range, the level of the pseudo-cholinesterase activity is very substantially lowered. The fall in the level of this enzyme in nerve tissue is present and maximal as early as one day after the ingestion of the tri-ortho-cresyl phosphate. The paralysis and demyelination on the other hand do not appear until later.

The inhibition of the pseudo-cholinesterase therefore precedes the onset of histologically detectable demyelination and paralysis, and so cannot be regarded as a result of changes in the myelin sheath induced by some other mechanism.

There is no evidence of any disturbance of pyruvate metabolism in birds poisoned with tri-ortho-cresyl phosphate: the blood pyruvate levels are unchanged and preparations of brain tissue from intoxicated birds which show a profound fall in the level of pseudo-cholinesterase are found to oxidize both glucose and pyruvate at the normal rate. It would seem, therefore, that in the case of the motor polyneuritis induced by poisoning with tri-ortho-cresyl phosphate, a fundamentally different biochemical disturbance exists from that found in vitamin B_1 deficiency or in an arsenical polyneuritis.

Unfortunately, we have at present no clear understanding of the physiological role played by the pseudo-cholinesterase. Its presence in relatively high concentrations in medullated nerves and in the

fibre tracts of the central nervous system suggests that it might have some role to play in connexion with the metabolism and turnover of myelin (Ord and Thompson, 1952), and that when it is inhibited, as by tri-ortho-cresyl phosphate, demyelination and signs of neurone dysfunction may ensue. This possibility would seem to be supported by a recent report of flaccid paralysis developing in 3 people exposed to a new organo-phosphorus insecticide (Bidstrup and Hunter, 1952) which is also a powerful inhibitor of pseudo-cholinesterase; in the brief report of the cases attention was drawn to the fact that the paralysis resembles that which follows poisoning by tri-ortho-cresyl phosphate.

The aspect of these findings that seems to be of significance is that here again we have evidence of an enzymic disturbance accompanying a peripheral nerve lesion, although of a very different type from the block in pyruvate metabolism that occurs in certain other neuropathies.

REFERENCES

BIDSTRUP, P. L., and HUNTER, D. (1952) *Lancet* (i), 262.
BLOCH, H. (1941) *Helv. med. acta*, **8**, (Suppl. 7) 15.
BUEDING, G., WORTIS, H., and STERN, M. (1942) *J. clin. Invest.*, **21**, 85.
CAVALLINI, D., FRONTALI, N., and TOSCHI, G. (1949) *Nature, Lond.*, **164**, 792.
EARL, C. J., and THOMPSON, R. H. S. (1952) *Brit. J. Pharmacol.*, **7**, 555.
JOINER, C. L., MCARDLE, B., and THOMPSON, R. H. S. (1950) *Brain*, **73**, 431.
ORD, M. G., and THOMPSON, R. H. S. (1952) *Biochem. J.*, **51**, 245.
PETERS, R. A. (1936) *Lancet* (i), 1161.
PLATT, B. S., and LU, G. D. (1939) *Biochem. J.*, **33**, 1525.
SARKAR, S. N. (1948) *Nature, Lond.*, **162**, 265.
THOMPSON, R. H. S., and JOHNSON, R. E. (1935) *Biochem. J.*, **29**, 694.
WILLIAMS, R. D., MASON, H. L., POWER, M. H., and WILDER, R. M. (1943) *Arch. intern. Med.*, **71**, 38.

Dr. W. B. Matthews: *Cryptogenic Polyneuritis.*

The literature of polyneuritis is largely concerned with the discovery of new causes of the condition or with the description of groups of cases of unknown ætiology that appear to form distinct clinical syndromes. There are comparatively few reports on the relative incidence of the numerous types of polyneuritis that have been described. It therefore seemed worth while to review those cases admitted to the Neurological Unit at the Manchester Royal Infirmary in the eleven-year period 1940–50 inclusive. I am grateful to Dr. F. R. Ferguson and to Dr. G. E. Smyth for permission to report on their patients.

The cases in this survey do not form a representative group of peripheral neuropathies for a variety of reasons. Only in-patients were considered, which excludes many minor manifestations of diabetic neuropathy in particular. The age incidence is probably weighted in favour of the older age groups, although some children are included. Most important is that the series undoubtedly contains a greater proportion of chronic or difficult cases than would be encountered on a general medical unit. Some patients were admitted during this period a considerable time after the onset of their disease so that in these cases the follow-up exceeds the eleven-year period.

When doubtful cases had been excluded 46 patients remained to be considered. The ætiological factors concerned are shown in Table I. The most striking feature is the large proportion in which

TABLE I.—ÆTIOLOGICAL FACTORS IN CASES OF POLYNEURITIS ADMITTED TO THE NEUROLOGICAL UNIT AT THE MANCHESTER ROYAL INFIRMARY, 1940–50

Carcinoma of breast	1
Carcinoma of bronchus	1
Ethyl alcohol	2
Methyl alcohol	1
Porphyria	1
Diabetes	2
Hyperemesis gravidarum	1
Diphtheria	1
Infective hepatitis	1
Measles	2
Mumps	1
Unknown	32
Total	46

TABLE II.—INFLUENCE OF AGE ON PROGNOSIS

Average age of patients at onset of attack:

Good prognosis	30·2 (range 5–48)
Bad prognosis	43·2 (range 21–61)

Age at onset	Good prognosis	Bad prognosis
Under 30	7	2
30–40	5	3
40–50	5	6
50 and over	0	4

no convincing cause could be found—some 70% in fact. Moreover, in many cases classified as of known ætiology the agent incriminated is more a well-recognized clinical association than a clearly understood causal agent. For example, an acute polyneuritis occurring three weeks after measles is classified as of known ætiology, while a similar attack following a non-specific infection is classed as of unknown ætiology.

It is with the 32 cases of cryptogenic polyneuritis that I shall deal. Recognized causative agents may have been overlooked in some instances, though many investigations were carried out. In chronic cases these were as thorough as knowledge of the pathogenesis of polyneuritis at that time permitted. While recognizing therefore that different unknown ætiological factors and mechanisms might be involved, it was hoped that a clinical study of these patients might throw some light on two important aspects. It was thought that on viewing the cases in retrospect it might be possible (1) to discover prognostic indications by which the course of the disease might have been predicted. Closely linked with this was (2) the possibility of distinguishing clinical syndromes that might later perhaps be found to be associated with specific causes or metabolic defects. I must say at the outset that the results were somewhat inconclusive.

(1) *Prognostic Indications*

The results of the follow-up of 31 of these 32 patients were that the prognosis was good in 15 patients and bad in 16, 7 patients having died of the disease. (One patient was lost sight of). Post-mortem examination in 5 of these still failed to show any cause for the condition. Although the term "bad prognosis" includes a variety of end-results I think that the distinction between complete recovery and permanent, progressive or fatal lesions is sufficiently clear-cut to warrant such a broad subdivision.

The prognosis was rather better in women but the difference was not significant. Age appeared to be an important prognostic factor. It can be seen from Table II that the mean age at the onset of the disease in those who recovered was 30·2 years, and in those who did not, 43·2, the difference being statistically significant. Amplifying this it can be seen that the prognosis becomes increasingly menacing with advancing age so that of those in whom the disease began after the age of 50 none recovered. In 2 cases of recurrent polyneuritis it was possible to include separate attacks. One patient recovered from attacks when aged 41 and 45 and the other recovered from severe attacks when 21 and 45 but died of his third attack at the age of 59. 2 patients had to be omitted owing to uncertainty of the significance of certain possibly premonitory symptoms.

The occurrence of a preceding non-specific infection or of fever during the attack was rare and neither appeared to have any bearing on the prognosis. The electrocardiogram was abnormal in only 2 of the 10 patients in whom it was examined. One otherwise healthy young man had a bundle branch block which was still present two years after his recovery and which may have been unrelated to his polyneuritis. The other patient, who showed non-specific changes in the chest leads, died after a progressive course of five months. Significant tachycardia was uncommon and usually either settled quickly on admission to hospital or was a terminal event.

The cerebrospinal fluid protein was found to have both normal and greatly raised values not only in patients who recovered quickly but also in fatal or extremely chronic cases. There seemed to be no foundation for the belief that a high protein indicates a good prognosis.

The extent of the paralysis was again found to be unhelpful beyond the obvious fact that bulbar involvement is an immediate danger to life. Patients with severe quadriplegia recovered, while one patient in whom paralysis was never marked outside the legs died from the resulting bedsores. In 2 patients who died the paralysis was markedly asymmetrical at the onset. It is also perhaps worth mentioning that in 2 patients in whom the disease subsequently followed an extremely chronic course there had been previous episodes of facial palsy. In one this may have been coincidental, but the other had no less than three such attacks, two on one side and one on the other.

The degree of sensory loss was also found to be no guide to the ultimate prognosis. A clinically pure sensory neuropathy was not, however, encountered as a recoverable lesion, but was seen twice as a permanent residue of an acute attack of motor and sensory neuropathy and once as a steadily progressive condition.

All patients received treatment similar in outline—physiotherapy and large doses of vitamin B_1. It could not therefore be said that treatment had any effect on the prognosis.

As might be expected the mode of onset was found to be of considerable value in prognosis. Following Magnussen (1946) the clinical course of the disease was divided into three stages: progressive, stationary and improving. Those in whom the progressive stage lasted less than eight weeks were classified as of acute onset, although it is obvious that the term, as defined, may imply something very different from the acute onset of poliomyelitis, for example. Table III shows that such a subdivision confirms the generally held opinion that cases with an acute onset have on the whole a better prognosis, but it is important to note that the distinction is far from absolute.

Onset of improvement.—This could always be dated with some accuracy. It can be seen from Table IV that there is a fairly sharp dividing line at three months. If there had been no improvement within this period recovery was much less likely to occur. Again there are exceptions, both those who began to improve within this period but who never recovered completely, and those whose disease was progressive or stationary for a longer period, but who subsequently recovered.

TABLE III

	Recovered	Died	Residual or progressive lesions
Acute onset ..	12	2	4
Slow onset	4*	5	5

*Includes two attacks in one patient.

TABLE IV

Time from onset to death or to the first sign of improvement	Recovered	Died	Residual or progressive lesions
Less than 15 days ..	2	2	1
„ „ 70 „ ..	8	2	4
„ „ 90 „ ..	12	2	4
More than 90 days or no improvement	4*	5	5

*Includes two attacks in one patient.

It cannot be said that reviewing these 31 cases in retrospect has brought to light any absolute prognostic indications. Any such attempt is overshadowed by the existence of recurrent polyneuritis. The only possibly significant fact with regard to this problem is that both the patients with recurrent attacks remarked that during the long intervals of good health between attacks they remained liable to short episodes of paræsthesiæ when over-tired, a symptom not complained of by patients who recover from a single attack of polyneuritis.

(2) *Different Clinical Entities*

On turning to the second object of this survey, the attempt to distinguish clinical entities, the difficulties are again great. These cases might be classified in a variety of ways according to the mode of onset, clinical features or end-result, but any such categories always showed a considerable degree of overlap. For such cases there are three descriptive titles in common use—acute infective polyneuritis, chronic progressive polyneuritis and recurrent polyneuritis. The first of these has received most attention, and comparatively minor clinical variants of a common picture have often been given distinctive names and rather rigid diagnostic criteria. The clinical features of the other classes are ill-defined. In the present series there are 18 cases that might reasonably be thought to come under the heading of acute infective polyneuritis, although the infective element was seldom evident. Of these 12 recovered, 2 died in the acute stage and 4 were left with residual lesions. 1 patient was left with a bilateral facial palsy; 1 with foot-drop and wasted hands; and 2 with incapacitating sensory ataxia which remained stationary for many years. In both these latter cases the initial severe paralysis had recovered, but 1 patient, five years after the initial acute attack, is now again becoming weak and wasted, but this time the onset has been gradual.

10 cases may be regarded as chronic progressive polyneuritis. The clinical course in these cases was extremely variable and the duration and outcome can only be summarized in Table V. There is an

TABLE V

Case No.	Clinical course
1	Death after five months
2	Progression for eight months. Recovery after two years
3	Death after twelve months
4	Progression for twelve months, then stationary for two years
5	Death after nineteen months
6	Progression for four years. Recovery after six years
7	Death after four years
8	Progression for fourteen years
9	Progression for sixteen years
10	Progression for twenty-four years

obvious clinical distinction between the disease steadily progressive over decades and the acute attack spending its force within a few weeks. It can be seen, however, that apart from the last 3, these cases form a fairly continuous series, and the distinction between the more acute of these chronic progressive cases and those classified as of acute onset becomes less obvious. Except in progressing for longer than an arbitrarily defined limit such cases may be indistinguishable. It must be doubted whether the descriptive titles of acute infective and chronic progressive polyneuritis do in fact describe distinct entities.

Of the remainder 2 are classified as recurrent polyneuritis with recovery between attacks, and one patient was altogether remarkable and could not be placed in any of the recognized categories.

In conclusion it may be said that this review has emphasized the limitations of the purely clinical approach to polyneuritis. Polyneuritis is a response of the nervous system to a great variety of stresses, many as yet unknown. By reason of this lack of specificity the study of variations of clinical detail within this pattern does not appear likely to throw much further light on cases of unknown origin or on the fundamental pathogenesis of polyneuritis.

REFERENCE

MAGNUSSEN, G. (1946) *Acta psychiat. Kbh.*, **21**, 561.