Papers and Originals

Polyneuritis*

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It would be hard to find a neurological subject of more general medical interest than polyneuritis. Every physician is responsible for the care of such patients, and the problems of aetiological diagnosis I will discuss are his inescapable concern. There is another reason for the selection of this subject. The fibres of the peripheral nerve are more accessible to direct examination than those more centrally situated, and they are at present the subject of intensive research by a variety of techniques—electrophysiological investigation, biopsy both of the peripheral nerves themselves and of the muscle-fibres supplied by them, and the experimental production of polyneuritic lesions in a variety of animals.

The standard textbooks of medicine and neurology enumerate a list of possible causes of polyneuritis, sometimes amounting to little short of a hundred, and covering every letter of the alphabet from Alcohol to Zoster. This is discouraging enough, but at some stage or other the ominous remark is also made that in more than half of all clinical cases the cause remains unknown, and this has certainly been my experience.

General Considerations

The common clinical syndrome of mixed sensorimotor polyneuritis is characterized by ascending paraesthesiae and peripheral impairment of sensation with flaccid weakness, loss of deep reflexes, and wasting. Pain is sometimes prominent, and, especially in acute cases, the muscles may be tender. The picture is familiar, though it is not always easy to decide whether peripherally occurring paraesthesiae are truly peripheral in origin or presage a more central lesion in the posterior columns of the spinal cord. In the earliest clinical stages both the tell-tale blunting of deep reflexes that bespeaks peripheral nerve disease and the increased briskness characteristic of spinal-cord involvement may be lacking.

It is tempting to think of polyneuritis as a lesion of the fibres of peripheral nerves, and easy to forget that these peripheral nerve fibres are in fact the long protoplasmic processes of the largest cells in the whole body—the axons of the anterior horn cells in the spinal cord and the dendrites of the bipolar sensory neurones of the posterior root ganglia respectively. Indeed, these cell processes, which subserve movement and sensation in the toes, may be three feet or more in length. They are entirely dependent for life and function on a continuing supply of protein and other substances synthesized in the parent cell and continually travelling down the fibre to the periphery. It is not surprising that such long fibres are proportionately vulnerable.

The term "polyneuritis," or its fashionable sesquipedalian synonym polyneuropathy, is used to describe the clinical results

of almost any lesion of these motor and sensory peripheral neurones, and they are applied whether the point of attack of the aetiological agent is the cell body itself or the nerve fibre in its length—a distinction of critical significance. When we think of polyneuritis in this way its multiple causation is hardly surprising. The concept is as all-embracing as if we were to consider together all the diseases of either the brain or the spinal cord.

The aetiological agents we must consider in relation to lesions of the peripheral nervous system are for the most part different from those concerned with the production of central lesions. There are exceptions, such as vitamin-B₁₂ deficiency: in sub-acute combined degeneration of the spinal cord a lesion which can begin as a polyneuritis ascends to involve the posterior and lateral columns of the cord, often produces asymptomatic changes in the electroencephalogram, and sometimes even causes a rapidly reversible organic psychosis. There are also a few lesions of the peripheral neurones that are traditionally excluded from the rubric of polyneuritis. Poliomyelitis, for instance, is in essence a disease with a highly selective incidence on the lower motor neurone, but it is excluded perhaps because its aetiology and pathogenesis are fairly well understood. Motor neurone disease is traditionally omitted, probably because its rather stereotyped natural history, its malignant prognosis, and especially a coincident involvement of the upper motor neurones distinguish it from all other forms. What the Americans rather graphically describe as "entrapment syndromes," where a peripheral nerve trunk is imprisoned in a fascial compartment, are similarly excluded. It is true that such lesions are sometimes symmetrical or nearly symmetrical, as when the median nerves are compressed in the carpal tunnels, or in lateral popliteal palsy, and also that occasional patients may suffer multiple lesions of this kind. There are families with this susceptibility, and the mechanism plays a part in the pathogenesis of certain cases of diabetic neuropathy. Much more often, however, entrapment lesions are single, and their self-evident origin in ischaemia mechanically induced by compression or friction excludes them from present consideration.

Pathology

Considering the clinical frequency of polyneuritis and its vast literature our knowledge of its histopathology is surprisingly sketchy, and much that is reliably known has been learned only recently. Except where it arises on the basis of a serious disease like cancer, collagenosis, or porphyria, only occasional cases come to necropsy, and even in these instances scrupulous neuropathological studies are few and far between. Other commoner forms of polyneuritis such as those occurring in diabetes, alcoholism, and drug intoxication are rarely fatal, and although the Guillain-Barré syndrome still has an appreciable mortality this has been greatly reduced by skilful management of the respiratory paralysis which is the usual cause of

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death, and for this reason our knowledge is now unlikely to be augmented by adequate necropsy studies of early cases.

From a pathological as well as a clinical viewpoint, it is important first to distinguish two undoubtedly authentic and quite different polyneuritic lesions.

Mononeuritis Multiplex

The first is mononeuritis multiplex, in which nerve trunks and their constituent axons are damaged by discrete and identifiable pathological lesions occurring at irregular intervals along their course. The outstanding example of this reaction is polyarteritis nodosa, where ischaemic areas in the length of the nerve trunk can be related to occlusive arteritic lesions in the vasa nervorum. Like most other lesions of polyarteritis, this neuropathy results from multiple infarction, and it is distinguished by asymmetry and involvement of major nerves. A painful partial left sciatic lesion may be followed by ulnar palsy on the right—a bizarre clinical sequence that makes sense only in its context of a systemic illness characterized by some degree of fever with a raised erythrocyte sedimentation rate and a polymorphonuclear leucocytosis, cachexia, abdominal joint and muscle pains, and often significant hypertension. Needless to say, the more diffuse the distribution of such multifocal lesions the more closely the clinical picture approaches that of the symmetrical polyneuritis into which it merges.

Furthermore, the great length of the nerve fibres to the periphery of the lower extremities makes them especially vulnerable to multiple ischaemic lesions along their course, evoking symptoms of interference with axonal conduction which begin at their periphery and slowly ascend with progression of the disseminated vascular lesion. Polyneuritis as such is of course usually unassociated with leucocytosis or a raised sedimentation rate. There are two other important causes of the mononeuritis multiplex syndrome—leprosy, in which peripheral nerves are grossly and microscopically involved by the granulomatous lesions of the disease; and diabetes, in which compression may augment the effects of ischaemia to produce scattered lesions affecting various peripheral nerve trunks.

Triorthocresyl Phosphate Poisoning

The second classical lesion is quite different and amounts to nothing short of a diffuse disease of neurones. A good example is poisoning by triorthocresyl phosphate. This produces a peripheral ascending polyneuritis generalized and symmetrical from the start. The compound is widely used in industry, and has several times evoked epidemic toxic polyneuritis as a result of food contamination, notably in the United States and North Africa. Here we have the advantage that extensive laboratory studies of experimental intoxication have been carried out in animals, and experimental triorthocresyl phosphate neuropathy can reasonably be regarded as a working model of one well-defined variety of human polyneuritis. Its own most important features are that it develops only after an interval of at least seven days and usually longer after ingestion; that it progresses rapidly for a few days, is predominantly motor in its incidence, and recovers slowly and often incompletely; and that it is characterized pathologically by a "dying back" (Cavanagh, 1964) of the peripheral extremities of the long neurones. This is not a demyelinating neuritis. The initial lesion is in the neurone, and the ascending myelin breakdown that ensues is secondary to decay of the axon, just as it is in the Wallerian degeneration that follows axonal division. The ways in which triorthocresyl phosphate and some other organophosphorous compounds poison the neurone are not known in detail, but it seems certain that their neurotoxic effects are due to secondary metabolites which suppress enzymatic reactions, essential in this particular instance especially for the health of the anterior horn cell.

Biopsy

The main contribution both of electrophysiological techniques and of surgical biopsy to the study of polyneuritis has been in sharpening clinical differentiation between flaccid weakness due to neuropathy and the very similar clinical syndromes that may result from primary diseases of muscle such as polymyositis. Even with the best ancillary techniques this may still be difficult, especially since lesions of both types may coexist, as they sometimes do in the "neuromyopathy" occasionally seen in patients with cancer—where the situation may be even further bedevilled by a partial "pseudomyasthenic" response of muscle weakness to neostigmine.

However, an attempt to systematize and clarify cannot be abandoned merely because the outlines of our concepts are somewhat blurred. Such indistinctness is one of the charms as well as one of the irritations of all biological studies. Nor should the occasional technical failures of these methods blind us to their real value as tools both of diagnosis and of research. A clinical case of unequivocal polyneuritis will occasionally yield an inexplicably myopathic electromyogram and vice versa, and the interpretation of muscle biopsy is no less subjective than clinical diagnosis and perhaps even more prone to excite argument. Motor conduction velocity may be normal in a severely paralysed nerve, or still markedly delayed where clinical recovery is almost complete. The possible fallacies of nerve biopsy can be imagined when we consider that even at necropsy there is often a striking discrepancy between the intensity of paralysis and the extent of nerve-fibre involvement. But only a physician unsophisticated enough to believe that any combination of ancillary tests can yield a definitive diagnostic formulation, or can be of value except as part of an expert clinical assessment, would discard such valuable aids to diagnosis on the grounds of their occasional inconsistencies.

Biopsy of the sural or some other accessible superficial nerve has long been of proved value in the investigation of the difficult group of obscure chronic and subacute polyneuropathies, and especially in the diagnosis of a few rare but morphologically distinct forms of polyneuritis. It will usually reveal the characteristic irregular deposits of glycoprotein amyloid material in and around the affected nerves that is typical of amyloid sensorimotor neuropathy, whether this is familial or associated with myelomatosis; and also the characteristically onion-like concentric lamellar thickening of the nerve sheaths seen in the rare familial hypertrophic interstitial polyneuritis first described by Dejerine and Sottas more than 70 years ago. Biopsy may also yield information of prognostic significance concerning the presence or absence of regeneration or remyelination.

But morphological studies of polyneuritic nerve have also been used as a basis for pathological classification. This concerns chiefly the differentiation of neuropathies secondary to axonal and therefore to neuronal damage, like those already described in connexion with poisoning by the organophosphorous compounds (and similar neuronal though less exclusively motor lesions in alcohol, arsenic, or drug intoxications), from a quite different group of essentially demyelinating neuropathies. In these the brunt of the damage is borne by the Schwann cells and their associated myelin sheaths, and the axons themselves are less conspicuously affected—a situation that obtains, for example, in diphtheritic polyneuritis and in the Guillain-Barré syndrome.

Segmental Demyelination

Professor Gilliatt and his colleagues (Cragg and Thomas, 1964; Fullerton, 1966) have extended the use of nerve biopsy, studying teased single fibres in length rather than cross-sections of nerve trunks, and attaching special importance to the long-recognized appearances of segmental demyelination limited by adjacent nodes of Ranvier, endeavouring also to correlate

morphological changes with electrophysiological observations. They have emphasized the difference between segmental demyelination and Wallerian degeneration in both human and animal material, regarding them as radically different forms of pathological reaction—even though it is known that the latter may succeed the former in prolonged compression of the nerve and that both may be encountered together in lead-poisoning and other neuropathies.

In segmental demyelination the axons appear normal on light microscopy, though the concept of an exclusive incidence of the lesion on the Schwann cell system is jeopardized by axonal abnormalities seen on electron microscopy. Segmental demyelination has been observed in diphtheritic, diabetic, and carcinomatous polyneuritis, as well as in the Guillain-Barré syndrome. It is often associated with a striking reduction of conduction velocity, but during recovery function is restored more rapidly than when this depends on regenerative sprouting. In contrast, it is paradoxical that in the peripheral Wallerian degeneration encountered in poisoning with exogenous substances like thalidomide or isoniazid, or endogenous toxins such as those circulating in porphyria, the axon is fragmented as well as the myelin sheath—and yet conduction velocity is sometimes little impaired. This may be because a few fibres escape the global lesion and continue to conduct normally.

Whether or not segmental demyelination deserves as specific an importance as is attributed to it by the Queen Square workers, there certainly seems to be a roughly quantitative relationship between demyelination and impaired electrical conductivity. Whatever the significance of these observations in relation to Gilliat's theoretical formulation they underline some important limitations of electrophysiological diagnosis. The disconcerting fact that conduction velocity may be entirely normal in severe polyneuritis of metabolic origin such as that seen in porphyria impairs the clinical value of the test. A reduced conduction velocity usually means polyneuritis, but a normal reading does not exclude the diagnosis.

Experimental Polyneuritis

The contribution of animal studies to toxic neuropathy has been mentioned in relation to triorthocresyl phosphate intoxication, and similar methods have been applied in isoniazid-, lead-, and thallium-poisoning, but animal experimentation has also clarified other varieties of polyneuritis.

Perivenous demyelinating "allergic" encephalomyelitis, reproducible in the animal by the injection of sterile brain emulsion, is now a routine tool of the experimental neuropathologist. The perivenous demyelinating lesion of this laboratory disease is very similar to that of human post-vaccinal or post-measles encephalomyelitis and more questionably related to multiple sclerosis. However, in 1955 Waksman and Adams produced a peripheral analogue of this experimental disease in the form of a demyelinating peripheral neuritis provoked in the rabbit by the injection of sterile extracts of peripheral nerve. The lesions of experimental allergic polyneuritis closely resemble those seen in the Guillain-Barré syndrome. They are characterized by vascular congestion and the focal aggregation of histiocytes and lymphocytes in the nerve trunks, and by demyelination that is maximal centrally in the spinal-nerve roots and is also seen less conspicuously and often segmentally in the peripheral nerves. The axons are less severely involved and conduction velocity is very variably affected.

Diphtheritic polyneuritis experimentally induced in the cat has also been the subject of a series of important laboratory studies (McDonald, 1963). The general picture is of a very similar lesion characterized by extensive demyelination maximal in the spinal roots and the proximal parts of the spinal and cranial nerves. Peripheral lesions are less conspicuous, comprising chiefly segmental demyelination. Here also axonal changes are inconspicuous.

Necropsy Evidence

If we consider the data obtained by biopsy and similar studies in the living patient, together with the information gained from the study of experimentally induced polyneuritis and that yielded by the reliable necropsy studies carried out over the past half-century or more, we can build up a pathological picture of polyneuritis as it presents in the clinic. Such a synthesis is bound to be incomplete. Human biopsy studies furnish, after all, only a snapshot of the periphery of a single nerve at one particular moment in the development of the lesion. Nor can experimental observations be extrapolated into the human situation without taking account of such remarkable variations in species susceptibility as the resistance of the rat and the vulnerability of the fowl to poisoning with triorthocresyl phosphate. Many necropsy studies, on the other hand, have paid insufficient attention to the different patterns of pathological reaction encountered along the length of the peripheral nerve, as where florid degeneration of Wallerian type at the extremity gives place to the milder changes of segmental demyelination in the more proximal part. Routine conduction-velocity studies may also overlook peripheral or inaccessibly proximal interruptions of conductivity. Furthermore, there are many aspects of polyneuritis that have until quite recently escaped the attention of the pathologist, such as the conditions of the sensory- and motor-nerve endings, the intimate vascularity of the peripheral nerves, and the peripheral autonomic disturbances encountered in diabetes.

The first category that emerges from this synthesis is of polyneuritis due to lesions of the supporting tissues and vascularity of the peripheral nerves. This includes polyarteritis and rheumatoid disease—where arteriolar changes are outstanding—and leprosy, xanthomatous neuropathy, amyloidosis, hypertrophic polyneuritis, Refsum's syndrome, and chronic recurrent corticosteroid-responsive polyneuritis.

The second is the "dying-back" neuropathy in which Wallerian degeneration occurs at the periphery of the longest nerve fibres as a result of neuronal poisoning. This is the predominant pattern in toxic lesions such as those induced by triorthocresyl phosphate, isoniazid, and arsenic; of nutritional neuropathies such as those of pellagra, beriberi, malabsorption, and alcoholism; and of acute intermittent porphyria.

A third fairly well defined group is that characterized by proximal demyelination, with a predilection for the nerve roots and especially the dorsal roots and root ganglia. Peripheral demyelination is variable but less conspicuous, and the group includes the Guillain-Barré syndrome and its analogue experimental allergic neuritis, and clinical and experimental diphtheritic neuritis.

In the fourth form the most conspicuous finding is simply a loss of neurones in either the anterior horns or the posterior root ganglia, associated with disappearance of the relevant fibres in the peripheral nerves. This finding is typical of some very chronic lesions such as peroneal muscular atrophy and hereditary sensory neuropathy, and is seen also in some chronic carcinomatous neuropathies. It may in fact represent merely the end-result of some more specific pathological process modified by its slow tempo and long duration.

Segmental demyelination has been found at some stage in several types of polyneuritis, and although it may ultimately prove to be nothing more than an initial stage of continuous loss of myelin its early and disproportionate incidence on the Schwann cell endows it with some degree of specificity. It is often conspicuous in lead neuropathy and is also common in diabetes, though the pathogenesis of diabetic neuritis is complex and poorly understood; vascular lesions play a part and neuronal damage has also been reported.

To build such an edifice of classification is of course to invite its destruction. Hardly any of these pathological reactions ever occur in isolation. Demyelination, for example, is common to many situations. It is present in neuronal poison-

ing, and even in the acute demyelinating polyneuropathies it may be accompanied by the death of nerve cells. Further study is necessary in the field of clinicopathological correlation and in the morphological study of human and experimental polyneuritis as well as in neurochemistry before a satisfactory classification can be achieved.

I would now like to leave these general questions of pathology and classification and briefly discuss a few important clinical varieties of polyneuritis.

Genetically Determined Polyneuritis

Peroneal muscular atrophy or Charcot-Marie-Tooth disease is the commonest hereditary form of polyneuritis, and although it is rare it is one of the commoner chronic polyneuropathies encountered in the clinic. Many cases go begging for a diagnosis, but non-recognition usually results from simple failure to inquire into the family history or to appreciate the significance either of the accompanying club feet or of the remarkably selective peripheral distribution of the muscular wasting, which affects the lower limbs first and most severely and does not extend beyond the mid-thigh. The absence of severe disablement after many years of slowly progressive nervous disease is also unique. Every form of inheritance has been described. Lesions in the lateral columns of the spinal cord are clinically silent, but the frequent coincidence of minor signs suggesting spinocerebellar ataxia of Friedreich's or similar type lends support to the view that the developmental faults underlying this group of disorders are closely related. The inborn metabolic or biochemical deviation that almost certainly underlies peroneal atrophy is quite unknown.

Chronic hypertrophic polyneuritis shows many similarities to Charcot-Marie-Tooth disease, including the occasional association of spinocerebellar signs, but it is distinguished by marked enlargement of the palpable nerves due to concentric thickening from proliferation of the Schwann cells and fibroblasts, and also by a possible connexion with neurofibromatosis. It is unusual also in that its course may be punctuated by acute or subacute exacerbations and remissions—a remarkable feature of a disorder which nearly always declares itself as frankly hereditary.

An even rarer condition in this small but important hereditary group is the hereditary sensory neuropathy described by Denny-Brown (1951). Here a strongly familial sensory neuropathy causing severe dissociated sensory loss in the feet leads to mutilating ulceration and is due to selective degeneration of the cells of the dorsal root ganglia—a sensory equivalent perhaps of the predominantly motor lesion of peroneal atrophy. Despite its infrequency this condition is of some practical as well as theoretical importance, since in the past trophic changes of this kind in the lower extremities have often been wrongly attributed to the excessively rare condition of lumbo-sacral syringomyelia. A further point of interest is that similarly circumscribed pathological changes are found in the sensory polyneuritis that occasionally complicates cryptogenic cancer in middle or later life.

You may reasonably wonder why I have spent time discussing such rarities, especially from the field of genetic disorders that is so often considered therapeutically sterile. I can illustrate my reason only by describing a still rarer syndrome—but in the meanwhile I would like you to recall the astonishing control of symptoms (the word "cure" is of course anathema to any self-respecting neurologist) that can be achieved in Wilson's disease by the use of penicillamine. Sufferers from this grave inborn error of metabolism can now be maintained in normal health by a remarkable triumph of clinical biochemistry. It is for this reason, if for no other, that Refsum's syndrome must be mentioned, because here we seem to have gone at any rate part of the way to unearthing a relevant metabolic abnormality. This recessively inherited syndrome, described by Professor Sigvald Refsum (1946), of Oslo, as hereditary ataxia poly-

neuriformis, comprises chronic sensorimotor polyneuritis, cerebellar ataxia, and atypical retinitis pigmentosa, and many cases have now been described. Refsum suggested that the disorder might prove to be a neurological manifestation of some form of systemic lipidosis, a view later supported by the finding of fat in the urine and a marked increase in serum fatty acid. It has now been established that there is a striking accumulation of an unusual fatty acid in various body tissues of patients with the disease, as well as in their blood and urine (Klenk and Kahlke, 1963; Kahlke, 1964). This substance, phytanic acid, appears to be an abnormal metabolite specifically related to this disorder and derived from dietary constituents, a concept that has opened the door to the possible control of the condition by dietary restriction (Eldjarn *et al.*, 1966).

Guillain-Barré Syndrome

First described by Landry in 1859 as acute ascending paralysis, this familiar and often dramatic condition has masqueraded under many terminological disguises. Its occasional tendency to occur in small epidemics, and an unsupported suspicion that it might be a manifestation of infection with a neurotropic virus, led to the term "acute infective polyneuritis"; occasional involvement of cranial nerves, characteristically with facial diplegia, to "polyneuritis cranialis"; and recognition of a maximal incidence of pathological change in the nerve roots to the currently favoured "polyradiculitis."

The absence of primary neuronal changes in itself rendered an origin in virus invasion unlikely, as did the failure to confirm early claims of transmission to experimental animals. Clinically the frequent relation of the syndrome to a variety of antecedent infections also suggested a less specific pathogenesis. Usually the preceding illness is nothing more than a banal upper respiratory infection, but the Guillain-Barré syndrome is also a rare but well-recognized sequel of influenza, measles, varicella, mononucleosis, infectious hepatitis, Jennerian vaccination, and serum injection. In the last instance it occasionally complicates or follows the commoner form of focal "serum neuritis" that is characterized by acute pain in the shoulder-girdle, followed by weakness and wasting with a predilection for the deltoid—the syndrome of "neuralgic amyotrophy." This condition is almost certainly due to a similar but more localized acute inflammatory lesion affecting especially the fifth and sixth cervical nerve roots on one or both sides.

The possibility that polyradiculitis might represent a peripheral analogue of post-infective encephalomyelitis received firm experimental support from Waksman and Adams's (1955) production of allergic neuritis in experimental animals injected with peripheral nerve extracts potentiated by Freund's adjuvant. There seems little reason to doubt the close relation of this allergic experimental disease to the human syndrome. We owe the most comprehensive account of the pathology of human polyradiculitis to Haymaker and Kernohan (1949), who mention the absence of histopathological changes in some acutely fatal cases, analogous perhaps with the similarly negative findings in cerebral syndromes fatal within hours of Jennerian vaccination. Within a few days oedematous changes are seen in the spinal nerve roots, rapidly followed by proximal myelin degeneration, and a little later (ninth to eleventh day) by focal cellular infiltration. The march of pathological events in experimental allergic neuritis is very similar. Waksman and Adams stress the disseminated perivascular distribution of the early lesions, again reminiscent of para-infective and experimental allergic encephalomyelitis, and the proximal incidence of demyelination in the rabbit. This proximal predilection is lacking in the guinea-pig, both in allergic and in diphtheritic neuropathies.

The Guillain-Barré syndrome develops rapidly over a period of hours or days. Weakness usually begins at the periphery of the lower limbs, is always flaccid, and ascends rapidly. In some instances, however, there is disproportionate weakness of proximal muscle groups, and the more frequent involvement of these than in most other forms of polyneuritis is probably an expression of the radicular nature of a lesion that affects nerve fibres irrespective of their length. Early and general loss of deep reflexes is frequent even where paralysis is limited. Peripheral paraesthesiae are common, but loss of sensation is usually inconspicuous and confined to some impairment of vibration and positional sense in toes and fingers. If urinary retention or an extensor plantar response appears it is fleeting. Disability usually increases over a period of days, remains static for a few weeks, and then begins to improve. Recovery is sometimes rapid but more often slow. It is, however, nearly always complete, and expert management of the acute and dangerous phase is therefore doubly important.

The young and totally quadriplegic patient kept alive by artificial respiration may be engaged in competitive athletics 18 months hence after a lengthy and tedious convalescence. Such a happy outcome is due almost entirely to recent improvements in the methods of assisted respiration, and it is predominantly to our colleagues in anaesthesia that we owe a recent reduction of mortality in this condition from 30% or even 50% to less than one in ten under optimal conditions. Polyradiculitis is a medical emergency, and until it has clearly ceased to progress the patient should be under close observation in a suitably equipped hospital. Respiratory and bulbar paralyses still account for some fatalities, but others are associated with the finding of focal necrotic and interstitial inflammatory lesions in the myocardium.

Classical Feature

A striking increase in the protein content of the spinal fluid is a classical feature, but it is far from specific, being found also, for example, in diphtheritic, diabetic, and porphyric polyneuritis. It is not invariable even in otherwise typical instances of the Guillain-Barré syndrome, and is quite often inconspicuous or absent in the early stages, when diagnostic difficulties are most likely to arise. Diagnosis does not usually present serious problems, though among those personally encountered must be recorded the differentiation of rapidly ascending quadriplegia due to this condition from that of acute myelitis—an issue resolved by the persistence of urinary retention and the finding of extensor plantar responses even before return of the deep reflexes. I have also seen the Guillain-Barré syndrome simulated by an initial attack of acute porphyria which declared itself by staining of the sheets in the box respirator in which the patient was admitted to hospital, and also more catastrophically by an acute mid-thoracic extradural abscess in which high fever, leucocytosis, and severe back pain did not attract due attention in a young woman with ascending and entirely flaccid sensorimotor paraplegia.

The outstanding benefits of modern management have overshadowed any possible contribution of steroid therapy to the improved prognosis of acute polyneuritis. Although corticosteroids and corticotrophin are widely employed, the capricious incidence and relative rarity of the syndrome have precluded adequately controlled trial. However, personal experience lends support to published evidence that they exercise an inconstant and unpredictable but sometimes apparently dramatic effect on the condition, and for this reason always deserve trial. Restoration of respiratory function and the striking return of deep reflexes within hours of their administration have been seen by too many sceptical neurologists to be discounted as coincidental. Subacute and chronic cases sometimes respond, but the greater frequency of therapeutic response in earlier cases suggests an effect on inflammatory oedema rather than on established demyelination. If there is no improvement

within a week of instituting treatment it should be abandoned. Relapse on withdrawal after satisfactory response is frequent enough to be highly suggestive of therapeutic efficacy. For this reason it is wise to withdraw the drugs, where they have proved effective, only gradually and after about six weeks.

A Related Syndrome

Recurrence of the acute Guillain-Barré syndrome after recovery is less common than relapse, but the possibly related syndrome of chronic relapsing corticosteroid-responsive polyradiculitis (Austin, 1958) is important because of its often excellent therapeutic response. Unfortunately it shades into a large group of obscure subacute and chronic polyneuropathies which so far defy classification and understanding. Reliable pathological studies of this heterogeneous material are virtually non-existent, and for this reason Dr. John Prineas and I are at present analysing a large series with a view to tentative subdivision on the basis of symptomatology and prognosis. Among subgroups that have so far emerged with some degree of definition are:

(a) Subacute and relapsing cases which ultimately recover irrespective of treatment, and which are clearly not of Guillain-Barré type.

(b) Very slowly progressive polyneuropathies which have shown no evidence of cancer or other systemic illness during a period of many years.

(c) Progressive and fatal cases where evidence of systemic disease appears in the form of signs such as hepatomegaly and plasma protein changes.

(d) Other fatal instances in which the development of dementia, cerebellar deficit, or lesions in the corticospinal tracts or posterior columns reveal involvement of the central as well as the peripheral nervous system.

Post-mortem evidence has so far contributed little to our understanding of these last two groups.

As might be expected, this series also comprises cases of chronic polyneuropathy that entirely defy classification, including two patients with progressive polyneuritis and total external ophthalmoplegia, as well as an appreciable group of patients in whom the firm establishment of a diagnosis of neuropathy has resisted exhaustive investigation, even in the presence of highly suggestive symptomatology.

Diabetes

Diabetic neuropathy continues to defy classification and even definition, doubtless because it comprises several different disorders of obscure pathogenesis. Neurological complications are more frequent in poorly controlled, though not necessarily severe, diabetes of considerable duration. Asymptomatic loss of ankle-jerks and diminished perception of vibration in the toes are common in middle-aged and elderly diabetics, as is a general reduction in motor-conduction velocity, and both findings suggest frequent subclinical neuropathy.

The occasional occurrence of mononeuritis multiplex in diabetes as a result of nerve-trunk lesions has already been mentioned, and represents one fairly well defined form of diabetic polyneuritis. The sciatic, lateral popliteal, median, and ulnar nerves are often affected, and the usual picture is of a painful partial lesion of the nerve with appropriate loss of power and sensation. Like the isolated cranial-nerve lesions that cause sudden painless diplopia in the diabetic and arteriopath, these lesions are ischaemic. Blood supply impaired by atherosclerosis and endarteritis is often further jeopardized by pressure and involves nerve fibres already affected by the subclinical conduction defect mentioned above.

The more usual diabetic syndrome is, however, a painful symmetrical subacute polyneuritis often limited to the lower

limbs. Burning pain in the soles of the feet, and shooting or aching pains in the calves, are especially troublesome at night. In this predominantly sensory form significant muscle weakness is uncommon, and curiously, in view of what has been said about the findings in subclinical cases, loss or painful alteration of superficial sensation is more conspicuous than impairment of vibration or positional sense. In occasional cases, however, profound impairment of these modalities produces a variant known as diabetic pseudotabes, and indeed neurosyphilis may also be mimicked by pupillary changes which may extend the whole way to an Argyll Robertson pupil. This is only one manifestation of a remarkable tendency of diabetic neuritis to affect the peripheral autonomic system—an involvement evident in such visceral disturbances as severe constipation punctuated by troublesome nocturnal or postprandial diarrhoea, postural hypotension, diminished sweating, ankle oedema, and a hypotonic bladder. Impotence possibly has a similar basis. Poor peripheral circulation and sensory loss both contribute to the penetrating ulcers and arthropathies that not infrequently affect the feet in chronic cases.

Although weakness and wasting are inconspicuous in this essentially sensory polyneuritis, there is another well-defined syndrome of diabetic amyotrophy (Garland, 1955) which is characterized by asymmetrical or unilateral weakness and wasting of the proximal muscles, usually of the lower limbs. The knee- and ankle-jerks are frequently absent. The thighs are often predominantly affected, and pain may be severe, though loss of sensation or autonomic disturbance are rare. The protein content of the spinal fluid is usually raised, and may be 200 mg. or more per 100 ml. The syndrome clearly arises from a lesion of the lower motor neurone, and whether an occasional extensor plantar response indicates spinal-cord involvement by the same process, or is due to some coincidental lesion such as arteriopathy or cervical spondylosis, is uncertain. The spinal-fluid changes, and the not infrequent extension of weakness and wasting to the muscles of the lower leg, suggest that diabetic amyotrophy originates in a lesion of the nerve roots.

A few other features of diabetic polyneuritis deserve mention. Mixed syndromes comprising the various elements outlined above are common. Since polyneuritis in most cases is a complication of neglected diabetes, it is only occasionally a presenting symptom of the metabolic disorder. Nor does the routine glucose-tolerance curve often help in the elucidation of severe sensorimotor polyneuritis. This syndrome is almost unknown in diabetes, and minor anomalies of glucose metabolism rarely deserve the aetiological significance frequently accorded in this context. Hardly any of our own chronic polyneuropathies of this type have subsequently developed frank diabetes.

The pathogenesis of diabetic neuropathy remains obscure. Arteriopathy is not invariable, and evidence of aneurine deficiency or therapeutic response to the vitamin are equally dubious. The apparent response of many patients to improved diabetic control, and perhaps especially the occasional intriguing appearance of acute polyneuritic symptoms during stabilization (so-called "insulin neuritis"), favour a major pathogenetic role for a disturbance of neuronal metabolism, but the nature of the deviation still eludes us.

Carcinoma

Recognition of the frequency and importance of non-metastatic neurological complications of malignant disease is recent, and in this connexion we owe much to Lord Brain and his London Hospital colleagues (Brain and Norris, 1965). These "neuromyopathies" cover a remarkable spectrum, involving every level of the nervous system, and ranging from intermittent confusional and depressive states to inflammatory degenerative muscle disorders. The contemporary epidemic of

bronchogenic cancer has enhanced their importance, and a search for cryptogenic neoplasms is now part of the investigation of any atypical neurological disorder of middle or later life.

Carcinomatous polyneuritis may precede the clinical onset of cancer by as much as four years, and although clinical improvement sometimes follows surgical removal of the growth the neurological signs often wax and wane independently of its progression. The neuropathic syndrome most specific to cancer is a rare form of exclusively sensory polyneuritis with pains and paraesthesiae which give place to a remorselessly progressive and total loss of all modalities of sensation that may ultimately involve the trunk and face as well as the limbs. This is due to fall-out of sensory neurones in the posterior root ganglia, followed by secondary degeneration of the sensory fibres of the peripheral nerves and the posterior columns. However, a mixed and less specific sensorimotor polyneuritis, often beginning distally with ill-defined pains in the lower limbs and frequently remittent, is very much commoner. The spinal-fluid protein is often increased, and myopathy, dementia, and cerebellar degeneration are frequent concomitants.

That these syndromes are in the broad sense toxic and not due to metastatic infiltration is no longer open to doubt, and the recent demonstration of complement-fixing antibodies to homologous nervous tissue in carcinomatous sensory neuropathy (Wilkinson, 1964), together with the presence of infiltration with inflammatory cells in the affected nerve roots, raises the question of a possible autoimmune pathogenesis analogous with that of experimental allergic neuritis.

Biochemical Aspects of Polyneuritis

The beginnings of a biochemical approach to polyneuritis have already been mentioned, especially in connexion with the exciting and important instance of Refsum's disease, with its hint of a possible biochemical basis for the less uncommon forms of hereditary polyneuritis.

The increasing number of drug-induced neuropathies to which our patients are exposed by the advance of modern pharmacology is already described in a considerable literature. The definable aetiology of such iatrogenic disorders renders them excellent subjects for experimental study, and it is not surprising that they have already furnished valuable basic information about the nervous system as well as new concepts in the more circumscribed field of neurotoxicity. The study, for example, of the predominantly sensory polyneuritis that may complicate isoniazid therapy—an unlooked-for by-product of the chemotherapeutic conquest of tuberculosis—has revealed an unexpectedly clear and intriguing relation between toxic susceptibility and constitutional background.

Polyneuritis is a common complication of long-term isoniazid therapy, and is related to dosage, though it affects rather less than half of all patients treated even with massive amounts of the drug (Hughes *et al.*, 1954). This is a pyridine derivative chemically related to pyridoxine, and the concurrent administration of this vitamin effectively protects against isoniazid neuropathy. However, the recent observation that other components of the vitamin-B complex are similarly effective suggests a relation that is something less than specific for pyridoxine (Devadatta *et al.*, 1960).

Investigation has shown that the population in general, as well as patients with tuberculosis, fall into two groups in relation to the metabolism of isoniazid. In about half, the drug is slowly inactivated and appears free in considerable amounts in the urine, while in the remainder urinary excretion is slight and the drug rapidly inactivated in the body. Slow inactivation is inherited as a recessive characteristic. Fast inactivators show a dominant mode of inheritance (Evans *et al.*, 1960). Slow inactivators furnish a disproportionately large number of cases of isoniazid polyneuritis, and the enzymatic reaction concerned is probably connected with acetylation of the drug. It seems

that high circulating levels of isoniazid based on this inherited metabolic variation induce neuropathy, as do the high levels of circulating nitrofurantoin sometimes encountered in the chemotherapy of chronic kidney infections in the presence of renal failure. But in the case of isoniazid the genetically determined basis of the toxic circulating levels is especially remarkable, and may have implications for other kinds of poisoning where familial susceptibility has been observed. Thalidomide neuropathy is an example from the field under discussion.

Other types of toxic neuropathy are at present the subject of active biochemical study, though the results so far obtained have thrown less light on the general problems concerned than in the two instances mentioned above. Morphological and physiological investigations present fewer intrinsic difficulties than attempts to unravel chemical pathogenesis, especially since we have so little certain knowledge of the intimate chemistry of the normal peripheral nervous system, but the biochemical approach undoubtedly has greater potentialities in relation both to aetiology and to ultimate therapeutic possibilities.

Summary

Although polyneuritis is usually regarded as a disorder of nerve fibres, these fibres are in fact the long processes of neurones situated in the spinal cord and posterior root ganglia. Some polyneuritic lesions primarily affect the nerve fibre at intervals along its length. In others peripheral dying back of

the fibre results from damage to the neurone itself. In a third group its myelin sheath is disproportionately affected.

The current contributions of electrophysiological investigation, tissue biopsy, and animal experiment to the study of peripheral nerve lesions are discussed, and a brief account is given of the application of concepts drawn from these fields to some of the commoner clinical forms of neuropathy.

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Interpretation of Levels of Strontium-90 in Human Bone

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Bones from various localities in Britain have been analysed for their content of strontium-90 since 1955. The results have been reported by Bryant and co-workers (1957, 1958a, 1958b, 1959a, 1959b, 1959c, Arden *et al.* 1960), and more recently by the Medical Research Council (1960-6). At intervals the results have been surveyed, and, in the light of what is known about the contamination of the "national diet" (Agricultural Research Council, 1959-65), deductions have been made about turnover of strontium in bone (Bailey, Bryant, and Loutit, 1960 ; Bryant and Loutit, 1961, 1964).

This communication is concerned particularly with new data derived since the considerable increase in fall-out following the 1961-2 nuclear-weapon detonations in the atmosphere.

Materials and Analytical Methods

The standard bone for assay in the national series has been the femur. However, for infants, as it has been shown that there is no difference in concentration of strontium-90 among different bones (Bryant and Loutit, 1961), any bone made available by the pathologist has been welcomed. Whenever possible the femur, whole or as a longitudinal section, has been used, and, less frequently, upper or lower sections. Occasionally other bones from adolescents have been supplied and analysed.

In addition, smaller surveys have been made on bones (vertebrae) collected on a more systematic basis in London in

1961 (Bartlett, Bryant, and Loutit, 1963) and 1963 and 1964 (Bartlett, Fletcher, and Loutit, 1966).

The method for assay of strontium-90 in bone after thermal ashing at 700° C. has continued to depend upon the preferential solution of calcium by fuming nitric acid and the removal of barium and radium to isolate the strontium. In appropriate cases the yttrium-90 daughter is separated. The activity of the strontium and yttrium is measured by using geiger counters arranged in anticoincidence with an overall background of less than 1 count per minute. The natural strontium content is determined spectrographically, but for samples arising from the beginning of 1964 a preliminary separation of strontium from calcium by cation-exchange chromatography has been introduced. The methods have been published elsewhere (Bryant, Morgan, and Spicer, 1959a ; Webb and Wordingham, 1963).

Results in National Series

Variation of Strontium-90 with Age

The mean concentrations of strontium-90 in picocuries per gram of calcium (pCi/g.Ca) according to age for bones analysed for each of the years 1956 to 1964 are given in Figs. 1 and 2. As in the earlier years, so in the last three, maximum values were observed at around 1 year of age. The values thereafter fell progressively with age to minima in adults.

The time taken to reach the maximum concentration was short. In previous discussions (Bryant and Loutit, 1961, 1964) the observed data in each year for those less than 2 years

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