POLYNEURITIS

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Diseases affecting the lower motor and sensory neurones, diffusely and usually symmetrically, are grouped together under the title polyneuritis. The term is imprecise, for many of these diseases affect structures other than peripheral nerves, e.g. spinal nerve cells, roots and muscles, and few of them are really inflammatory disorders. To overcome this inaccuracy, such terms as polyradiculoneuropathy and neuromyopathy have been coined but the older word still serves, with better euphony perhaps, provided it is used merely in the sense of a condition in which lesions of peripheral nerves occur. Its retention may be advisable, too, until such time as the pathogenesis of the various types of the disease have been more fully elucidated. From a clinical viewpoint, the disease is a syndrome, easily recognized as such, but often requiring much time and care in the investigation of its aetiology. Classification of the disorder on aetiological lines, e.g. toxic, metabolic, infective types, etc., is usual in neurological texts, but this cuts across pathogenesis and it seems preferable to attempt a division on pathological grounds. Three main groups may be distinguished: (a) parenchymatous, (b) interstitial, and (c) vascular (Greenfield, 1958).

(a) Parenchymatous Types of Polyneuritis

These are two in number: (i) those in which the neurone degenerates as a whole or in its peripheral part—*primary neuronal degeneration*; and (ii) those in which demyelination of the nerve fibres occurs in segments—*segmental demyelinating neuropathy* (Fisher and Adams, 1956). The first comprises those types of polyneuritis in which some metabolic or dietetic deficiency results in degenerative or atrophic changes. The classical example is beri-beri, and it was from experimental work in connection with this disease that the B group of vitamins was discovered. In animals, several of these vitamins seem necessary for the preservation of an intact peripheral nervous system; in man, only five are of relevant clinical importance—thiamine, pantothenic acid, pyridoxine, nicotinic

acid and vitamin B₁₂. Thiamine is a constituent of the coenzyme cocarboxylase, which is necessary for the oxidation of pyruvic acid formed in the metabolism of glucose by nerve cells. It is also concerned in the synthesis of acetylcholine in nerve fibres. Its deficiency, therefore, results in neuronal degeneration and the accumulation of an excess of pyruvate in the blood. This may be present in the fasting state or it may be brought out by a loading dose of glucose. Joiner, McArdle and Thompson (1950) describe the use of such a 'pyruvate metabolism test' in the investigation of cases of polyneuritis. Lack of thiamine may be a contributory factor in the polyneuritis of chronic alcoholism and in those cases which complicate chronic disease of the gastro-intestinal tract. Its action as a coenzyme has to be integrated with that of another enzyme, lipoic acid (Sinclair, 1956). This substance is thought to be formed in the liver and it has the property of forming stable compounds with a variety of organic and inorganic substances, e.g. arsenic, mercury, carbon disulphide, acetaldehyde and acetoacetate. Sinclair suggests that the polyneuritis produced by such substances is similar to that of thiamine deficiency in so far as the same underlying enzyme systems are affected. He also thinks that diabetic polyneuritis may be in part due to the inactivation of lipoic acid by ketones.

Pantothenic acid as part of coenzyme A is intimately concerned with the metabolism of pyruvate as well as thiamine, but it is so widely distributed in food that its deficiency in man is unsubstantiated. It has been claimed to cure the 'burning feet' syndrome, but this is doubtful, and it has been used with apparent benefit in the treatment of vestibular neurone damage caused by streptomycin.

Pyridoxine deficiency in animals produces *inter alia* epileptic fits and peripheral nerve degeneration. In man this vitamin forms a stable compound with isoniazid (I.N.A.H.), which blocks its action. Hence a polyneuritis may occur and, in fact, in this country, I.N.A.H. is probably the

commonest cause of a chemically induced neuropathy.

Deficiencies of nicotinic acid and vitamin B₁₂ also produce peripheral neuropathies, usually overshadowed by spinal cord changes, in pellagra and subacute combined degeneration of the cord respectively, but the exact pathogenesis is not yet known. Even less is known of the cause of the polyneuritis associated with carcinoma, reticulosis and sarcoidosis, but it is also thought to be due to some metabolic disturbance.

Finally, primary degeneration of peripheral nerves may occur as an hereditary disease—peroneal muscular atrophy (Charcot-Marie-Tooth's disease). Presumably again the fault is biochemical, though nothing is known of its nature.

The second type of parenchymatous polyneuritis is segmental demyelinating neuropathy. In this condition, involvement of nerve fibres is patchy and in the early stages limited to internodal segments of the myelin sheath, with preservation of the sheath proximal and distal to the lesion. Axon degeneration does not occur until a late stage is reached and, therefore, in less severe cases recovery can occur. This curious pattern of involvement probably occurs because the primary toxic damage is to the sheath of Schwann and it is seen in the polyneuritis of diphtheria, lead and acute porphyria.

(b) Interstitial Types of Polyneuritis

This group comprises inflammations of the peri- and endoneurial tissues and the pressure effects of acute and chronic oedema on nerves and spinal roots. Its most important varieties are those diseases which appear to have an allergic aetiology—acute infective polyneuritis (the Guillain-Barré syndrome), polyneuritis complicating serum and vaccine therapy and possibly acute brachial radiculitis (neuralgic amyotrophy). Only in the first of these have adequate pathological studies been made (Haymaker and Kernohan, 1949). The initial change is one of oedema of the roots and proximal parts of the spinal nerves, followed by degeneration of myelin sheaths and axons and later by lymphocytic infiltration. The allergic hypothesis has been strengthened by the work of Waksman and Adams (1955, 1956), who were able to produce an experimental allergic neuritis in animals by the injection of homologous peripheral nerve tissue with suitable adjuvants. The sequence of pathological events was similar to that in acute infective polyneuritis. It is in this group of disorders that steroid therapy has proved of great value.

Other rare conditions of interstitial type are the polyneuritis of primary amyloidosis, the hereditary hypertrophic polyneuritis of Dejerine and Sottas,

Refsum's disease and primary infection of nerves such as in leprosy and trypanosomiasis.

(c) Vascular Types of Polyneuritis

Peripheral nerves may be damaged in generalized vascular disease of the limbs—atheroma, Buerger's disease, frostbite and immersion foot. The nutrient arteries of nerves may, however, be specifically affected, for example, in polyarteritis nodosa. This results in necrosis of fibres distal to the segment affected. Such changes may be diffuse, giving rise to a symmetrical polyneuritis, or they may be scattered irregularly to produce a series of peripheral nerve palsies—mononeuritis multiplex.

This grouping of types of polyneuritis cannot be extended to all varieties of the disease. So little is known of the pathogenesis of some that accurate classification is impossible. This applies in particular to one of the most common—diabetic polyneuritis. The pathological changes here suggest that possibly all three types may be seen in this disease. The accompanying table summarizes this classification and is modified from Greenfield (1958).

Clinical Diagnosis

By and large, polyneuritis presents no great problem in diagnosis. Variations in symptoms and signs occur, of course, between different types of the disease but these are quantitative rather than qualitative and depend on the tempo of events and relative differences in the involvement of motor and sensory fibres. Only rarely is the distribution of lesions of diagnostic help, e.g. the peculiar ciliary and palatal paresis of diphtheritic polyneuritis. This discussion, therefore, will be mainly concerned with general principles only. Motor nerve involvement produces those features of a lower motor neurone lesion—weakness, wasting and a diminution or loss of tendon reflexes. Sensory nerve involvement is more variable in its presentation depending on the type of fibre damaged. Symptoms consist of pain, paraesthesiae, numbness and unsteadiness, objectively in loss or impairment of the modalities of touch, pain, temperature, vibration and joint sense, together with an increase of muscle tenderness. In most types of polyneuritis, the longest nerve fibres are earliest affected so that these symptoms appear distally in the extremities and usually in the legs before the arms. On the motor side this gives rise to a bilateral foot drop with a steppage gait, and in the upper limbs to weakness of hand muscles and wrist and finger drop. On the sensory side a characteristic glove and stocking type of loss occurs. Rarely, impairment of joint sense may overshadow other types of sensory loss

CLASSIFICATION OF TYPES OF POLYNEURITIS

(a) **Parenchymatous**(1) *Primary Neuronal Degeneration*

- (a) Disturbance of pyruvate oxidation in the neurone.
Beri-beri, chronic alcoholism, arsenic and mercury poisoning, polyneuritis of gastro-intestinal disease.
- (b) Other B vitamin deficiencies.
Pellagra, subacute combined degeneration of the cord, pyridoxine deficiency (I.N.A.H. poisoning).
? pantothenic acid deficiency (streptomycin poisoning).
- (c) Less well understood metabolic disorders of the neurone.
Polyneuritis associated with carcinoma, reticulosis and sarcoidosis.
- (d) Hereditary neuropathies due to abiotrophy or nutritional failure of the neurone.
Peroneal muscular atrophy (Charcot-Marie-Tooth's disease).
Hereditary sensory neuropathy (Denny Brown).

(2) *Segmental Demyelinative Neuropathy*

(Toxins chiefly affecting the sheath of Schwann and myelin.)

Diphtheria, lead, acute porphyria.

(b) **Interstitial**

- (a) Allergic and post-infectious polyneuritis (causing oedema $\pm$ inflammation of nerves).
Acute infective polyneuritis, serum and vaccine neuritis, ? acute brachial radiculitis (neuralgic amyotrophy).
- (b) Metabolic disorders.
Hereditary hypertrophic polyneuritis (Dejerine and Sottas), Refsum's disease, primary amyloidosis.
- (c) Interstitial inflammation of nerves.
Leprosy, trypanosomiasis, pyogenic.

(c) **Vascular**

Polyarteritis nodosa, atheroma, Buerger's disease, ? diabetic polyneuritis.

and give rise to a sensory ataxia—a pseudo-tabetic picture occasionally seen in diabetes, alcoholism and carcinoma, and in the hereditary sensory neuropathy of Denny Brown. In long-standing cases of sensory loss, trophic ulceration of the feet may occur.

Usually, disorder of motor and sensory function proceeds concurrently and to a more or less equal extent, but in some conditions one type of fibre is predominantly involved so that an almost pure motor or sensory syndrome is produced. Motor polyneuritis, for example, characterizes some cases of acute infective polyneuritis, acute porphyria and carcinoma, but in most of these conditions, even when sensory symptoms are absent, muscle tenderness is always increased. Chronic cases of motor polyneuritis may present the most difficult diagnostic problems and their differentiation from such diseases as progressive muscular atrophy, polymyositis and muscular dystrophy may require electrodiagnosis by means of intensity duration

curves and electromyography and also at times a muscle biopsy examination. Conversely, other types of polyneuritis present as sensory disorders with little or no muscle weakness, e.g. diabetes and subacute combined degeneration of the cord. Such discrepancy between motor and sensory involvement may therefore be a useful clue to causative diagnosis. Speed of onset may likewise aid differentiation—acute poisoning and allergic disorders may give rise to widespread signs in a matter of hours or days, chronic metabolic deficiencies and chronic intoxications produce polyneuritis developing slowly over weeks or months.

Palpation of peripheral nerves deserves emphasis for it is often omitted. Tenderness may be a useful corroborative sign and enlargement a vital diagnostic one.

Cranial nerve involvement, especially the seventh, is a not infrequent addition to peripheral neuritis—especially in acute infective polyneuritis and sarcoidosis—and mental changes may also occur. Heart failure is a hazard common to some types—beri-beri, diphtheria and acute infective polyneuritis.

Pathological investigations play an all-important part in the diagnosis of obscure cases. C.S.F. examination usually reveals a high protein content without any increase in cells, but may be normal even in acute cases. Urine examination confirms a diagnosis of diabetes, porphyria and some exogenous poisons. Carcinomatous neuropathy must always be considered in the middle-aged. Bronchial carcinoma is the most frequent cause and a routine chest X-ray is necessary. In such cases, however, the polyneuritis may antedate the appearance of the cancer, so that serial films may be required. Chest films may also reveal evidence of reticulosis and sarcoidosis. Subacute combined degeneration of the cord may begin with symptoms of a polyneuritis before there are any changes in the peripheral blood or bone marrow. In suspected cases, who will always show a histamine-fast achlorhydria, the diagnosis can be made either by an estimation of the serum B₁₂ level (values below 100 μg . per ml. indicate vitamin B₁₂ deficiency but are usually very much lower in S.A.C.D.) or by means of a radioactive B₁₂ test. Briefly, in this a known quantity, approximately 1 mgm., of radioactive B₁₂ is taken by mouth and the amounts subsequently excreted in urine and faeces are estimated. In S.A.C.D. little or no absorption occurs from the gut, so that at least 80 per cent. is recovered from the faeces. These are most useful tests to make at a stage in the disease when treatment is usually fully curative.

Gastro-intestinal function may occasionally need investigation—polyneuritis occasionally compli-

cating such conditions as steatorrhoea, ulcerative colitis, tuberculosis and gastrectomy.

Finally, when other tests fail, a biopsy of a digital nerve in the foot may be required and is diagnostic in such conditions as primary amyloidosis and hypertrophic polyneuritis.

Treatment of polyneuritis must be both symptomatic and where possible specific. General measures include suitable analgesics for pain, correct splintage for paralysed limbs, physiotherapy and walking appliances where necessary. Specific therapy to correct metabolic or vitamin deficiency is often difficult to assess and has led to much controversy, due largely to an insufficient realization that where nerve fibres are destroyed, recovery can only occur by the long process of regeneration, and this cannot be influenced by any known remedy. Hence the effects of specific therapy can only be obvious in reversible lesions and this emphasizes the need for early diagnosis. It is usual to employ multi-vitamin B preparations either orally or by injection, rather than single vitamins. Special antidotes to particular poisons are few, but mention must be made of the use of dimercaprol (B.A.L.) in arsenic and metallic poisoning and in those cases of polyneuritis with a disturbed pyruvate metabolism which do not respond to thiamine.

In allergic types of polyneuritis and in polyarteritis nodosa, steroid therapy is necessary and will be discussed below.

Acute Infective Polyneuritis

A full discussion of particular types of polyneuritis is beyond the scope of this article, but some special mention must be made of this disease—the commonest cause of polyneuritis in this country. Reference has already been made to its probable allergic aetiology. Frequently, it begins as a 'second illness,' following by a week or more some seemingly banal infection usually of the respiratory tract. The onset is sudden, with fever and backache, followed within a day or two by pains in the limbs, muscular weakness and distal sensory symptoms. Unlike most other types of polyneuritis, the weakness may start proximally and spread distally. In other cases paralysis ascends from the feet to involve trunk, arms, head and neck (Landry type). Sensory symptoms are often minimal and sometimes absent, though muscle tenderness is always increased. The speed of evolution of the paralysis varies considerably from mild cases with progressive weakness over a period of weeks to fulminating cases dying from respiratory failure in a matter of days. C.S.F. examination usually shows an increase of protein but may be normal in the early stage. Occasionally the cell content may be increased. In non-fatal

cases the spread of the disease is self-limited—recovery begins and eventually, after months, is complete, except in elderly patients where some degree of permanent paralysis may occasionally be seen. Relapses and recurrences of the disease sometimes happen. Prognosis has been greatly changed in recent years by (i) steroid therapy and (ii) methods of artificial respiration to tide patients over the acute phase. In a majority of patients, though not all, the disease seems to be controlled by steroid hormones. In some a quite dramatic disappearance of weakness occurs, in others improvement does not begin until the second week of therapy, whilst in a minority the disease progresses, in spite of treatment (Jackson, Miller and Schapira, 1957; Graveson, 1957). To be effective, it must be given at the earliest possible opportunity before irreversible damage has occurred and in large amounts. Very severe cases require parenteral therapy either with hydrocortisone sodium succinate 100 mg. intravenously twice daily or long-acting A.C.T.H. 40 units daily intramuscularly for the first few days. Less severe cases will respond to oral treatment with cortisone or prednisone. Cortisone is given in doses of 300 mg. daily for two days, then 200 mg. daily for two days, continuing thereafter for two to three weeks with 100 mg. daily. The comparable doses of prednisone are 60, 40 and 20 mg. daily. Improvement can best be judged in those muscles only slightly affected. When the drug is discontinued, weakness will recur within 24 to 48 hours if the disease process is still active and the drug has then to be continued for another week or two. The variable response to steroids suggests that the disease may not be an entity but a syndrome of multiple aetiology.

Patients with respiratory and/or bulbar involvement should be transferred to respiratory units where possible, there to undergo artificial respiration when needed, either in a tank respirator or by intermittent positive pressure respiration through a tracheotomy. By these means, the mortality of this condition has in recent years been considerably reduced.

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