PROGRESSIVE HYPERTROPHIC POLYNEURITIS.

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THIS rare disease was first recognised as an entity by Dejerine and Sottas in 1893, four years after Gombault and Mallet had recorded a characteristic example, the true nature of which was not realised, under the title of "A case of tabes occurring in infancy." Since then a number of papers on the subject have been written, particularly by French authors, and cases have recently been reported by Slauck, von Mellin and others.

Progressive hypertrophic polyneuritis is a disease which may be manifest at any age and is often familial. The main feature is thickening of the peripheral nerves, which are often palpable and which present characteristic histological changes. There is muscular atrophy of the feet or hands, or of both, but it is usually more marked in the feet. The condition tends to be progressive and the muscles of the proximal parts of the limbs may be affected later. Deformities frequently arise, of which pes cavus, claw-hand and kyphoscoliosis are the most common. Diminution or absence of the tendon reflexes is the rule and sensory changes are not infrequent.

French authors have endeavoured to classify the disease into types.

Type 1. (Gombault-Dejerine.)—Characterised by muscular atrophy of the extremities, most marked in the distal parts, commencing and predominating in the lower limbs, accompanied by fibrillary twitchings and disturbances of the electrical reactions. Nystagmus and marked kyphoscoliosis are present and what may be described as tabetic signs, viz., lightning pains, anæsthesia of varying degree, Romberg's sign, Argyll Robertson pupils and absent tendon-jerks.

Type 2. (Pierre Marie-Boveri.)—In this variety similar muscular atrophy of the limbs is present without fibrillary twitchings, motor incoordination, Romberg's sign, Argyll Robertson pupils or nystagmus. The tendon-jerks, however, are absent and marked kyphoscoliosis, intention tremor and scanning speech occur.

Type 3. (Roussy-Cornil.)—This form is distinguished by being non-familial and commencing in adult life.

A number of cases may be placed in these groups but others have been observed which show wide variations, and many authors have not followed the above classification. In any case a fourth type must be included if the classification is to approach completeness.

Type 4. Harris and Newcomb, Natrass and other writers have recorded cases of recurrent attacks of interstitial hypertrophic neuritis in which the nerves have shown similar histological appearances to those which occur in the other varieties of the condition.

Harris and Newcomb's case was non-familial and occurred in a male, aged 52, who had recurrent attacks of paralysis during six years. The signs and symptoms included weakness of the legs, bilateral foot-drop, wasting of the intrinsic muscles of the hand and some degree of anæsthesia. The knee-jerks arm-jerks, abdominal and plantar reflexes were absent and the affected muscles showed R.D. Their conclusion is expressed as follows: "It seems that the Dejerine-Sottas type of familial hypertrophic interstitial neuritis should be distinguished as a separate group from recurrent polyneuritis, to which our case appears to belong, though the interstitial hypertrophic neuritis found in the nerve-trunks and spinal nerve-roots in our case forms a remarkable link between the two groups, and it is conceivable that a similar underlying cause may be responsible for all of them, an auto-toxæmia such as is the probable cause of hæmatoporphyrinuric neuritis."

CHARACTERISTICS OF THE DISEASE.

Age and mode of onset.—In the majority of cases the onset of the disease is first noticed by the development of pes cavus in childhood; later, focal atrophy of the muscles of the feet and legs is present; wasting of the intrinsic muscles of the hands generally occurs after an interval of some years. Occasionally the first signs are not observed until adult life when the hands may be first affected.

Yokomori recorded the cases of a father and son in the former of whom the symptoms appeared at the age of 44 and in the latter at 26. Dide and Courjon reported five cases in 1919 and claimed that they represented a type of the condition not previously described. All their cases occurred in adults between the ages of 30 and 40; the muscles of the hands only were affected in all except two in which pes cavus was also present. The tendon reflexes were normal, the median and ulnar nerves are stated to have been thickened but there was no sensory loss. No pathological examination was made and in its absence and in view of the atypical nature of the cases it is doubtful whether they can be included as examples of progressive hypertrophic neuritis (cf. de Bruyn and Stern).

Heredity.—Heredity plays an important part in the incidence of the malady, although a number of sporadic cases have appeared, as may happen in other hereditary and familial conditions, e.g. Friedreich's ataxia, peroneal muscular atrophy and congenital cystic disease. A family history is obtainable, however, in almost all the cases in which the symptoms are present in childhood but less frequently when the condition has commenced in the adult.

Muscular atrophy and deformities.—The typical appearances are atrophy of the muscles of the feet and intrinsic muscles of the hands; as the disease

progresses the muscles of the legs and forearms may also be involved. The muscular atrophy, therefore, is distal. Fibrillary twitchings commonly occur. Associated with this muscular atrophy are the deformities generally described as claw-hand and club-foot. Hyperextension at the metatarsophalangeal and acute flexion at the interphalangeal joints frequently renders it impossible to determine with accuracy the nature of the plantar response if it is present. Equinovarus deformity is sometimes seen. Kyphoscoliosis is of common occurrence and may be very pronounced.

Reflexes.—In all the cases described the tendon reflexes are either very markedly diminished or entirely absent. There are few references to the abdominal reflexes but in one of Russell and Garland's cases they were absent and in another they were sluggish. In the present series they were abolished in Case 1 but brisk in the others. These patients with absent abdominal reflexes were all adults in whom the disease had been present for some years and it is probable that this is a later development of the condition. On the other hand absence or diminution of the tendon reflexes occurs at an early age and may be found before any muscular atrophy or deformities are noticed (Case 3 in present series).

The plantar responses vary. In the majority of cases they are absent. In three of Russell and Garland's cases they are stated to have been flexor and in one definitely extensor.

Sensory disturbances.—These vary considerably. In a few instances no sensory loss has been detected: in others it has been well marked and of the glove and stocking variety, light touch being lost, sensibility to pain and temperature blunted and sense of position impaired. These changes tend to occur later in life and are progressive.

Pains in the limbs of lightning character are not uncommon. Vasomotor disturbances such as sweating of the hands and feet may occur and were present in Russell and Garland's first case and in Case 1 of this series.

Electrical reactions.—There has been some change in the electrical reactions in the majority of cases in which these reactions were tested. Most commonly there is no response to faradism in the affected muscles or the response is very sluggish. The response to galvanism is also sluggish. Changes in the electrical reactions probably occur late in life and become more marked as the disease progresses. They may be absent in childhood.

Cerebellar signs.—Nystagmus is referred to in a number of cases but does not appear to be a marked or characteristic feature of the disease. Intention-tremor is mentioned by Marie, and some clumsiness and incoordination of movement may be present: this, however, is probably not greater than can be accounted for by muscular weakness and peripheral sensory loss. Scanning speech was present in one of the original cases described by Dejerine and Sottas and in one by Marie but does not appear to be common.

Pupil reactions.—In three cases the pupillary reactions are stated to have

been sluggish or of the Argyll Robertson variety, but in the majority they are normal. Changes in the optic discs are not described and clinically the cranial nerves are unaffected, but Dejerine and Thomas state that both the cranial nerves and the cervical sympathetic are increased in volume. Marie and Bertrand also noted enlargement of the cervical sympathetic, with early pathological changes and characteristic changes in the vagus. Marie mentions the occurrence of slight exophthalmos.

Nerves.—An important feature of the disease is enlargement of the peripheral nerves. Clinically those most frequently enlarged are the internal cutaneous of the forearm, the ulnar, the saphenous and the superficial cervical nerves. They are increased in volume and are often hard on palpation and may actually be visible under the skin. On the other hand hypertrophy of the accessible nerves may be inconspicuous and may be observed only if sought for or at autopsy.

In this connection it must be remembered that peripheral nerves may be visible or palpable in other conditions and in apparently normal individuals. In a diabetic, aged 58, seen recently, the knee-jerks were sluggish, the ankle-jerks absent and the plantar responses flexor. The left internal saphenous nerve was hard and easily palpable just above the ankle joint. Again, a boy of 19 admitted to hospital with symptoms of gastritis had very sluggish knee- and ankle-jerks, a flexor plantar response and a minor degree of flat foot. Both internal saphenous nerves were easily visible and palpable above the ankle but there were no other signs or symptoms to suggest any nervous disease.

PATHOLOGY.

The pathological changes which occur are fully described and discussed by de Bruyn and Stern and the following is a brief summary of their findings.

The changes are mainly incident upon the peripheral nerves and spinal ganglia. In the former both the interstitial and neural elements are hypertrophied and in the distal portions of the nerves there is much loss of myelin. The characteristic features of the disease-process in the nerves is the presence of masses of tissue, either nucleated or non-nucleated, arising from the sheath of Schwann and constituting hypertrophy of this sheath.

Other authors have described these masses as 'onion bulbs' from their laminated appearance, resembling the cut section of an onion. This lamination was absent from de Bruyn and Stern's case and they suggest that they had observed a different stage in the same morbid process. Similar masses may be present in the spinal ganglia. Marie and Bertrand detected many signs of degeneration in the ganglion-cells and this has been confirmed by de Bruyn and Stern. Degeneration in the posterior columns of the spinal cord has been described in the majority of cases and is considered to be a sequel to the pathological process in the nerves. Some authors have described atrophy of the cells of the anterior horn (Souques and Bertrand, Yokomori, Dejerine and Thomas).

DIAGNOSIS.

The conditions which progressive hypertrophic polyneuritis most resembles are hereditary ataxia (Friedreich's disease), and peroneal muscular atrophy of the Charcot-Marie-Tooth type.

Friedreich's disease is characterised by the absence of tendon-jerks; an extensor plantar response; deformities, pes cavus and scoliosis being the most common; cerebellar signs including ataxia, nystagmus and speech defects. Muscular wasting is not as a rule present, but in a few instances symmetrical wasting of the foot muscles and intrinsic muscles of the hands has been reported. Such cases may be confused with peroneal muscular atrophy or may have been unrecognised cases of progressive hypertrophic neuritis, which itself closely resembles peroneal muscular atrophy. In the latter disease, however, the knee-jerks may be retained, there is no extensor plantar response, kyphoscoliosis does not occur, nor are sensory changes marked. There are no pupillary changes, incoordination of movement or nystagmus. The enlargement of nerves with typical histological changes is peculiar to hypertrophic interstitial neuritis and it is stated that the electrical reactions show more marked changes than in peroneal muscular atrophy.

Hoffmann, Raymond and other writers have affirmed that these conditions are clinical varieties of the same malady; Dejerine and Marie, however, oppose this view.

Symonds and Shaw observed claw-feet with absent tendon-jerks occurring in seven individuals in one family. The main features of their cases were bilateral pes cavus and, in three, wasting of the hand muscles. The tendon-reflexes were absent and the plantar responses, when obtained, flexor. There were no sensory changes. The condition of the peripheral nerves is not mentioned. These writers also refer to seven members of a family with acquired pes cavus and total abolition of the tendon-jerks and, in several, atrophic weakness of the hand muscles, recorded by Roussy and Levy, who regarded their cases as distinct from Friedreich's disease on the one hand and peroneal muscular atrophy on the other. Symonds and Shaw, however, regard both series as a *forme fruste* of Charcot-Marie-Tooth's disease.

It is evident that progressive hypertrophic polyneuritis bears a close clinical resemblance to some examples of peroneal muscular atrophy; but it must be admitted that the true relationship between them and other similar diseases is at present unknown, and any attempt to classify them is speculative.

It is well known that in any hereditary condition varieties occur which appear to be peculiar to a family and do not accord with the classical descriptions of the malady.

Until further pathological evidence is available to prove their etiological connection, progressive hypertrophic polyneuritis stands out as a sufficiently definite clinical entity to merit description as a separate disease.

COURSE AND PROGNOSIS.

The disease as a rule is a very chronic one, especially in those cases which start in childhood. The deformities, muscular atrophy and enlargement of the nerves are slowly progressive and the associated weakness may ultimately render the patients helpless. Many live to an advanced age. The patients in seven cases collected from the literature were over the age of 50 years, the eldest 74. In de Bruyn and Stern's case, however, death ensued three years after the onset of the condition. Generally there is no shortening of life.

TREATMENT.

A number of cases have received orthopædic treatment for pes cavus in childhood but it is doubtful if any benefit accrued. The progressive nature of the malady renders the prospects for orthopædic surgery unfavourable. The differential diagnosis between this condition and simple deformities therefore becomes of importance to the surgeon.

In the cases of the present series walking is quite satisfactory and all that is required is special boots to fit the deformed feet.

No treatment is known which influences the progress of the disease.

PERSONAL CASES.

CASE 1. A. U., male, age 50.

He states that his father had clubbed feet and also some deformity of the hands. His grandfather had some abnormality of the feet. One elder sister has had clubbed feet all her life, and deformity of the hands. She has a son aged 21 who has a tendency to clubbed feet. His other brothers and sisters are normal.

History.—He first noticed trouble with the feet at the age of nine or ten years. Wasting of the hand muscles has been present for many years but this has caused him no inconvenience until recently, when the wasting has become more marked. He complains specially of weakness of the thumb muscles. Occasional sharp pains in various parts of the body have occurred and sweating of the hands is excessive.

Examination. Muscular system.—There is general muscular maldevelopment. Some kyphoscoliosis is present in the dorsal region, with convexity to the right, and slight lordosis in the lumbar region. There is no focal wasting of the arm muscles. Wasting is present in the muscles of the thenar and hypothenar eminences and interossei of both hands. Fibrillary twitchings are occasionally seen in the triceps and latissimus dorsi.

There is marked weakness of opposition of the thumb and little finger and also of adduction of the thumb. A lesser degree of weakness is also present in dorsiflexion of the wrists.

In the lower limbs the musculature is of subnormal development. Fibrillary twitchings have been seen in the calf muscles from time to time. Pes cavus is present in both feet and is more marked on the right side (fig. 1). The great toe is hyperextended at the metatarsophalangeal joint and acutely flexed at the interphalangeal joint.

FIG. 1.—Case I.

Central nervous system.—Cranial nerves normal. Optic discs normal. No nystagmus. Speech is rather slow but no definite abnormality is present.

Reflexes.—The abdominal reflexes are absent. All tendon-jerks are very sluggish indeed. The right knee-jerk is absent and there is only a flicker of the quadriceps on the left side. Both plantar responses are absent.

Sensory system.—There is slight blunting of sensation to touch, pin-prick, heat and cold. Possibly slight diminution of vibration sense in the left leg. Large and small joint sense is normal. Some incoordination noticed on sliding the heel down the opposite shin, which is more marked in the right leg. Romberg's sign negative. No definite intention-

tremor, but there is some incoordination of the hands on attempting to pick up a pin. The gait is somewhat clumsy and tends to be on rather a wider base than normal, probably due to the deformity of the feet.

Cutaneous nerves.—There is visible enlargement of the internal cutaneous nerve of the right forearm and of the internal saphenous nerves of both feet, most marked just above the ankle joints (fig. 2). The right ulnar nerve is unduly palpable and is enlarged.

FIG. 2.—Case I. The internal saphenous nerve is visible above the right internal malleolus.

Electrical reactions.—The arm and leg muscles respond to faradism and galvanism, but a much stronger current than normal is required to evoke any response.

CASE 2. A. U., male, aged 12.

Pes cavus was first noticed at the age of two to three years but he has not complained until recently when he found that ordinary boots and shoes gave some discomfort to the feet.

Examination.—He walks well and there is no ataxia. Bilateral pes cavus is present and some general muscular atrophy of the legs (fig. 3). There is no sensory loss other

than slight defect of postural sensibility of the toes. All tendon-jerks are very sluggish and both ankle-jerks are absent. The plantar responses are both extensor. The abdominal reflexes are brisk. There is no tremor, Romberg's sign is negative and the finger-nose test is satisfactory. Cranial nerves normal. Optic discs normal. There is no deformity of the back. Electrical reactions normal. There is thickening of the external saphenous nerve on the left side, above the ankle joint.

FIG. 3.—Case II.

CASE 3. C. U., female, aged 5.

No previous history of importance. The parents have noticed no abnormality. Well nourished. Slight webbing of the second and third toes of each foot. No definite club foot is present but there is a high arch on each side. Cranial nerves normal. No nystagmus. Optic discs normal. Walking is on rather a wide base but no ataxia has been noticed. Romberg's sign negative. No muscular wasting. The arm-jerks are very sluggish and the right knee- and ankle-jerks are absent. The right plantar response is equivocal. Abdominal reflexes brisk. There is no visible or palpable hypertrophy of nerves.

M. U., female, aged 7, and F. U., female, aged 16 months, the other two children, are both entirely unaffected and no abnormal physical signs were detected.

Cases 1 and 2 were shown at the Neurological Section of the Royal Society of Medicine and are recorded in the *Proceedings* of the Section.

BIOPSY.

A portion of the right internal cutaneous nerve (Case 1) was removed from the forearm, under local anæsthesia. By kind permission of Dr. J. Godwin Greenfield a microscopic examination of the nerve removed was carried out in the laboratory of the National Hospital, Queen Square. The report received is as follows. The piece of nerve resected, about 2" in length, was rather thicker than a normal internal cutaneous nerve. After fixation in formolsaline, longitudinal and transverse frozen and celloidin sections were made.

In frozen sections stained with Scharlach R and counterstained with hæmatoxylin, the nerve-fibres appeared to be widely separated. The perineurium was greatly thickened, while the endoneurium was so much thickened that each endoneural sheath appeared as a wide concentric ring enclosing the myelin sheath. Occasionally two myelin sheaths were contained within one such endoneural sheath. No lamellar arrangement of the endoneurium was observed. The myelin sheaths were present, and took the stain of normal myelin, but in some parts of the section the thickened endoneurium enclosed clear spaces devoid of myelin. Between the endoneural sheaths there were small areas of a structureless, unstained tissue which contributed to the wide spacing of the nerve-fibres.

In celloidin sections stained with hæmatoxylin and counterstained with Van Gieson's stain there was considerable shrinkage of the tissues inevitable in the process of preparation. In spite of this, wide separation of the nerve-fibres was still evident, and the thickening of the peri- and endoneurium was striking. The nuclei of the endoneurium were seen to be greatly increased in number. The indeterminate tissue between the nerve-fibres stained a faint yellow with this stain. It contained no nuclei. Sections stained by the Weigert Pal method and counterstained with Van Gieson's stain showed that the majority of the nerve-fibres were well myelinated.

In these sections the wide separation of the nerve-fibres was more evident than in the other celloidin sections, as the preliminary mordanting with chrome salts had reduced shrinkage to a minimum. In some areas of the sections thickened endoneural sheaths enclosed myelin sheaths which were thinner than the normal myelin sheaths of sensory fibres.

By Kernohan's modification of Bielschowsky's method the majority of the axis-cylinders appeared normal.

The histological features of this nerve are typical of hypertrophic interstitial neuritis; they conform almost exactly to those described in the biopsy on Russell and Garland's second case. This similarity of the histopathological picture suggests that the disease process has reached approximately the same point in the two cases.

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