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MOTOR NEURONE DISEASE

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THE story of motor neurone disease goes back more than a hundred years, to the latter half of the 19th century, and the days of the great clinical neurologists of France. Of the many famous names linked to this story three are pre-eminent: Charcot—physician and neuropathologist, and great teacher, who became even more renowned for his studies of hysteria (Fig. 1); Duchenne, the one from Boulogne, who came from a family of fishermen and seafarers (Fig. 2); and Dejerine, great clinical neurologist, and pioneer in the study of localization of function in the brain (Fig. 3).

Progressive degenerative lesions affecting both upper and lower motor neurones of the spinal cord and brain stem were described as separate diseases, distinct one from another, under the titles of *progressive muscular atrophy*, a spinal disease of lower motor neurones (Aran, 1850; Duchenne, 1858); *progressive bulbar palsy*, a disease of bulbar lower motor neurones (Wachsmuth, 1864); and *amyotrophic lateral sclerosis* (Charcot and Joffroy, 1869), a disease of both lower and upper motor neurones. *Progressive ophthalmoplegia* (Hutchinson, 1879; Gowers, 1879; Brissaud, 1895) was formerly considered to be a nuclear disease analogous to the cases of progressive bulbar palsy originally described by Duchenne (1858) as 'primary labio-glosso-laryngeal paralysis'. The nuclear origin of progressive bulbar palsy was demonstrated by Charcot, and the association with amyotrophic lateral sclerosis by Dejerine (1883). Chronic poliomyelitis, nuclear amyotrophy and progressive spinal muscular atrophy are other synonyms which have been used to describe the diseases now grouped by many authorities under the name of *motor neurone disease*. The Werdnig-Hoffmann paralysis of *infantile progressive spinal muscular atrophy* is usually added to this grouping, the original cases being described in 1891 and 1893. The unity of these several conditions has been criticized by Wilson (1954), who considers the term motor neurone disease 'ætiologically vague and pathologically unspecific'. The clinical picture and progress of these diseases often remain distinct throughout life, and there is a tendency for this clarity of outline to become blurred by nosological fusion into a single disease entity. Despite the probable pathological unity there is much to be said for retaining within the overall heading of motor neurone disease, the original individual names for diseases which have many clinical differences and differing prognoses.

General Ætiology

Though cases of motor neurone disease may occur in childhood and adolescence (van Bogaert, 1925), it is a disease mainly of early middle life, from about the age of 30 to 50 years. Cases of bulbar palsy occur twice as commonly in women as in men, but progressive muscular atrophy and Charcot's disease affect men far more often than

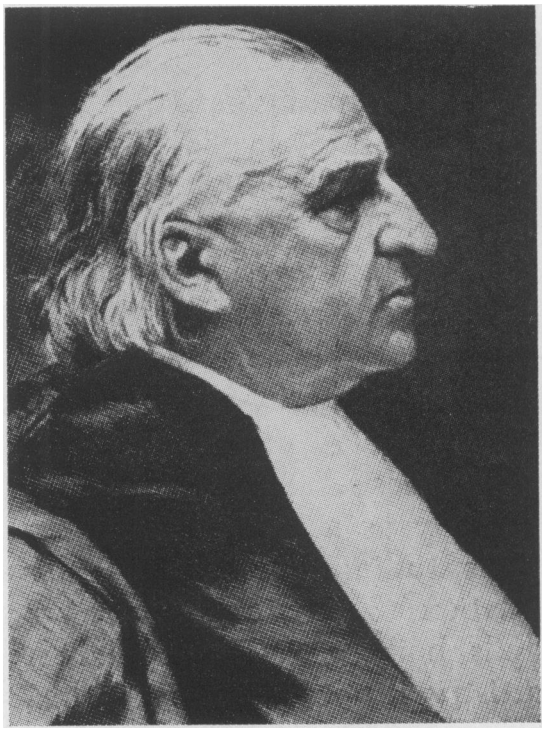

FIG. 1.—Jean Martin Charcot (1825-1893)
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FIG. 2.—Guillaume Benjamin Amand Duchenne (1806-1875)

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women, in the proportion 2 to 1 and 3 or 4 to 1 respectively. Occasional familial cases are reported (Osler, 1880; Hammond, 1881; Holmes, 1905), but are uncommon in western countries. On the island of Guam, and others of the Marianas Islands in the Pacific, Koerner (1952), Arnold, Edgren and Palladino (1953), Kurland and Mulder (1954, 1955) and Kurland (1957) have reported a remarkable incidence of the disease, with a frequency 100 times more than normal, 1% of the adults being affected and 10% of all deaths being due to motor neurone disease. Familial cases here, with a high incidence in young people, are very common. These reports have brought into prominence possible racial and heredo-familial factors, which were previously considered unrelated in this disease.

Cases occurring after acute poliomyelitis, and at varying times after syringomyelia and epidemic encephalitis, have been frequently reported (Carr, 1926; Ornsteen, 1930; Greenfield and Matthews, 1954). The possibility of a deficiency factor has been pointed out by Ask-Upmark and Meurling (1955). Neurosyphilis and lead poisoning occasionally produce spastic paralysis and wasting, which may imitate motor neurone disease, but distinguishing features can usually be found. Fatigue and trauma (Jelliffe, 1935), whether from direct injury or concussion (Alpers and Farmer, 1949), or past injection therapy, seem to have a bearing in precipitating the onset of motor neurone disease at a particular site, e.g. injections into the buttocks or upper arms in lumbar and shoulder-girdle types of progressive muscular atrophy respectively. In most cases preceding incidents are probably coincidental, occurring by chance only, the majority of cases occurring idiopathically and belonging to the class of 'primary endogenous systematized degeneration' (Wilson, 1954).

Progressive Muscular Atrophy—Varieties and Clinical Features

The progressive muscular atrophy of Aran and Duchenne, with its distinctive features of nuclear amyotrophy and without clinical evidence of pyramidal disease, continues to be seen frequently. The classical variety of symmetrical wasting and weakness of the small muscles of the hands is found in many of these cases (up to 50%—according to Wilson), involving interosseous and lumbrical, thenar and hypothenar muscles, with progression proximally to the forearm and later the upper arm muscles. Not infrequently weakness and wasting start first in the muscles of the shoulder girdle (Vulpian-Bernhardt's proximal type)—the supraspinati, infraspinati and latissimus dorsi being affected—with extension to deltoid and pectoral muscles later. The presence of fasciculation distinguishes this variety from the proximal myopathies. The brachio-radialis muscles, the upper third of the trapezii, and the sterno-mastoid muscles often remain unaffected until the later stages of the disease. This proximal or scapulo-humeral type often pursues a relatively mild course (Swank and Putnam, 1943).

A pelvic girdle onset is also not uncommon, with extension both to the lumbar muscles and muscles of the thighs. Wasting of gluteus medius and minimus muscles produces characteristic hollowing of the outer portions of the buttocks, with resulting prominence of the greater trochanters; atrophy of the erector spinæ muscles emphasizes the vertebral spines and the diamond-shaped outline of the sacrum. Wasting of the quadriceps muscles brings out the anatomical features of individual muscles, with the long strap of the sartorius muscle standing out strongly on knee flexion and emphasizing also the hollowing above the patellæ from the wasted vastus medialis portions of the quadriceps muscles. Both gait and posture are affected early in this variety, the patients adopting an unsteady forward-bending

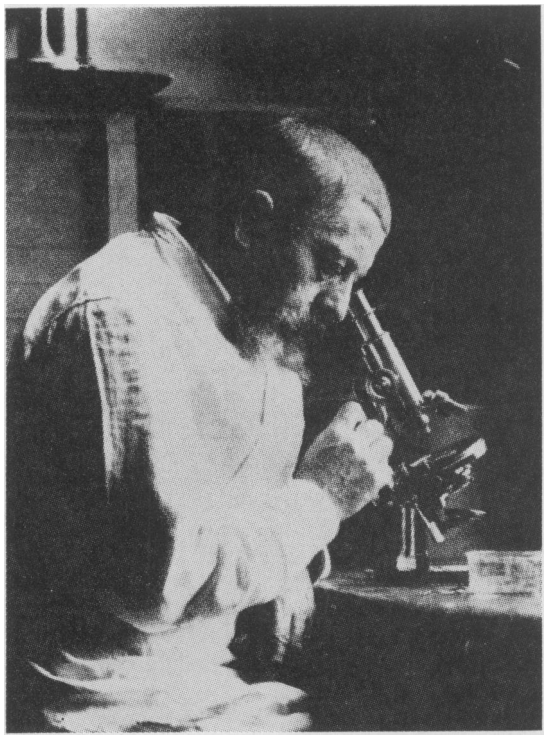

FIG. 3.—Joseph Jules Dejerine (1849-1917)
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attitude to maintain balance with weakening muscles.

Rarely, onset with peripheral leg wasting imitates peroneal muscular atrophy. Lack of symmetry of wasting is found only in the early stages of the disease, but for a time a hemiplegic picture may be found. A generalized tetraplegic variety, purely atrophic, affecting all four limbs with spread later to the trunk and bulbar muscles, is perhaps more common than is realized. Occasionally, this tetraplegic variety is associated with severe limb pains imitating a polyneuritis, but with preservation of reflexes until a late stage.

In clinically pure cases of progressive muscular atrophy, weakness and severe lack of tone with flaccidity of muscle groups, and progressive reduction of reflexes are usual, especially where muscle wasting is severe. Tonic wasting with active reflexes suggests the later development of Charcot's disease. All varieties show active fat atrophy as well, and this sometimes appears to precede the muscle wasting. In the later stages of atrophy, whether regional or generalized, the muscles of respiration become involved, with wasting and weakness of intercostal muscles and diaphragm, and of the *oblique* abdominal muscles. The recti abdominis muscles seem rarely to be affected. Muscle wasting and weakness are invariably accompanied by fasciculat on—the spontaneous flicker of groups of muscle fibres supplied by a degenerating motor unit—muscle twitching which can be demonstrated or increased by preliminary limb contraction against mild resistance. Fasciculation undoubtedly increases after exertion, and despite some statements to the contrary (Wechsler, 1958) seems to be more frequent and generalized in rapidly progressive cases, and has therefore definite prognostic as well as diagnostic value.

Atrophic spread to the bulbar muscles is common and occurs in up to 50% of cases clinically (Swank and Putnam, 1943). Some cases present initially with Duchenne's labio-glosso-laryngeal paralysis. Post-mortem many cases show anatomical spread of degeneration, without having produced associated symptoms during life. In these bulbar cases the tongue becomes flabby, shrunken and wrinkled, lying in the floor of the mouth and showing prominent fasciculation. There is difficulty in putting out the tongue, or moving it from side to side. Eating, as well as speaking, becomes difficult. The lips and chin are involved, together with the palate and extrinsic muscles of the pharynx and larynx. Dysarthria results from defective articulation, pronunciation of dentals (d, t), labials (b, f, m, p, v), linguals (l, n. r) and palatals (g, k) is lost, and slurred speech gives way to unintelligible noises. The voice becomes' monotoned' or monotonous, swallowing becomes increasingly difficult, and inhalation of food and nasal regurgitation are further symptoms which develop later as the dysphagia becomes more severe (Wilson, 1954). The progression of *primary* atrophic bulbar cases is rapid and death is usual within a year of onset. Secondary cases may deteriorate rather more slowly over a period of two to three years. Involvement of the upper brain stem with resulting nuclear ophthalmoplegia is rare. Here ptosis and gradual paralysis of external ocular muscles may complicate bulbar palsy, or very rarely be a primary manifestation of the disease. Progressive ophthalmoplegia has been reported ir younger cases with a distinct familial incidence. Most of these, however, are now considered to be of myopathic origin (Kiloh and Nevin, 1951).

As previously noted, familial cases of progressive muscular atrophy occurring in childhood are recognized under the title of Werdnig-Hoffmann paralysis or progressive spinal muscular atrophy of infancy, and must be included in the general grouping of cases showing chronic degenerative atrophy of lower motor neurones (see Case No. 4). Normal at birth, weakness and

wasting commence at about six months in the muscles of the back and shoulder and pelvic girdles, spreading later to the intercostal muscles and peripheral muscles of the limbs. Fasciculation of muscle occurs and tendon reflexes diminish. The muscles are flaccid. Recently, identity with Oppenheim's amyotonia congenita has been suggested (Brandt, 1950), particularly on pathological grounds, though profound lack of tone and lack of fasciculation is characteristic of these floppy babies.

General Symptoms and Signs of Amyotrophic Lateral Sclerosis

The advent of spasticity of the limbs in motor neurone disease profoundly affects the progress and prognosis of the case. Whereas in the earliest stages the presence of upper limb weakness and wasting of small muscles suggests the more restricted anatomical diagnosis of progressive muscular atrophy, with usually its more prolonged clinical course, the recognition of spasticity of muscle indicates the development of Charcot's disease with the classical picture of amyotrophic lateral sclerosis. Stiffness of muscles and increased reflexes are then found with varying degrees of clonus. The muscle spasticity is found predominantly in the lower limbs, accompanying and usually following small muscle weakness and atrophy of the upper limbs. Occasionally spasticity is the presenting feature, and atrophy of muscle may be delayed and be minimal, or even absent, throughout the course of the disease. These uncommon cases are often referred to as cases of primary lateral sclerosis, described by Erb as 'spastic spinal paralysis', and may indeed be a different disease entity. Wasting of spastic muscles in classical Charcot's disease occurs in only slight degree after one or two years, and is due to spread of cord cell involvement from lateral to anterior horns. Variations of this picture of upper limb wasting and lower limb spasticity are, however, commonly found. Tendon reflexes may be exaggerated in the arms, wrists and fingers, with muscle spasticity, and 'tonic wasting' of buttocks, thighs and lower limbs, with prominent fasciculation of muscle, may occur in the presence of very brisk reflexes.

Bulbar spread is invariable, occurring usually in the later stages of the disease, but may be early and predominate (Alpers, 1958). Occasionally it is of spastic type, and instead of the wasted lower facial, tongue and laryngeal muscles of progressive bulbar atrophy a condition of spastic weakness of these muscles is found from supranuclear neurone involvement. A brisk jaw jerk, small spastic tongue and stiff lower facial muscles are found. The emotional picture of pseudo-bulbar palsy, with its inappropriate and uncontrolled paroxysmal laughing and crying, sometimes accompanies these findings (Davison and Kelman, 1939; Wechsler, Sapirstein and Stein, 1944). Perhaps most commonly a combined upper and lower motor neurone bulbar lesion is found, with dysphagia and dysarthria of both spastic and atrophic type. Ocular involvement of spastic type is difficult to assess, for even the atrophic variety of nuclear ophthalmoplegia is now felt, as previously noted, to be allied to the familial muscular dystrophies. Ptosis, enophthalmos, and small pupils of oculo-sympathetic Horner's paralysis have been reported (Wechsler, 1958) from spread of the degeneration to the lateral horns of grey matter in the thoracic cord, involving sympathetic ganglion cells there, but must be very rare.

Objective sensory changes are uncommon, but have been reported (Wechsler, Brock and Weil, 1929; Davison and Wechler, 1936; Friedman and Freedman, 1950; Lawyer and Netsky, 1953). Early, severe and long-persisting cramp-like pains in the muscles of the back and shoulders, as well as of buttocks and legs, are however not uncommon, and transitory neuritic 'lightning' pains also occur as in pure progressive muscular atrophy. Both are often reported by patients as due to 'rheumatism'. They can be very disabling in themselves. Numbness and 'pins and needles' in the feet and fingers are also complained of in the earlier stages of the disease. The hands and feet of atrophied spastic limbs are often cold and cyanotic. Involvement of sphincters is very rare and late in appearance, and presents with either retention or incontinence. Rarely also urgency of micturition occurs, and in cases showing fasciculation suggests pyramidal tract involvement (Swank and Putnam, 1943). Impotence may develop. Mental changes occur, but are rare (Davison and Wechsler, 1936).

The syndrome of Jakob (1923), with the unsatisfactory title of 'spastic pseudosclerosis', described also by Creutzfeldt (1920) and later by Davison (1932), Worster-Drought, Hill and McMenemey (1933) and others, shows a clinical picture of muscular atrophy with fasciculation and spastic paralysis of either bulbar or spinal type, giving rise to dysarthria and weak stiff limbs. Extrapyramidal symptoms of tremor, Parkinsonian rigidity and poverty of movement, and mental symptoms with gradual loss of intellect, progressing to dementia, are also found. The presence or development of these latter features distinguish this special syndrome from the accepted grouping of motor neurone disease, and justify separation from it.

Illustrative Case Record of Jakob-Creutzfeldt Disease

O. D., female, aged 54 years. She first attended on 15.12.61 with a history of increasing forgetfulness for the previous 12 months, dragging of the feet for about nine months, and progressive weakness of all her limbs for the last six months. On examination she showed severe dysarthria, increased jaw jerk, and severe spastic weakness of all limbs, with mild wasting of the forearms and hands without sensory loss. No fasciculation of muscle. B.P. 145/80 mm. Hg. X-rays of skull and spine normal. CSF normal. EEG abnormal, with bilateral theta activity in occipital areas supporting clinical diagnosis of basilar artery insufficiency. On 9.3.62 air encephalograms at Churchill Hospital, Oxford, showed widespread atrophy of cerebrum, midbrain and cerebellum. Dr. Spalding considered that despite a speech 'resembling that characteristically heard in severe motor neurone disease', the above findings and mild dementia indicated a diagnosis of Jakob-Creutzfeldt disease.

In the following summarized case reports a diagnosis of motor neurone disease has been made on clinical grounds, supported by routine X-rays and CSF examinations, with EMG records in several cases, but without autopsy confirmation. These patients usually die at home, where consent for post-mortem examination is either not obtained or not given.

Case No. 1.—W. A., male, aged 52 years. Symptoms were present for six months before he was first seen on 17.1.58. Weight 13 st. 8 lb. He complained of pains in the limbs at night, with flushing of feet and twitching of legs. On examination he showed auricular fibrillation, B.P. 130/90 mm. Hg, no neurological signs, hæmoglobin 109%, ESR 3 mm./hr. X-ray of chest normal. On 25.4.58, with a weight of 11 st. 10 lb., anxiety state was present, and possibly fasciculation of leg muscles. By 23.7.58 he complained of weakness of the legs and showed generalized fasciculation of muscles of the legs, arms and shoulders, increased after exercise. There was partial left foot drop, and both arms were weak. CSF—protein 70 mg./100 ml., globulin negative, no cells. On 18.8.58 wasting of small muscles of both hands and of quadriceps muscles was noted. Seen by Dr. Ritchie Russell on 8.9.58, who confirmed diagnosis of MND. Eleven months later, on 30.7.59, there was marked wasting of trapezii, pectorals, forearm and interossei muscles, and of thigh and leg muscles. Bilateral foot drop and wrist drop were present, with generalized fasciculation. Knee and ankle reflexes absent and plantars flexor. He died several days later. Post-mortem examination not obtained.

Diagnosis: Progressive muscular atrophy.

Case No. 2.—J. B., male, aged 69 years. He attended on 18.10.61 complaining that 18 months previously he had noticed 'flopping' of the left foot. A limp gradually developed, and later weakness of the left leg and left arm. On examination there was weakness of dorsiflexion of the left foot, wasting and weakness of both quadriceps muscles, especially of the vastus medialis portions, with prominent fasciculation. Reflexes were normal, but the right plantar response was extensor. Wasting and weakness of all shoulder girdle muscles, including deltoid and pectoral muscle groups, with gross fasciculation, was also noted. Heart and lungs normal. Seen again on 5.3.62 he showed severe weakness of arms and shoulder girdle muscles; walking was difficult.

Diagnosis: Amyotrophic lateral sclerosis.

Here the rapid progress of the disease over a period of two years, with positive Babinski response, despite normal reflexes and absence of spasticity, indicate the more serious diagnosis of amyotrophic lateral sclerosis. The family doctor has since noted that this patient saw an E.N.T. specialist two years ago because of an unexplained difficulty in swallowing, which later seemed to clear. This suggests mild bulbar palsy at the onset of the disease, which is uncommon.

Case No. 3.—L. B., female, aged 48 years. She complained of progressive loss of power of the right hand and 'jumping' of the upper arm muscles for the previous eight months. No pain or sensory symptoms. On examination, 10.10.58, there was wasting of right supraspinatus, infraspinatus, trapezius, and deltoid muscles, with active fasciculation and wasting of thenar and hypothenar muscles and both quadriceps muscles. Sensory loss right hand of ulnar distribution, possibly an associated ulnar nerve lesion. Knee and ankle reflexes were exaggerated, with clonus. Plantar responses flexor. On 25.5.59 there was obvious spastic paraplegia and extensor plantar responses. By 13.5.60 spastic tetraplegia was evident, the legs were paralyzed and very little movement was left in the arms and hands. Swallowing was difficult, with some choking on eating, speech slow and cough defective. There was mild euphoria. She died in January 1961. No autopsy.

Diagnosis: Amyotrophic lateral sclerosis; bulbar palsy.

Case No. 4.—K. C., male, aged 5 years. He is under the care of Dr. Wigglesworth and was admitted to the Hospital for Sick Children, Great Ormond Street, at 18 months, in August 1958. Birth weight 8½ lb., movements always weak, sitting up at 5½ months, no attempt to stand; general hypotonia, reflexes all absent. Plantars equivocal. Muscle biopsy right quadriceps—appearances of progressive muscular atrophy. Electromyogram, September 1961, showed fibrillation and fasciculation potentials, and a gapped action pattern, with giant polyphasic potentials supporting a diagnosis of motor neurone disease.

Diagnosis: Infantile progressive spinal muscular atrophy (Werdnig-Hoffmann).

The original differential diagnosis in this case lay between muscular dystrophy, amyotonia congenita, and progressive muscular atrophy. This boy's mother's uncle is R. T., Case No. 11, who has amyotrophic lateral sclerosis.

Case No. 5.—A. D., female, aged 63 years. She was first seen on 16.9.59 after complaining of weakness of the left arm and twitching of both arms for the previous three months. On examination weakness and wasting, and hypotonia of all muscles of left arm. No sensory loss. On 21.10.59 fasciculation and wasting of left shoulder girdle muscles was quite severe, with lesser wasting of right shoulder girdle and considerable fasciculation of right biceps. ESR 15 mm./hr., WR and Kahn negative. X-ray of cervical spine showed severe cervical spondylosis. Seen by Dr. Spalding on 12.1.60, who confirmed diagnosis of MND. By 16.3.60 there was wasting of muscles of buttocks and thighs and weakness of the left leg. Some bowel frequency, perhaps autonomic diarrhœa. On 5.10.60 marked

fasciculation of lips and tongue neck and shoulder girdle muscles was noted, and there was difficulty with swallowing. Admitted to Salvation Army Home in January 1961. Died later.

Diagnosis: Progressive muscular atrophy; bulbar palsy.

Case No. 6.—J. I., male, aged 57 years. First seen on 7.9.53, complaining of tremors, numbness and heaviness of the legs for previous three months. On examination he showed brisk leg reflexes and right ankle clonus, plantars flexor, no wasting, no sensory loss, and CSF normal. X-rays of cervical, thoracic and lumbar spine normal. Not seen again until 5½ years later, when on 16.2.59 he complained of pains in the right arm, aching and shaking of the legs, especially at night, and of difficulty in walking for the previous three years. On examination buttocks and thighs were wasted and showing fasciculation, the right leg was spastic, with increased reflexes bilaterally, partial right foot drop, and right extensor plantar response. By 19.12.60 the right arm was weak but spastic, and the right shoulder painful. On 18.12.61 fasciculation was noted in the right calf: he walked with difficulty.

Diagnosis: Amyotrophic lateral sclerosis.

This case illustrates the difficulty in determining the total duration of the disease, and the importance of noting the date of the earliest symptoms complained of by the patient which can be certainly related to the disease.

Case No. 7.—H. L., male, aged 73 years, plumber. First seen on 13.3.59 complaining of leg weakness and muscle pains for the previous six weeks. On examination there was considerable wasting of leg muscles, left quadriceps and right adductors, with fasciculation. Eversion of right foot was weak, increased leg reflexes and left extensor plantar response were noted. No sensory loss. Interosseous muscles of hands and flexors of forearms wasted. Arm reflexes brisk. CSF normal; X-ray of chest clear; lumbar spine lipping. Re-examined on 23.6.61. Marked quadriceps wasting with fasciculation, and brisk reflexes noted. On 9.2.62: tires easily; uses walking stick.

Diagnosis: Amyotrophic lateral sclerosis.

Case No. 8.—J. N., male, aged 57 years. He was examined on 18.9.58, after a complaint of weakness and aching in the knees for the previous two years. Considerable wasting of right quadriceps and anterior tibial muscle groups of both legs noted, with active fasciculation of left calf, brisk leg reflexes, and bilateral extensor plantar responses. There was wasting also of both glutei and shoulder girdle muscles, right more than left. Bilateral dorsal interosseous muscle wasting. Sensation normal. Investigations: X-rays of skull, chest, cervical and lumbar spine normal. CSF normal, chest clear, electromyogram records inconclusive. On 8.2.62 right foot cold and cyanotic, with foot drop, hand grips poor.

Diagnosis: Amyotrophic lateral sclerosis.

Case No. 9.—A. H., female, aged 66 years. She attended on 4.7.57, complaining of backache, weakness of the right leg, and of difficulty in walking for the previous 12 months. On examination she showed bilateral claw hands, which were cold and cyanosed, and wasting of small muscles of hands and forearms with fasciculation. The arm reflexes were brisk, and there was partial right foot drop. On 7.9.57 CSF normal, X-ray of cervical spine showed degenerative changes, dorsal and lumbar spine and pelvis were normal, and chest clear. Re-examined at patient's home on 5.3.58, when there was complete paralysis of the right leg, with foot drop, weakness of the left leg and diminution of reflexes, flexor plantar responses, dysphagia, weak voice and ineffective cough, and congestive changes in the chest. Patient died some days later. Her daughter is A. O., Case No. 10.

Diagnosis: Progressive muscular atrophy; bulbar palsy.

The degenerative changes of cervical spondylosis are common, and spinal cord compression may occur with myelopathy and brachial neuritis. An amyotrophic lateral sclerosis syndrome may be simulated, but objective sensory changes are usually found.

Case No. 10.—A. O., female, aged 41 years. First seen on 22.6.61. Weight 8 st. 7½ lb., usually 10 st. She complained of weakness of arms, shoulders and legs, with twitching movements, for past six months. On examination, wasting of shoulder girdles and small muscles of hands, with extensive fasciculation, increased jaw jerk, brisk leg reflexes, right ankle clonus, and bilateral extensor plantar responses were noted. Electromyograms characteristic of anterior horn cell degeneration. Glucose tolerance curve and CSF normal. On 18.1.62, weak voice, swallowing difficult, arms and legs very weak. Attended in wheel-chair.

Diagnosis: Amyotrophic lateral sclerosis; bulbar palsy.

This case illustrates the occasional familial history found in the disease. The patient's mother also died from motor neurone disease at the age of 63 years (Case No. 9, A. H.).

Case No. 11.—R. T., male, aged 39 years. First seen on 11.4.60, this patient complained of weakness of the legs for the previous six months, together with shooting pains in the thighs, weakness of the arms, and aching in the wrists and elbows. One year previously he was kicked in the back whilst playing football, and this was followed by pain for several weeks. On examination, sensation was normal, there was wasting and weakness of both quadriceps muscles, with increased knee and ankle reflexes. Plantar responses equivocal. On 25.4.60 ankle clonus, bilateral extensor plantar responses, fasciculation of quadriceps and deltoid muscles noted. Arm reflexes brisk. X-rays of spine and CSF normal. On 12.6.61 weakness of legs and fasciculation left thigh noted. On 8.1.62 condition fair.

Diagnosis: Amyotrophic lateral sclerosis.

This patient's joint and muscle pains had suggested to his doctor a rheumatic polyarthritis. His brother's daughter has a boy who suffers from progressive spinal muscular atrophy (Case No. 4, K. C.), and further illustrates the familial history occasionally found. The apparent association with trauma is worth noting.

These 11 cases briefly reported form part of a group of 17 cases of clinical MND who have been under observation in the Kettering area during the past five to six years. The remaining six cases have been excluded on grounds of insufficient evidence because the supporting investigations were incomplete. All were considered to be cases of clinical PMA, with cramp-like pains, weakness and wasting of upper or

lower limbs, shoulder or pelvic girdles, showing prominent fasciculation, variable reflexes, flexor plantar responses and objectively normal sensation. X-rays of skull, chest and spine and CSF and blood tests were normal. Muscle biopsy and EMG records, glucose tolerance curve, creatinine studies, and perhaps ^{131}I thyroid up-take tests are necessary in these cases, which probably also require autopsy proof of the extent of the cord cell damage. Clinically pure PMA is more difficult to substantiate than the combined lesion of ALS.

In my experience subjective sensory symptoms of cramps, neuritic-type pains, aching and heaviness of the limbs and paræsthesiæ are prominent in motor neurone disease, especially in the PMA variety, and may be present for several months before as well as after the onset of muscle weakness and wasting. This feature has perhaps lacked emphasis because the specific pathological change involves predominantly motor pathways.

Anatomy and Pathology of Motor Neurone Disease

Pathologically as well as clinically, motor neurone disease shows many variations from the classical picture of an upper and lower motor neurone degeneration extending from the Betz cells of the cerebral cortex, through the internal capsule, pons and medulla, to the spinal cord. This cortico-spinal involvement is often only partial, frequently patchy, and is far from being as systematized as originally thought (Wilson, 1954).

In the *cerebral hemispheres* the agranular cortex of the frontal and precentral areas often shows some atrophy, most marked in the 3rd and 5th cortical layers, the latter containing the large pyramidal Betz cells. The middle third of the corpus callosum, containing crossed association fibres, shows degenerative changes, together with the pyramidal fibres in the posterior limb of the internal capsule. This degeneration may be only partial, and not extend outwards beyond the midbrain. Occasionally lesions have been found in the extra-pyramidal system (cf. Jakob's syndrome) with involvement of the corpus striatum. In the *medulla* the cranial nerve nuclei show cellular changes similar to those of the Betz cells and peripheral anterior horn cells, the 12th, 10th, 7th and 5th nerve nuclei showing most damage. Degeneration has also been described in Deiter's nucleus and in the vesticulo-spinal, rubro-spinal and tecto-spinal tracts, as well as in certain ascending tracts, particularly the spino-cerebellar tract. Involvement of cells of Clarke's column is found less frequently. In the *spinal cord* the predominant degenerative changes are found in the antero-lateral columns, and in the cells of the anterior horns especially of the cervical and lumbar enlargements.

Severe involvement of root fibres passing from the anterior horn cells, sometimes, however, only as far as the cord margin, has been stressed by Holmes (1909) and by Wilson (1954). In other words, the intra-spinal portion of the nerve roots, those parts bare of neurilemma, may degenerate heavily—beyond the cord margins the myelin may show little degeneration. The dorsal columns, though only rarely involved (Davison and Wechsler, 1936), do show occasional demyelination in amyotrophic lateral sclerosis, and this was emphasized at the Paris Symposium during the Charcot Centenary in 1925. It may, however, be coincidental. The degree of atrophy of cells and fibres often does not correspond one with the other: in some cases muscle wasting and anterior horn-cell degeneration may both be severe, and the peripheral nerve show only mild changes. Many of these findings suggest a far from systematized purely motor degeneration. As a rule peripheral nerves show varying amounts of myelin sheath degeneration, depending upon the acuteness of the disease, and in relation to the degree of muscular atrophy the number of *large* nerve fibres present may be markedly reduced. At least one-third of the motor nerve fibres may be destroyed before the muscle shows any clinical signs of atrophy. Wohlfart and Swank (1941) have shown the presence of regenerating nerve fibres, a condition known as 'sprouting', occurring in fibres adjacent to other degenerating fibres. It has been suggested that this collateral *regeneration* and nerve-sprouting of knobs may be stimulated by release of some substance from the adjacent degenerating fibres. The more scattered the degenerating nerve cells, the better seem to be the conditions for collateral sprouting. Wohlfart (1957) feels that sprouting of nerve fibres must be an important factor in delaying the wasting and weakness of muscle in diseases showing progressive degeneration of lower motor neurones. The muscles show disseminated neurogenic atrophy, with groups of normal fibres intermingled with atrophic shrunken fibres arranged in small bundles. The latter become fragmented, with increase of sarcolemmal nuclei, which later show clumping and pyknosis. The motor end-plates disappear early. Striation of the muscle fibres persists until the late stages. There is a relative lack of fibrosis and fattiness.

Differential Diagnosis of Motor Neurone Disease

From the foregoing account of the different ways in which motor neurone disease may present

it is seen that muscle wasting, spasticity of muscle and varieties of bulbar palsy are pre-eminent in the clinical picture. Muscle wasting, localized to a particular group of muscles, may usher in any one of the three varieties of motor neurone disease. In progressive muscular atrophy, as has been seen, this wasting may affect any muscle grouping, but especially may it be noticed first in the small muscles of the hands, the shoulder or pelvic girdles, the bulbar muscles, or uncommonly the leg muscles.

In the differential diagnosis of these many ways of presentation, it is immediately apparent that a detailed knowledge of applied anatomy of the nervous system is required. In the earliest stages, before the pattern of wasting has fully developed, clear-cut diagnosis may be difficult. Especially is this so in wasting confined to the small muscles of the hands, where recognition of individual lesions of ulnar and median nerves, with their characteristic wasting and sensory loss, is vital in excluding them from general spinal cord diseases. Similar diagnostic difficulties may arise in wasting of lower limb muscles, though here not so much in wasting of the small muscles of the feet as of the leg and thigh muscles.

Acute lesions of the cervical spinal cord include *poliomyelitis*, which occurs usually before middle age, is rapid in onset, non-progressive, and causes asymmetrical paralysis of large as well as small muscle groups. In *cervical cord compression* from tumours, or as a result of osteophytosis or severe disc lesions, cerebro-spinal fluid changes may be found. Root pains are common in *syphilitic meningo-myelitis*, and with this and *cervical rib pressure*, and in *syringomyelia*, objective sensory changes are found. Cervical rib compression of the inner cord of the brachial plexus causes muscle wasting, limited to partial rather than whole muscle atrophy, corresponding to C.8 and Th.1 segmental areas. Th.1 lesions may be accompanied by cervical sympathetic paralysis irrespective of the underlying disease. Segmental wasting from localized degenerative anterior horn cell changes may follow motor neuritis from injections of various kinds, often involving shoulder or pelvic girdle muscles. With the residual, often symmetrical, wasting of peripheral neuritis objective sensory changes are also found.

Carcinomatous neuropathies may cause peripheral sensory and motor lesions, which require recognition (Denny-Brown, 1948), and may be illustrated by the following two cases, which were considered originally to be cases of motor neurone disease.

Case No. 1.—E. C., male, aged 64 years, was first seen on 27.11.61, complaining of weakness of the left leg, twitching of the left thigh, occasional cramps, and pins and needles in the legs, present for the past year. On examination there was slight muscle wasting of both thighs, with occasional fasciculation, and absent knee and ankle reflexes. The plantar responses were flexor. There was no objective sensory loss. Early clubbing of the fingers was noted. EMGs (Dr. Birkbeck) showed 'moderately gapped action patterns: no fibrillation'. On 29.11.61 CSF and EEG normal, ESR 9 mm./hr., and there was no anæmia. On 1.12.61 X-ray of chest showed an opacity at the left hilum, and on 11.1.62 left upper lobectomy was carried out (Mr. Grimshaw). Path. report: 'Poorly differentiated carcinoma'.

Case No. 2.—A. H., male, aged 62 years, first attended on 23.3.59 with a complaint of paræsthesiæ of the legs with weakness, and weight loss, noticed over the previous six months. On examination no abnormal physical signs were noted, and blood tests, X-rays of chest, thoracic and lumbar spine were normal. On 29.4.59 CSF was normal and fasciculation was noted in both legs, and on 12.8.59 he was re-admitted to hospital because of obstructive jaundice, with palpable gall-bladder. Fasciculation of muscles of arms and thighs and obvious wasting of quadriceps muscles was also noted. Serum bilirubin 8.5 mg./100 ml., alkaline phosphatase 67 units. At laparotomy on 22.8.59 (Mr. Phillips) carcinoma of head of pancreas was found, with hepatic secondaries. Cholecyst-jejunostomy was carried out; the patient died shortly afterwards.

In both these cases the possibility of carcinoma arising coincidentally in patients with progressive muscular atrophy might be considered, but the time of onset and progress of the two diseases suggest an ætiological relationship in each case.

Chronic lead poisoning can present a neurological picture not unlike that of motor neurone disease of both atrophic and combined amyotrophic-spastic varieties—with small muscle wasting, fasciculation, and sometimes increased reflexes and spasticity. The general clinical features of lead poisoning and the occupational history serve to indicate the ætiology.

Distinct from diabetic polyneuritis of sensory type, with pain, loss of tendon reflexes, ataxia, sensory loss and trophic changes in the feet, a syndrome of *diabetic amyotrophy* has been reported on several occasions during the past ten years. Pain, with weakness and wasting in the limb muscles and sometimes in the pelvic and shoulder girdle muscles, occurs over a period of several months. Depression of reflexes is usual, and objective sensory loss is not found. Fasciculation has been reported. The syndrome appears to be completely reversible (Garland, 1957) and may not be entirely related to good diabetic control.

Wasting occurring in the *familial muscular dystrophies* is usually proximal in its distribution, but the rare distal type of muscular dystrophy of Gowers and the later age-group type of Nevin, may both resemble progessive muscular atrophy

and cause difficulty for some years in differential diagnosis. Muscle fasciculation is, however, never found in the myopathies. *Dystrophia myotonica* may show peripheral weakness and wasting, but the characteristic delay in muscle relaxation and the associated features of genital atrophy, baldness, cataract and sterno-mastoid weakness clearly distinguish it from motor neurone disease. In *peroneal muscular atrophy* the muscle wasting involving the feet and legs affects later the hands and forearms, but here is accompanied by sensory changes. Werdnig-Hoffmann's progressive spinal muscular atrophy, including the so-called amyotonia congenita of Oppenheim, are now grouped together as cases of motor neurone disease occurring in infancy and childhood (Brandt, 1950).

The local muscle wasting of *chronic joint diseases* such as rheumatoid arthritis rarely causes difficulty in differential diagnosis, and the pain and paræsthesiæ and partial muscle wasting of the *carpal tunnel syndrome*, often previously misdiagnosed as due to cervical rib or thoracic inlet syndrome, is rarely confused with the weakness and wasting, without sensory loss, of progressive muscular atrophy.

Apart from clinical assessment in the differential diagnosis of motor neurone disease help may be obtained from muscle biopsy and from electrical tests, including electromyographic records. The muscle changes in neurogenic atrophy have been briefly noted above and are to be distinguished from those of the myopathies, including polymyositis. In the muscular dystrophies some muscle fibres are shrunken, others are large and swollen with loss of striation; the sarcolemmal nuclei migrate into the substance of the fragmented fibres, and fatty infiltration and connective tissue replacement are other changes which differ from those of denervated muscle. In polymyositis evidence of inflammatory changes is found, with cellular infiltration and phagocytosis. Necrosis and fragmentation of swollen muscle fibres may be severe, and alongside this evidence of concurrent muscle regeneration may also be seen.

Electrical tests of value in assessing muscle denervation include faradic-galvanic tests, the determination of rheobase and chronaxie, plotting of strength/duration curves, the muscle response to slowly rising currents, and the motor conduction velocity of nerves. The assistance which may be given by electromyogram records is referred to below.

Recent Trends

The present-day picture of motor neurone disease may be viewed from clinical, histopathological, electrophysiological and biochemical aspects. In summary, the *clinical* features of the disease in its various forms have been thoroughly described during these past 100 years. As emphasized by Swank and Putnam (1943), the different types of motor neurone disease vary considerably in the speed of progress of the disease, though all cases are uniformly fatal. Familial cases have been reported. Cases presenting during life as clinically pure examples of progressive muscular atrophy, often generalized or tetraplegic, affect men three times as often as women, and tend to progress slowly with a duration of 5 to 15 years or more (Muller, 1952; Wechsler, 1958; Alpers, 1958; Magee, 1960). In them subjective sensory symptoms are common, often early and severe and troublesome. A lumbar type of amyotrophy, distinct from myopathy, is not uncommon. In amyotrophic lateral sclerosis or classical Charcot's disease the stiffness and spasms of spasticity and the subjective sensory symptoms of trophic changes are predominant. The disease is unremitting and progresses rapidly, with a fatal outcome within three years. Uncommon cases occur in which the disease presents during life with lateral sclerosis only. These cases of spastic paraplegia progress more slowly, over a period of 5 to 10 years, before death occurs. Progressive bulbar palsy is found twice as commonly in women as in men. Three-quarters of the cases occur as an extension of pre-existing motor neurone disease, either progressive muscular atrophy or amyotrophic lateral sclerosis, one-third of these as a terminal event; 25% occur as the presenting feature of motor neurone disease, and in them the disease is rapidly progressive, death occurring within 12 months from the onset of symptoms.

Pathologically, the degenerative changes in the anterior and lateral columns of the spinal cord become progressively less severe as the condition ascends to the brain stem and brain (Davison, 1941). The disease is not confined to the motor neurones, for other tracts, afferent as well as efferent, are involved in some cases. The spinocerebellar tracts and cells of Clarke's column, and occasionally the extra-pyramidal tracts, may all show irregular changes of demyelination. The histological picture of degeneration and the later 'sprouting' of regenerating nerve fibres have been described above.

Experimentally, the important distinction between fibrillation and fasciculation, so admirably made by Denny-Brown and Pennybacker (1938), has helped considerably in understanding further the mechanisms involved at the neuro-muscular junction. Several days after the nerve fibre dies individual muscle fibres show twitching or fibrillation, which is thought to occur from the local

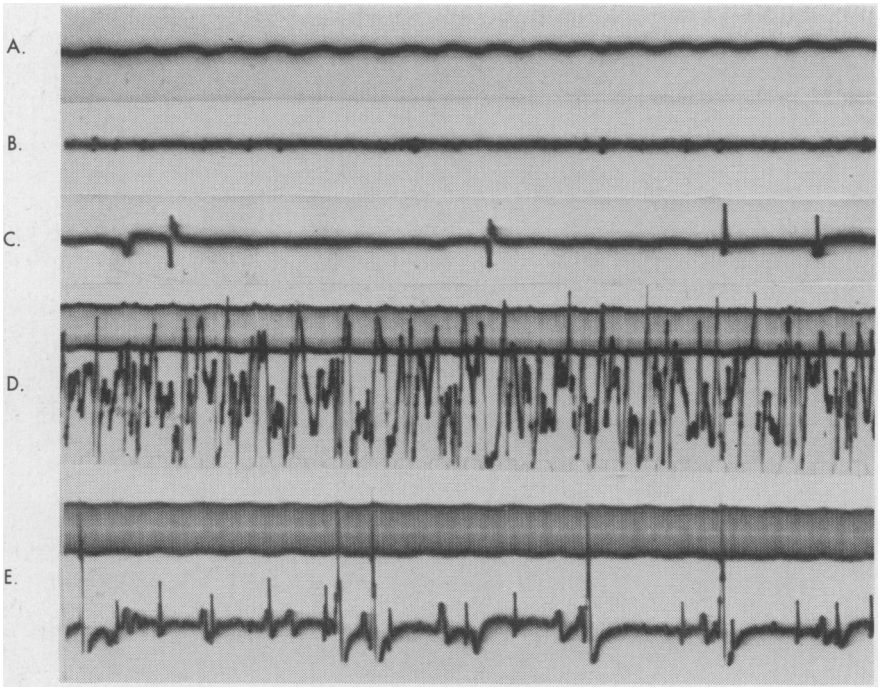

FIG. 4.—A. Electromyogram of *normal resting muscle*, showing absence of electrical activity.
B. Electromyogram of *normal actively contracting muscle*, showing crowded interference pattern.
C. Electromyogram of *resting muscle in motor neurone disease*, showing fibrillation potentials.
D. Electromyogram of *resting muscle in motor neurone disease*, showing fasciculation potentials.
E. Electromyogram of *actively contracting muscle in motor neurone disease*, showing poor frequency response of abnormal motor units (cf. Fig. 4, B).

action of persisting acetylcholine (Adams, Denny-Brown and Pearson, 1953). It is, however, fasciculation, or coarse contraction of a group or bundle or fasciculi of muscle fibres from a single degenerating motor nerve and its cell, that is usually noted on examination or sometimes complained of by the patient suffering from motor neurone disease. When the nerve fibre has completely degenerated, fasciculation no longer occurs. The site of origin of these fasciculations is, however, probably in the region of the myoneural junction, and not at the anterior horn cell (Forster and Alpers, 1944). The clinical and electromyographic differences between this ominous fasciculation in motor neurone disease and the benign fasciculation of myokymia were pointed out by Denny-Brown and Pennybacker, and have been emphasized by Schwab, Stafford-Clark and Prichard (1951). In myokymia the fasciculations are gross, coarse and slow, and involve most or all the motor units in a fasciculus. Occurring in voluntary muscle, the syndrome includes cramps and emotional tension, and there is no weakness or wasting of the affected muscles. In motor neurone disease the larger nerve fibres and cells degenerate much earlier than the smaller fibres (Wohlfart and Swank, 1941; Wohlfart, 1949). 'Sprouting', or regenerating fibres, delay progression of muscle wasting for some time. Fig. 4 illustrates electromyograms which show these features of fibrillation and fasciculation, both in the resting muscle and during active contraction. Stimulated by the work of Buchthal and Clemmesen (1943), the study of electromyography during the past 20 years has played an increasingly important role, both experimentally and clinically in the differentiation of neuromuscular disorders.

A diagnosis of motor neurone disease cannot be made from electromyogram records alone. However, anterior horn cell degeneration is suggested by spontaneous fasciculation and by the

loss of whole motor units on voluntary contraction, the surviving motor units being either normal in size or synchronized to give high voltage polyphasic potentials. Fibrillation potentials may be found in chronic spinal atrophy, but are more often seen in partial or complete peripheral nerve lesions. In the myopathies on voluntary effort relatively normal interference patterns can still be obtained, but the individual motor unit potentials are reduced both in size and duration; some are very rapid, and the polyphasic potentials are proportionately increased in number (Kugelberg, 1947). In polymyositis, where electrical tests show no slowing of conduction velocity or abnormalities of excitability of the peripheral nerves as in the neuropathies, automatic frequency analysis of the electromyogram again shows marked increase in high frequency or short duration action potentials of small polyphasic character (Lambert, Sayre and Eaton, 1954).

Though clearer recognition of the varieties of the disease and better understanding of the clinical and neuro-pathological features have occurred in recent years, the underlying cause of motor neurone disease remains unknown. Inflammatory and toxic causes seem unlikely. The concept of premature ageing of the nervous system, Gower's 'abiotrophy'—like the label 'idiopathic epilepsy—was a negative idea, lacking stimulus to further research. Present-day opinion inclines to the view that motor neurone disease is due to a biochemical abnormality in the nutrition of nerve cells and fibres, whereby a disturbance is caused in the enzyme systems concerned with their metabolism.

From the *biochemical* aspect of the many enzyme systems involved in the metabolism of nervous tissue, acid phosphatase activity is considerable in both nerve cells and axons of nerve fibres, and disappears rapidly on division of the cell from its fibre. It is present in non-medullated as well as medullated nerve fibres. Adenosine triphosphatase (ATP) is directly involved in the energy production of muscular contraction. Cholinesterase is the enzyme responsible for the breakdown of acetyl-choline, both at the neuromuscular junction and along the surface of the nerve fibres, as depolarization occurs during nerve conduction. Pseudocholinesterases are found mainly in the walls of blood vessels and in relation to glial cells. Anti-cholinesterases are found (choline acetylase and others) which allow persistence of action of acetyl-choline as required. There is some suggestion that the enzyme acetyl-cholinesterase may play a part in demyelination (Lumsden, 1957).

Work done with the electron microscope has shown that acetyl-choline, manufactured by the mitochondria which collect at the nerve endings, is stored in synaptic vesicles, which flow from the pre- to the post-synaptic membrane on receipt of the nervous impulse (de Robertis and Bennett, 1955). Release of acetyl-choline by cholinesterase is promoted by calcium ion, and retarded by magnesium ion. Fig. 5 illustrates an electron microscope photograph of part of a nerve ending, showing some of these features. Whittaker (1962), in a fascinating account of the structure and function of the synapse, has described the new techniques which have been developed in separating and studying the constituents and biochemical make-up of nerve endings. This increasing knowledge of the anatomy and metabolism of nerve cell, nerve fibre and synapse, as revealed by the electron microscope and by studies of the enzyme systems involved, may later advance our knowledge of motor neurone disease.

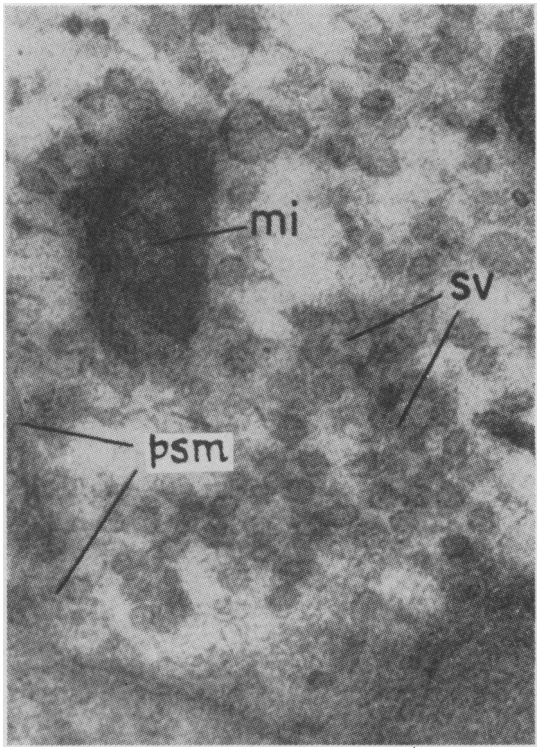

FIG. 5.—Electron micrograph of *part* of nerve ending in neurohypophysis of the toad, showing synaptic vesicles (SV) and mitochondria (mi). psm = presynaptic membrane.

(From de Robertis, E. (1961): Histophysiological Aspects of Signal Transmission in the Nervous System. The Role of the Synaptic Vesicles, *Triangle*, **5**, 76. Reprinted with permission of the author and the Editorial Board of *Triangle*, the Sandoz Journal of Medical Science.)

Of trace metals, no less than 14 have been found constantly in the brain and shown to play

a part in cell metabolism and myelin formation. They may act as both enzyme activators and inhibitors. Copper, for instance, may play a catalytic role in the synthesis of the phospholipids of cell membrane, and therefore in myelin production (cf. 'swayback', a demyelinating disease of lambs in Australia, which results from copper deficiency in the diet). Inhibition of cytochrome oxidase, an important enzyme concerned with cellular respiration, also occurs in copper deficiency, and this, too, may affect phospho-lipid syntheses (Lumsden, 1957). Cholesterol forms an essential part of the lipo-protein complex of the myelin sheath, which has a lamellar structure, with lipid and protein layers alternating. This is thought to be responsible for the high electrical resistance and insulating capacity of the myelin sheath, allowing high conduction velocity. This function is lost in demyelinating nerve fibres. Somewhere in the complex metabolism of myelin, with its multiple enzyme activity, catalytic trace metals and lipo-protein structure, lies a defective link responsible for the demyelination which forms one of the important features of motor neurone disease and of other nervous diseases. As we have seen, this neuro-biochemical abnormality appears capable of transmission on a familial basis. It seems likely that the discovery of the ultimate cause of motor neurone disease now lies in the hands of the neuro-biochemists.

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