Chronic spinal muscular atrophy

JOHN PEARCE AND D. G. F. HARRIMAN

From the Departments of Neurology and Neuropathology, The General Infirmary at Leeds

For many years, neurologists have been aware of the occasional occurrence of motor neurone disease of prolonged duration. Although the aetiology of this disease is still unknown, the descriptions of hereditary amyotrophic lateral sclerosis (reviewed by Espinosa, Okihiro, Mulder, and Sayre, 1962) and the high incidence of motor neurone disease occurring in the Chamorros of the Mariana Islands, with and without the Parkinsonism-dementia syndrome, have reawakened interest in these disorders with particular regard to a possible genetic aetiology (Engel, Kurland, and Klatzo, 1959; Hirano, Kurland, Krooth, and Lessell, 1961).

It is generally acknowledged that varying combinations of amyotrophic lateral sclerosis (Charcot), progressive muscular atrophy (Duchenne and Aran), and progressive bulbar palsy (Duchenne) constitute the syndrome of motor neurone disease; this almost always presents in patients after the age of 40 and terminates fatally within two to four years. Males are affected twice as often as females, whereas the sex incidence is equal in hereditary amyotrophic lateral sclerosis. A further distinguishing feature is the survival for many years of some patients afflicted by hereditary amyotrophic lateral sclerosis. Espinosa et al. (1962) and Wohlfart and Gamstorp (1960) consider that the sporadic form of motor neurone disease is a distinct and separate syndrome and not identical with the dominantly inherited familial form.

Infantile progressive spinal muscular atrophy (Werdnig-Hoffmann disease) differs from motor neurone disease in other ways. It has an early onset and rapid course, although occasionally patients survive in a hopelessly crippled state into early adult life; in contrast to motor neurone disease the spinal cord shows no pyramidal tract degeneration and brain-stem nuclei and cerebellar tracts are involved. In motor neurone disease, recent studies, using the more refined techniques of Marchi staining (Smith, 1960), have shown widespread tract degeneration in the brain. Occasional cases of pure anterior horn cell degeneration have been described (Lawyer and Netzky, 1953; Bonduelle and Bouygues, 1958): in one verified example of 'progressive spinal amyotrophy' (Alajouanine, Boudin, Bertrand, and Scherrer, 1950) and another of 'familial progressive bulbar-spinal muscular atrophy' (Magee, 1960) there was no pathological evidence of pyramidal tract degeneration so that it is tempting to conclude that a pure anterior horn cell degeneration of prolonged course may exist, but proof must await post-mortem examination by more modern methods.

An uncommon variant of chronic anterior horn cell degeneration was described by Wohlfart, Fex, and Eliasson (1955) and by Kugelberg and Welander (1956). This syndrome was characterized by (1) wasting, weakness, and hyporeflexia predominantly affecting the proximal muscles and simulating muscular dystrophy; (2) an onset in childhood or adolescence; (3) a very slow rate of progression; (4) a hereditary transmission as a non-sex-linked recessive gene; and (5) a neurogenic pattern on muscle biopsy and electromyography. In a recent review Smith and Patel (1965) were able to discover 60 reported examples. The average age of onset was 9 years of age and the average duration of the disease was over 18 years. A positive family history was obtained in 71% of patients. Almost all patients had proximal weakness; distal weakness was present in 31% of patients in the upper limbs and in 25% of patients in the lower limbs. Fasciculations were present in over one third, and electromyography showed a neurogenic lesion in every patient recorded. In 70% of patients, there was evidence of neurogenic atrophy in the muscle biopsy.

Wohlfart (1942) had already described three cases which he at first considered to be a transitional form between peroneal muscular atrophy and muscular dystrophy.

The evidence therefore suggests that the Wohlfart-Kugelberg-Welander syndrome is an inherited disorder of childhood or adolescence with a slow rate of progression, and that its basis lies in chronic degeneration of the anterior horn cells of the spinal cord. Magee and DeJong (1960) reported three patients who differed slightly. Transmission was as a simple dominant gene; there was reasonable evidence that the disease became static for a period of many years, and instead of hyporeflexia, the deep tendon reflexes were normal. These authors thought that the retention of reflexes was probably
not of major consequence. Tsukagoshi, Nakanishi, Kondo, and Tsubaki (1965) reported a further five patients with this syndrome who also showed differences: (1) the onset of the disease appeared to be in adult life; (2) bulbar palsy was present in three of the five patients; and (3) although the pattern of inheritance was not clear, a dominant gene appeared to be operative in at least one of the four families.

In a review of 53 patients suffering from amyotrophic lateral sclerosis, Lawyer and Netzky (1953) recorded two patients of unusual interest. The first (case 7), who survived for four years, was a woman aged 54 in whom a muscle biopsy showed atrophy of motor units and 'dystrophic' changes in muscle fibres of normal size. The second patient (case 8) commenced with the disease at the age of 37, but survived till 72 when death was due to serum hepatitis. The early onset and prolonged course correspond precisely with those in our own patients to be described. Moreover pyramidal deficit became apparent in this patient only after an interval of 30 years.

All these reports illustrate the overlap between classical amyotrophic lateral sclerosis and spinal muscular atrophy, and reasons will be given to support the view that they represent intermediate forms of a range of degenerative diseases which merge into one another.

It is apparent that the many variations which have been recorded in this group of diseases have led to a state of confusion. The present report attempts to classify the adult spinal muscular atrophies and draws attention to histological myopathic features which may develop as a result of longstanding, progressive denervation.

CASE 1  W. R., a man, aged 69 (NPB.229/65), in 1918, following a period of transient low back pain, first noticed weakness of the left leg when riding a pedal cycle. It may have remained static for some time, but in 1926 he started to walk with a limp. At some ill-defined time in the next 20 years, he gradually became aware of slight weakness of the right leg, and of weakness and wasting of the muscles around both shoulders. His general health remained good. His parents died at the...
ages of 78 and 82 without neurological illness, and were unrelated. There were no siblings and his grandparents, cousins, uncles, and aunts suffered from no neuromuscular disease of which he was aware. Two sons and one daughter in their 40s were alive and well.

The cranial nerves were normal, and in particular there was no wasting of the tongue. There was marked wasting and weakness of the shoulder girdle muscles greater on the left side (Figs. 1 and 2). The weakness and wasting involved the deltoids, spinati, pectorals, biceps and triceps muscles and to a less extent the extensors of the wrist and fingers and the intrinsic muscles of the hands. There was constant fasciculation in all of the wasted muscles, most marked proximally. The deep tendon reflexes were normal in the upper limbs. In the legs there was diffuse weakness and wasting of the glutei, hip flexors, quadriceps, and hamstrings (Figs. 3 and 4). The anterior tibial and peroneal muscles were wasted and weak on the left side with a resultant dropped foot. There was slight weakness and wasting of the muscles below the knee of the right side. Both knee and ankle jerks were absent, the left plantar response flexor and the right equivocal or extensor. Sensation was normal.

Investigations for systemic diseases were negative as were radiographs of the chest, cervical and lumbar spine.

Chromosomal studies were normal, the modal number being 46; sex chromatin negative.

The cerebrospinal fluid was normal.

Electrophysiological studies Electromyography showed evidence of a widespread neurogenic lesion of central type in all four limbs.

Nerve conduction studies were within normal limits.

- **Serum enzymes** S.G.O.T. 24 units (laboratory normal 14 to 41 units); S.G.P.T. 28 units (laboratory normal 1 to 32 units); creatine kinase 2-6 units (laboratory normal 0-5 to 4 units).

**Histology** Motor-point muscle biopsies were performed under local anaesthesia by the method previously described (Harriman, 1961). Occasionally (where stated) a simple muscle biopsy was performed. The right deltoid was light red and just reacted at the muscle surface motor point to a galvanic current of 3V/0-05 msec. (normal 1-5V/0-02 msec.). The muscle fascicles consisted of fibres of normal or large calibre, sometimes with central nuclei. Occasionally there were examples of fibre necrosis with attendant macrophages (Fig. 5). The perimysium was in places broad, and contained fat and occasional muscle nuclear clumps, as if whole muscle fascicles had virtually disappeared (Fig. 6). There were no large groups of narrowed fibres. Some of the large fibres in longitudinal
FIG. 5. Right deltoïd of case 1 (longitudinal section). Fibre necrosis. Haematoxylin van Gieson stain (H.V.G.).

FIG. 6. Right deltoïd of case 1 (transverse section). Broad perimysium containing a few clumped nuclei, remnants of muscle fibres (at arrows). Haematoxylin van Gieson.

FIG. 7. Right deltoïd in case 1 (longitudinal section). Rows of internal nuclei parallel to fibre cleavage. Haematoxylin van Gieson.
section showed parallel orientation of the internal nuclei as a prelude to cleavage (Fig. 7). The motor nerve supply showed pronounced branching of subterminal fibres and collateral innervation indicating neurogenic disease. A simple muscle biopsy was performed on the left vastus internus. It showed marked atrophy, and fascicles consisting mostly of adipose tissue and scattered nuclear clumps in islets of sarcoplasm (so-called 'muscle giant cells'). There were no groups of narrowed fibres, although in one or two fascicles scattered narrow fibres were numerous; an intact intramuscular nerve was included. In this muscle atrophy was too advanced for diagnosis.

**CASE 2** S. B., a man aged 42 (NPB.189/63 and NPB.50/64), seven years ago, or possibly earlier, noticed weakness of the feet. For four years both legs felt weak, and he had difficulty in getting out of low chairs. Sometimes painful 'cramp' occurred in all four limbs. In the last three years wasting of the legs became obvious, especially the left.

Weakness was noticed in the arms for two years, and caused difficulty in gripping and lifting objects. His general health had remained excellent, and he had no relevant previous illness. There were seven brothers and two sisters none of whom had any neurological disease; his parents were unrelated.

The cranial nerves, facial muscles and tongue were normal on examination. The limbs showed asymmetrical, proximal, and distal atrophy, with profuse fasciculation. In the upper limbs gross weakness and wasting were present, greater on the right side, affecting the serratus anterior, spinati, biceps, brachioradialis, long extensors of the wrists and fingers, and the intrinsic hand muscles. Sensation was not impaired, and the deep tendon reflexes were preserved and equal in both arms. The sternomastoids, trapezi, and pectoral muscles were spared.

Weakness was present in upper and lower abdominal muscles, but the abdominal reflexes were normal. In the lower limbs weakness, wasting, and fasciculation were most marked in the quadriceps, anterior tibials, peronei, gastrocnemius, and soleus muscles. The right leg was more affected than the left, and the distal muscles were more involved than the proximal. Sensation was again normal. The knee jerks were normal and equal, but both ankle jerks were significantly depressed. The plantar responses were flexor. Coarse fasciculation was observed in the wasted muscles on numerous occasions, but only in the last 18 months.

Many laboratory tests (including those of the cerebrospinal fluid) were repeatedly within normal limits.

*Serum enzymes* S.G.O.T. 22, 15 units; S.G.F.T. 24, 19 units; aldolase 13-3, 9-0, 2-6 units; creatine kinase 14-6 units.

*Electrophysiological studies* The pattern obtained was identical in all muscles examined, and consisted of discrete polyphasic motor unit activity, the amplitude of potentials being 6 to 9 mv. Nerve conduction studies were within normal limits. Identical findings were found on a second examination, and were strongly suggestive of a central neurogenic lesion such as motor neurone disease.

*Histology* A muscle biopsy was taken on 1 June 1963. The exposed left gastrocnemius was yellow and was unfortunately thought unsuitable for motor point biopsy. The fascicles consisted largely of fat, but there were a few areas where muscle fibres were relatively numerous and showed haphazard variation in calibre (Fig. 8), hypertrophied fibres with parallel rows of central nuclei, fibre splitting, and 'muscle giant cells' (Figs. 9 and 10). There were no groups of narrowed fibres. A few small basophil fibres were encountered. At this stage a histological diagnosis of muscular dystrophy was suggested.

A year later a second biopsy of the right palmaris longus was performed. The exposed muscle was red with a brown tinge, responding to 2V at 0-05 msec. The muscle fibres in general were of normal calibre, but there were a few larger fibres with central nuclei and a few isolated narrow fibres. Vital staining of the motor nerve supply showed collateral innervation, beading of subterminal fibres, and growth cones, and indicated neurogenic disease.

The widespread wasting and weakness, the profuse fasciculation and the electromyographic studies all clearly indicated degeneration of anterior horn cells. Motor neurone disease is, however, uncommon in the 30s, and after five years it would be most unusual to find a patient without upper motor neurone signs, without bulbar involvement, and still able to work. This patient therefore suffered from an anterior horn cell lesion of unusually early onset and remarkably slow progression.

The high serum aldolase and creatine kinase values and the first muscle biopsy suggested the possibility of a myopathic lesion (Pearce, Pennington, and Walton, 1964), but the overall picture, including the second biopsy, indicated a neurogenic amyotrophy with unusual 'myopathic' features.

**CASE 3** W.H., a man aged 62 (NPB.253/65), noticed weakness of his right leg when he was aged 24. There may have been slight weakness earlier in his life, but he was able to run and play football at school without difficulty. There was no noticeable change, but in 1941 when aged 38 he was discharged from the army because of weakness of the right leg. At 48 his walking further deteriorated, and because of the development of a dropped foot on the left side a caliper was fitted. Examination then disclosed slight weakness of the dorsiflexors of the right foot, gross weakness and wasting of the anterior tibial and peroneal muscles of the left leg, a depressed left ankle jerk, no sensory loss, and flexor plantar responses.

At 62 his disability was still mild, and he had worked in an iron foundry for the previous 20 years. The unrelated parents died in their 70s, and his five brothers, uncles, aunts, and cousins had no symptoms similar to his own.

The cranial nerves, including muscles of the face, neck, and tongue, were normal. Early weakness and wasting were now detected in the small muscles of the hands; proximal upper limb muscles were normal. Variable fasciculation was repeatedly observed in both upper
FIG. 8. *Left gastrocnemius in case 2 (transverse section) to show haphazard variation in fibre calibre of muscle surviving within adipose and condensed collagenous tissue. Haematoxylin van Gieson.*


limbs, and the deep tendon reflexes were all pathologically brisk. The abdominal muscles and reflexes were normal.

In the right lower limb, there was moderate weakness and wasting in the proximal muscles, and slight in the distal; the left lower limb showed an opposite distribution, with slight proximal weakness and gross distal involvement producing a flail paralysed foot. Profuse fasciculation was seen in both legs. The knee jerks were normal and equal, the right ankle jerk normal, the left ankle jerk absent. The right plantar response was extensor, the left flexor. Sensation was normal.

Many laboratory tests were negative. Radiographs and examinations of the cerebrospinal fluid showed no significant abnormalities.

*Serum enzymes* S.G.O.T. 12 units, S.G.P.T. 9 units, and creatine kinase 7-6 and 2-4 units.

*Electrophysiological studies* Electromyography showed discrete motor units with amplitude up to 10mv on voluntary contraction. There was a tendency to superimposition of abnormally large discrete motor units. Conduction in the left lateral popliteal nerve was within the normal range but the action potential was of very small amplitude; the right lateral popliteal nerve conducted normally. These findings indicated a neurogenic lesion of central type in both the arm and leg muscles.

*Histology* The exposed right vastus internus was dark red and reacted normally. Most fascicles were composed of large round or polygonal fibres, often showing central nuclei, and included a few scattered nuclear clumps (Figs. 11 and 12). The internal nuclei in a few of the largest fibres were arranged in several parallel rows and led to fibre cleavage. The motor innervation showed evidence of neurogenic disease by branching of sub-terminal axons and collateral innervation (Fig. 13).

*The sural nerve* Stained by the Palade and Marchi techniques, the sural nerve showed no loss of myelinated fibres and no sign of active degeneration (Fig. 14). The conclusion was of central neurogenic atrophy without evidence of lower sensory neurone degeneration.

**CASE 4** G. K., a man aged 64 (NPB.327/65), thought he was born with weakness of the left arm, and although, as examination showed, this was not the case, it was clear that he had had weakness of the left arm since childhood.

---

**FIG. 11.** Right vastus internus in case 3 (transverse section). Large fibres with internal nuclei and variation in fibre size. Haematoxylin van Gieson.

**FIG. 12.** Right vastus internus in case 3 (longitudinal section). A few 'muscle giant cells' and large fibres with internal nuclei. Haematoxylin van Gieson.
At school he was teased because he could not bend his left elbow properly, and he always found it difficult to take his handkerchief from his breast pocket. He was unable to climb ropes in the gym at school, but was able to play football without difficulty. He thought the weakness of the left arm had not progressed. In 1931, at the age of 31, he noticed difficulty in running, which would cause him to fall quite suddenly. During the next 30 years, the weakness of the legs gradually progressed and he tended to fall, particularly if he changed the speed of his walking or attempted to run. In the last 10 years, he noticed wasting of the legs, particularly on the left side, and in 1962 a diagnosis of multiple sclerosis was made by a general physician. In 1965 he was still able to walk for a quarter of a mile unaided. He had no sensory symptoms, and speech and swallowing were always normal.

His general health was good apart from a perforated peptic ulcer which was repaired on two occasions and he had had a benign tumour of the bladder treated surgically. His parents were unrelated and two brothers and one sister were alive and well. His marriage was sterile.

Examination showed no abnormality in the cranial nerves. In the upper limbs there was wasting and weakness of the shoulder girdle muscles, the left much more than the right where fasciculation was well marked. The tendon reflexes were absent in both arms and sensation was normal. The abdominal reflexes were brisk and equal. There was diffuse weakness of both lower limbs involving proximal and distal muscles, but wasting was confined to the anterior tibial groups. There was mild claw deformity of both feet, the left leg was weaker than the right and fasciculation was present. The knee and ankle jerks were pathologically brisk on both sides and the plantar responses sharply extensor. There was no sensory or cerebellar deficit.

An E.M.G. showed definite changes of central neurogenic type in both arms and legs, most marked on the left side.

S.G.O.T. was 26 units, S.G.P.T. 9 units.

Histology The exposed left vastus internus had a brown tinge and reacted at 2-3V., 0-02 msec. Many muscle fascicles were normal, but in some there were isolated nuclear clumps or 'muscle giant cells' scattered between normal and hypertrophied fibres (Fig. 15). A number of these contained internal nuclei and showed fibre cleavage. There were no groups of equally narrowed muscle fibres. The motor nerves showed collateral innervation (Fig. 16), and intramuscular growth cones typical of partial denervation.
Chronic spinal muscular atrophy

DISCUSSION

Although Wohlfart was not the first to describe the syndrome of motor neurone disease of long duration, he was certainly responsible for first drawing attention to its neurogenic basis, and for emphasizing its superficial similarity to muscular dystrophy. For this reason it is suggested that if an eponym must be used Wohlfart's syndrome is the most appropriate. Since the clinical features are diverse, and the cause unknown, it seems reasonable to adopt 'spinal muscular atrophy' as a generic term; it emphasizes the feature common to all the variants, and can be suitably qualified.

In the earlier descriptions the following characteristics were reported (Wohlfart, 1942; Wohlfart et al., 1955; Kugelberg and Welander, 1956): proximal muscular atrophy; slow rate of progression; fasciculation; onset usually in childhood or adolescence; inheritance as an autosomal recessive and the neurogenic nature of the disease confirmed by muscle biopsy and electromyography. Signs of bulbar and pyramidal tract involvement were absent.

To these features have been added: (1) the occasional inheritance as a dominant gene; (2) apparent lack of progression of the disease; (3) uniformly normal instead of diminished deep tendon reflexes (Magee and DeJong, 1960); (4) the onset of the disease in adult life; (5) the presence of bulbar palsy (Tsukagoshi et al., 1965).

The present report includes the features of onset in adult life; sporadic occurrence with no evidence of a hereditary basis; gross asymmetry of muscles involved in the same patient; both proximal and distal muscle wasting; signs of pyramidal tract lesion; myopathic change in muscle biopsies and serum enzyme studies.

AGE OF ONSET The age of onset in three of our cases was in early adult life. In only two of the 58 patients
reviewed by Smith and Patel (1965) was the onset after the age of 20. In the past this has been considered to be an important feature of this syndrome although occasional exceptions, such as the two already mentioned, and those of Tsukagoshi et al. (1965), have been reported. Spinal muscular atrophy can occur at almost any age, and an onset in early adult life is quite compatible with this diagnosis.

FAMILY HISTORY As has been previously mentioned, most examples of the syndrome appear to be inherited as a simple autosomal recessive. Occasional cases, such as some of those reported by Kugelberg and Welander (1956), have a negative family history. A dominant inheritance was present in the family described by Magee and DeJong (1960). The disease in all of the patients reported in the present paper appears to occur sporadically, and in three patients recently reported by Gross (1966).

PATTERN OF MUSCLE INVOLVEMENT In our patients, there was a considerable degree of asymmetry in the pattern of muscle involvement. This is a known feature in the sporadic form of motor neurone disease, but in most of the examples of Wohlfart’s syndrome it has not been stressed.

In most of the recorded cases, the proximal distribution of the muscle wasting has been emphasized. It was certainly present in our patients, but considerable distal amyotrophy could coexist.

Distal amyotrophy was recorded in six of the 16 patients reported by Kugelberg and Welander (1956) and hence the term ‘hereditary proximal neurogenic muscular atrophy’ (Tsukagoshi et al., 1965) is not a strictly accurate designation.

PYRAMIDAL SIGNS Pyramidal signs have been apparent in two of our patients as shown by brisk deep tendon reflexes and an extensor plantar response. This feature has not been previously reported. Magee (1960) suggested that the preservation of deep tendon reflexes did not necessarily imply pyramidal disease in patients who have in addition lower motor neurone signs. The reverse argument is equally true: lower motor neurone disease may mask overt corticospinal lesions since an intact lower motor neurone pathway is necessary for the production of alterations of tone, tendon reflexes, and abnormal superficial reflexes. It is suggested that such lesions may well have been present in the patients described by Magee, and possibly in some of the other reported cases. Although the brunt of the disease is borne by the anterior horn cells, there may well coexist lesser lesions in the corticospinal pathways such as occur in the sporadic form of motor neurone disease.

SERUM ENZYME STUDIES Two of the patients (cases 1 and 2) showed slight abnormalities of serum muscle enzymes. Elevations of serum levels of creatine kinase and aldolase, and in lesser degree of the transaminases, are characteristic of muscular dystrophy. The elevation implies a leakage of muscle enzymes into the serum through a damaged muscle cell membrane. In acquired myopathies raised enzyme levels are relatively uncommon, and in neurogenic muscular atrophy very rare (Pearce et al., 1964; Pearce, 1965). The abnormal levels in the patients reported here are interpreted as being indicative of destruction of the cell membrane, a result of neurogenic atrophy of unusually long duration. This corresponds to the histological findings in these patients.

MYOPATHIC FEATURES All of the adult patients showed ‘myopathic’ features in their muscle biopsies, and in case 2 they were so marked as to lead to an initial diagnosis of muscular dystrophy which we now believe to be incorrect. The discovery of what purports to be a myopathy in a patient, who is otherwise on clinical, genetic, and electromyographic grounds suffering from a neurogenic disorder, is of some diagnostic importance and requires to be discussed in some detail.

By myopathic features we mean those histological changes which are ordinarily seen in primary disorders of muscle such as muscular dystrophy and chronic polymyositis, and include haphazard variation in calibre of fibres, fibre splitting, central migration of sarcolemmal nuclei, muscle giant cells, fibre necrosis, phagocytosis, and regeneration. (We are not considering here large interstitial inflammatory cell collections which we regard as more specifically myositic.) But none of these lesions is specific, individually or even in combination, and a diagnosis of muscular dystrophy, for example, on histological grounds can only be made under favourable circumstances before the disorder is advanced.

In view of the lack of specificity it is not surprising to find each of these changes at one time or another in known neurogenic disease. As a rule denervation of human muscle results in equal narrowing of those muscle fibres supplied by the affected axon, and in the case of disease of the anterior horn cell entire motor units show the well-known atrophy of large groups of fibres. Narrowed fibres may persist for years, but at some unspecified time may undergo further change and result in nuclear clumps, muscle giant cells, or disappear completely. This sequence has been seen by one of us (D.H.) occasionally in a large series of motor point muscle biopsies and is emphasized by Adams (1964), amongst others. Experimental denervation is followed by degenera-
tive changes (Denny-Brown, 1960). When fibres hypertrophy to compensate for denervation of others, it is not uncommon for nuclei to migrate internally and even for segmentation (fibre splitting) to occur. It may be seen in motor neurone disease as well as in the myopathies, and internal nuclei in large fibres are described in clinical neurogenic disease by Greenfield, Shy, Alvord, and Berg (1957). There appears to be a difference in the end result of one episode of denervation (as in poliomyelitis) and a progressive denervation. In the first, denervated units are at the same stage of atrophy, whereas in the second different units and subunits show varying degrees of narrowing. Poliomyelitis may lead to such severe atrophy that only a few hypertrophied fibres with internal nuclei persist in a sea of fat (as we have seen 40 years after the infection), but typical myopathic features are not seen as a late sequel to poliomyelitis (Sissons, 1965). The remaining myopathic features of muscle necrosis and regeneration are without specificity of any sort and are found in many conditions, including neurogenic disease.

Although myopathic changes are not common in progressive degenerations of the lower motor neurone, they have been reported both singly and in combination. In case 7 of Lawyer and Netzky (1953), there was motor unit atrophy and in addition 'definite dystrophic changes'. Their illustration shows nuclear aggregation in part of a muscle fibre of normal size, and a very large fibre with internal nuclei. We do not agree that this is sufficient for a diagnosis of dystrophy. They believed that primary disease of the central nervous system and of muscle may have been coincidental. Magee and DeJong (1960) reported in one of their cases of neurogenic muscular atrophy of 37 years' duration large fibres with internal nuclei surviving in adipose tissue. Tsukagoshi et al. (1965) mention myopathic features such as 'central nuclei, necrosis, architectural abnormalities, and round cell infiltration' in addition to the more usual pattern of group atrophy in their five cases. The observations of Wohlfart (1942) agree: he reported 'slight dystrophy-like changes microscopically'. Slight but similar changes were seen in case 5 of Wohlfart et al. (1955), and the authors stated that the significance of these changes was not clear. They felt that the appearance might be secondary to a neurogenic lesion of long duration, but that it was not possible to exclude a combination of neurogenic changes and primary myopathy. Garvie and Woolf (1966) have recently reported two families affected by the 'Kugelberg-Welander' syndrome. In one patient, a woman aged 32 years examined 30 years after the onset, considerable variation in the diameter of muscle fibres was described. In one of the three patients reported under the title of 'proximal spinal muscular atrophy', Gross (1966) was impressed by myopathic features, shown by enzyme studies and histology. The muscle necrosis and basophilia described we consider to be entirely non-specific.

In progressive neural muscular atrophy or Charcot-Marie- Tooth disease neurogenic denervation occurs over particularly long periods of time and features which resemble myopathy are known to occur. In comparing muscle biopsies from 17 patients with Charcot-Marie-Tooth disease with those from 14 patients with amyotrophic lateral sclerosis, Hasse and Shy (1960) found that 10 of the first group and one of the second showed a mixed neuropathic and myopathic picture. Similar findings were reported in one case by Lucas and Forster (1962).

The association of myopathic changes with prolonged neurogenic disease is thus established, and appears to us to be too frequent to be an association of different diseases, either by chance or by genetic linkage. Two important factors in their development are the progressive nature of the degeneration of the lower motor neurone and its chronicity. Other unknown factors must also operate as myopathic changes are not inevitable. If at times muscle biopsy

**TABLE I**

**CLASSIFICATION OF THE SPINAL MUSCULAR ATROPHIES**

<table>
<thead>
<tr>
<th>Form of the Disease</th>
<th>Eponym</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor neurone disease in Chamorros</td>
<td>Kurland and Mulder</td>
<td>Dominant</td>
</tr>
<tr>
<td>Infantile spinal muscular atrophy</td>
<td>Werdnig and Hoffmann</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Hereditary (juvenile) amyotrophic lateral sclerosis</td>
<td>Holmes</td>
<td>Dominant</td>
</tr>
<tr>
<td>Juvenile spinal muscular atrophy</td>
<td>Wohlfart, Kugelberg and Welander</td>
<td>Autosomal recessive, dominant</td>
</tr>
<tr>
<td>Non-hereditary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortico-striato-spinal degeneration</td>
<td>Jakob and Creutzfeld</td>
<td></td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Charcot and Joffrey</td>
<td></td>
</tr>
<tr>
<td>Progressive bulbar palsy</td>
<td>Duchenne</td>
<td></td>
</tr>
<tr>
<td>Adult spinal muscular atrophy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
reveals a myopathic picture in neurogenic disease, it is obvious that staining of the innervation will help in differentiating the two conditions. This was illustrated by Garvie and Woolf (1966) and in our cases. Attention is drawn to the myopathic changes in order to indicate a possible source of diagnostic confusion.

In reviewing the variants of this syndrome it becomes apparent that there exists a wide range of disorders whose common factor is chronic degeneration of the upper and lower motor neurones. The genetic pattern of inheritance, the anatomical distribution of the disease, and the natural history vary considerably in the different groups and form the basis on which the individual syndromes have been delineated.

Table I is an attempt to classify the spinal muscular atrophies on a clinico-genetic basis which is limited by our present ignorance of the fundamental aetiological factors.

**SUMMARY**

Four patients suffering from unusually prolonged spinal muscular atrophy are described. Although similar to the syndrome described by Wohlfart, Kugelberg, and Welander, several differences are reported. These include sporadic occurrence in adult life, gross asymmetry, distal and proximal distribution, pyramidal signs, and a myopathic type of change on muscle biopsy.

The histological features of prolonged neurogenic atrophy are discussed, and it is suggested that changes simulating a primary myopathy may result from this process.

A classification of the spinal muscular atrophies is suggested.

The patients described are under the care of Dr. Hugh Garland, to whom our thanks are due. We are indebted to Dr. D. Taverner for the electrophysiological studies. The histological sections were prepared by Miss P. M. Allen and Miss P. L. Stocks.

**REFERENCES**


