

Syndrome of Continuous Muscle Fibre Activity

HISTOCHEMICAL, NERVE TERMINAL AND END-PLATE

STUDY OF TWO CASES

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SUMMARY

Twelve years ago two patients with a syndrome of continuous muscle fibre activity were described and the site of the abnormal discharge localised to the motor nerve terminals. These cases have been restudied electrophysiologically, by muscle histology and histochemistry and by motor nerve terminal and end-plate preparations. The neurological nature of the disorder is confirmed, and the relevant effects of drugs acting on motor nerve terminals discussed. The original cases responded dramatically to diphenylhydantoinate, and one of the patients has improved to a point where he no longer requires therapy, thus confirming the acquired nature of the disorder.

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In 1961 the electromyographic and clinical findings of two patients were recorded under the title 'A syndrome of continuous muscle fibre activity' by Isaacs.⁵ The cases were both males, one a boy aged 12 years and the other a man of 53 years, who presented with symptoms and postural disturbances resulting from involuntary continuous muscle activity, characteristic of the fully-developed stage of this disorder (Figs 1 and 2). This syndrome has since been confirmed by several well-documented case reports.^{3,4,9,10,12,15,20,21} The cases were quite distinct from the myotonias and occurred sporadically. The aetiology remains unknown, though Wallis *et al.*²⁰ suspected dichlorophenoxyacetic acid (2,4-D) poisoning in one case. The condition is progressive unless treated with diphenylhydantoinate as suggested by Isaacs⁵ or with carbamazepine as reported by Mertens and Zschocke¹² in 1965. Prior to the description of this disorder in 1961, such cases must have been classified as myotonia or myokymia since the characteristic and specific nature of the persistent discharge from the motor nerve terminals was not appreciated.

CLINICAL DESCRIPTION

The condition affects males and females of any age. The patients complain of stiffness of the muscles, and difficul-

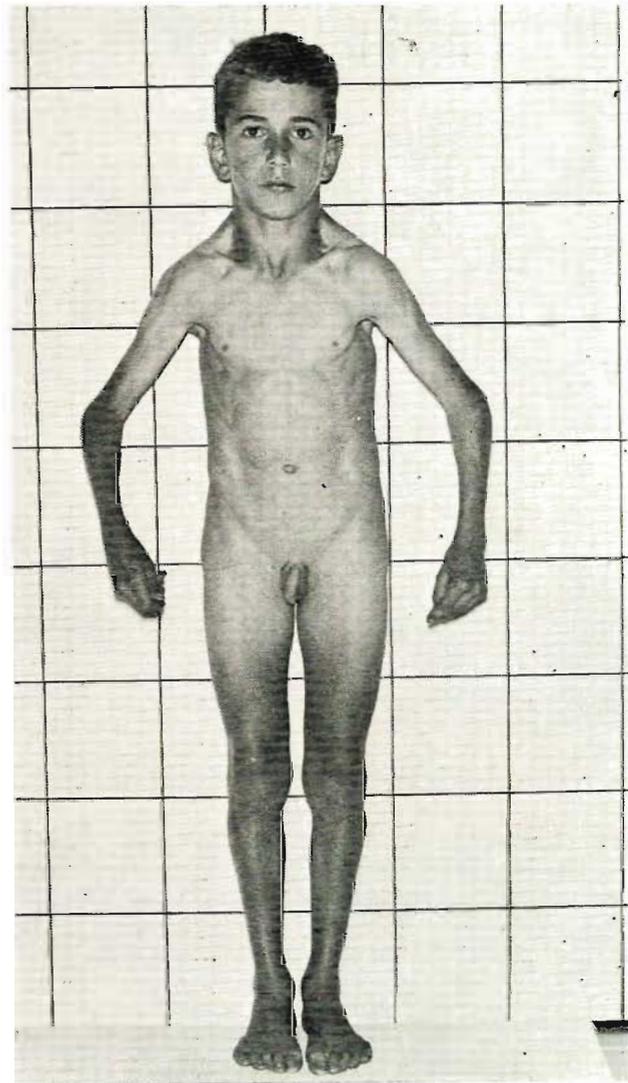


Fig. 1. Patient 1 before treatment.

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ty with voluntary movement, owing to a great increase in resistance within the muscles themselves. They complain of difficulty with chewing and occasional difficulty with breathing. There are no complaints of sphincteric or sensory disturbances.

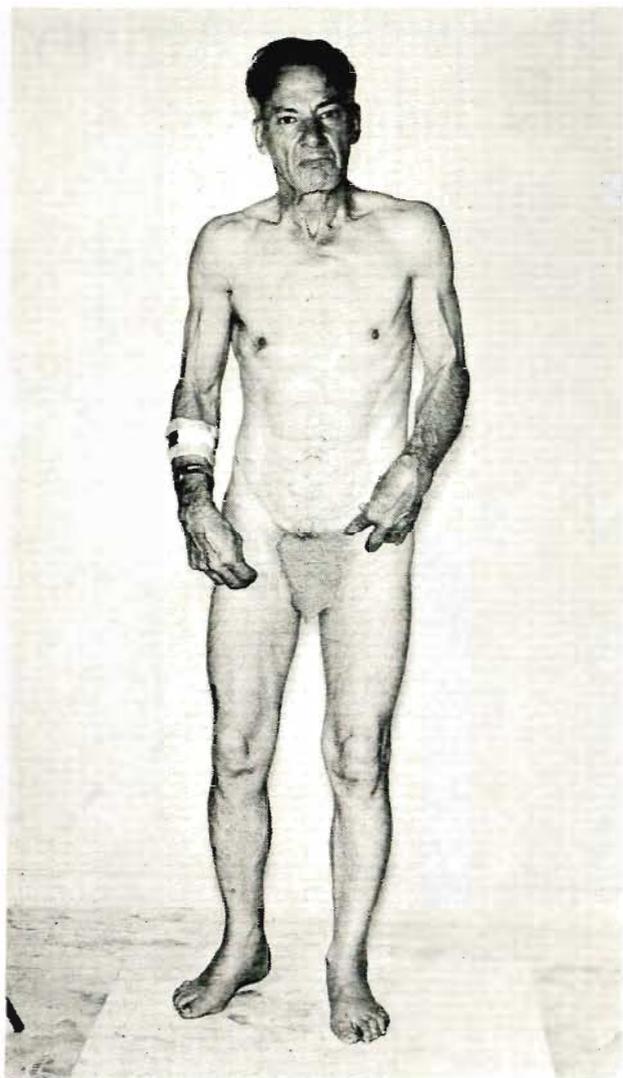


Fig. 2. Patient 2 before treatment.

On examination the sensory nervous system is completely normal but the voluntary muscles are in a state of continuous involuntary contraction. In addition to this involuntary activity there is evidence of continuous fasciculation, some fine and some coarse, occurring in the muscles. The fasciculation is particularly noticeable in the facial muscles and especially in the eyelids. The fasciculations are variable in place and intensity, and the occurrence of synchronous fasciculation activity causes the occurrence of interspersed occasional undulations over wider areas of the muscle, an appearance which was referred to as myokymia by Schultze¹⁷ in 1895. Passive movement of the limbs meets with increasing resistance as the muscles are stretched. The continuous involuntary activity causes the voluntary movements to be slow and restricted, and this is particularly noticeable in the more peripheral muscles. Because of the abnormal workload all voluntary movements fatigue very rapidly. The extra-ocular

muscles do not seem to be affected and swallowing remains normal, though jaw movements may be slow and stiff. Respiratory movements are restricted and dyspnoea may be evident on exertion. The abnormal activity of the muscle persists during sleep. The tendon reflexes are usually unobtainable owing to the continuous state of muscle activity, but the cremasteric reflexes can usually be elicited. The patients feel warm and, particularly in the summer months, sweat excessively.

INVESTIGATIONS

Blood, cerebrospinal fluid, X-ray films, enzyme and metabolic studies of these patients were normal.^{8,9,20,21} The basal metabolic rate was markedly raised because of abnormal muscle activity. Electrocardiograms were normal and demonstrated the interference from the limb and chest muscle activity.

The key to diagnosis of the syndrome rests with the electrophysiological investigations. Electromyography demonstrates the state of continuous activity of the muscles. The recordings reveal a persistent, rapid dysrhythmic discharge, consisting of a mixture of motor unit activity and low-voltage short-duration activity, which was thought to indicate both single muscle fibres and motor units with varying degrees of fibre depletion (Figs 3 - 5). Recruitment of motor unit activity on voluntary contraction is difficult to assess, but in less involved muscles appears to be normal. A period of electrical silence follows each period of strenuous activity and lasts for 10 - 20 sec. There is no evidence of myotonia. In less involved muscles occasional repetitive bursts of closely situated motor unit activity

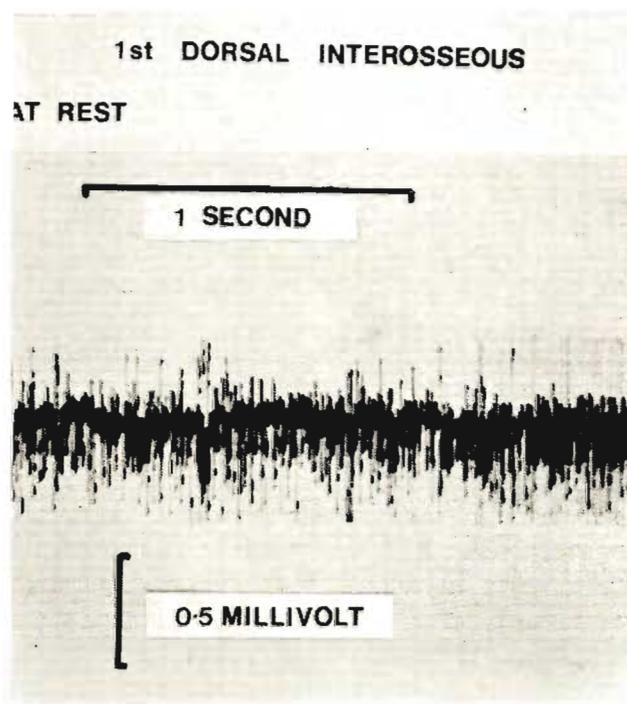


Fig. 3. Spontaneous motor unit activity.

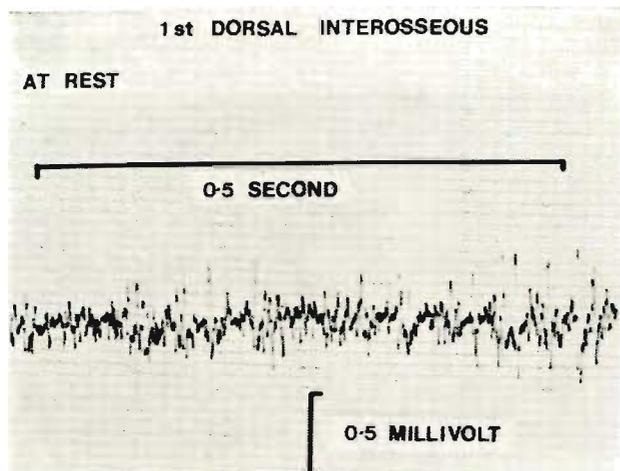


Fig. 4. Fractionated motor unit activity.

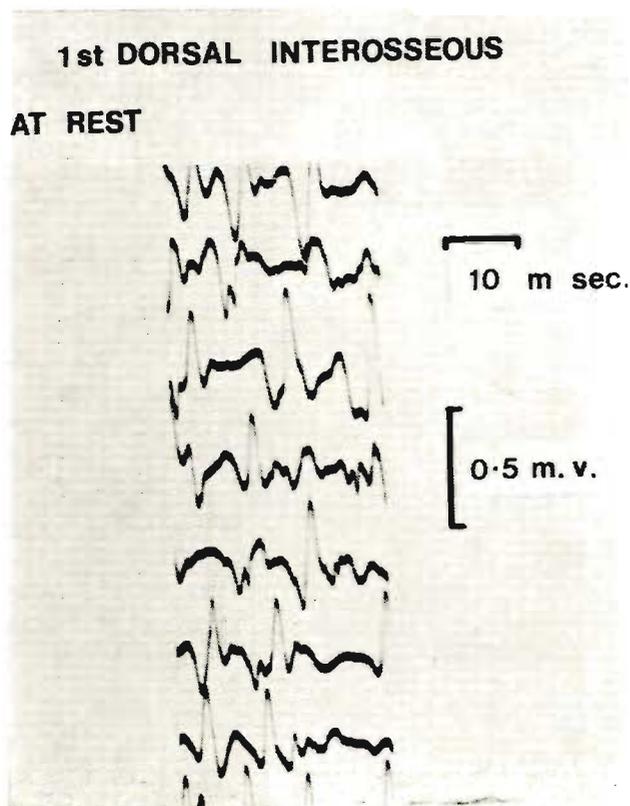


Fig. 5. Single fibre activity.

are obvious, and these give rise to the coarse undulating movements seen in the muscle. Nerve conduction in both motor and sensory fibres was found to be at the lower limits of normal and the terminal latencies may be prolonged.^{9,20}

The site of the abnormal discharge causing the muscle fibre activity was originally located at the motor nerve terminals by the use of the various blocking procedures.³ The use of myoneural blocking or depolarising agents

causes the continuous activity to disappear, indicating the dependence of the involuntary muscle activity on neural transmission. The use of procaine nerve blocking, both proximal and more distal, as well as spinal anaesthesia, does not abolish the activity, indicating that the major area of spontaneous discharge is located in or near the motor nerve terminals. Conventional muscle biopsy sections stained with haematoxylin and eosin show the presence of scattered atrophic fibres and marked variation in fibre size in the rest of the muscle.¹

THE PRESENT STUDY

Since the original cases have been followed for just on 12 years, it was decided to subject them to further muscle studies. In patient 2, now aged 65 years, treatment was discontinued 2 years ago since his symptoms had gradually improved to a level where therapy was no longer necessary.

Biopsy specimens were obtained under local anaesthesia, muscle tissue being removed from the posterior third of the left deltoid and anterior tibial muscles. Separate pieces were used for histochemical analysis and for motor nerve terminal and end-plate study. The histochemical analysis included phosphorylase, NAD diaphorase, myofibrillar ATPase, and mitochondrial ATPase stains. In addition to this the muscle was stained with haematoxylin and eosin, with a trichrome stain as modified by Engel and Cunningham,² and a PAS stain for glycogen, together with a salivary diastase-digested control. The motor nerve terminals and end-plates were stained by chloro-auric acid using a modification of the Ranvier method.

The histological and histochemical findings were practically identical in both cases. The haematoxylin and eosin sections revealed considerable variation in muscle fibre size with average diameters varying between 10 and 180 μm . There were numerous aggregates of muscle cell nuclei, the remnants of atrophied fibres. The glycogen content of the cells was normal and there was no evidence of nemaline rod formation. The feature of the histochemical staining was the very significant grouping of individual cell types, and only in very few areas was any semblance of the normal checkerboard pattern maintained (Figs 6-8).

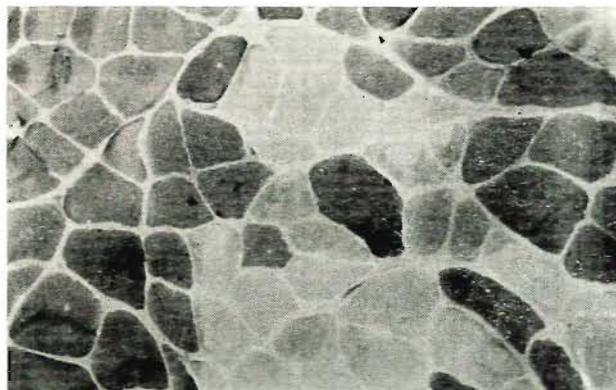


Fig. 6. Note abnormal grouping of individual fibre types (myofibrillar ATPase $\times 100$). Serial section with Fig. 7.

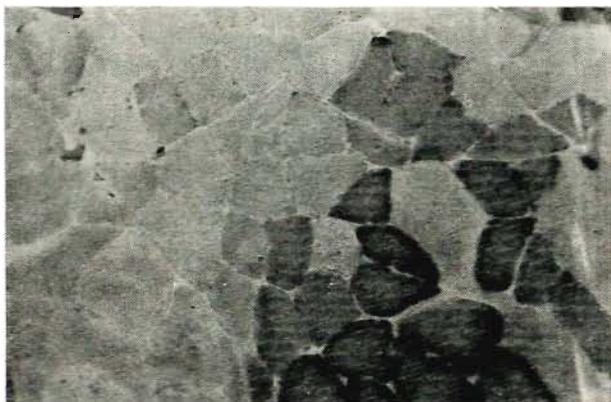


Fig. 7. Note abnormal grouping of individual fibre types (NAD diaphorase $\times 100$). Serial section with Fig. 6.

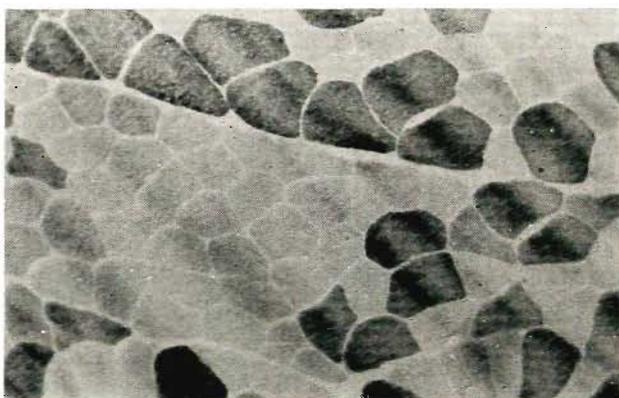


Fig. 8. Abnormal grouping of individual fibre types (myofibrillar ATPase $\times 100$).

The motor nerve terminals and end-plates showed evidence of grossly excessive terminal branching. There was ample evidence of multiple innervation of single muscle fibres with innervation ratios in some of the squash preparations of 1,4:1 (Figs 9 and 10)—the normal innervation ratio being 1,2:1. The end-plates varied considerably in size and shape from 15 to 70 μm in length (Fig. 11). Many ultraterminal branches were obvious. In the preparations the intramuscular portions of the motor nerves could be extensively studied, and only in very few areas were the axons found to be abnormal, showing evidence of occasional axonic spheres (Fig. 12). The internodal distances varied between 170 and 50 μm . The shorter distances occurred towards the motor nerve terminals.



Fig. 12. Bulbous swelling of a motor nerve axon (Ranvier $\times 1000$).

DISCUSSION

Originally, on the basis of electromyographic studies, Isaacs⁵ suggested that the site of pathology lay in the



Fig. 9. Branching of motor nerve terminal to supply end-plates to two muscle fibres.



Fig. 10. Terminal branching of motor nerve terminal with multiple innervation of muscle fibres.



Fig. 11. Terminal branching of the motor nerve terminal. Note the variation in size of the end-plates.

motor nerve terminals. It was considered that this anatomical subdivision was the site of the continuous discharge which resulted in a state of continuous acetylcholine (AC) release at rest, and that the quantity of AC released was sufficient to effect postsynaptic depolarisation and resulted in the continuous motor unit, single fibre and fractionated motor unit activities. This continuous muscular activity in turn caused the clinical manifestation of sweating, which reflected the increased metabolic activity.

It was found that this abnormal discharge from the motor nerve terminals responded dramatically to the administration of diphenylhydantoinate (DPH).⁸ So dramatic was this response that two totally incapacitated patients were returned to normal activity within a period of two months.

By applying this pharmacological knowledge some insight is gained as to the level and nature of the spontaneous discharge. Woodbury²² in 1955 suggested that DPH exerted its suppressive activity by facilitating the active extrusion of intraneuronal Na^+ , and suggested that DPH had an effect on the action of the membrane sodium pump. Recent work by Pincus and Rawson¹³ on the nerve fibres of the walking legs of lobsters, confirmed that DPH lowers the intracellular concentration of sodium. Lewin and Bleck¹¹ and Pincus and Lee¹¹ maintained that the major anticonvulsant action of DPH relates to its ability to limit cation entry and thereby reverse post-tetanic potentiation (PTP). The phenomenon of PTP occurs as a result of increased release of transmitter substance, which is dependent upon calcium. The Ca^{++} has to move into the presynaptic area during the period of repetitive stimulation, and DPH has an indirect effect upon Ca^{++} entering the cell during this period of stimulation. Rises in intracellular Na^+ concentration cause an increase in Ca^{++} concentration.² DPH, therefore, by limiting Na^+ inflow, may by the same process limit Ca^{++} influx. In normal therapeutic dosage DPH acts specifically on the motor nerve terminals, an action which has been clearly demonstrated by Raines and Standaert¹⁶ in their work on the cat soleus neuromuscular preparation. In the cat it is possible to establish a state of spontaneous discharge which is similar to the spontaneous discharge of our patients, by applying tetanic stimuli to the nerves of the tonic muscles. This produces a state of hyperexcitability, which causes subsequent single impulses to the nerve to evoke a repetitive spontaneous response in the tonic muscle involved. This hyperexcitability can be prevented and controlled by the administration of DPH.

Further evidence which assists in determining the site of the spontaneous discharge is obtained by utilising certain stimulatory drugs such as veratrine and neostigmine. These drugs are capable of evoking spontaneous motor unit and fractionated motor unit activity, and the site of the generation of the spontaneous activity has been shown to be the motor nerve terminals by Riker and Okamoto.¹⁸

Pharmacological evidence favours the localisation of the site of spontaneous discharge to the motor nerve terminals. Though DPH in therapeutic dosage has little or no effect upon conduction in peripheral nerves under normal circumstances, it may well take on a significant role when

the motor nerve fibres have been previously damaged, and where such damage has presumably given rise to areas of hyperexcitability which discharge spontaneously, a more widespread action of DPH may be evident.

Both Wallis *et al.*²⁰ and Welch *et al.*²¹ found evidence of atrophy of a small number of fibres in the right sural nerve in one of their patients, and on this basis suggested the possibility of sensory nerve involvement. This observation is contrary to the clinical findings since no evidence of objective sensory change has been found. Only in one of the adequately reported cases²⁰ was tingling of the feet encountered, and this symptom was of short duration. The sural nerve is an unfortunate choice for a biopsy since it is very frequently abnormal in otherwise normal subjects, being subjected to considerable trauma relating to ankle movements; in fact, the distal end of any long nerve is a poor region to study, as shown by Arnold and Harriman.¹ One must therefore obtain more evidence of sensory nerve involvement from other sites before sensory nerve pathology can be included in this syndrome.

The present investigations confirm the neuropathic nature of the disorder, and the abnormal grouping of individual fibre types is an indication of denervation with subsequent reinnervation. Reinnervation was confirmed by studies on the motor nerve terminals — excessive terminal branching being evident, and many muscle fibres found to be multiply innervated. Axonic spheres were only found in the elderly patient, and as such cannot be regarded as evidence of more proximal nerve involvement. Proximal involvement was suggested by Willis *et al.*²⁰ who reported the work of Swift, who recorded and electronically counted the number of spontaneous muscle potentials occurring within the adductor digiti quinti of their patient. Nerve blocking at the level of the elbow reduced the frequency of the potentials by 53%, and to 13% where the same nerve was blocked at the wrist, indicating that a significant amount of spontaneous activity arose from the motor nerve between the levels of the elbow and the wrist. It is a feature of the syndrome^{8,9,12} that the spontaneous activity is considerably enhanced by voluntary contraction, and that the spontaneous discharges continue at an increased rate for a considerable period of time after such voluntary activity. The blocking of the peripheral nerve to a muscle at a proximal site leads to some decrease in the spontaneous activity, but it is difficult to decide just how much of this decrease is due to the absence of the aggravating effect of voluntary activity on the one hand, or elimination of proximal areas of spontaneous discharge in the nerve itself on the other. Even if such proximal sites of spontaneous discharge are eliminated by blocking the ulnar nerve at the level of the wrist, the decrease in spontaneous activity observed, if one can be sure that the procaine has not diffused into the area of the muscle, may largely be due to the absence of this proximal facilitatory action on the hyperexcitable and spontaneously discharging centres in the motor nerve terminals. Spontaneous discharging areas in the motor nerve terminals may produce both contraction of single muscle fibres by orthodromic activity and motor unit activity by antidromic circuiting. This depolarising mechanism could also account for the occurrence of fractionated units. The occurrence of occasional repetitive bursts of closely situated motor

unit activity do not resemble the high voltage symmetrical bursts of activity seen in myokymia of spinal and brain stem origin, but may be a peripheral manifestation of a similar irritative process.

It was observed⁹ that the terminal latencies improved with time in patients on treatment, suggesting either that the nerve disorder corrects itself in time, or that the return to normal posture following muscle relaxation removes pressure on the distal parts of the nerve. The latter mechanism is considered most likely.

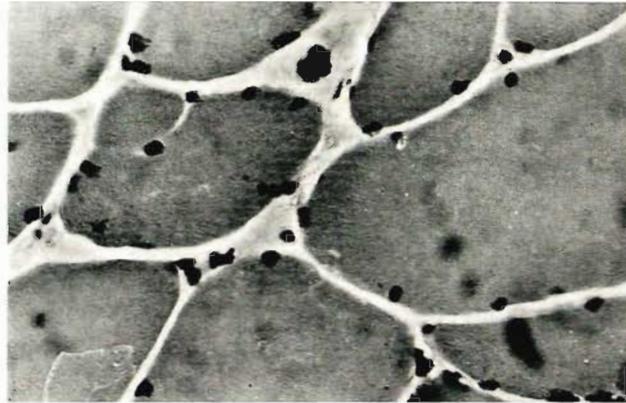


Fig. 13. Note the variation in fibre size, some fibres having hypertrophied to 180 μm . There is evidence of an increased number of nuclei and remnants of atrophic fibres (H. and E. $\times 1000$).

The marked variation in muscle fibre size, and particularly the formation of the very large fibres (Fig. 13), is regarded as a manifestation of disturbed trophic function of the motor nerves. Such trophic action was regarded by Drachman⁶ in 1968 as a function of the spontaneous quantal release mechanisms. It is also possible that continued and excessive acetylcholine activity on the muscle fibres may induce a myopathic change, as has been shown by Fenichel *et al.*,⁷ who produced myopathic changes in rat muscle by inhibiting cholinesterase activity.

The over-all evidence suggests that the abnormality in the syndrome of continuous muscle fibre activity occurs mainly in the motor nerve terminal. Involvement of the motor axon as a whole, though to a lesser degree, is probable.

The aetiology is likely to be a specific reaction to some insult to the motor fibres of the peripheral nervous system, the brunt of the affection being sustained by the motor nerve terminals, that non-myelinated portion of the motor nerve which was shown by Song¹⁹ in 1967 to be particularly susceptible to trauma. The nature of the insult remains unknown, though Wallis *et al.*²⁰ questioned the possible causative effect of 2,4-D poisoning in one case. The possibility that some chemical agent may be responsible for this syndrome is highlighted by the drug, 2-(1-aziridiny)-1-vinylethanol, which according to Zager

*et al.*²¹ produces continuous fasciculations which can be abolished by curare and suppressed by DPH.

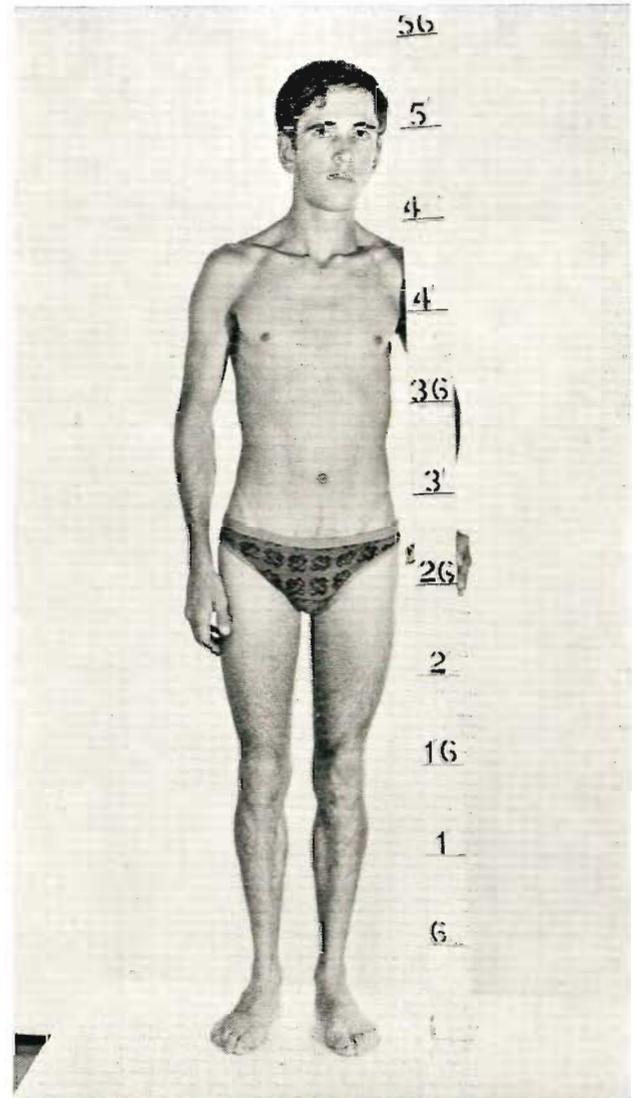


Fig. 14. Patient 1, a recent photograph. There is no evidence of abnormal neuromuscular activity.

From a clinical and symptomatic point of view, both cases are in excellent health (Figs 14 and 15). In one of the cases we have been able to discontinue the administration of DPH since the disease has gradually remitted to a point where the patient preferred to be without therapy. Clinically his movements are normal and only occasional fasciculations are obvious. Electromyographic study reveals that the muscles are now almost silent at rest (Fig. 16), but the spontaneous discharge becomes evident after the aggravating effect of a voluntary contraction (Fig. 17). The evolution and remission of this syndrome over the period of 12 years in this case confirms the acquired nature of the condition.

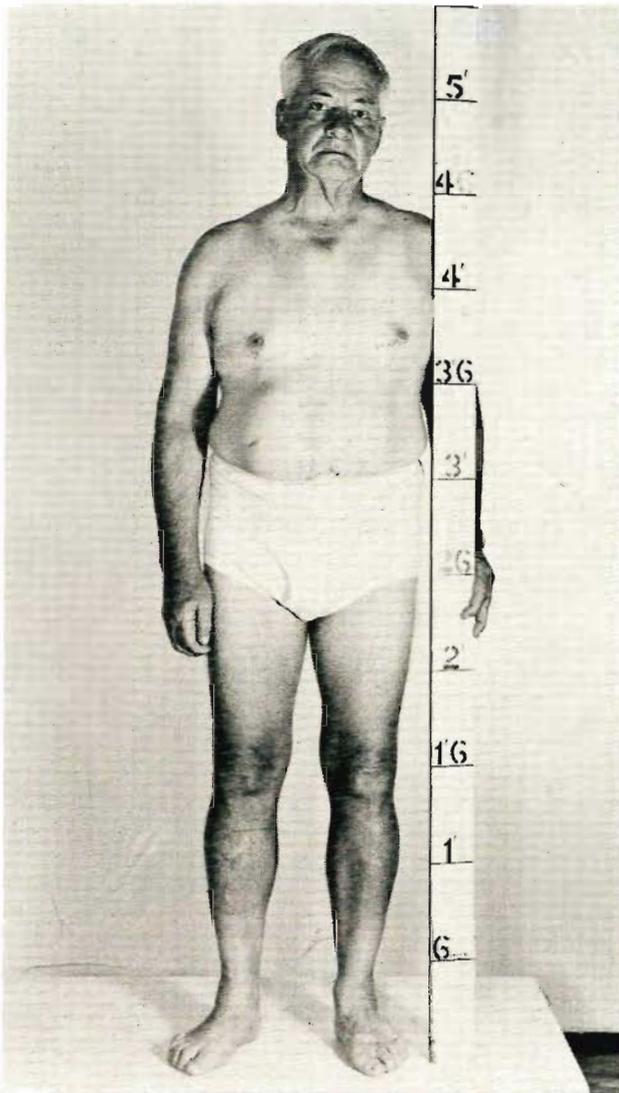


Fig. 15. Patient 2, a recent photograph. There is no evidence of abnormal neuromuscular activity.

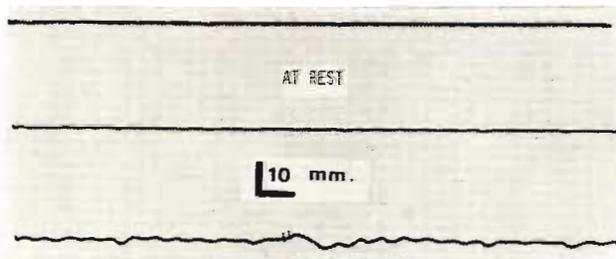


Fig. 16. Tracings from top to bottom are recordings from the extensor communis, flexor sublimis and abductor pollicis brevis muscles at rest.

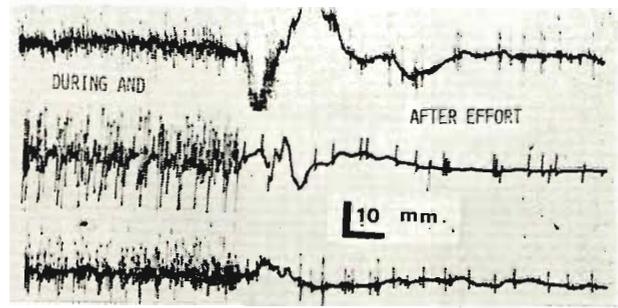


Fig. 17. The same muscles as in Fig. 16. Recordings obtained using concentric needle electrodes during and after strenuous short-duration hand closure. The onset of relaxation is indicated by the deflection in the base lines. Note the presence of spontaneous discharge occurring after the voluntary contraction.

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