ELECTROMYOGRAPHIC STUDY OF MUSCULAR WEAKNESS IN CHRONIC RENAL FAILURE*

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Charcot,[1] in 1870, noted the association between disease of the nervous system and chronic renal failure. The details of this association, however, have only been established in the past few years, when Asbury *et al.*[2,3] finally established the entity of uraemic polyneuropathy.

When one refers to neuropathy in chronic renal failure, one is referring specifically to the neuropathy consequent on the metabolic disturbances. Systemic conditions such as amyloid disease, lupus erythematosus, polyarteritis nodosa and diabetes mellitus which may involve both kidney and nerve tissue are excluded.

The neurological manifestations of chronic renal failure are mainly peripheral and consist of symmetrical sensory and motor impairment, the longest nerves being most severely affected. The sensory changes consist of paraesthesia—often preceded by burning and followed by numbness. Occasionally pain is the major neuropathic manifestation. This may be severe and intractable and is sometimes described as muscular. Intractable pain has also been noted in a few cases with advanced neuropathy after a prolonged programme of haemodialysis, an unfortunate manifestation of inadequate sensory recovery. The motor manifestations vary from a slowly progressive weakness to dramatic widespread paralysis associated with generalized muscle wasting. When this occurs, it does so as a rule in severe uraemic states and has appeared on occasions to have been precipitated by the first period of haemodialysis.

There is no constant association between the severity of the chronic renal failure and neuropathy, though most cases occur when creatinine clearance is reduced to less than 20 ml./min. Time appears to be the other important factor, and when time is coupled with severity the incidence of neuropathy rises sharply.

Pathologically there is a patchy degeneration of the myelin and, to a lesser extent, degeneration of the axis cylinders. In the more acute lesions demyelination may be the sole lesion, while in the more chronic cases widespread Wallerian degeneration of the peripheral nerves is found. Unlike diabetic neuropathy, the autonomic nervous system does not seem to be involved in chronic renal failure. Cranial nerve lesions are rare and occur only in the most severe cases. They appear to be related to cerebral oedema, as rapid recovery of such lesions has been noted when the patient's level of cerebral function improves with treatment.

Ewer *et al.*[4] described a 'tetanic neuropathy'. This is an unusual form of neuropathy in which there is severe muscular spasm, very similar to that seen in tetanus. The feet become fixed in the equinovarus position and the spasm may be severe enough to tear the muscle fibres. Bleeding into the rectus muscle has been observed and may give rise to pain and simulate an acute abdominal emergency. The lesion here appears to be a central one affecting interneuronal and anterior horn cells and occurs in these cases as a terminal manifestation.

Electromyographic studies have been well documented and have been used to follow the progress of the neuropathy in chronic renal disease.[5] Electromyographic recordings have also served to confirm the clinical findings and they afford objective means of assessing the disability. Not infrequently changes may be found on electromyography before they are clinically obvious as shown by Preswick and Jeremy.[6] The presence of neuropathy is in itself an urgent indication to intensify the treatment of chronic renal failure. This usually means frequent periods of haemodialysis. With adequate therapy the neurological changes may be halted and in some cases reversed. Improvement, unfortunately, does not always occur and is inversely related to the degree of axon destruction. Sometimes improvement is extremely slow and has been noticed only after transplantation.[5]

The electrophysiological manifestations of the uraemic neuropathy are typically those of denervation. Denervation activity of varying degree is found when the involved muscles are explored with needle electrodes while volitional activity shows a varying degree of fall-out of motor-unit activity. Strength/duration graphs are a useful and simple means of following denervation, but this method has been largely replaced by more sophisticated electromyographic techniques. This is unfortunate, as the investigations are complementary.

Muscular weakness in chronic renal failure is not always the result of neuropathy. In order to elucidate this point, the electrophysiological testing has been extended to encompass the observation of fatigue during isometric contraction.

PHYSIOLOGY

In considering muscular contraction and, in particular, the changes in the electromyographic pattern of fatigue, one should possess a working knowledge of the integrative activity of the central and peripheral mechanisms which drive and modulate the anterior horn cells of both α and γ systems. When we learn to assess normal neurological control and take into account motivation and the myoneural junction we will be better equipped to observe the primary muscular causes of contractile failure.

For the purpose of this introduction a brief survey of some of the major contributions which have enhanced our understanding of the peripheral neurological mechanisms governing muscle contraction and, in particular, isometric contraction will be made.

Adrian and Bronk[7] were able to show a linear relationship between the tension that develops during muscle contraction and the stimulating frequency. The initial experiments were performed on the tibialis anticus muscle of the cat. Further experiments done by stimulating popliteal nerves which had been cut proximally, showed

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that the linear relationship held good between the frequencies of 15 - 40/second. Stimulation rates above this limit produced a further increase in tension but the response was unpredictable and non-linear. Studies recording the impulses to the diaphragm in cat phrenic nerves in which all but a few fibres were sectioned, revealed an increased motor-unit activity which varied between 15 and 90/second.

Adrian and Bronk[8] developed the first concentric needle electrode. With this electrode coupled to the electromyogram they were able to examine the triceps muscle in man. Their electromyographic studies revealed the expected increase in motor-unit frequency with increasing tension, but they also noted the recruitment of other units during this activity. The upper discharge rate at which other motor-units were recruited was noted to be of the low order of 14/second. They concluded that voluntary contraction in man is maintained 'by a series of nerve impulses which range from 5 - 50 or more a second in each nerve fibre, and that the gradation in force is brought about by changes in the number of fibres in action'.

Lindsley[9] emphasized the role of recruitment during muscular contraction and demonstrated that the integrated voltage-tension curve was largely a function of recruitment. Margaria[10] stated that there is a limiting frequency to the firing of individual motor-units—a limit which in normal muscle lies between 20 and 25/second. This again emphasizes that when the tension is increased beyond the limiting frequency any relationship between tension and such firing frequency breaks down.

Weddell *et al.*[11] established that paretic muscles respond with a much higher motor-unit frequency than normal muscles. This explains the high response rates in the phrenic nerve diaphragm studies of Adrian and Bronk.[8] Das Gupta[12] took this interesting finding a step further and demonstrated that the abnormally high contraction frequency was a response common to all weak muscle, irrespective of the cause.

Muscle spindle γ efferent control was studied by Eldred *et al.*[13] They examined the action potentials of single spindle afferents coming from the gastrocnemius and soleus muscles of the cat. It was noted that de-efferentation led to a sudden drop in spindle discharge, while de-afferentation did not diminish this activity and, furthermore, still showed evidence of bias at all tensions ranging from zero upwards. It was further noted that the gamma system could be stimulated through reflexes such as the pinna reflex (i.e. pinching the ear which causes contraction of the limb muscles). With de-afferentation of the limb muscles the responses to pinna stimulation caused a normal response in the spindle as shown by recordings from the afferent nerve fibres, but the limb muscles failed to contract. This experiment indicated the sequence and dependence of the extrafusal muscles on the gamma servo-loop system during reflex stimulation.

It has been accepted that the basis for muscle spindle activity is to feed back information about length and velocity. This helps with the orientation of the static limb, while information about the rate of change of muscle fibre length is necessary for movement. These functions of the spindle would seem to meet most requirements but, according to Simpson,[14,15] do not satisfy the conditions found either during isotonic contraction where tension may rise at constant length or during isotonic contraction at constant velocity. With this in mind, Simpson has attributed a tension-sensitive function to the spindle with an independent tension servo-loop control. Simpson believes that a facilitatory tension-sensitive end-organ is situated in the nuclear chain region of the spindle which is so abundantly supplied with secondary nerve endings, while the inhibitory control is a function of the Golgi tendon organ. Supportive evidence for a tension servo-loop control has been provided by Jansen and Matthews[16] in their studies on the effect of fusimotor activity on the static responsiveness of the primary and secondary endings of muscle spindles in the decerebrate cat, and by the work of Das Gupta[12] who conducted experiments on muscle during isometric contraction. Das Gupta injected the muscle belly of contracting muscle with 2% procaine and noted a fall in the spindle discharge rate to between 15 and 18/second, as well as an increase in the regularity of the discharge. As no change in muscle length occurred, the change was attributed to alterations in the tension-sensitive system.

Das Gupta and Simpson[17] have been able to demonstrate that the relationship between tension and frequency of motor-unit activity is in fact not linear but that a linear relationship exists between the number of muscle fibres contracting/unit time and tension during isometric contractions. This relationship also holds good for isotonic contraction at constant velocity.[18]

Edwards and Lippold[19] studied the effects of fatigue on isometric contraction and found that the integrated voltage/tension graph remained linear though the slope of the curve became progressively steeper, i.e. a proportionate increase in the integrated voltage above the normal with increasing tension was demonstrated.

Lenman[20,21] studied the association between integrated activity and tension during isometric contraction in subjects with muscular weakness. He was able to show that an abnormal though proportionate increase in the integrated voltage occurred for given tensions in the patients with weakness of myopathic origin. On the other hand, no such alteration in the slope of the curve occurred when the cause of the weakness was neuropathic. Lenman and Potter[22] reported on the abnormal prominence of the electrical change associated with fatigue in patients with myopathic disorder.

Over the past 5 years I have examined the progressive qualitative changes in the electromyographic pattern during isometric contraction. These changes were followed through the early and late stages of fatigue. A clearly individual pattern emerges distinguishing between the normal, the neurological and the myopathic.

MATERIAL AND CLINICAL PICTURE

Fifteen patients in chronic renal failure, complaining of severe muscular weakness, were studied. The weakness was such that the patients had difficulty in walking unaided and none was capable of climbing more than five 9-inch steps. Renal pathology was established by biopsy

and fell into the following groups: Post-streptococcal glomerulonephritis, 8 cases; polycystic disease, 2 cases; and pyelonephritis, 5 cases, of which 2 were associated with the interstitial nephritis and papillary necrosis of long-term phenacetin consumption. The ages ranged from 17 to 56 years and the sexes were approximately equal. Other uraemic cases which were seen with similar weakness over the same period but associated with diseases which are known to affect the nervous system, were excluded. Examples of these excluded cases were patients suffering with disseminated lupus erythematosus, diabetes mellitus and chronic alcoholism.

End-stage chronic renal failure had been present for periods varying between 4 and 18 months. Renal disease (excepting those cases with polycystic disease) had been present for periods varying from 2 to 15 years. The blood calcium levels were normal, with elevation of the phosphate. Blood magnesium levels were normal, as were serum vitamin B_{12} and folic-acid levels. The blood urea at the time of examination varied between 90 and 275 mg./100 ml. Most patients were on a modified Giovanetti diet with vitamin and methionine supplementation.

Four of the patients referred by the Renal Unit of Johannesburg General Hospital were already on their haemodialysis programme. Four had had repeated periods of peritoneal dialysis during temporary periods of exacerbation. The balance of the patients had been controlled by diet. The patients under review had received no neurotoxic medications or cortisone during the 3 months preceding the onset of the severe muscular weakness. Care was taken to verify this.

Of the 15 cases, 11 complained of altered sensation in the extremities. The altered sensation varied from slight numbness and paraesthesia to severe sensory loss which was present in 5 cases. In one of these cases there was an additional complaint of excruciating pain in the limbs. This pain was situated especially in the legs and the patient claimed that it felt as though it was in the muscles. The pain was aggravated by movement and made sleep very difficult. The remaining 4 cases did not complain of, or show, objective evidence of sensory impairment. The tendon reflexes were markedly depressed or absent in all cases.

METHOD

A Disa electromyograph and Disa Multistim stimulator served as the basic equipment. The muscles were explored with concentric needle electrodes Disa 13 K 51. The motor nerve conduction studies were based on the principle of Hodes *et al.*[23] The sensory conduction was estimated either orthodromically or antidromically by the evoked-potential technique of Dawson.[24]

The stimulating pulse employed varied between 40 and 250 volts. A square wave was used with a 0·3-msec. duration. The recordings were made with stimuli at least 25% above the threshold levels. The Disa electromyograph was coupled with a 14-inch Airmec oscilloscope screen which gave greater accuracy in the immediate timing of latency by means of a second pulse and a clearer picture of individual motor-units. The climatic environment is a warm one and the buildings are adequately heated in winter, so that the ambient temperature of the laboratory was never below 25°C. Patients were kept in this environment for 30 minutes before testing, so that peripheral limb temperature factors affecting nerve conduction were minimized.

The isometric contraction studies were all carried out on the abductor pollicis brevis muscle of the dominant side. Other muscles were studied at the same time but the abductor pollicis brevis was favoured as its nerve supply is consistent (from the median nerve) and the tension required to produce fatigue within 7 minutes in normal controls was reasonably small. The isometric load was achieved with the hand strapped in the supine position. A 2-lb. lead weight was suspended by means of a sling over the interphalangeal joint and a pointer then clipped over the thumb. The thumb was then taken through the full range of abduction and the half-excursion point was noted. The electrode needle or needles were then placed in position and the patient was asked to pull the weight up to the half-abduction position and hold it in this position by keeping the pointer at a determined spot on a vertical ruler. A stop-watch timed the procedure and recordings were made every 30 seconds for up to 7 minutes or until the patient, despite encouragement, was unable to maintain the position.

The presence of denervation was judged by the occurrence of spontaneous activity away from the area of the motor end-plate. The spontaneous activity consisted of diphasic or triphasic potentials with a duration of 4 msec. or less, and positive potentials.

The deltoid muscle was explored in all cases for polyphasic motor-unit potentials. The electrodes were inserted in 4 separate sites and a minimum of 20 separate motor-units were observed in each muscle. Potentials possessing 4 phases and more were considered to be polyphasic.

RESULTS

Electromyography

In the 11 cases with clinical evidence of peripheral neuritis, focal areas of denervation were found on searching with needle electrodes. As was expected, the most distal muscles showed the brunt of the disease. Recruitment of motor-unit activity on volition was abnormal and in the most severe cases only isolated functioning motor-units were present. Of the remaining 4 cases, 1 showed minimal evidence of denervation in the extremities, and 3 showed no evidence of denervation and there was no evidence of pseudomyotonia or increased irritability of the muscle fibres.

The polyphasic counts were on the high side and ranged between 6 and 15% of the total activity. The highest counts were found in those cases with neuropathy having intensive haemodialysis. This may represent early reinnervation.

Nerve Conduction

These results are shown in Table I. All were abnormal except cases 13, 14 and 15. It was noted that, with these exceptions, the weakness correlated well with the abnormality in nerve conduction. Fig. 1 demonstrates the normal latencies, good sensory nerve potential peaks and normal

TABLE I. NERVE CONDUCTION (METRES/SECOND)

	Motor		*Sensory*			
No.	*Median nerve*	*Lat. popliteal nerve*	*Median nerve*	*Lat. popliteal nerve*	*EMG*	*Fatigue pattern*
1	38	32	41	Not obtained	Denervation	Neuropathic
2	35	29	35	Not obtained	,,	Neuropathic
3	45	35	47	36	,,	Mixed
4	30	18	Not obtained	Not obtained	,,	Neuropathic
5	40	27	43	30	,,	,,
6	21	14	Not obtained	Not obtained	,,	,,
7	24	13	,,	,,	,,	,,
8	18	Not obtained	,,	,,	,,	,,
9	25	18	20	,,	,,	,,
10	29	21	Not obtained	,,	,,	,,
11	37	29	40	,,	,,	,,
12	43	32	44	,,	,,	,,
13	55	46	56	50	Nil	Myopathic
14	58	42	60	46	,,	,,
15	50	43	52	44	,,	,,

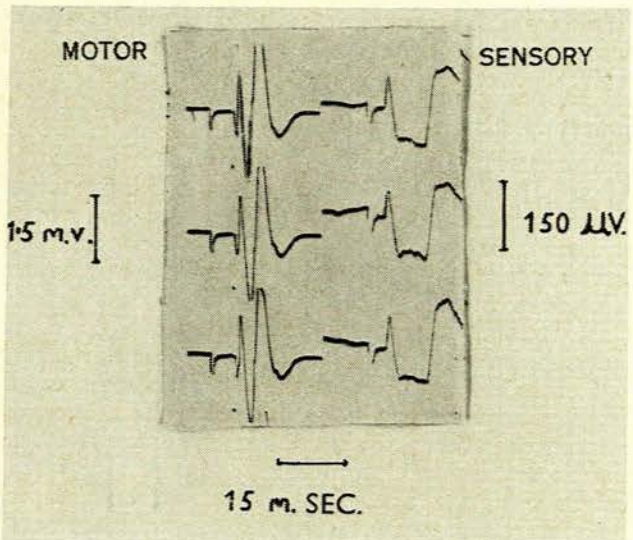

Fig. 1. Normal motor and sensory conduction and induced activity in a case of uraemic myopathy. Median nerve stimulation at wrist.

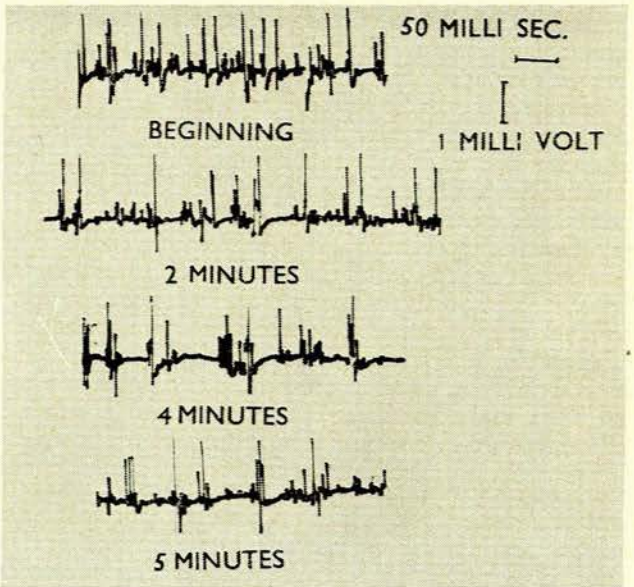

Fig. 2. Motor-unit activity recorded during isometric contraction from a patient with neuropathy. Note the marked fall-out of motor-unit activity.

dispersion of motor-unit activity following nerve stimulation in case 14.

Fatigue Study

The 12 cases with clinical evidence of neuropathy showed considerable fall-out of motor-unit activity. The motor activity remained discrete and showed insignificant voltage change up to the onset of fatigue, but the motor-unit amplitude tended to fall when the tension could no longer be maintained. Fig. 2 demonstrates the fall-out of motor-unit activity in a typical case of neuropathy. Fig. 3 demonstrates the activity after 3 minutes of isometric contraction. Deterioration between the upper and lower traces illustrates the advancing neuropathy over a 3-month period. The 3 remaining cases (i.e. those without clinical or EMG evidence of neuropathy) gave an entirely different pattern. The motor-unit activity during isometric contractions fused into progressively widening

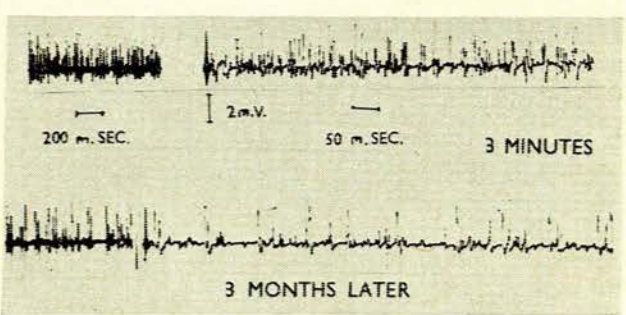

Fig. 3. Deterioration in the motor-unit activity over a period of 3 months in uraemic neuropathy.

patterns showing an early increase in voltage which persisted until the muscle tension fell. Following the fall in tension the voltages fell progressively, though the widened bizarre patterns of activity persisted. Fig. 4 demonstrates

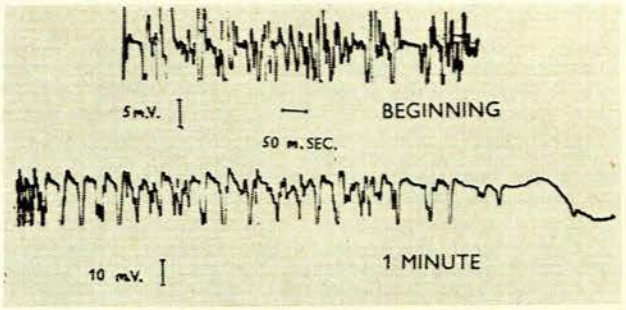

Fig. 4. Motor-unit activity in myopathy. Note the marked widening of the motor-units and early fatigue.

the typical pattern of myopathic weakness seen during isometric contraction. The trace illustrates fatigue which has occurred within one minute of isometric contraction.

DISCUSSION

The cases with clinical evidence of uraemic neuropathy were quite typical. Case 3 is an example of those cases emphasized by Preswick and Jeremy[6] where the peripheral neuropathy was picked up electrodiagnostically before a clinical diagnosis could be made. The extreme weakness in this case was thought to be due to a combined neuropathic and myopathic abnormality.

The cause of neuropathy in chronic renal disease is, unfortunately, still too frequently iatrogenic. Many of the drugs used in the treatment of renal infection are neurotoxic and it is not widely appreciated that the usual dosage of antibiotics such as kanamycin, streptomycin, colimycin, etc., must be reduced in renal failure and at the same time a close watch kept on the blood levels of these substances. It is not unusual to find that half the usual initial dose given to a patient in chronic renal failure suffices for 3 days and more. Bacteriostatic and bacteriocidal chemicals such as nitrofurin should never be used in chronic renal failure for the treatment of urinary tract infection, as the urinary concentration is inadequate, while the blood levels rise dangerously. Fig. 5 depicts the severe muscle wasting in a 27-year-old female treated for pyelonephritis with neurotoxic drugs. She died as a result of the neuropathy.

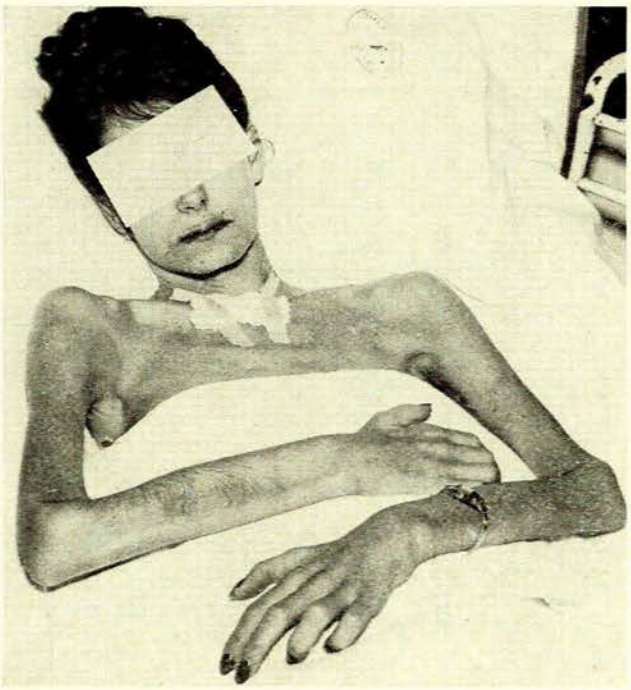

Fig. 5. Wasted muscles and covered tracheostomy resulting from neurotoxic drugs in chronic renal failure.

Neurotoxicity may be an unexpected finding and all new drugs must be carefully watched in chronic renal failure. I have recently seen the sudden and unexpected onset of peripheral neuritis in two otherwise well-controlled cases in chronic renal failure. In both cases the blood urea estimations were less than 45 mg./100 ml. Both cases were on allopurinol therapy with a dosage of 300-400 mg./day. We were unable to get blood level estimations done by our local laboratories or by the manufacturers. Stopping the drug appears to have arrested the rapidly progressive condition and the cases are being followed with nerve conduction studies. Allopurinol was suggested as a cause of neuropathy by Glyn and Crofts.[25]

The diagnosis of myopathy in uraemia rests largely on the clinical finding of severe muscular weakness, the absence of peripheral neuritis both clinically and electrodiagnostically and the presence of the abnormal electromyographic fatigue pattern on isometric contraction. The renal pathology in the cases with myopathic weakness was pyelonephritis in 2 and post-streptococcal glomerulonephritis in the other.

For the study of the electromyogram during isometric contractions the position of 50% abduction was chosen as the fixed point of testing for the abductor pollicis brevis muscle, as it has been shown by Miwa and Matoba[29] that motor-unit activity varies with the degree of muscular shortening even though the tension remains constant. Liberson *et al.*,[27] conversely, have shown that when the degree of muscle shortening remains constant a linear relationship between tension and integrated voltage holds true.

With disease of the peripheral nerve there is little change in the voltage of the motor-unit activity, which persists to the point of fatigue, when the voltage may show only a slight increase and then a fall, or more often a progressive fall, in the more severe cases. With peripheral nerve disease the mechanism of recruitment is faulty owing to loss of available motor-units, and it follows that synchronization is less likely to occur. Because of the depleted motor-unit population, fatigue occurs early.

In the case of myopathy, there is no reduction in the number of motor-units but the muscle fibres are weaker than normal. The weakness results in early fatigue which is heralded by increased firing rates, maximum recruitment and marked synchronization. The voltage of the integrated

electromyogram rises abnormally for the tension produced, as has been shown by Lenman.[20,21] The electromyographic tracing shows a rapid rise in motor-unit potential voltage with marked widening as the motor-unit activity overlaps dramatically with progressive fatigue (Fig. 4). Induced activity by nerve stimulation at this stage produces a very brief rise in tension or no rise at all. In addition to the above mechanism it is suspected that in some cases slight slowing of muscle cell membrane conduction has occurred. Investigation into this aspect is currently progressing.

The electromyographic pattern of fatigue has been used in my unit over the past 5 years as a method of confirming the presence of myopathic weakness in cases of diverse aetiology. The procedure is simple and informative. The observation of the qualitative electromyographic change is characteristic and integrated voltage correlation is unnecessary for practical purposes. Fig. 6 is a composite

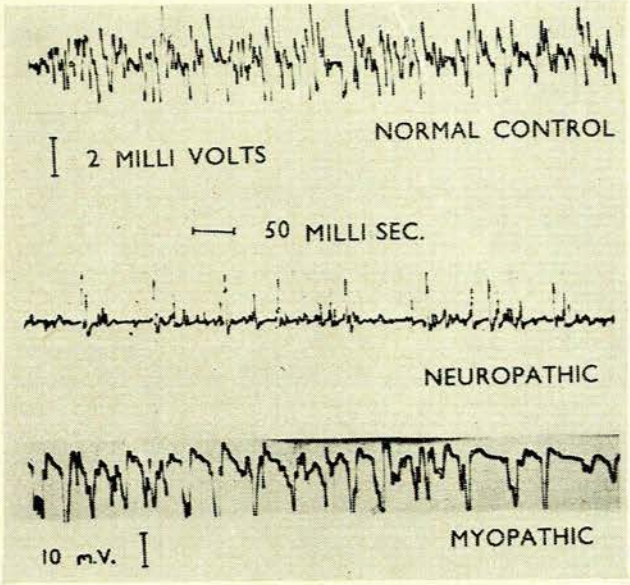

Fig. 6. Motor-unit activity after one minute in normal, neuropathic and myopathic subjects.

figure showing the characteristic change seen in neuropathy and myopathy compared with the normal pattern during isometric contraction.

There are two main drawbacks to the use of isometric contraction in the diagnosis of myopathy. Firstly, concomitant peripheral nerve disease modifies the response. Secondly, one must exclude cases with upper motor neurone disease where an abnormal amount of synchronization of motor-unit activity may be found.

SUMMARY

A study of the changing electromyographic pattern during isometric contraction is described. These changes have been useful in confirming the presence of myopathy as the cause of severe weakness in 3 uraemic subjects. The technique is simple and the qualitative electromyographic changes described help to separate the neuropathic and myopathic from the normal. The fatigue studies are complementary to routine electromyographic and nerve conduction studies.

I wish to thank the Medical Superintendents of the South Rand and Johannesburg Hospitals for permission to publish these cases; Drs K. Furman and B. Goldberg for referring the cases from the renal units; and the Photographic Unit of the Department of Medicine, University of the Witwatersrand, for the photography.

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