THE MUSCLE LESION IN THYROTOXICOSIS

being a clinical, electromyographic and pathological investigation of the muscular weakness and atrophy associated with hyperthyroidism

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INTRODUCTION AND REVIEW

Attention was first drawn to muscular weakness as a symptom of thyrotoxicosis by Graves (1935) and Basedow (1840). However, it was not until 1885 that Du Cazal presented a patient with the simultaneous onset of thyrotoxicosis and severe muscle atrophy (Sattler 1952). Ten years later, in 1895, Burthurst described "A case of Graves' Disease Associated with Idiopathic Muscular Atrophy", which concerned a man aged 20 who complained of difficulty in walking and of generalised muscular weakness for 14 months. He had the typical features of thyrotoxicosis, with exophthalmos and moderate enlargement of the thyroid gland, but in addition he had wasting and weakness of the deltoid muscles, biceps brachii, thenar eminences and the gluteal muscles and there was weakness of the serratus anterior. One of the most characteristic features of his weakness was that he was unable to raise himself from the lying or kneeling positions without using his arms.

Since Du Cazal wrote the first report 73 further cases of definite marked muscular atrophy in hyperthyroidism have been recorded in the literature (for references see Table 1) and the condition was first referred to by MacKenzie (1940) as "chronic thyrotoxic myopathy".

Since 1894, when Müller reported 4 thyrotoxic patients with nasal speech and dysphagia and one patient with hallucinations, many different types of neuro-muscular disorder associated with hyperthyroidism have been described. These have been classified by Logothetis in a recent review article (1961) and are presented

here in a slightly modified form:

A. Myopathies resulting from hyperthyroidism

1. Acute thyrotoxic myopathy
2. Chronic thyrotoxic myopathy
3. Endocrine ophthalmoplegia

B. Myopathies sometimes associated with hyperthyroidism

1. Myasthenia Gravis
2. Periodic Paralysis

C. Neurological manifestations in thyrotoxicosis

1. Acute thyrotoxic "encephalomyopathy"
2. Optic nerve lesions and retinopathy
3. Thyrotoxic crisis and coma
4. Upper motor neurone syndromes
5. Thyrotoxic electrocortical dysrhythmia and seizures
6. Thyrotoxic tremor and chorea
7. Parkinsonism in thyrotoxicosis

D. Psychiatric manifestations in hyperthyroidism

This discussion will be confined to the various muscular complications which are associated with thyrotoxicosis.

Acute Thyrotoxic Myopathy and Encephalomyopathy

These two are being considered together because many authors describe the same clinical findings under either heading. The first papers in the English literature on the acute paresis of thyrotoxicosis were by Laurent (1944), Waldenström (1945), Sheldon and Walker (1946) and Strong (1949). However, Waldenström, in addition to describing his own 10 cases, quoted a large number of patients with similar features which had been culled mainly from the German literature of the previous 50 years. The clinical picture was of the sudden onset of bulbar palsy in a patient who may have had antecedent thyrotoxic symptoms for several months or even years. In many of the cases cited by Waldenström (1945) there was severe diarrhoea and vomiting and also clear evidence of thyrotoxic crisis and coma, and this latter association has been described in subsequent case reports (Chapman and Maloof 1956, Gimlette 1959, Heinrich, McCabe, Nicely and Elder 1962). Eight out of 10 of Waldenström's patients had atrial fibrillation. Other features which have been noted are aching in the limbs and paraesthesiae (Gimlette 1959). In most of the articles which have been written since 1945 the authors have indicated that there was generalised muscle weakness in addition to the ptosis, difficulty with speech, dysphagia and the nasal regurgitation of fluids, though ophthalmoplegia does not seem to have been a prominent feature. The tendon reflexes were variable, being reported as brisk or totally absent, and in one case there was evidence of an upper motor neurone lesion (Heinrich et al. 1962). Sanghvi, Gupta, Banerjee and Bose (1959) described the acute onset of

paraplegia, hypokalaemia and nephropathy in a thyrotoxic patient in whom the paralysis showed no response to treatment with potassium but was completely cured by thyroidectomy.

Fasciculation was seen in Heinrich et al.'s case and fibrillation was reported in the shoulder muscles of Strong's (1949) patient, but, since fibrillation consists of the contraction of individual muscle fibres and is not visible through the skin (Thomas 1963, p. 315) it is suggested that the spontaneous activity seen in this patient was possibly fasciculation or even myokymia (see p. 21).

Pathological reports are scanty, but in Waldenström's review an enlarged thymus was noted on three occasions and degeneration and haemorrhage into the cranial nerve nuclei in three cases. Microscopic examination of the brain in Chapman and Maloof's (1956) second patient revealed slight to moderate swelling of oligodendroglia in the subcortical white matter. Muscle histology has been commented on three times. Strong (1949) found only evidence of oedema in biopsies of ocular and temporal muscles, whereas Gimlette's (1959) first case showed widespread degeneration of muscle fibres with foci of lymphocytes and Sanghvi et al. (1959) found evidence of fibre degeneration with vacuolisation, sarcolemmal nuclear proliferation and loss of striations in swollen fibres.

Electromyography appears to have been done on only two occasions and in both patients the pattern was that of a myopathy (Gimlette 1959).

A fatal outcome was almost the rule in the earlier cases, but Waldenström (1945) was able to obtain a full remission of symptoms using iodine followed by partial thyroidectomy. Later, with the development of effective antithyroid drugs and radioactive iodine, complete recovery has been obtained with medical treatment (Strong 1949, Chapman and Maloof 1956, Gimlette 1959, Heinrich et al. 1962), thus tending to disprove Waldenström's (1945) theory that the condition was caused by a lack of iodine.

The objection has been raised by Millikan and Haines (1953) that many of the earlier cases described in the literature may have been myasthemia gravis coincident with thyrotoxicosis, but is difficult to prove or disprove their contention. However, neostigmine gave dramatic relief from the bulbar symptoms in three of the more recent cases (Laurent 1944, Sheldon and Walker 1946).

Chronic Thyrotoxic Myopathy

Clinical Features. Seventythree cases of chronic thyrotoxic myopathy have been reported in the literature (see Table 1). Melville (1959) doubted whether the term "chronic" should be applied since many of the cases had a history of only about 9 months' duration. However, an analysis of the cases shows that the mean duration of the myopathy was 11.1 months in men and 16.7 months in women, so the description seems quite justified. The normal ratio of females to males with thyrotoxicosis is 4:1 (Williams 1962, p. 170), but in the reported cases of chronic myopathy there were, in fact, more males than females (38:35) and this suggests that the lesion is more common in men.

There was no significant difference between the two sexes, so far as age was concerned, nor in the severity of weight loss or the height of the basal metabolic rate, and the pattern of muscles affected was much the same in both sexes. From this one must assume that the longer duration of thyrotoxic symptoms and myopathy in members of the female sex was due to their greater ability to tolerate ill-fortune.

In 23% of the patients the muscle lesion was so prominent that thyrotoxic symptoms were not a cause of complaint. In most of the rest, however, the onset of muscle symptoms was concurrent with those of hyperthyroidism. Most characteristically patients had noticed difficulty in climbing stairs or trying to rise out of a chair, some could not hold their arms up long enough to comb their hair, some had had great fatigue while walking along the level, while a fewer number had no specific muscle groups affected,

TABLE 1

Analysis of 73 cases of thyrotoxic myopathy reported in the literature.

	Male			Female			Statistical Analysis of differences between male and female cases
	Number of cases with adequate data	Number of cases positive	Analysis	Number of cases with adequate data	Number of cases positive	Analysis	
Number of patients	38			35			
Mean age	38		49.4 yrs.	35		45.8 yrs.	
Age range			20-69 yrs.			11-70 yrs.	
Mean duration of myopathy	34		11.1 mths.	28		22.5 mths.	$0.05>P>0.025$
Mean duration of thyrotoxicosis	28		11.3 mths.	30		25.3 mths.	$0.025>P>0.0125$
Mean weight loss	32		36.5 lbs.	21		33.2 lbs.	
Presence of goitre	35	28	80%	27	26	96.3%	
Presence of proptosis	37	14	37.8%	27	13	48.1%	
Presence of ophthalmoplegia	37	3	8.1%	27	1	3.7%	Numbers insufficient for x^2 analysis.
Mean basal metabolic rate	32		+49%	28		+47%	
Glucose tolerance diminished	15	*11	73.3%	8	‡ 5	62.5	
Urinary creatine excretion	17		154.0mg./ 24hrs.	18		350.0mg./ 24hrs.	$0.05>P>0.25$

* 3 diabetic curves with oral glucose tolerance test.

‡3 diabetic curves with oral glucose tolerance test.

Table 1 continued.

	Male			Female			Statistical analysis of differences between male and female cases
	Number of cases with adequate data	Number of cases positive	Analysis	Number of cases with adequate data	Number of cases positive	Analysis	
Urinary creatinine excretion	7		1009.4 mg./ 24hr.	7		661.0 mg./ 24 hr.	0.025>P>0.0125
Muscles affected							
Proximal alone	35	13	37.1%	28	15	53.6%	
Proximal and distal	35	16	45.7%	28	9	32.1%	
Proximal, distal and cranial	35	5	14.3%	28	3	10.7%	
Proximal and cranial	35	1	2.9%	28	1	3.6%	
Cases with bulbar involvement	38	8	21.1%	35	4	11.4%	$x^2 = 0.62$ 0.50>P>0.40
Cases with antecedent upper respiratory tract infection.	38	4	10.5%	35	0	0%	
Cases with fasciculation or fibrillation.	36	15	41.7%	* 31	1	3.2%	$x^2 = 8.48$ 0.05>P>0.001
Improvement in strength with neostigmine.	17	4	23.5%	12	1	8.3%	
Cases with fasciculation who improved with neostigmine.	9	4	44.4%	1	1	100%	
Cases with fasciculation who did not improve with neostigmine.	9	5	55.5%	1	0	0%	

* One case of fasciculation not included because of old poliomyelitis in affected limbs.

Bathurst (1895), Ayer, Means and Lerman (1934), Starling and Brain (1938), Darke, Hunt and Brain (1938), Parsons and Twort (1939), MacKenzie (1940), del Castillo, de la Balze and Caul (1940), Morgan and Williams (1940), McEachern and Ross (1942), Froment, Jeune and Duverne (1942), Bartels and Pizer (1944), Thorn and Eder (1946), Froment, Gallavardin and Devic (1946), Devic, Froment, Guinet and Devic (1947), Sanderson and Adey (1949), Quinn and Worcester (1951), Zierler (1951), Sanderson and Adey (1952), Millikan and Haines (1953), Kite, McLintock and Graves (1954), Sacrez, Lauseeker and Isch (1955), Hoffenburg and Eales (1956), Collings and Lienhard (1957), Bostrom and Hed (1958), Hed, Kirstein and Lundmark (1958), Melville (1959), Ellis and Carey (1961), Whitfield and Hudson (1961) and Havard (1962).

but complained of a generalised weakness. Severe paresis affecting all muscle groups was precipitated in one patient (Collings and Lienhard 1957) by a glucose tolerance test and was relieved by the administration of potassium chloride. In the 73 patients movements least affected were those of the hand. Only two patients spontaneously complained of weakness of the hands. Five patients out of the total had indeed no complaints at all which were related to the muscles.

Four of the men had had upper respiratory tract infections before the onset of severe muscular weakness (Ayer et al. 1934, MacKenzie 1940, Morgan and Williams 1940) and two patients had had thirst and polyuria (McEachern and Ross 1942, Zierler 1951). It is interesting to note that Zierler's patient had a daily urinary output of 4-5 litres and a serum potassium of 2.0 mEq/litre suggesting that the hypokalaemia may have caused renal tubular damage. Additional features preceding and accompanying muscle weakness were diarrhoea in 10.9% of the patients (del Castillo et al. 1940, Morgan and Williams 1940, MacKenzie 1940, Devic et al. 1947, Zierler 1951, Sacrez et al. 1955, Ellis and Carey 1961, Whitfield and Hudson 1961), and vomiting in two cases. Two patients described by Sanderson and Adey (1952) and by Millikan and Haines (1953) had had cramps in their legs, while Hoffenburg and Eales (1956) described a man with pain and stiffness in his muscles and contractures, and muscular aching was noted by Whitfield and Hudson (1961).

There was proximal involvement of muscle in all the cases described in the literature. In 44% these were the only ones

affected by the myopathy, in a further 40% there was evidence of distal involvement and in the remaining 16% weakness of bulbar muscles also occurred and there was no significant difference in its incidence between the two sexes. Difficulty in speaking was the most common symptom and consisted of dysphonia, hoarseness, weakness of speech or an alteration in the quality of the voice. Dysphagia was the second commonest sign of bulbar involvement and the nasal regurgitation of fluids occurred in one patient.

41.7% of the men were noted to have spontaneous muscle movements, compared with only 3.2% of the women. Although the movements were variously described by the authors as fasciculation or fibrillation, the latter are unlikely to have been seen, as was explained earlier. Harman and Richardson (1954) considered that in many of these patients the muscle twitching was in fact myokymia. That the twitching was myogenic and not neurogenic was suggested by McEachern and Ross (1942) who blocked the nerve to the affected muscle with novocaine and observed its continuance. Millikan and Haines (1953) reported a normal innervation in one of their patients who had muscle twitching. Nearly one-sixth of those in whom neostigmine or edrophonium was tried derived some increase in muscle strength and half of those who had fasciculations developed greater strength following their administration. Both Kite et al. (1954) and McEachen and Ross (1942) linked the fasciculations with the improvement in power following neostigmine and postulated that the fasciculations were due to an undue sensitivity of the motor end plate in a state of abnormal metabolism.

Tendon reflexes were mostly normal. As nearly an equal number were hyperactive as were diminished and a small number were absent. Devic et al. (1947) described two cases in which there were, in addition to muscle wasting and weakness, extensor plantar responses and paraplegia. One died the day after operation, the other recovered fully following thyroidectomy.

73.3% of the men and 62.5% of the women had evidence of impaired tolerance to glucose. Two of these patients were known diabetics and it is probable that most of the rest had "thyroid diabetes", with a return to the normal state after remission of their thyrotoxicosis. The high incidence of impaired glucose tolerance is probably an indication of the severity of the thyrotoxicosis in these patients.

Rather more men than women had ophthalmoplegia (8.1%:3.7%), but the numbers are too small for statistical analysis. Part of any difference could perhaps be accounted for by the greater incidence of nodular goitre (Plummer's Disease) in the women (4 cases), which characteristically is not accompanied by ophthalmoplegia, as compared with the men (1 case).

INVESTIGATIONS

Biochemistry. Apart from the constantly raised basal metabolic rate, protein bound iodine or I^{131} uptake, there have been no constant biochemical features in the reported cases. Five patients had slightly raised serum calcium levels and two had hypocalcaemia, but the vast majority were quite normal. A serum potassium of 2.0 mEq/l was reported in one patient. Five patients (2 with testicular atrophy) on whom urinary 17 ketosteroid estimations were carried out gave values at the lower limit of normal

(Thorn and Eder 1946), apart from one man whose output was only 2.7 mg./24 hours. Sanderson and Adey (1952) reported a Robinson-Power-Kepler test which was positive on two occasions and returned to normal after treatment of the thyrotoxicosis and one of Thorn and Eder's (1940) cases was found to have atrophy of the zona glomerulosa of the adrenal cortex at postmortem. Sanderson and Adey found evidence of impaired adrenal function in one of their patients and suggested that the cause was subnormal production of adrenocorticotropic hormone (1952), whereas Daughaday and Farr (1951) postulated a primary defect of adrenal responsiveness in thyrotoxicosis.

Creatine and Creatinine Excretion. Creatine excretion in normal adult men is usually almost absent and in adult women the upper limit of normal is 50 mg./24 hours (Documenta Geigy 1962). The normal range of creatinine excretion for normal adults is 1.071-3.219 g/24 hours with a mean of 2.145 g/24 hours (Documenta Geigy 1962).

Table 1 shows that in the 73 cases of chronic thyrotoxic myopathy reported the mean creatine excretion in men was 154.0 mg./24 hours, whereas it was 340.0 mg./24 hours in women. Statistical analysis reveals this difference as being significant. The figures for creatinine excretion were 1.009 g/24 hours for males and 0.661 g/24 hours for females, the differences not being statistically significant. Two of each sex had no creatinuria. These were the cases of Zierler (1951) and Sanderson and Adey (1952). Pipberger and his colleagues (1955) also reported absence of creatinuria in 5 out of 13 thyrotoxic patients, and so it would

appear that the pattern of excretion of creatine and creatinine in hyperthyroidism is extremely variable. It seems likely that the creatinuria and the low excretion of creatinine are partly due to decreased muscle mass, and thus impaired storage of creatine which is manufactured by the liver and kidneys, and partly to impaired utilization of creatine by the muscles (Wilkins and Fleischmann 1946). This is borne out clinically by the demonstration of impaired creatine tolerance in thyrotoxic patients (Thorn and Eder 1946).

Electrocardiography. Apart from atrial fibrillation, the electrocardiogram rarely showed any unusual features. However, on three occasions inversion of the T wave was noted and Morgan and Williams (1940) described "slight myocardial damage" in one of their patients.

Electromyography. Electromyographic investigation of chronic thyrotoxic myopathy has been carried out in only a small number of patients. The most characteristic finding has been a reduction in duration and voltage of motor unit potentials (Sanderson and Adey 1949, 1952, Sacrez et al. 1955), a large number of which were disintergrated in appearance (Hed et al. 1958, Whitfield and Hudson 1962, Havard 1962) and there has been one report of the presence of fibrillation (Hed et al. 1958). Millikan and Haines (1953), on the other hand, reported that there was no abnormality in the electromyogram (E.M.G.) of any of their four patients on whom it was carried out.

A few other descriptions of the E.M.G. in thyrotoxicosis have appeared in the last 15 years. Garcia Austt, Torrents and Mussio-Fournier (1949), working in Montevideo, could find no features which distinguished the E.M.G. of hyperthyroid patients from normal, but they did note that the frequency was lower in 52% of 17 thyrotoxics than in 50 normals at the onset of the contraction of quadriceps against a load of 3 Kg. They found that with successful treatment of the thyrotoxicosis the frequency increased and the tracing went back towards normal or became completely normal. They also said that there was some correlation between the initial frequency of the E.M.G. and the height of the B.M.R.. Gimlette (1959), on the other hand, found a high frequency of the action potentials on volition, and discovered that a majority of the thyrotoxic patients he tested had the "myopathic pattern" described by Bauwens (1955). Evidence of myopathy, consisting of a shortening of the duration of action potentials, a reduction in voltage and an increase in polyphasicity, was found by Pipberger, Kalin and Wegmann (1955) in 12 out of 13 thyrotoxic patients. Some electromyograms were carried out on several muscles and an analysis of the results showed a clear preference for the proximal muscles of the limbs as compared with the distal. One of the patients was found to have fibrillation potentials on E.M.G.

These findings are typical of myopathy, no matter what the cause (Kugelberg 1947), 1949, Buchthal and Pinelli 1953, Pinelli and Buchthal 1953, Eaton and Lambert 1957). The presence of fibrillation in the patients of Pipberger *et al.* (1955) and Hed *et al.* (1958) does not necessarily indicate denervation (Guy et al.

1950, Eaton and Lambert 1957) and it has been shown by Adrian and Gelfan (1933) that fibrillation can result from ionic differences across the muscle fibre membrane. Buchthal and Rosenfalck (1963) reported finding fibrillation potentials in half the muscles of patients with muscular dystrophy, a condition in which the muscles are known to contain a low concentration of potassium (Blahd, Bauer, Libby and Rose 1953, Horvath, Berg, Cummings and Shy 1955) but in which the serum content of that ion is quite normal. Recently workers in Japan have discovered a significant reduction in the intracellular content of potassium in muscle obtained by biopsy from thyrotoxic patients, with a concomitant rise in the sodium concentration. (Satoyoshi, Murakami, Kowa, Kinoshita, Noguchi, Hoshina, Nishiyama and Ito 1963).

Pathology. Askanazy wrote the first description of the muscle lesion of thyrotoxicosis in 1889. He noticed infiltration of fat cells between muscle fibres, atrophy of muscle fibres with a decrease in their diameter, proliferation and clumping of muscle nuclei, loss of striation and vacuolisation. Cardiac and smooth muscle showed no abnormality. Since 1898 a few further reports have appeared. Many described much the same findings as Askanazy (Dudgeon and Urquhart 1926, Morgan and Williams 1940, Bartels and Pizer 1944, Quinn and Worcester 1951, Boström and Hed 1958, Havard 1962), but in addition aggregations of lymphocytes have been noted in 5 articles (Dudgeon and Urquhart 1926, Liechti 1938, Thorn and Eder 1946, Hed et al. 1958, Whitfield and Hudson 1961). Eppinger (1937) found capillary thickening and pericapillary oedema. Devic et al. (1947) described an alteration of the mitochrondria

in the region of the motor and plates and demyelinisation and vacuolisation of minor nerves was seen in one of Hed et al.'s (1958) patients. Cöers and Woolf, using an intravital staining technique, also found changes in the terminal nerve fibres, mainly profuse distal sprouting, often with the formation of multiple end plates on single muscle fibres.

Hed et al. (1958) noticed the presence in the muscle tissue of iron loaded phagocytes. The presence of subsarcolemmal semilumar accumulations of metachromatic substance observed by Asboe-Hansen, Iversen and Wichmann (1953) in thyrotoxics, but most markedly in those with progressive exophthalmos, has not yet been confirmed. The reason for this may be that the phenomenon was only visible in muscles fixed in basic lead acetate which precipitated acid mucopolysaccharides, and was not found in tissue fixed in aqueous media, such as formalin (Iversen, Asboe-Hansen and Carlsen 1953).

However, there have been several reports of biopsies carried out on patients with thyrotoxicosis which have shown no abnormality (Morgan and Williams 1940, Sanderson and Adey 1949, Millikan and Haines 1953, Kite et al. 1954, Collings and Lienhard 1957, Adams et al. 1962).

Prognosis. Some of the early cases died of respiratory paralysis, but virtually all of the others made a full recovery from their myopathy, largely due, no doubt, to the more effective modern forms of treatment for hyperthyroidism. The rapidity of the recovery of muscle power has sometimes been remarkable. Peycelon (1946) described a patient who 3 days after thyroidectomy

was able to lift both legs off the bed and hold them vertically, a thing which had been quite impossible before the operation. Ellis and Carey (1961) had a patient whose strength was returning after two weeks' treatment with propylthiouracil and most other authors noted a return to normality over the course of several months, once treatment had been initiated.

ENDOCRINE OPHTHALMOPLEGIA

This condition, which is only indirectly related to the thyroid gland, as it may occur in hypothyroidism, Cushing's syndrome or in apparently euthyroid individuals, is characterised by progressive exophthalmos, oedema of the lids and conjunctivae, weakness of the extraocular muscles, usually those serving elevation, convergence and lateral movement, and occasionally papilloedema and corneal ulceration. There seems to be little connection between endocrine opthalmoplegia and the other muscle syndromes of hyperthyroidism, both on clinical and experimental grounds. It has been pointed out that severe involvement of the eye occurs more frequently following successful treatment of the thyrotoxicosis than during the course of the disease itself and it sometimes arises in a patient suffering from hypothyroidism (Asboe-Hansen et al. 1952, Brain 1959).

Physiologists have shown that the administration of thyroid extract or thyroxine to experimental animals did not, by and large, produce exophthalmos, but that the latter could be initiated by the administration of anterior pituitary extracts, especially when the animals had had a previous thyroidectomy carried out (Brain 1959).

Asboe-Hansen et al. (1952, 1953) measured the serum level of thyrotropin and found it to be significantly raised in 9 out of 10 patients with progressive exophthalmos. More recently Kinderen, Houtstralanz and Schwarz (1960) and Dobyns, Wright and Wilson (1961) isolated a substance which they called the "exophthalmos producing substance". It was believed to be an entity quite separate from that of thyrotropin and there seemed to be a good correlation between the presence or absence of exophthalmos and the presence or absence of the substance in the serum of thyrotoxic patients. The fact that the eye condition often regresses considerably following pituitary stalk section or hypophysectomy (McCullagh, Clamen and Gardner 1957) provided confirmatory evidence as to the pituitary origin of endocrine ophthalmoplegia.

Pathological changes have been described by several authors, both in the extrinsic muscles of the eye and in the skeletal muscles. Askanazy (1898) found similar changes in both sites. Dudgeon and Urquhart (1926) observed lymphorrhages, sometimes perivascular, proliferation of interstitial cells and atrophy of muscle fibres in the extrinsic eye muscles, where the changes were most marked, in the deltoid and the biceps, and in the myocardium, where they occurred less frequently. Dudgeon and Urquhart drew attention to the similarity between these findings and those of myasthenia gravis (Buzzard 1905). They also remarked that the thymus was enlarged in three out of their eight cases of exophthalmic goitre. Similar changes were produced in the skeletal muscle of thyroidectomised guinea-pigs by Paulson (1939) who gave 30 daily injections of antuitrin T, and the work was confirmed by Dobyns (1946) who also noted, using special stains, that the muscle fibres

were loaded with small droplets of fat. There seemed to be a close correlation between the amount of fat found in the muscle fibres and the degree of weakness produced in the guinea-pig and it was also notable that the fatty change and weakness occurred as a relatively acute phenomenon, becoming less marked as the injections of antritrin T were continued. Dobyns had earlier pointed out (1945) that thyrotropic hormone had toxic effects on animals even before there was any effective thyroid response.

Reference has already been made to the presence in patients with progressive exophthalmos of semi-lunar accumulations of mucopolysaccharide under the sarcolemmal covering of the skeletal muscle fibres (Asboe-Hansen et al. 1952). Two papers by Ludwig, Boas and Soffer (1950) and by Asboe-Hansen and Iversen (1951) described the finding of an accumulation of mucopolysaccharides, in particular hyaluronic acid, in the orbital tissues. Later Iversen and Asboe-Hansen (1952) explained the mechanism of protrusion of the eyeballs as being due to the water-binding action of the mucopolysaccharides in the orbital tissues. Whether extensive muscle paralysis can be produced purely secondarily to the retro-orbital oedema with its resultant exophthalmos, venous occlusion (Naffziger 1932, Dobyns 1950) and muscle stretching is not clear, but it seems likely that there is also some primary muscle lesion in ophthalmoplegia as it may occur without any clinically demonstrable exophthalmos (Logothetis 1961). In the 73 cases of thyrotoxic myopathy reported in the literature 5 patients with exophthalmos had abnormal skeletal muscle histology and in two it was normal. (There was one patient with ophthalmoplegia in each group.) Of the patients without exophthalmos 14 had an abnormal muscle

biopsy and 4 were reported on as being normal. There was no difference in the histological picture between the patients with exophthalmos and those without.

THYROTOXICOSIS AND MYASTHENIA GRAVIS

The combination of myasthenia gravis and thyrotoxicosis was first described by Remak in 1899 (Logothetis 1961) and since then it has been reported in more than 50 cases (Adams et al. 1962).

It has been estimated that 1% of thyrotoxics have myasthenia gravis at some time in the course of their disease (Grob 1963) and that the incidence of thyrotoxicosis preceding, accompanying or following the clinical onset of myasthenia gravis is 5% (Millikan and Haines 1953). Millikan and Haines found that 80% of the patients with this combination were women and that the type of myasthenia was the same as that found in patients without thyrotoxicosis. It responded to neostigmine, which, however, had no effect on any associated endocrine ophthalmoplegia.

Some authors have attempted to find factors which are common to both conditions. Cohen and King (1932) commented on the hypertrophy of lymphatic tissue, the occasional presence of lymphocytosis and the finding of lymphorrhages in muscle tissue. In addition the presence of atrophy or even necrosis of the muscle fibres was noted by Russell (1953). An enlarged thymus is found in half the thyrotoxic patients who come to postmortem examination (Williams 1962, p. 157) and in recent autopsy studies approximately one third of the patients with myasthenia gravis had thymomas and a further quarter had hyperplasia of the thymus (Castleman and Norris 1949, Rowland, Aranow and Hoefer 1957). Cohen and King (1932) also compared the not infrequent occurrence of glycosuria and lowered glucose tolerance in thyrotoxics with the definite lowering of carbohydrate tolerance in myasthenia gravis.

The relationship of myasthenia gravis and thyrotoxicosis described in the literature is complex. Millikan and Haines (1953) reported that in their cases 48% of the patients developed hyperthyroidism before the myasthenia gravis. In 32% the relationship was the reverse and in 20% the conditions occurred simultaneously. Although McEachean and Parnell (1948) described a 'see-saw' relationship between the diseases, the myasthenia increasing as the thyrotoxicosis receded and vice-versa, other reports have been divided unevenly between the protagonists (Thorner 1939, Cohen 1946, Maclean and Wilson 1954) and those who described the opposite turn of events or no obvious intraction. (Thorn and Tierney 1941, Kowallis et al. 1942, Flynn 1944, Green 1949, Millikan and Haines 1953, Osserman and Silver 1961.) Adams et al. (1962, p. 599) take the view that, whatever the factors are which cause the occurrence of the two diseases at the same time, the thyrotoxicosis does not make the myasthenia gravis worse per se, but merely adds on the weakness of hyperthyroidism to that of the former condition. Thus the response to neostigmine cannot be expected to be total.

THYROTOXICOSIS AND PERIODIC PARALYSIS

More than 200 cases of concurrent thyrotoxicosis and periodic paralysis recorded in the literature have recently been reviewed by Engel (1961), who found that most cases were of a sporadic rather than a familial nature and tended to occur at an older age (Grob 1963b, p. 167) than in the uncomplicated type of periodic paralysis. In rather more than 80% of the cases the thyrotoxicosis antedated or appeared at the same time as the periodic paralysis.

Serum potassium levels have been reported as being low in some, but not all, patients with the combination of the two diseases (Talbott 1941, Goldberg and Barnett 1961). Most cases remit once the thyrotoxicosis is brought under control. To emphasize that there is a direct relationship between thyroid overactivity and the degree of paralysis a man (Hildebrand and Kepler 1941) with a family history of periodic paralysis, and who had himself suffered minor and infrequent attacks, developed hyperthyroidism and immediately the attacks began to get severe and more frequent. Hildebrand and Kepler and also Ziegler (1949) infused potassium intravenously into patients in an attack with known hypokalaemia, but without producing any response.

MISCELLANEA

Generalised Myokymia in Thyrotoxicosis

This form of muscle twitching has been reported only once in association with thyrotoxicosis (Harman and Richardson 1954), though the authors regard the cases reported by Morgan and Williams (1940) and McEachean and Ross (1942) as exhibiting myokymia. Possibly some of the other cases of thyrotoxic myopathy reported as having fasciculations had in fact myokymia. The myokymia, which may occur in normal people, especially under conditions of fatigue, is observed as coarse muscular twitchings, easily visible through the skin. The spontaneous activity continues after spinal or high nerve block, but is stopped by curare and is not increased by prostigmine, thus placing the origin somewhere in the peripheral nerve. Electromyographic studies show that nerve excitability is increased, but that there is no evidence of a lower motor neurone lesion.

Muscle Rigidity and Spasm with Thyrotoxicosis

Werk, Sholiton and Marnell (1961) presented the case of a man who exhibited the "stiff man" syndrome - originally described by Moersch and Woltman (1956) - and thyrotoxicosis. This middle-aged man complained of weakness, stiffness in his muscles and difficulty with swallowing. Investigations confirmed hyperthyroidism and treatment with radioactive iodine improved his stiffness to some extent, but did not abolish it. There was a large amount of psychological overlay in this patient, and it is hard to know whether the stiffness represented a true association with thyrotoxicosis, though in two cases of thyrotoxic myopathy described by Sanderson and Adey (1952) and by Millikan and Haines (1953) muscle cramps were a prominent feature and a patient with pain and stiffness in his muscles was reported by Hoffenburg and Eales (1956)

Myotonic Dystrophy

Two cases of thyrotoxicosis occurring in patients with myotonic dystrophy have been noted (Berkman 1935, Leach 1962). In both cases there was a marked improvement in strength following treatment of the hyperthyroidism; in one case coincident bulbar symtoms also disappeared and in the other the degree of myotonia was lessened. It is not suggested that there is any relationship between the two conditions other than that of chance, but it seems likely that both were cases of myotonic dystrophy with superadded thyrotoxic myopathy.

AIM OF THE THESIS

This review of the literature has brought out some similarities which occur between the various skeletal muscle conditions associated with overactivity of the thyroid gland. These similarities are summarised in Table 2 and it can be seen that the condition of acute thyrotoxic myopathy ("encephalomyopathy") resembles very closely that of chronic thyrotoxic myopathy, the only difference being the more frequent sudden onset of bulbar symptoms in the former. The muscle histology is almost identical.

The resemblance between the acute and chronic forms of myopathy and both myasthenia gravis and periodic paralysis is not quite so striking, but it will be noted that the degeneration of muscle fibres and vacuolisation within the fibre have been described in all four conditions. Also, cases have been reported in each disease in which there was some upset of potassium metabolism and attention is drawn to the enlargement of the thymus in both thyrotoxicosis and myasthenia gravis.

Experience in the Metabolic Clinic, Royal Victoria Hospital, Belfast had suggested that muscle involvement was common in thyrotoxicosis and it was decided, therefore, to carry out a detailed investigation of a series of consecutive, unselected patients presenting at the Metabolic Clinic with proven hyperthyroidism in an attempt to discover more about the nature of the muscle lesion.

It was thought that the most likely explanation for the occurrence of the various muscular disorders was a constant derangement of muscle metabolism in thyrotoxic patients. This

TABLE 2.

Some similarities between the muscle lesions associated with thyrotoxicosis

Acute thyrotoxic Myopathy and Encephalo-myopathy	Chronic Thyrotoxic Myopathy	Myasthenia Gravis	Periodic Paralysis
	Sometimes an antecedant upper respiratory tract infection.	Upper respiratory tract infection may be an aetiological agent (Simpson 1960)	
Diarrhoea and vomiting	Diarrhoea and vomiting		
Spontaneous activity seen in muscles	Spontaneous activity seen in muscles		
Bulbar involvement usually	Often bulbar involvement	Usually bulbar paresis	Rarely bulbar paresis
Upper motor neurone lesions reported	Upper motor neurone lesion on one occasion		
Hypokalaemia reported	Hypokalaemia reported one case precipitated by glucose and relieved with potassium chloride.	33% experienced some increase in strength following potassium chloride (Grob 1963, p. 154).	Hypokalaemia precipitated by carbohydrate.
Unknown	Glucose tolerance diminished	Glucose tolerance diminished	
E.M.G. Myopathy	E.M.G. Myopathy	E.M.G. Myopathy	E.M.G. - Myopathy during an attack. (Shy, Wanko, Rowley and Engel 1961).
Muscle pathology Degeneration of muscle fibres Vacuolisation Sarcolemmal nuclear proliferation Loss of striations	Muscle pathology Degeneration of muscle fibres Vacuolisation Sarcolemmal nuclear proliferation Loss of striations Lymphorrhages	Muscle pathology Atrophy of muscle fibres Vacuolisation Sarcolemmal nuclear proliferation Loss of striations Lymphorrhages	Muscle pathology Degeneration of isolated muscle fibres Vacuolisation (Adams et.al. p. 647)
Thymic enlargement	Thymic enlargement	Thymic enlargement	

would produce weakness, followed later by secondary atrophy of the muscle fibres and would unmask those people who also had latent myasthenia gravis or periodic paralysis.

The main criterion for the presence of a myopathy in the patients studied was the electromyogram. Muscle biopsies were made in order to assess any histological abnormalities and to try to relate the muscle fibre population and diameter to the electromyographic findings.

METHODS

Patients. Fifty-four consecutive patients presenting at the Metabolic Clinic, Royal Victoria Hospital, Belfast, on whom a diagnosis of thyrotoxicosis was proven, were examined and investigated by the author for involvement of their muscles. The investigations carried out were electromyography, muscle biopsy, urinary creatine and creatinine excretion, serum calcium and potassium, 2-hour post-prandial blood glucose and electrocardiography. Whenever possible the diagnosis of thyrotoxicosis was substantiated by means of I^{131} uptake and excretion studies done over 48 hours, but occasionally I^{132} neck uptakes were performed on outpatients living at a distance, and at times estimations of the basal metabolic rate only were made on a few patients who had recently ingested iodine in one form or another.

If the severity of the thyrotoxicosis warranted it, the patient was admitted to hospital: otherwise the investigations were carried out as an outpatient.

Because of the extreme nervous tension and anxiety in some patients it was not always possible to do all the investigations on some individuals. However electromyographic studies were satisfactorily completed in all.

Clinical Examination. A detailed history was taken in order to establish, as accurately as possible, the duration of thyrotoxic symptoms and their relationship to the onset of any muscular complaints. Patients were questioned closely about their ability to perform movements with all major muscle groups and were asked about difficulty in carrying out familiar everyday actions such as combing

the hair, hanging up washing, climbing stairs etc.

As well as a full clinical examination to establish the signs of thyrotoxicosis and any associated pathology, particular attention was paid to all muscle groups in the body. The muscles were examined for evidence of atrophy which was graded as none (o), slight (+), moderate (++) or marked (+++).

A commonly used grading of muscular power is that of the Medical Research Council (1949), but this was found unsatisfactory as the severity of the weakness in the patients being studied was confirmed to M.R.C. grade 4. A similar classification to that for atrophy was therefore used, viz. no loss of power (o), some weakness against resistance by the examiner's hand (+), moderate weakness (++) and marked weakness (+++). Since clinical experience in the earlier part of the survey had suggested that the iliopsoas was more often affected than the quadriceps group, Lahey's (1926) test was modified so that the patient lay down in bed and, holding the knee straight raised the leg to an angle of 45° and maintained it in this position until able to do so no longer. The test was performed at the initial examination before and after the intravenous injection of 10 mg. of edrophonium chloride (Tensilon).

Visible spontaneous muscle activity was searched for with the patient in a state of complete relaxation.

The thyroid gland was carefully palpated in order to determine whether the goitre was diffuse or nodular.

Evidence of ophthalmoplegia was looked for and the degree of proptosis measured with a Keeler exophthalmometer at the initial and subsequent visits.

Electromyography. Electromyography was done at the time of the first examination and was repeated four months after the patient had been rendered euthyroid. One proximal muscle was sampled in each patient and the two muscles chosen were deltoid and rectus femoris. The triceps was tested on one patient. Over a third of the patients also had an electromyogram done on abductor digiti quinti.

Controls were obtained for each of the muscles tested. The controls consisted of people of all age groups who were either completely healthy or had no neuromuscular pathology, primary or secondary (e.g. diabetes mellitus, Addison's Disease, malignant neoplasms etc.).

Care was taken while doing follow up electromyograms on treated patients to ensure that the area of muscle near the biopsy site was not sampled.

The examinations were done with a D.I.S.A. three channel electromyograph. The amplifiers had a frequency range of 2 to 10,000 c.p.s. (Guld 1951) defined by 3 db. discrimination, the input impedance was 100 megohms shunted with 60 pF (single ended) and the noise level was less than 1.5 μV r.m.s. with a shorted input. Concentric needles, consisting of a platinum lead embedded in Araldite within a stainless steel cannula, were used. The area of the platinum surface was 0.07 sq. mm. The tip of the needle was cut obliquely at an angle of 15°. An 0.65 mm. diameter, 42 mm. long needle was used for proximal muscles and an 0.45 mm. diameter, 30 mm. long needle for distal muscles. The same needles were used on both the thyrotoxic patients and the controls.

The electrode impedance was kept as low as possible by checking it every two months. If the noise level was greater than 15 μV peak to peak the electrode was placed in 0.9% NaCl solution and 6 volts D.C. was applied for two seconds between the platinum electrode and the cannula.

The electromyogram was checked regularly for the accuracy on the cathode ray tubes of the time base and amplitude. This was done with the built in square-wave calibrator. Minor adjustments were rarely necessary.

The electromyograms were done by using three needle electrodes simultaneously. Each needle was inserted at random into the selected muscle and recordings were taken at minimal effort. Each needle was then advanced 1 cm. in the proximal muscles and at least 0.5 cm. in the abductor digiti quinti and the procedure was repeated. After the needles had been pushed in for a further 1 cm. and recordings had been taken, they were withdrawn and inserted twice more in other parts of the muscle, with three depths at each insertion. Thus, in all, 27 different parts of each muscle were sampled (Buchthal and Rosenfalck 1955). Intramuscular temperatures were not taken, but the patients were examined in a room kept at a constant temperature of 22°c, since it has been shown that cooling increases the action potential duration and also the percentage of polyphasic forms (Buchthal and Pinelli 1951).

Recordings were taken at sweep speeds corresponding to 1 m. sec. per mm. with an amplification such that 1 mm. on the cathode ray screen was equivalent to 10 μV. The paper speed was 5 cm. per sec. If the whole potential could not be seen, the amplification was increased until it could be. The action potential

duration was only measured at an amplification of 10 μV/mm. in order not to miss minor deflections from the base line.

At the end of the sampling procedure a recording was taken of the pattern of activity at full effort.

The films were developed and analysed for action potential duration and amplitude and the degree of polyphasicity. Each action potential was identified three times and the duration was measured from the first to the last deflection from the base line. The amplitude was measured as the peak to peak deflection (Buchthal, Guld and Rosenfalck 1954). The mean of the three readings was regarded as the characteristic for that potential. Any potential with five or more deflections across the base line was categorized as a polyphasic potential, but it also had to be identified three times before it was accepted as such. All the potentials in the record which could be identified three times were measured and sufficient length of record was taken to ensure that this included at least 20 different potentials, other than polyphasics. The mean duration and amplitude for the whole muscle and the percentage of polyphasic potentials was then calculated. Polyphasic potentials were not included in the calculations to determine mean action potential duration and amplitude (Buchthal 1957).

The pattern at maximum effort was classified as a normal interference pattern, mixed pattern or single motor unit potentials. The peak to peak voltage was measured whenever it was felt that the record represented the maximum contraction of which the patient was capable.

Motor nerve conduction velocities. Studies were carried out on the ulnar nerve of 12 patients. The 3 recording electrodes were placed in the abductor digiti quinti and the nerve was stimulated at the wrist and also above the elbow with the D.I.S.A. Multistim. The stimulus given was twice the threshold stimulus for that patient. The latency from the wrist to the muscle and the conduction velocity between the elbow and the wrist was calculated for each needle and an average of the three was then taken. Control measurements were done on subjects of all ages who were either normal or had no neuromuscular disease.

Muscle biopsy. Biopsy was carried out on the proximal muscle which had been examined electromyographically. The biopsy was always done on a part of the muscle which had not had electrodes inserted into it.

Control biopsies were done, usually on patients undergoing operation for varicose veins or inguinal hernia. Unfortunately it was rarely possible to obtain tissue from the rectus femoris or deltoid muscles.

The biopsy was performed according to the method suggested by Buchthal, Guld and Rosenfalck (1955). In the patients 2% xylocaine without adrenaline was used for skin anaesthesia; in the controls the operation was always under general anaesthesia. A piece of muscle 1.5 cm. x 0.5 cm. x 0.5 cm. was removed. The muscle sample was not touched with instruments or swabs, ligatures being tied round each end and the muscle tissue being divided distal to the ligatures. The biopsy specimen was stretched out on a piece of cork, pinned at each corner with a wooden sliver

and placed in 4% neutral formaldehyde at 37°c. These precautions were taken in order to minimise damage done to muscle tissue and also to prevent the fibres from going into a state of severe contraction. The fixing medium was maintained at 37°c. for 24 hours, then allowed to cool to room temperature.

After fixation the specimen was embedded in paraffin and sections 5 μ thick were cut both perpendicular to and in the plane of the muscle fibres. They were stained with haematoxylin and eosin and van Gieson. The sections were examined for histological abnormalities and, on suitable specimens, the muscle fibre population and mean diameter were measured. Only sections in which there was a true cross-section of the muscle fibres, that is one in which the fibres appeared round or polyhedral, were used for these estimations. The fibre population was measured by counting all the fibres in 35 squares of a grid incorporated in the microscope eyepiece. The size of this area on calibration was 1.05 sq. mm. and so the density could be calculated. The fibre diameter was measured with a scale, each division of which represented 25 μ. This was also incorporated in the microscope eyepiece. A hundred fibres were counted except in a few instances where there were insufficient fibres which were truly cross-sectional.

Urinary creatine and creatinine excretion. Twenty-four hour samples of urine were collected both before treatment and four months after the patient had become euthyroid. The creatine and creatinine estimations were done by the Auto-analyzer standard method (1962).

Serum calcium. Serum calcium was measured with the flame photometer (Fawcett and Wynn 1961).

Serum potassium. Estimations of serum potassium were made using the Auto-analyzer standard method (1961).

Blood glucose. The Auto-analyzer standard method (1960) was used for blood glucose estimations. The blood samples for these were taken two hours after a meal containing at least 100 g. of carbohydrate.

R E S U L T S

The Patients. Fifty-four consecutive thyrotoxic patients were examined, investigated and followed-up during the course of the survey. Tables 3 and 7 summarise the main features, details of which can be found in Appendix Tables 1 and 2.

Forty women and 14 men were seen, giving a female to male sex ratio of 2.9:1. The mean age of the patients was 47.9 years, and there was no significant difference between the mean ages of the male and female patients.

Fifty per cent of the patients gave a history of some muscle weakness. The most common symptom was that of difficulty in going up stairs (15 patients). A slightly smaller number of patients (13) complained of weakness of the arms, in particular the proximal muscles. The women often complained of being unable to brush or comb their hair without resting, and of excessive fatigue when putting up curtains or taking things from high shelves. The men, especially the manual workers, had noticed a decline in their ability to lift or push heavy objects and often required help in performing tasks which previously they had been quite capable of managing alone. There were no complaints of weakness affecting the bulbar muscles. There was no statistical difference between the ages of patients with muscular weakness and those without (Table 3).

79.6% of the patients had noticed the onset of typical thyrotoxic symptoms as the first feature of their illness: in 3.7%, weakness had been the presenting feature. In 16.7% of the patients there was a simultaneous onset of the usual thyrotoxic

TABLE 3

The main characteristics of the patients, with particular reference to muscle weakness. (See Appendix Table 1)

	Males			Females			Whole Series	Statistical analysis of differences between male and female patients
	No. of patients	No. of cases positive	Analysis	No. of patients	No. of cases positive	Analysis		
No. of patients	14			40			54	
Mean age			46.8 yrs			48.3 yrs	47.9 yrs	0.8>P>0.7
Age range			27-64 yrs			15-69 yrs	15-69 yrs	
% patients with history of weakness	14	8	57.1%	40	19	47.5%	50.0%	$X^2 = 0.666$ 0.35>P>0.30
Mean duration of weakness	14	8	4.2 months	40	19	5.3 months	5.0 months	0.60>P>0.50
Mean duration of thyrotoxic symptoms	14		6.4 months	40		6.7 months	6.6 months	0.95>P>0.90
Mean weight loss	14		17.5 lb.	40		17.5 lb	17.5 lb	
Onset of toxic symptoms first	14	11	78.6%	40	32	80.0%	79.6%	
Onset of weakness first	14	0	0%	40	2	5.0%	3.7%	
Simultaneous onset	14	3	21.4%	40	6	15.0%	16.7%	
Muscles involved								
Proximal alone	14	8	57.1%	40	26	65.0%	63.0%	
Proximal and distal	14	3	21.4%	40	7	17.5%	18.5%	
None	14	3	21.4%	40	7	17.5%	18.5%	
Mean age of patients with muscular involvement	14	11	47.1 yr	40	30	50.9 yr	49.9 yr	0.5>P>0.4
Presence of ophthalmoplegia	14	1	7.1%	40	3	7.5%	7.4%	

symptoms with those of muscle weakness. In all three groups there were no differences between males and females.

Of the patients who had had some complaints of weakness there was, in fact, no difference between the duration of their thyrotoxic symptoms and that of their weakness ($0.2 > P > 0.1$).

The same mean weight loss of 17.5 lb. occurred in both men and women and, as Table 4 shows, there was no correlation between the age of the patient and the amount of weight lost.

Clinical Examination

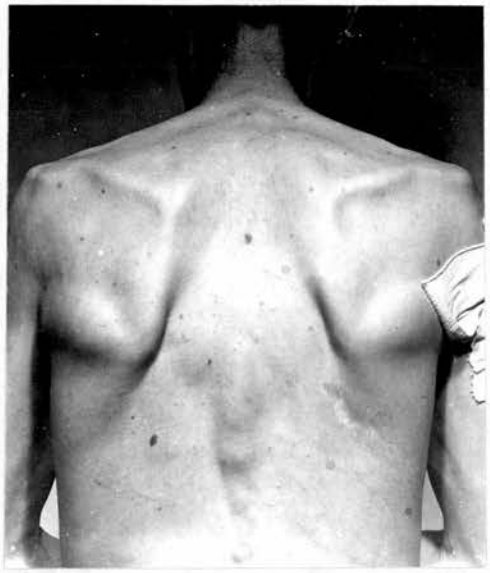
63% of the patients were found to have weakness and/or wasting of proximal muscles alone, 18.5% had involvement of both proximal and distal muscles, and the remaining 18.5% had a completely normal skeletal musculature. Two patients had slight slight atrophy without any weakness and 12 had weakness without any sign of wasting. In the other patients with muscle involvement, the wasting and weakness was usually of equal degree.

There was no difference in the mean age of those patients with muscle involvement compared with those without. Table 5 shows the number of patients in whom each muscle was involved, and it can be seen that the muscles of the shoulder girdle were more often affected than those of the pelvic girdle and, in particular, that extensors were twice as commonly affected as flexors. Figs. 1a and 2a show two patients with marked wasting of the shoulder and pelvic girdles respectively, and these can be compared with photographs taken four months after becoming euthyroid (Figs. 1b and 2b).

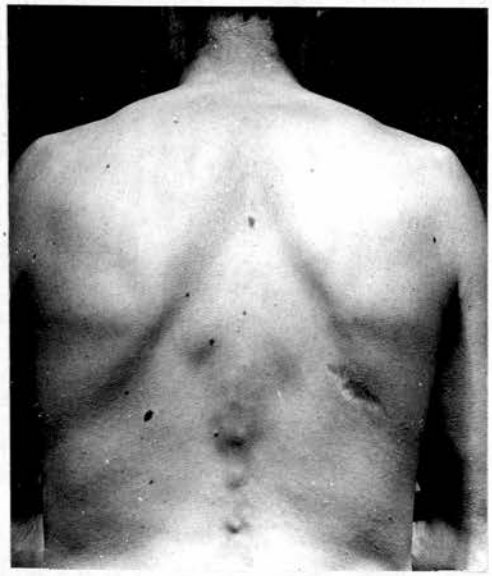
Table 4

Relationship between the age of the thyrotoxic patients and the amount of weight lost.

$\bar{x}$	47.9 yrs.
$\bar{y}$	17.5 lbs.
b_{yx}	0.011
r	0.032
Degrees of freedom	52
P	> 0.1 Not significant at P = 0.5



(a)

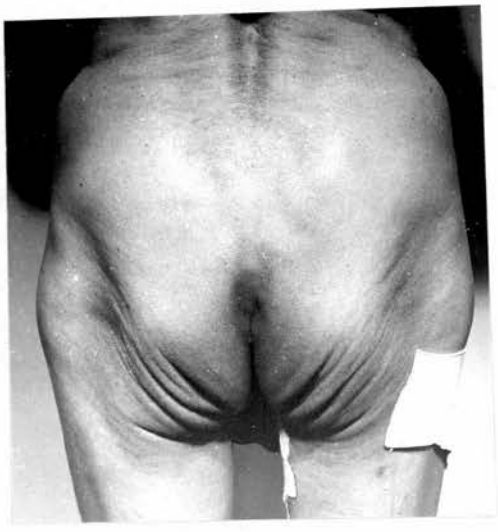


(b)

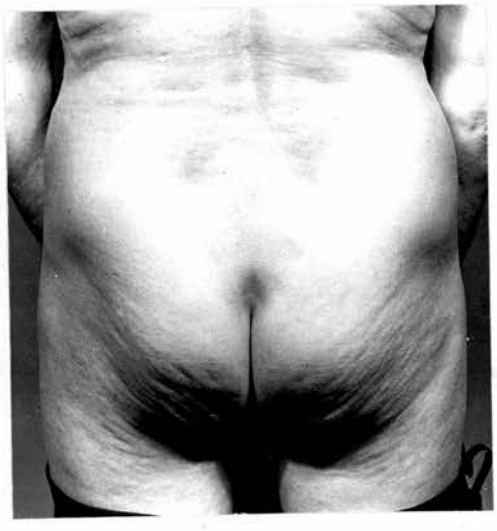
Fig. 1. Case No. 22. Male aged 38.

(a) Showing marked wasting of shoulder girdle muscles while thyrotoxic.

(b) Four months after becoming euthyroid.



(a)



(b)

Fig. 2. Case No. 15. Male aged 64.

(a) Showing wasting of gluteal muscles while thyrotoxic.

(b) Four months after becoming euthyroid.

Table 5

The frequency with which the various muscles were affected by weakness and/or atrophy.

Muscle	No. of patients
Supraspinatus	33
Triceps	33
Deltoid	30
Infraspinatus	28
Biceps br.	28
Iliopsoas	26
Quadriceps	11
Glutei	9
Extensors of wrist	6
Thenar muscles	6
Serratus anterior	5
Pectorals	4
Hypothenar muscles	4
Temporalis	3
Flexors of wrist	3
Sternomastoid	2
Biceps femoris	2
Interossei	2
Flexors of fingers	1

The tendon reflexes were normal in 29 patients (53.7%), brisk in 23 (42.6%) and reduced in 2 (3.7%). No sensory abnormalities were found.

Effect of Edrophonium. The length of time for which 19 patients could maintain each leg at an angle of 45° to the horizontal was measured and the average of the two taken. The patients were then given 10 mg. of edrophonium chloride (Tensilon) intravenously and the test was repeated. Table 6 shows that the edrophonium produced no significant increase in strength (Appendix Table 3).

Ophthalmoplegia. One of the 14 men (7.1%) and three of the 14 women (7.5%) had ophthalmoplegia. Each of the three women had other diseases in addition to her thyrotoxicosis. One had diabetes mellitus, another diabetes mellitus and pernicious anaemia and the third had concurrent myasthenia gravis, affecting only her eyes. As Fig. 3 shows, her ptosis responded well to the injection of edrophonium, but her ophthalmoplegia persisted.

Investigations
(Table 7 and Appendix Table 2)

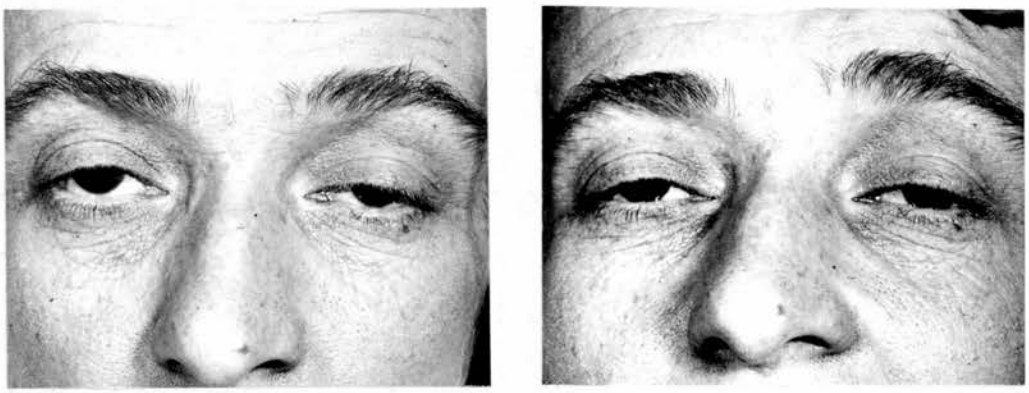
The presence of thyrotoxicosis was proved in all the patients by means of thyroid I^{131} or I^{132} uptakes, and occasionally by estimations of the basal metabolic rate or serum protein bound iodine alone (Appendix Table 2).

Electrocardiography. Electrocardiograms were done in 50 of the 54 patients, and the results are summarised in Table 8. 18% of the patients had an abnormal rhythm, usually atrial

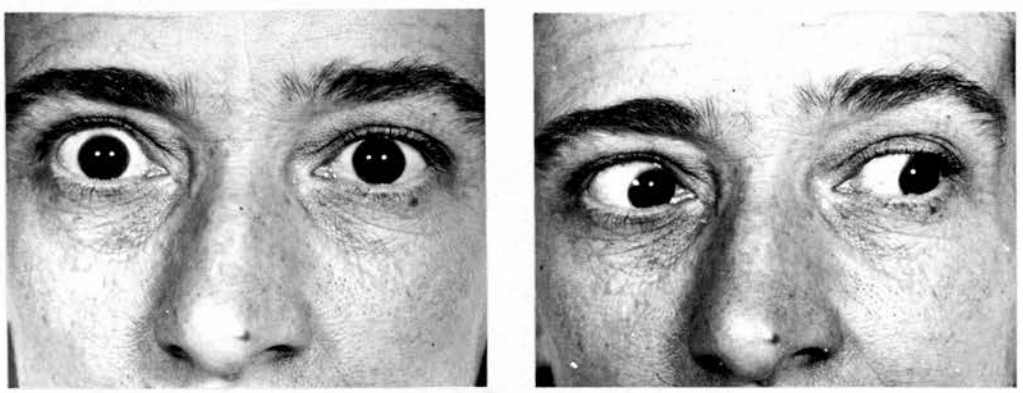
Table 6

19 Thyrotoxic patients
Time legs could be maintained in elevation
before and after the administration of
edrophonium (Tensilon).

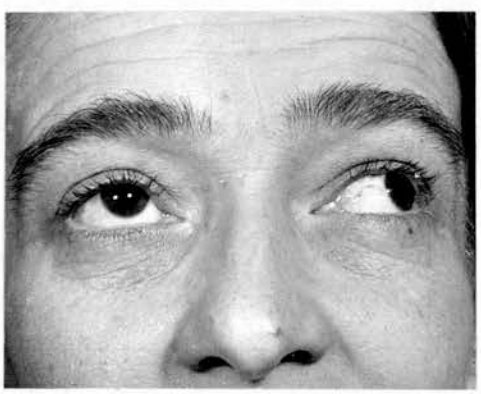
	Leg raising. Mean duration secs.	Standard error of difference	t	Degrees of freedom	P
Before edrophonium	58.9 ± 20.9	9.31	1.144	36	0.3> P > 0.2 Not significant at P = 0.05
After edrophonium	69.6 ± 34.8				



(a) (b)



(c) (d)



(e)

Fig. 3. Case No. 28. Female aged 35 with concurrent thyrotoxicosis and myasthenia gravis. (a) Showing ptosis. (b) Patient attempting to look to the left. (c) and (d) following the intravenous injection of edrophonium. (e) One month later, showing ophthalmoplegia unresponsive to edrophonium.

TABLE 7

The patients: biochemical data.

	Males			Females			Whole series	Statistical analysis Males/ females
	No. of patients	No. of cases positive	Analysis	No. of patients	No. of cases positive	Analysis		
Mean 2 hour post-prandial blood glucose	11		106.5 mg %	34		112.7 mg %	111.2 mg %	
% patients with hr. blood glucose > 110 mg %	11	4	36.4%	34	15	44.1%	42.2%	
Serum calcium mg %							10.0 ±0.5	
Serum potassium m Eq/l							4.3 ±0.5	
Urinary creatinine mg/24 hr.	14	12	311.7 ±289.9	40	32	246.7 ±207.9	264.4	0.3>P>0.2
Urinary creatinine mg/24 hr.	14	12	1132.5 ±437.2	40	32	863.4 ±590.8	936.8	0.2>P>0.1

Table 8

Analysis of the electrocardiograms of 50 thyrotoxic patients.

E.C.G. normal	2	4%
Sinus tachycardia	36	72%
Atrial fibrillation	7	14%
Atrial ectopic beats	1	2%
Atrial flutter	1	2%
Left ventricular hypertrophy	19	38%
Q_3, aVL	3	6%
Flat T wave	3	6%
ST depression	2	4%

fibrillation, and all of these except one had significant associated skeletal muscle weakness. 6% had Q waves in leads 3 and aVL, 6% had flattened T waves in various leads and 4% had ST segment depression. The vast majority had sinus tachycardia (72%), and just over half of these patients showed evidence on the electrocardiogram of left ventricular hypertrophy.

Blood Glucose. Estimations of the blood glucose two hours after a meal containing at least 100 grammes of carbohydrate were done on 45 patients. The mean value was 111.2 mg.%, and 42.2% of the patients had a value which was abnormally raised, that is above 110 mg.%, indicating diminished glucose tolerance (Williams 1962, p. 616).

Serum Calcium. Estimations were performed on 49 patients. The mean value was 10.0 mg.% and all the patients lay within the normal range of 9.5 - 10.5 mg.%, except for three patients whose values were between 9.0 and 9.5 mg.% and six others who had mild hypercalcaemia, the highest level being 11.9 mg.%.

Serum Potassium. Estimations on 48 patients gave a mean value of 4.3 mEq./1. Three had values which were just below the lower limit of normal of 3.5 mEq./1, and four others had values above 4.8 mEq./1, which is the upper limit of normal.

Urinary Creatine and Creatinine Excretion. Twenty-four hour excretion of creatine and creatinine was measured in 44 patients. The mean excretion of creatine was 264.4 mg./24 hours, and there was no significant difference between the values for men and those for women. The normal range for creatine

using the Auto-analyzer standard method (1962) is 0 - 200 mg./24 hours. Six out of the 12 men and 17 out of the 32 women had figures within the normal range. The lowest figure for a thyrotoxic patient was an excretion of 8 mg. of creatine in 24 hours.

The mean figure for creatinine excretion was 936.8 mg./24 hours, and again there was no significant difference between male and female patients in this respect. Most of the values for the men lay below, or at, the lower limit of the normal range for their sex, which is 1.0 - 2.4 grams, done by the Auto-analyzer standard method (1962). The figures for the women patients were similarly related to the normal range for females (0.7 - 1.3 grams).

Electromyography

Electromyograms were carried out on all 54 patients. A proximal muscle was tested in each patient - in 29 patients the deltoid muscle was chosen, in 24 the rectus femoris and in one case the triceps. In 21 patients abductor digiti quinti was also sampled.

Deltoid
(Appendix Tables 4 and 5)

Action Potential Duration. Table 9 and Fig. 4 show that in the control subjects there was a highly significant correlation between age and the mean action potential duration, the duration becoming greater with advancing years. All of the 29 thyrotoxic patients tested had mean action potential durations which were significantly different from the predicted for their age (Table 10).

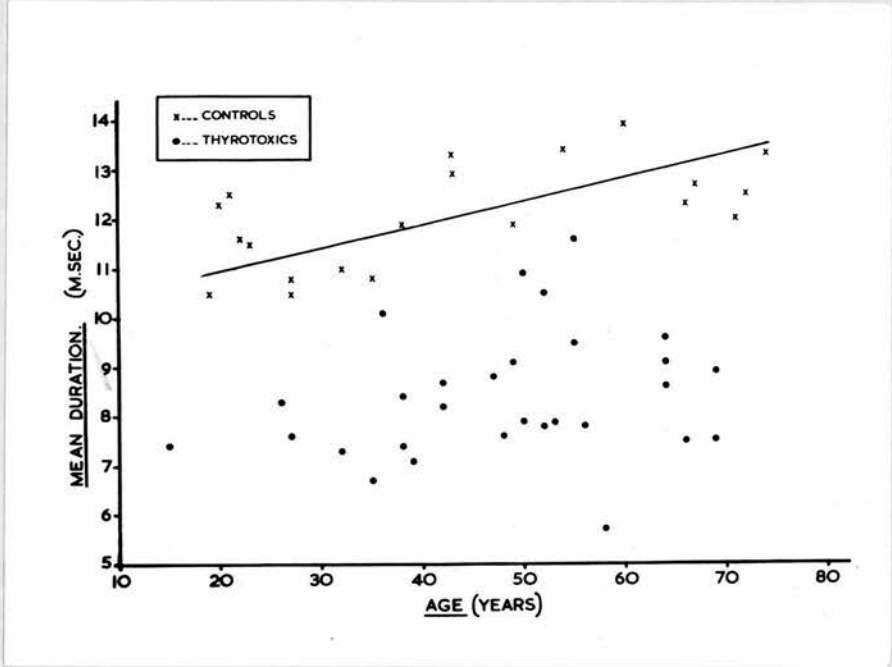


Fig. 4. Deltoid. Graph showing the relationship between age and mean action potential duration in control subjects and in thyrotoxic patients.

TABLE 9

Control Subjects. Deltoid. Correlation between age and mean action potential duration

No.	Age yrs.	Mean Duration m sec.	Statistical Analysis
1	27	10.8	
2	49	11.9	
3	43	13.3	
4	43	12.9	$\bar{x}$ = 42.1 yrs.
5	67	12.7	$\bar{y}$ = 12.0 m sec.
6	71	12.0	
7	35	10.8	$b_{y.x}$ = 0.048
8	32	11.0	S.D. = 0.46 m sec.
9	38	11.9	r = 0.90
10	72	12.5	
11	60	13.9	0.001 > P
12	74	13.3	Highly significant
13	54	13.4	at P = 0.05
14	21	12.5	
15	66	12.3	
16	20	12.3	
17	23	11.5	
18	22	11.6	
19	19	10.5	
20	27	10.5	
21	21	10.5	

TABLE 10

Thyrotoxic patients. Deltoid. Table showing the deviation of the observed mean action potential deviation from the predicted.

Case No.	Age yrs.	Observed mean action potential duration m sec	Predicted mean action potential duration m sec	Deviation of observed from predicted m sec	Statistical significance of deviation	
					t	P
1	42	8.7	12.0	3.3	6.976	P< 0.001
4	47	8.8	12.2	3.4	7.203	P< 0.001
10	38	7.4	11.8	4.4	9.301	P< 0.001
11	50	7.9	12.4	4.5	9.533	P< 0.001
12	48	7.6	12.3	4.7	9.978	P< 0.001
13	32	7.3	11.5	4.2	8.860	P< 0.001
14	26	8.3	11.2	2.9	6.066	P< 0.001
15	64	9.6	13.1	3.5	7.231	P< 0.001
17	69	7.5	13.3	5.8	11.812	P< 0.001
18	64	8.6	13.1	4.5	9.297	P< 0.001
19	66	7.5	13.2	5.7	11.704	P< 0.001
20	39	7.1	11.9	4.8	10.191	P< 0.001
22	38	8.4	11.8	3.4	7.218	P< 0.001
24	56	7.8	12.7	4.9	10.294	P< 0.001
25	55	9.5	12.6	3.1	6.500	P< 0.001
26	52	7.8	12.5	4.7	9.915	P< 0.001
28	35	6.7	11.7	5.0	10.593	P< 0.001
29	53	7.9	12.5	4.6	9.704	P< 0.001
30	49	9.1	12.3	3.2	6.956	P< 0.001
31	50	10.9	12.4	1.5	3.177	0.005>P>0.001
32	52	10.5	12.5	2.0	4.219	P< 0.001
35	15	7.4	10.7	3.3	6.720	P< 0.001
37	36	10.1	11.7	1.6	3.397	0.005>P>0.001
38	58	5.7	12.8	7.1	14.853	P< 0.001
45	55	11.6	12.6	1.0	2.100	0.05>P>0.01
48	27	7.6	11.3	3.7	7.756	P< 0.001
49	42	8.2	12.0	3.8	8.067	P< 0.001
50	69	8.9	13.3	4.4	8.961	P< 0.001
53	64	9.1	13.1	4.0	8.264	P< 0.001

Action Potential Amplitude. There was no association between age and the mean amplitude of the action potentials (Table 11), and, although the average amplitude in the thyrotoxic patients was lower at 95.8 μV than that of the control subjects at 112.4 μV, there was no statistical significance in this difference (Table 12).

Polyphasic Potentials. The mean percentage of polyphasic potentials measured in the deltoid muscle of control subjects was 9.6%, and the percentage found in the patients was significantly higher at 19.8% (Table 13 and Fig. 5).

Spontaneous Activity. Fibrillation potentials were observed only once in the deltoid muscle of a thyrotoxic patient. Fasciculation was observed on one occasion in a different patient.

Electromyogram on Maximal Volition (Appendix Table 7). All the deltoid EMG's showed a normal interference pattern on maximal effort. The mean peak to peak voltage was not significantly lower than that of controls (Table 14).

Rectus Femoris
(Appendix Tables 4 and 6)

Action Potential Duration. As with the deltoid muscle, the correlation in the control EMG's between age and action potential duration was highly significant (Table 15 and Fig. 6). However, although 20 (83.3%) of the thyrotoxic patients had mean action potential durations which were significantly different from the predicted for their age, four patients had values which were within the normal range (Table 16).

Table 11

Deltoid. Control subjects.

Relationship between age and mean action potential amplitude (see Appendix Table 5).

$\bar{x}$	42.1 yrs.
$\bar{y}$	112.4 uv.
b_{yx}	-0.525
r	0.318
Degrees of freedom	19
P	> 0.1 Not significant at P = 0.05

Table 12

Deltoid electromyograms

Comparison of the mean action potential amplitude of thyrotoxic patients with that of controls (see Appendix Tables 3 and 4).

	Mean amplitude μv.	Standard error of difference	t	Degrees of freedom	P
Controls n = 21	112.4 ± 32.8	11.279	1.470	48	0.2 > P > 0.1 Not significant at P = 0.05
Thyrotoxics n = 29	95.8 ± 48.7				

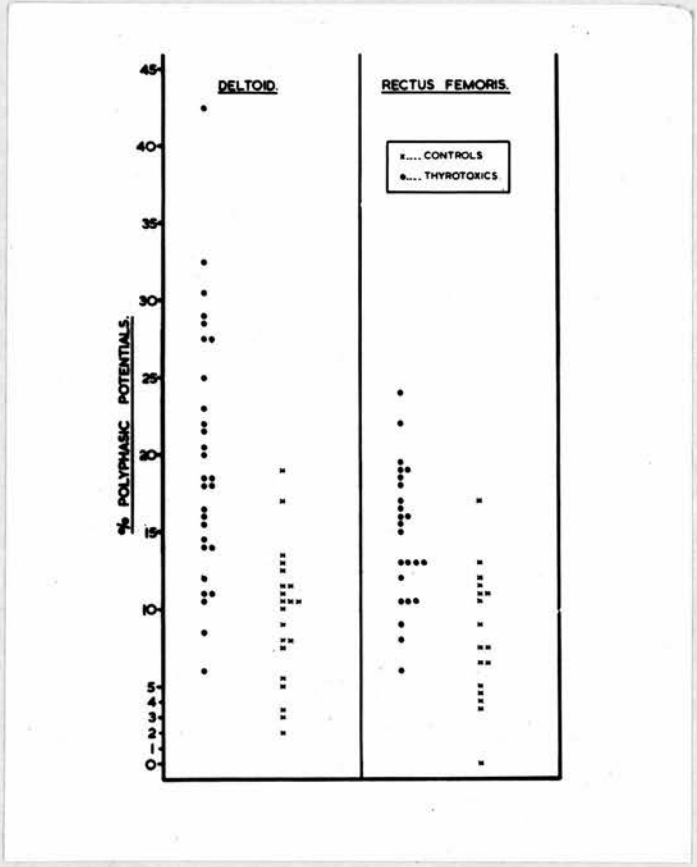


Fig. 5. Deltoid and Rectus femoris. Showing the differences in the percentage of polyphasic potentials between thyrotoxic patients and control subjects.

Table 13

Deltoid electromyograms

Difference in the mean percentage of polyphasic potentials between thyrotoxic patients and controls.

(Appendix Tables 5 and 4)

	Mean % polyphasic potentials	Standard error of difference	t	Degrees of freedom	P
Controls n = 21	9.6 ± 4.3	1.965	5.178	48	P < 0.001 Highly significant at P = 0.05
Thyrotoxics n = 29	19.8 ± 8.2				

Table 14

Deltoid electromyograms.

Mean amplitude of the interference pattern in the thyrotoxic patients and in the controls.

	Mean amplitude mv	Standard error of difference	t	Degrees of freedom	P
Thyrotoxics n = 9	3.7 ± 1.2	0.687	1.812	23	0.1 > P > 0.5 Not significant at P = 0.05
Controls n = 16	4.9 ± 1.9				

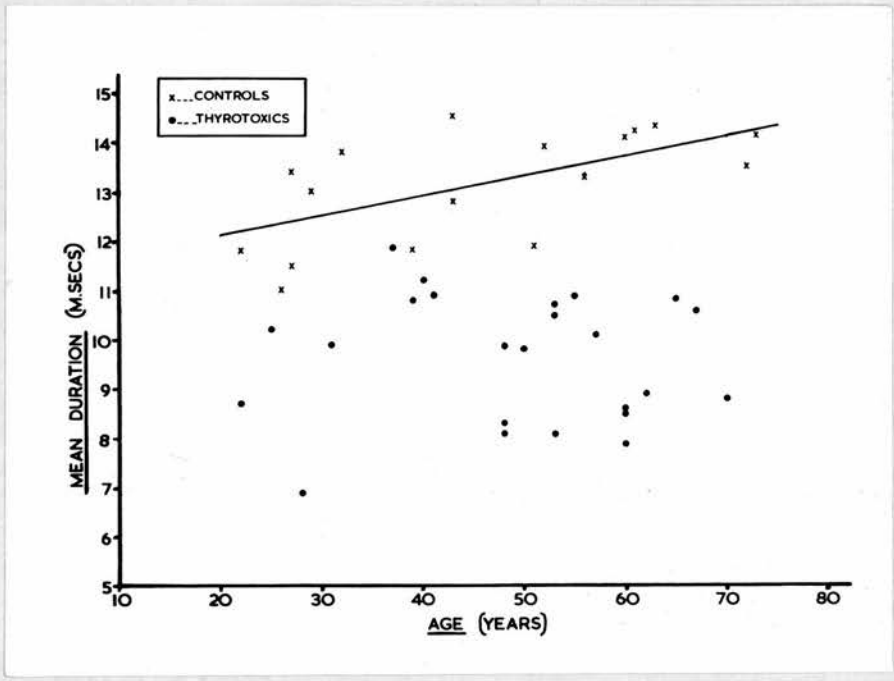


Fig. 6. Rectus femoris. Graph showing the relationship between age and mean action potential duration in control subjects and in thyrotoxic patients.

TABLE 15

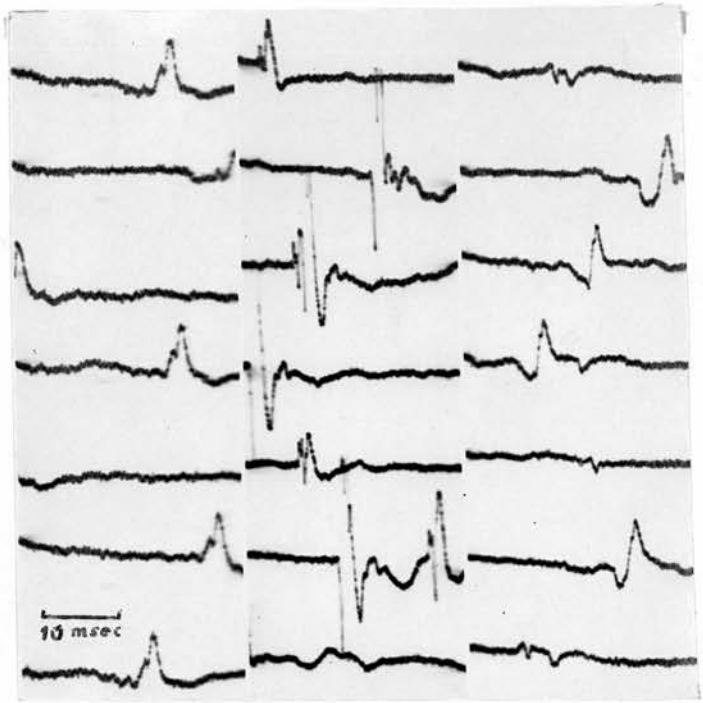
Control Subjects, Rectus femoris, Correlation between age and mean action potential duration.

No.	Age yrs.	Mean Duration m sec.	Statistical Analysis
1	22	11.8	
2	56	13.3	$\bar{x}$ = 45.6 yrs.
3	61	14.2	$\bar{y}$ = 13.1 m sec.
4	72	13.5	
5	60	14.1	by.x. = 0.041
6	43	12.8	S.D. = 0.92 m sec.
7	63	14.3	r = 0.61
8	52	13.9	0.01>P > 0.001
9	73	14.1	Highly sig-
10	43	14.5	nificant at
11	39	11.8	P = 0.05
12	51	11.9	
13	27	13.4	
14	32	13.8	
15	29	13.0	
16	26	11.0	
17	27	11.5	

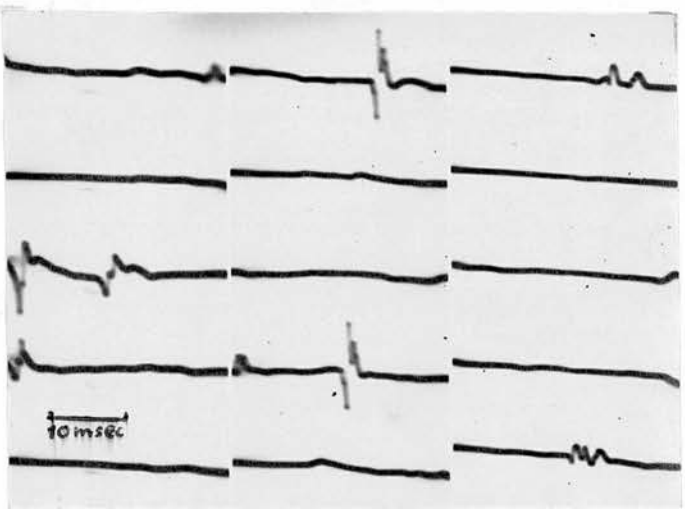
TABLE 16

Thyrotoxic patients. Rectus femoris. Table showing the deviation of the observed mean action potential duration from the predicted.

Case No.	Age yrs.	Observed mean action potential duration m sec	Predicted mean action potential duration m sec	Deviation of observed from predicted m sec	Statistical significance of deviation	
					t	P
2	48	8.1	13.2	5.1	4.411	$P < 0.001$
5	60	8.5	13.7	5.2	5.469	$P < 0.001$
6	22	8.7	12.2	3.5	3.390	$0.005 > P > 0.001$
7	57	10.1	13.6	3.5	3.611	$0.005 > P > 0.001$
8	37	11.9	12.8	0.9	0.901	$0.4 > P > 0.3$
9	53	10.7	13.4	2.7	2.836	$0.02 > P > 0.01$
16	50	9.8	13.3	3.5	3.670	$0.005 > P > 0.001$
21	70	8.8	14.1	5.3	5.264	$P < 0.001$
23	53	10.5	13.4	2.9	3.049	$0.01 > P > 0.005$
27	55	10.9	13.5	2.6	2.690	$0.02 > P > 0.01$
33	28	6.9	12.4	5.5	5.629	$P < 0.001$
34	31	9.9	12.5	2.6	2.709	$0.02 > P > 0.01$
36	48	9.9	13.2	3.3	3.484	$0.005 > P > 0.001$
39	25	10.2	12.3	2.1	2.125	$0.1 > P > 0.05$
40	65	10.8	13.9	3.1	3.133	$0.01 > P > 0.005$
41	48	8.3	13.2	4.9	5.174	$P < 0.001$
42	53	8.1	13.4	5.3	5.578	$P < 0.001$
43	60	7.9	13.7	5.8	5.980	$P < 0.001$
44	62	8.9	13.8	4.9	5.000	$P < 0.001$
46	67	10.6	14.0	3.4	3.390	$0.005 > P > 0.001$
47	40	11.2	12.9	1.7	1.770	$0.1 > P > 0.05$
51	39	10.8	12.8	2.0	2.147	$0.05 > P > 0.025$
52	41	10.9	12.9	2.0	2.128	$0.1 > P > 0.05$
54	60	8.6	13.7	5.1	5.253	$P < 0.001$



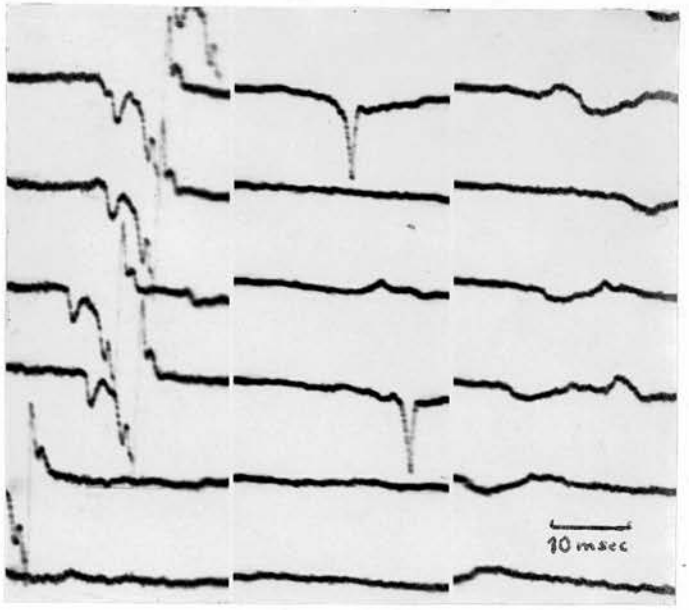
(a)



(b)

(c)

Fig. 7. Part of EMG done on the rectus femoris of case 7.
(a) Amplification at 10 μV/mm (b) Amplification at 20 μV/mm
(c) Interference pattern. Amplification at 100 μV/mm.



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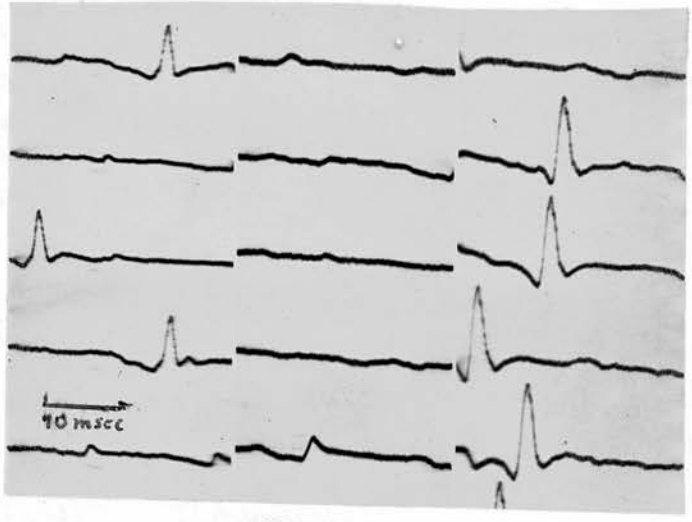

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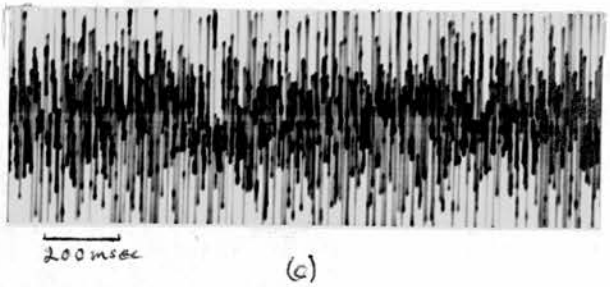

(c)

Fig. 8. Part of EMG done on rectus femoris of control subject (No. 3) (a) Amplification at 10 μV/mm (b) Amplification at 20 μV/mm (c) Interference pattern. Amplification at 100 μV/mm

Action Potential Amplitude. There was no correlation between age and action potential amplitude amongst the controls (Table 17), and a comparison of their figures with those of the thyrotoxics (158.9 μV and 151.5 μV respectively) showed that there was no real difference (Table 18).

Polyphasic Potentials. The controls had a mean percentage polyphasicity of 8.2 and that of the thyrotoxic patients was significantly higher than this at 14.8% (Table 19 and Fig. 5).

Spontaneous Activity. No evidence of fibrillation or fasciculation was found in the EMG's done on rectus femoris.

Electromyogram on Maximal Volition. An interference pattern was seen in all the patients except three who had a mixed pattern on maximal effort. There was a highly significant reduction in voltage (mean 2.5 mV) compared with controls (mean 4.5 mV) (Table 20).

Triceps

This muscle was sampled in one patient and in two controls, details of whose electromyograms are given in Table 21.

Neither the patient nor the controls had any evidence of spontaneous activity, and all three subjects showed a normal interference pattern on maximal effort.

No statistical analysis has been done on the EMG's of triceps because of the small numbers, but it is probably that there was a reduction in the patient's action potential duration and an increase in the percentage of polyphasic potentials.

Table 17

Rectus femoris electromyograms. Control subjects.

Relationship between age and mean action potential amplitude (see Appendix Table 6).

$\bar{x}$	45.6 yrs.
$\bar{y}$	158.9 μv.
b_{yx}	0.947
r	0.243
Degrees of freedom	15
P	>0.1 Not significant at P = 0.05

Table 18

Rectus femoris electromyograms

Comparison of the mean action potential amplitude of thyrotoxic patients with that of controls (see Appendix Tables 4 and 6)

	Mean amplitude μv.	Standard error of difference	t	Degrees of freedom	P
Controls n = 17	158.9 ± 66.2	24.839	0.295	39	0.8 > P > 0.7 Not significant at P = 0.05
Thyrotoxics n = 24	151.5 ± 84.0				

Table 19

Rectus femoris electromyograms

Difference in the mean percentage of polyphasic potentials between thyrotoxic patients and controls.

	Mean % polyphasic potentials	Standard error of difference	t	Degrees of freedom	P
Controls n = 17	8.2 ± 4.3	1.403	4.679	39	P < 0.001 Highly significant at P = 0.05
Thyrotoxics n = 24	14.8 ± 4.5				

Table 20

Rectus femoris electromyograms.

Mean amplitude of the interference pattern in euthyroid patients and in controls.

	Mean amplitude mV.	Standard error of difference	t	Degrees of freedom	P
Euthyroid patients n = 15	3.9 ± 1.9	0.707	0.745	28	0.5 > P > 0.4 Not significant at P = 0.05
Controls n = 15	4.5 ± 2.0				

Table 21

Electromyograms of the Triceps

	Age yr.	Sex	Action Potential Duration m sec.			Action Potential Amplitude μV			% Polyphasics	
			Total	No.	Mean	Total	No.	Mean	No.	%
Patient Case No. 3	25	F	156	20	7.8	2270	20	113	8	28.6
Control 1	24	F	248	25	9.9	3540	25	141	3	10.7
Control 2	26	F	261	23	11.3	6700	24	279	4	16.0

Abductor Digiti Quinti
(Appendix Tables 4 and 8)

Action Potential Duration. Unlike the two proximal muscles already described, there was no correlation in the EMG's done on abductor digiti quinti between age and mean action potential duration (Table 22). Of the 21 thyrotoxic patients tested, only 9 (42.9%) had a mean duration which lay outside the normal range of 9.3 ± 2.1 m. sec. (Table 23 and Fig. 9). All the 9 patients had abnormal proximal electromyograms.

Action Potential Amplitude. The mean amplitude for controls was 154.9 μV and that for the thyrotoxic patients 129.9 μV, but statistical analysis did not reveal any significant difference between these figures at the P = 0.05 level (Table 24).

Polyphasic Potentials. The patients had a higher degree of polyphasicity (13.6%) than the controls (9.9%), and this difference was significant (Table 25 and Fig. 10).

Spontaneous Activity. Fasciculation was seen in 3 patients, one of whom had it in 7 of the 27 positions sampled. Fibrillation potentials were observed in 3 cases.

Correlations

Sex. Taking the deviation of the observed mean action potential duration from the predicted for each patient as an indication of the degree of abnormality of the electromyogram, a comparison of the male and female patients (Table 26) shows that there was no significant difference between the two groups.

TABLE 22

Control Subjects. Abductor digiti quinti. Correlation between age and mean action potential duration.

No.	Age yrs.	Mean Duration m sec.	Statistical Analysis
1	32	10.2	
2	43	7.6	
3	21	9.9	
4	23	7.9	
5	22	9.0	$\bar{x}$ = 43.3 yr.
6	71	9.7	$\bar{y}$ = 9.3 m sec.
7	68	11.3	
8	57	9.4	b_{yx} = 0.014
9	55	9.5	
10	42	8.7	r = 0.249
11	43	8.4	
12	26	10.7	P >0.1
13	65	8.7	No correlation
14	27	8.4	
15	55	9.2	
16	29	8.4	
17	64	10.0	
18	37	10.3	

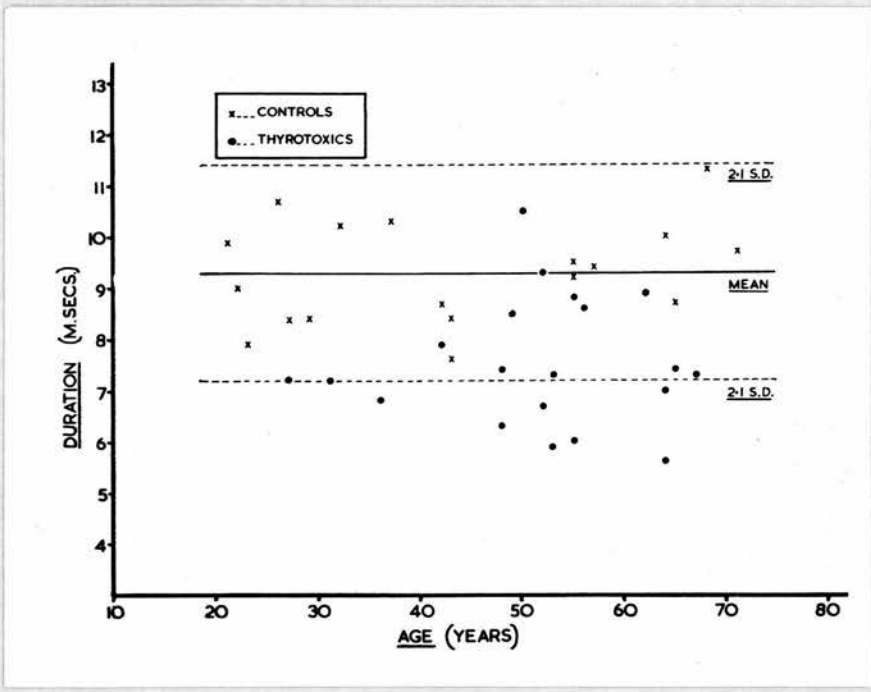

Fig. 9. Abductor digiti quinti. Graph showing the mean action potential duration in thyrotoxic patients and in control subjects.

TABLE 23

Thyrotoxic patients. Abductor digiti quinti. Table showing the deviation of the mean action potential duration from the normal.

Case No.	Age yrs.	Mean Duration m sec.	Deviation from mean for controls m sec.	Values >2.1 S.D.
18	64	7.0	-2.3	+
23	53	11.0	+1.7	0
24	56	8.6	-0.7	0
25	55	6.0	-3.3	+
26	52	6.7	-2.6	+
29	53	5.9	-3.4	+
30	49	8.5	-0.8	0
31	50	10.5	+1.2	0
32	52	9.3	0	0
34	31	7.2	-2.1	+
36	48	7.4	-1.9	0
37	36	6.8	-2.5	+
40	65	7.4	-1.9	0
41	48	6.3	-3.0	+
42	53	7.3	-2.0	0
44	62	8.9	-0.4	0
45	55	8.8	-0.5	0
46	67	7.3	-2.0	0
48	27	7.2	-2.1	+
49	42	7.9	-1.5	0
53	64	5.6	-3.7	+

Table 24

Abductor digiti quinti electromygrams

Comparison of the mean action potential amplitude of thyrotoxic patients with that of controls (see Appendix Tables 4 and 8)

	Mean amplitude uv.	Standard error of difference	t	Degrees of freedom	P
Controls n = 18	154.9 ± 66.0	15.965	1.567	37	0.2 > P > 0.1 Not significant at P = 0.05
Thyrotoxics n = 21	129.9 ± 29.4				

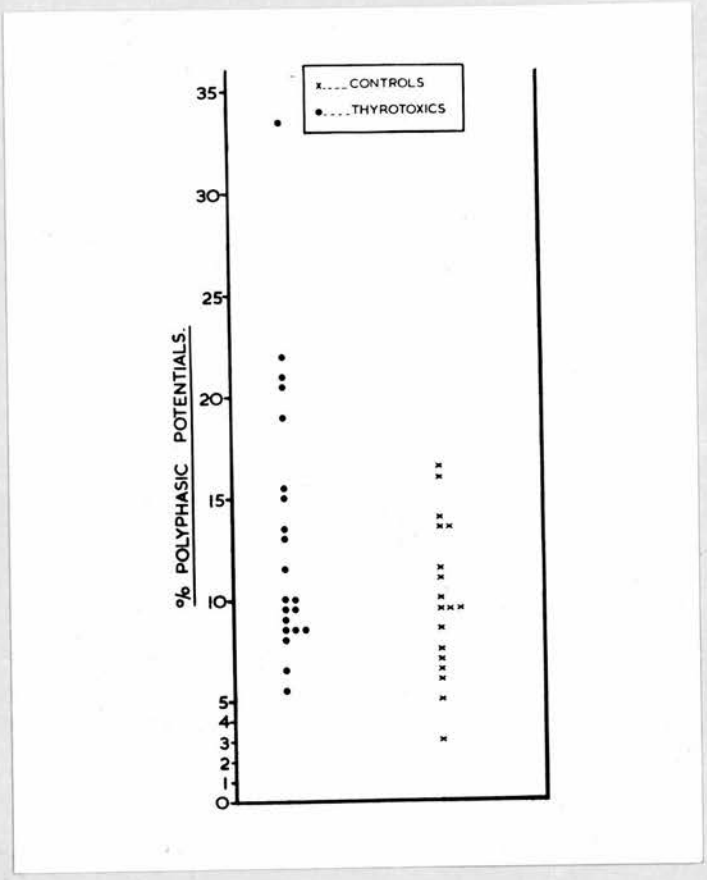

Fig. 10. Abductor digiti minimi. Showing the differences in the percentage of polyphasic potentials between thyrotoxic patients and control subjects.

Table 25

Abductor digiti quinti electromyograms

Difference in the mean percentage of polyphasic potentials between thyrotoxic patients and controls.

	Mean % polyphasic potentials	Standard error of difference	t	Degrees of freedom	P
Controls n = 18	9.9 ± 3.8	1.733	2.135	37	0.05 > P > 0.025 Significant at P = 0.05
Thyrotoxics n = 21	13.6 ± 6.5				

Table 26

Comparison of the deviation of the observed mean action potential duration from the predicted in male and female thyrotoxic patients.

	Mean deviation from predicted m.sec.	Standard error of difference	t	Degrees of freedom	P
Males n = 14	3.2 ± 1.1	0.417	1.618	52	0.2 > P > 0.1 Not significant at P = 0.05
Females n = 40	3.9 ± 1.4				

Age. There was no correlation between age and the deviation of the mean action potential duration from the predicted (Table 27) in the EMG's done on the deltoid muscle, all groups being equally affected (Fig. 4), but there was an association in the recordings taken from the rectus femoris (Table 28). It can be seen from Fig. 6 that the patients under the age of 45 were less severely affected than those in the older age groups, and statistical analysis (Table 28 and Fig. 11) show that this correlation in rectus femoris is significant.

Duration of Thyrotoxicosis. Tables 29 and 30 reveal no association between the time for which the patient had thyrotoxic symptoms and the severity of the electromyographic findings. (Appendix Tables 12 and 13)

Severity of Thyrotoxicosis. Using the level of the serum protein bound iodine in 31 patients as an indication of the severity of the thyrotoxicosis, a comparison of this with each patient's deviation of observed mean action potential from the predicted revealed that there was no correlation at all (Table 31 and Appendix Table 14).

Weight Loss. An analysis of the EMG's done on the deltoid and rectus femoris muscles revealed no positive relationship between the severity of the electromyographic action potential deviation and the amount of weight lost by the patient (Tables 32 and 33 and Appendix Tables 12 and 13).

Clinical Weakness of the Muscle Sampled. There was a significant difference between the mean action potential deviation in

Table 27

Deltoid. Thyrotoxic Patients.

Relationship between age and the deviation of the observed mean action potential duration from the predicted (see Table 10).

$\bar{x}$	48.0 yrs.
$\bar{y}$	3.9 m.sec.
b_{yx}	0.002
r	0.09
Degrees of freedom	27
P	> 0.1 Not significant at P = 0.05

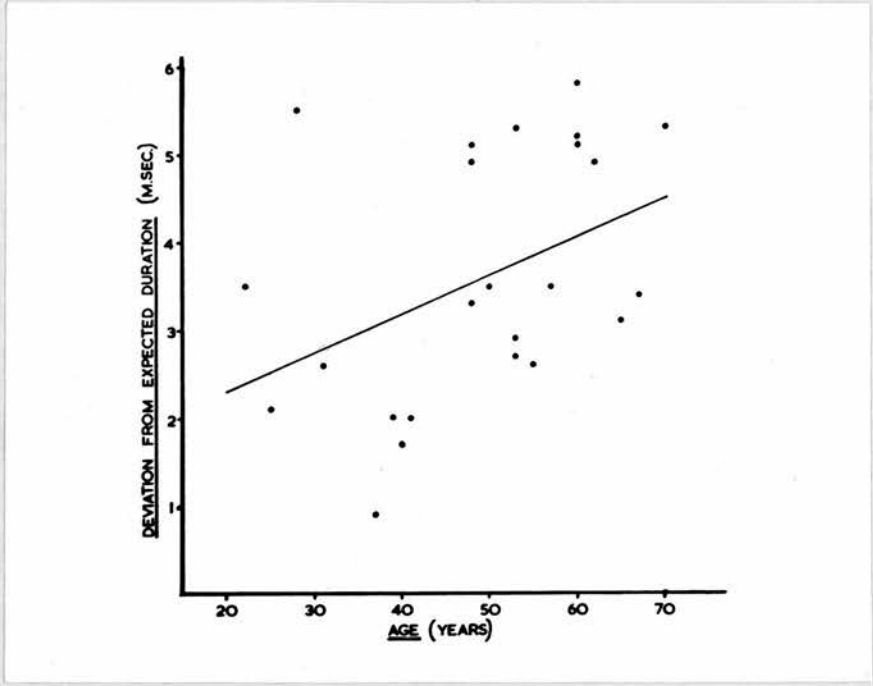

Fig. 11. Rectus femoris. Graph showing a correlation in thyrotoxic patients between age and the deviation from the expected mean action potential duration.

Table 28

Rectus femoris. Thyrotoxic patients

Relationship between age and the deviation of the observed mean action potential duration from the predicted (see Table 16)

$\bar{x}$	48.8 yrs.
$\bar{y}$	3.6 m.sec.
b_{yx}	0.044
r	0.417
Degrees of freedom	22
P	$0.05 > P > 0.01$ Significant at $P = 0.05$

Table 29

Deltoid. Thyrotoxic patients.

Relationship between the duration of the thyrotoxicosis and the deviation of the observed mean action potential duration from the predicted (see Appendix Table 12).

$\bar{x}$	6.0 months
$\bar{y}$	3.9 m.sec.
b_{yx}	-0.021
r	0.095
Degrees of freedom	27
P	> 0.1 Not significant at P = 0.05

Table 30

Rectus femoris. Thyrotoxic patients.

Relationship between duration of thyrotoxicosis and the deviation of the observed mean action potential duration from the predicted (see Appendix Table 13).

$\bar{x}$	7.4 months
$\bar{y}$	3.6 m.sec.
b_{yx}	-0.065
r	0.241
Degrees of freedom	22
P	> 0.1 Not significant at P = 0.05

Table 31

Relationship between serum protein bound iodine and the deviation of the observed mean action potential duration from the predicted
(see Appendix Table 14)

$\bar{x}$	11.4 µg.%
$\bar{y}$	3.9 m.sec.
b_{yx}	0.050
r	0.084
Degrees of freedom	31
P	> 0.1 Not significant at P = 0.05

Table 32

Deltoid. Thyrotoxic patients.

Relationship between weight loss and the deviation of the observed mean action potential duration from the predicted (see Appendix Table 12).

$\bar{x}$	17.7 lb.
$\bar{y}$	3.9 m.sec.
b_{yx}	0.035
r	0.270
Degrees of freedom	27
P	> 0.1 Not significant at P = 0.05

Table 33

Rectus femoris. Thyrotoxic patients.

Relationship between weight loss and the deviation of the observed mean action potential duration from the predicted (see Appendix Table 13).

$\bar{x}$	17.6 lb.
$\bar{y}$	3.6 m.sec.
b_{yx}	0.009
r	0.071
Degrees of freedom	22
P	> 0.1 Not significant at P = 0.05

those patients who had clinical weakness of the deltoid muscle as compared with those who had none (Table 34). Although the difference between the two groups was even larger in patients whose rectus femoris was examined clinically and electromyographically, a statistical analysis did not reveal this as being significant, probably because of the smaller number of patients (5 out of 24) who exhibited weakness of this muscle. (Appendix Table 15)

Extent of Muscle Involvement. If the degree of EMG change was compared with the extent of the involvement of the muscles by weakness and/or atrophy, it can be seen from Table 35 that there was a significant difference between those patients who had proximal involvement and those who had none. Moreover, there was an even greater difference between those patients who had weakness and atrophy of the distal as well as the proximal muscles compared with those who had no muscle involvement. (Appendix Table 11)

Nerve Conduction Velocities and Latencies (Appendix Table 9)

Tables 36 and 37 show that there were no significant differences in 12 patients between the conduction velocities in the ulnar nerve, measured from the elbow to the wrist, or in the latencies from the wrist to the abductor digiti quinti as compared with the results for controls.

Muscle Biopsy

Thirty patients had a muscle biopsy carried out, and the results are shown in Table 38. Only 14 of the sections were found to be suitable for an estimation of mean fibre diameter and fibre population per square mm., largely because of the difficulty in

Table 34

Comparison of the deviations of the observed mean action potential duration from the predicted in those thyrotoxic patients with clinical weakness of the sampled muscle and those without (see Appendix Table 15).

Muscle	Weakness	Mean deviation m.sec.	t	Degrees of freedom	P
Deltoid	Present n = 15	4.5 ± 1.4	2.661	27	0.02 > P > 0.01 Highly significant at P = 0.05
	Absent n = 14	3.3 ± 1.1			
Rectus femoris	Present n = 5	4.6 ± 1.1	1.878	20	0.10 > P > 0.05 Not significant at P = 0.05
	Absent n = 17	3.2 ± 1.6			

Table 35

Relationship between the extent of muscle involvement (atrophy and/or weakness) in thyrotoxicosis and the deviation of the observed mean action potential duration from the predicted (see Appendix Table 11).

Muscle involvement	Mean deviation m.sec.	Standard error of difference	t	Degrees of freedom	P
Proximal only n = 34	3.9 ± 2.6	0.472	2.260	42	0.05 > P > 0.025 Significant at P = 0.05
None n = 10	2.8 ± 1.2				
Proximal and distal n = 10	4.2 ± 1.3	0.545	2.587	18	0.02 > P > 0.01 Significant at P = 0.05

Table 36

Ulnar nerve: Controls and thyrotoxic patients

Conduction velocities measured between the elbow and the wrist.

	Nerve conduction velocity m.sec.	Standard error of difference	t	Degrees of freedom	P
Controls n = 15	58.7 ± 8.7	4.5	0.746	25	0.5 > P > 0.4 Not significant at P = 0.05
Thyrotoxics n = 12	62.1 ± 14.5				

Table 37

Ulnar Nerve: Controls and thyrotoxic patients

Latencies to abductor digiti quinti,
with stimulation at the wrist.

	Mean Latency m.sec.	Standard error of difference	t	Degrees of freedom	P
Controls n = 15	2.8 ± 0.4	0.158	1.265	25	0.3 > P > 0.2 Not significant at P = 0.05
Thyrotoxics n = 12	2.6 ± 0.4				

TABLE 38

The results of muscle biopsy on 30 thyrotoxic patients.

Case No.	Muscle biopsied	Fibre diameter (μ)			No. fibres per m.m.^{2}	Histology
		Total	No.	Mean		
1	Delt.	4389	77	57	136	Normal
2	Rect. fem.	4326	103	42	329	Normal
3	Triceps	4040	101	40	482	Normal
4	Delt.	-	-	-	-	Normal
5	Rect. fem.	4100	100	41	388	Normal
6	Rect. fem.	-	-	-	-	Normal
7	Rect. fem.	-	-	-	-	Infiltration of fat between muscle fibres.
8	Rect. fem.	-	-	-	-	Normal
10	Delt.	-	-	-	-	Proliferation of connective tissue between muscle bundles
11	Delt.	-	-	-	-	Normal
12	Delt.	-	-	-	-	One lymphorrhage
13	Delt.	4264	104	41	449	Two lymphorrhages
15	Delt.	3900	100	39	487	Degenerating fibres with macrophages and lymphocytes.
16	Rect. fem.	4284	102	42	413	Normal
18	Delt.	3978	102	39	429	Normal
19	Delt.	-	-	-	-	One degenerating fibre with macrophages
24	Delt.	3740	85	44	426	Normal
25	Delt.	-	-	-	-	Normal
29	Delt.	-	-	-	-	Normal
30	Delt.	-	-	-	-	Normal
31	Delt.	-	-	-	-	Normal
36	Rect. fem.	3230	85	38	396	Normal
37	Delt.	2640	66	40	290	Normal
38	Delt.	2482	73	34	-	Normal
39	Rect. fem.	3627	93	39	554	One lymphorrage
40	Rect. fem.	-	-	-	-	Normal
41	Rect. fem.	-	-	-	-	Normal
43	Rect. fem.	-	-	-	-	Normal
47	Rect. fem.	-	-	-	-	Normal
48	Delt.	3589	97	37	446	Normal
	Mean			41	398	

Delt. = Deltoid

Rect. fem. = Rectus femoris

getting an exact cross-section. Table 39 lays out the results of those control biopsies which were judged to be adequate for measurement.

Fig. 12 shows that, apart from one patient, all the thyrotoxics had mean muscle fibre diameters which were, on average, 12 microns smaller than those of the controls (Figs. 13, 14, 15, 16). No statistical analysis has been done because the biopsies were carried out on different muscles.

Fig. 17 demonstrates the increased number of muscle fibres per square mm. in the thyrotoxic patients compared with the control subjects (mean 398 and 287/square mm. respectively). The inference is that when the muscle fibres become smaller they get more crowded together.

Histology. Seven out of the 30 patients (23.3%), apart from any reduction in fibre diameter, also had some histological abnormality. Many showed an apparent increase in sarcolemmal nuclei (Figs. 18 and 19) due to the crowding together of atrophied fibres. However, when cross-sections were examined the number of nuclei per fibre was not found to exceed the upper limit of normal of 8 (Fig. 20).

Degenerating muscle fibres, infiltrated with macrophages and lymphocytes, were seen in 2 patients (Fig. 21). Four perivascular lymphorrhages were seen (Figs. 22, 23 and 24) and the other histological changes were confined to the infiltration of fatty tissue between the muscle fibres of one patient (Fig. 25) and the proliferation of connective tissue between the muscle bundles in another (Fig. 26).

TABLE 39

The results of muscle biopsy on control subjects.

No.	Age	Sex	Condition	Muscle biopsied	Fibre diameter (μ)			No of fibres per m m^2
					Total	No.	Mean	
1	51	M	Normal	Delt.	5050	101	50	243
2	49	M	Normal	Delt.	4080	80	51	231
3	37	F	Varicose veins	Sart.	3920	98	40	455
4	33	F	Varicose veins	V. med.	5253	103	51	287
5	22	M	Varicose veins	Sart.	4717	89	53	343
6	54	M	Inguinal hernia	Sart.	5300	100	53	194
7	37	M	Hydrocoele	Sart.	5616	104	54	305
8	43	M	Varicose veins	Add. L.	3843	63	61	268
9	33	M	Inguinal hernia	Sart.	4550	91	50	-
10	57	M	Varicose veins	Sart.	5187	91	57	292
11	27	M	Inguinal hernia	Sart.	4510	82	55	323
12	57	M	Inguinal hernia	Sart.	4628	89	52	302
13	29	F	Varicose veins	Sart.	3894	66	59	197
Mean							53 ± 5	287 ± 71

Delt. = Deltoid. Sart. = Sartorius.

V. med. = Vastus medialis. Add. L. = Adductor longus.

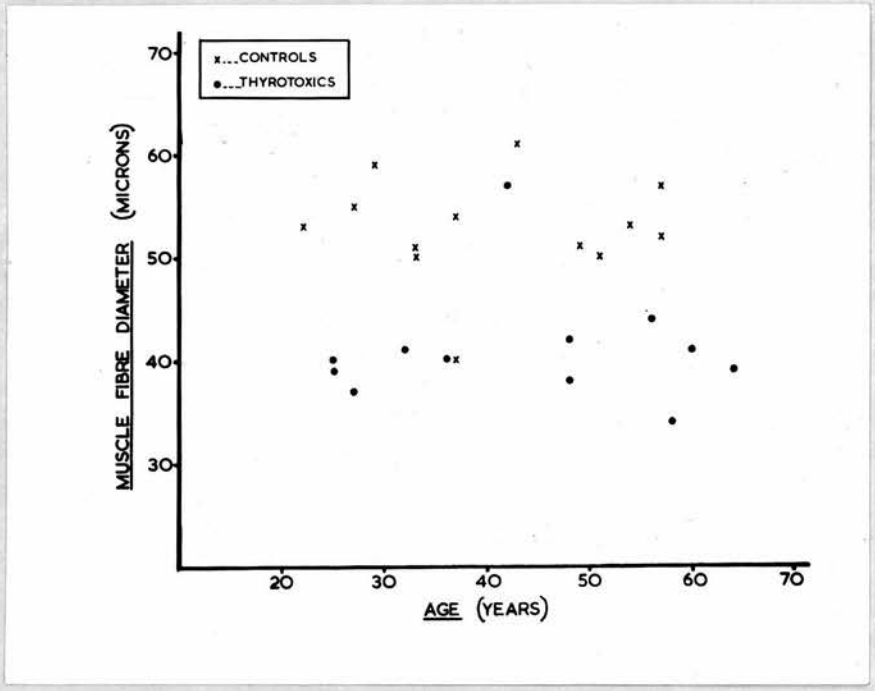

Fig. 12. Showing the differences in mean muscle fibre diameter between thyrotoxic patients and control subjects.

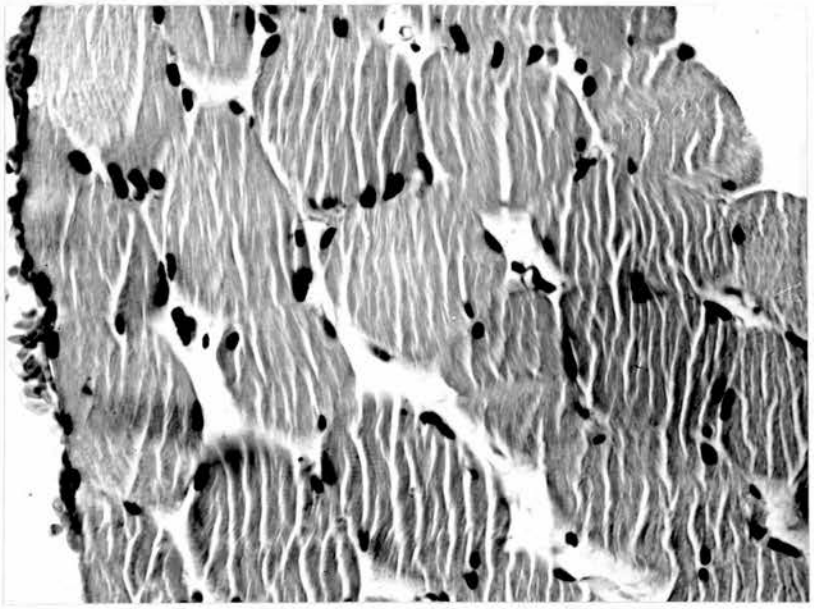

Fig. 13. Case No. 5. Mean muscle fibre diameter 41 μ (H. and E., x 475)

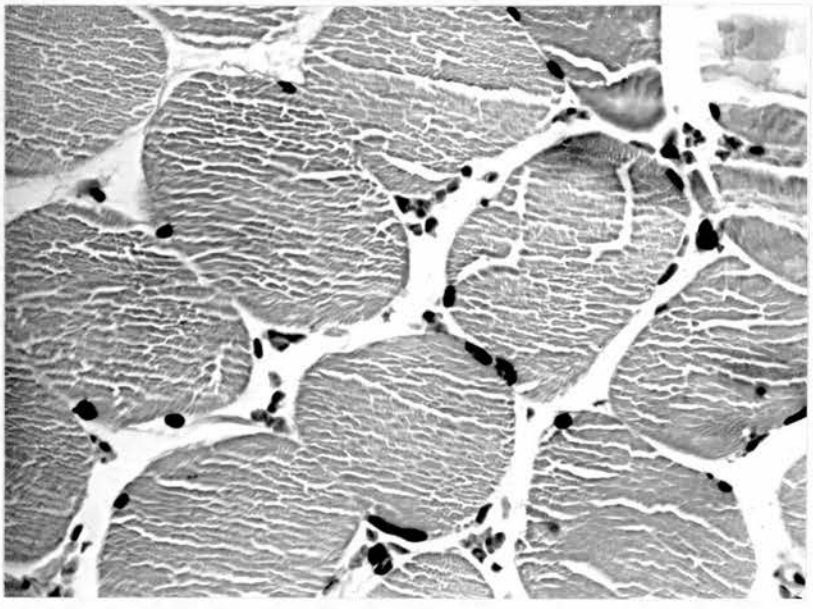

Fig. 14. Control biopsy No. 7. Mean muscle fibre diameter 54 μ (H. and E., x 475)

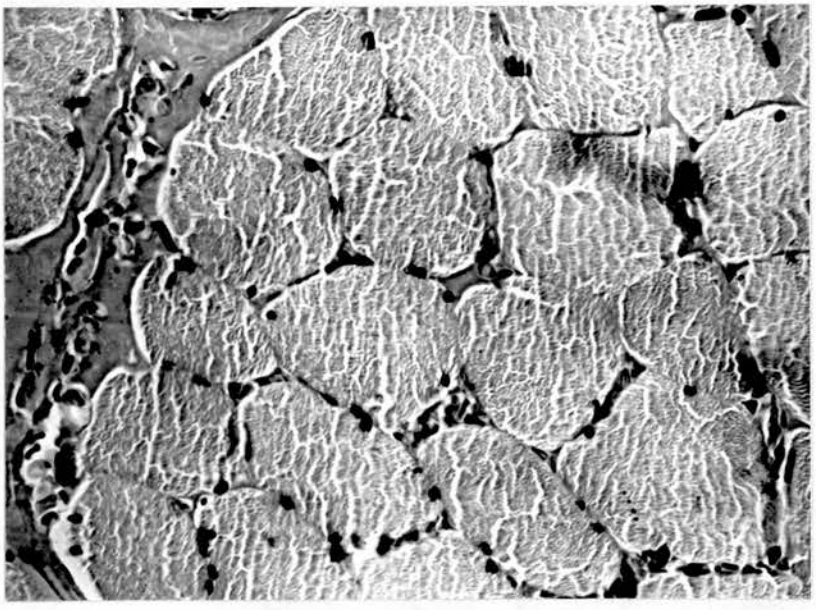

Fig. 15. Case No. 48. Mean muscle fibre diameter. 37 μ (H. and E., x 475)

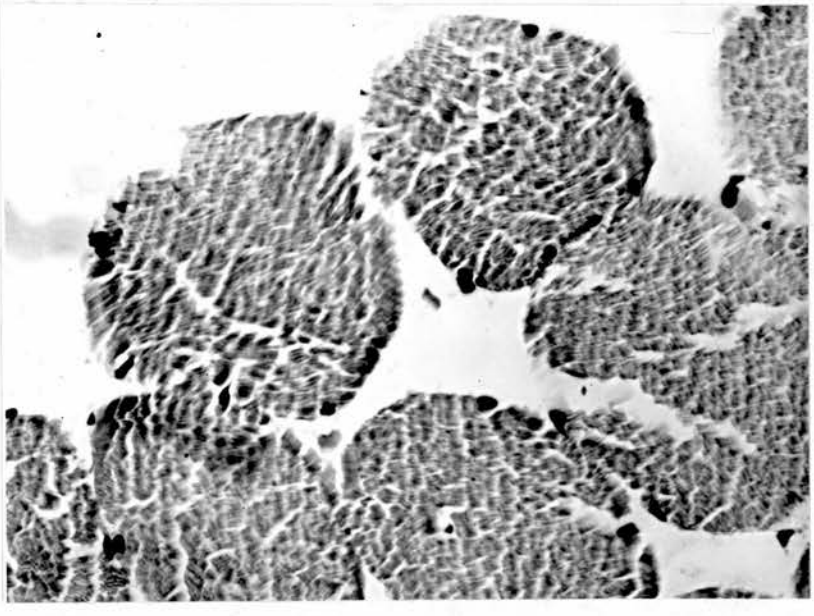

Fig. 16. Control biopsy No. 10. Mean muscle fibre diameter 58 μ (H. and E., x 475)

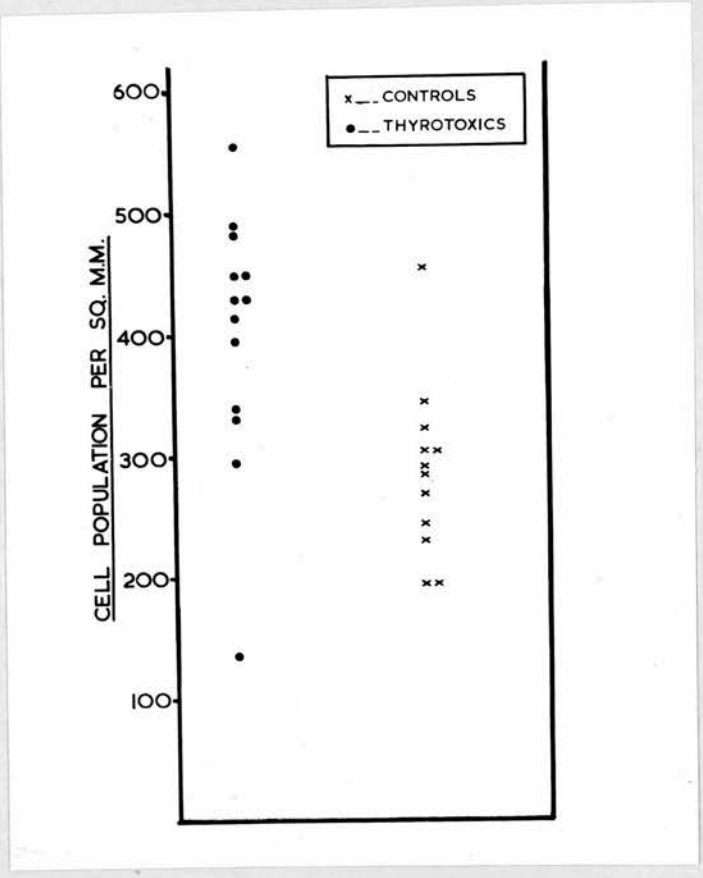

Fig. 17. Showing differences in the number of muscle fibres per square mm. between thyrotoxic patients and control subjects.

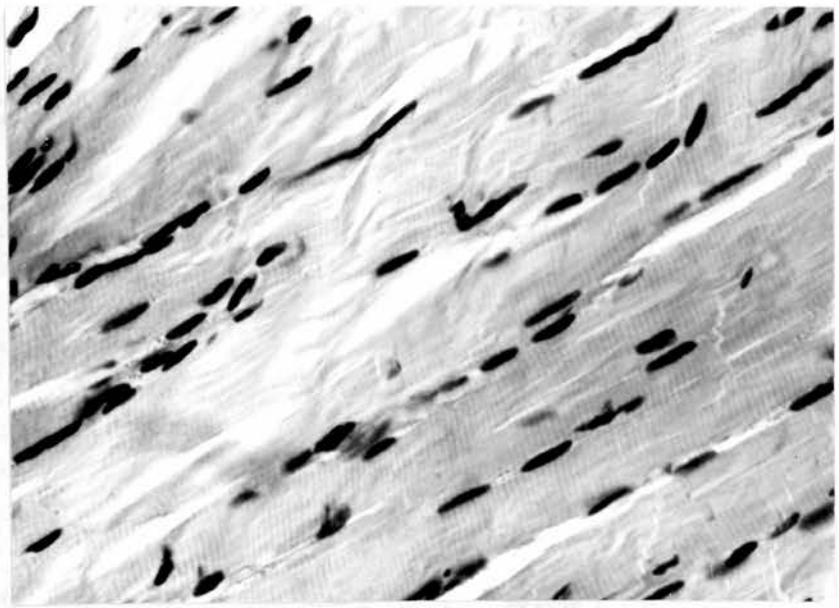

Fig. 18. Case No. 15. Longitudinal section showing an apparent increase in sarcolemmal nuclei (H. and E., x 475)

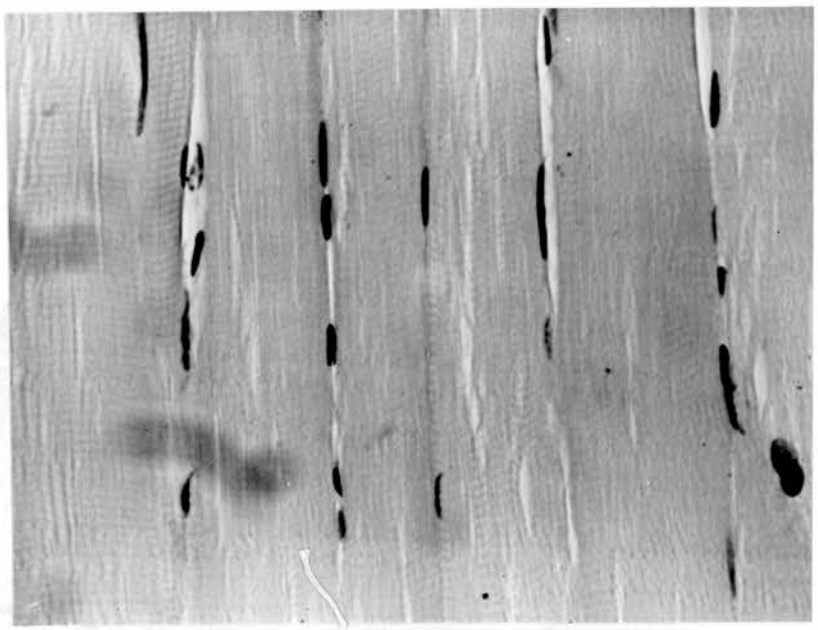

Fig. 19. Control biopsy No. 13. Longitudinal section showing a normal number of sarcolemmal nuclei (H. and E., x 475)

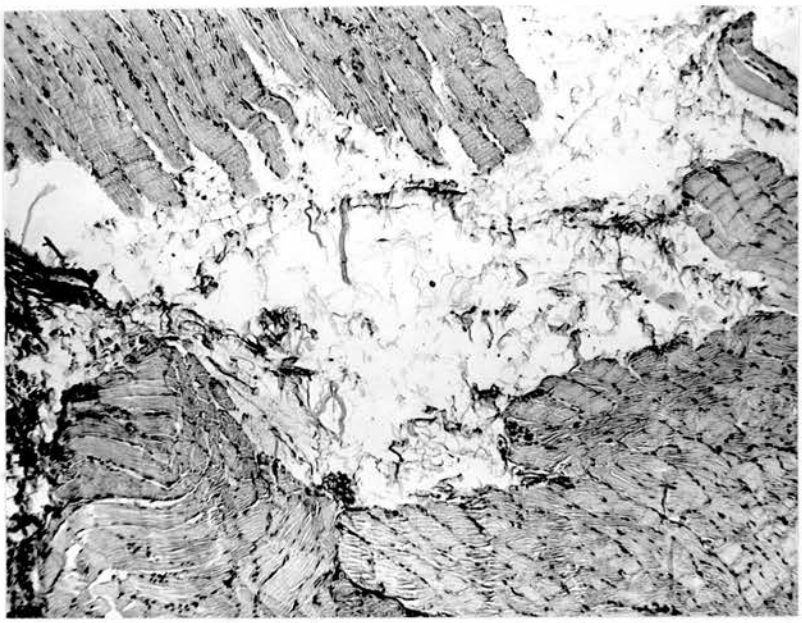

Fig. 26. Case No. 10. Proliferation of connective tissue between muscle bundles (Van Gieson, x 75).

No comment is made on the presence or absence of muscle fibre striations, because it cannot be said with certainty that striations are absent unless the section is specially stained or is examined under polarised light.

There was no significant difference in the EMG changes between those who had abnormal histology and those without (Table 40).

Follow-up Studies (Appendix Table 10)

Clinical State. All the patients except two were followed up by the author, and at the time of writing they are euthyroid. The average time taken to become euthyroid was 2.1 months from the start of treatment. Muscle power had returned to normal in about the same time (mean 2.2 months), but muscle atrophy took a significantly greater time (mean 2.8 months, $t = 2.290$, $0.025 > P > 0.02$) to disappear after the patient had become euthyroid.

Degree of Proptosis (Appendix Tables 1 and 10). Between the time the patient was first seen and a time four months after he or she had become euthyroid, serial measurements with the exophthalmometer of the degree of proptosis showed a mean increase of 1.5 mm. in 31 patients, taking the average for both eyes. In 9 patients the eyes had receded by a mean of 1.2 mm. and in a further 6 there was no change.

Creatine and Creatinine Excretion (Appendix Table 10)

Creatine excretion was measured in 8 male patients four months after they had become euthyroid. All the values lay within the normal range of 0 - 200 mg./24 hours and had a mean of

Table 40

Relationship between the presence of abnormal histology and the deviation of the observed mean action potential duration from the predicted (see Tables 10, 16 and 38).

Histology	Deviation from predicted m.sec.	Standard error of difference	t	Degrees of freedom	P
Abnormal n = 8	4.1 ± 1.1	0.584	0.684	28	0.5 > P > 0.4 Not significant at P = 0.05
Normal n = 22	3.7 ± 1.5				

48.5 ± 26.2 mg./24 hours. Four of the 23 women in whom creatine excretion was estimated had values just above the upper limit of normal. The mean for women was 98 ± 85.1 mg./24 hours.

Creatinine excretion, studied on the same patients, showed that all the men except one (0.820 g./24 hours) had values lying within the normal range of 1.0 to 2.4 g., with a mean of 1.368 ± 0.033 g./24 hours. Only 3 of the women had creatininuria in excess of the upper limit of normal of 1.3 g. The mean value for creatinine excretion in the women was 1.046 ± 0.031 g./24 hours.

Electromyography

Thirty-six patients had electromyograms repeated on the same muscles as before. The follow-up EMG's were done four months after the patients had become euthyroid.

Deltoid (Appendix Tables 4 and 5)

Action Potential Duration. Table 41 and Fig. 27 show that 14 out of the 21 patients (66.6%) on whom EMG's were repeated had an action potential duration which did not differ significantly from the predicted for their age. Six patients (28.6%) were still below the lower limit of normal, but had improved considerably on their original action potential duration. One patient developed a duration which was significantly above the upper limit of normal. In making the calculations, the assumption was made that the patients were still the same age as at the time of their first EMG. In fact, the majority of patients had their follow-up EMG done 7 - 9 months later, and the longest interval was 11 months. Any error caused by this in calculating the predicted action potential duration would not be more than 0.1 m. sec.

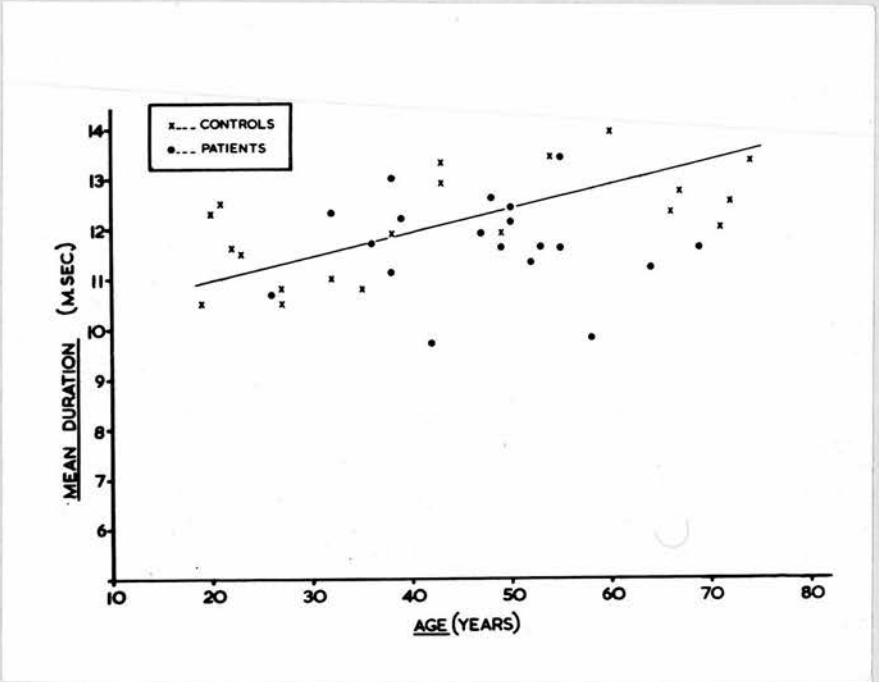

Fig. 27. Deltoid. Follow-up electromyograms. Graph showing the relationship between age and mean action potential duration in patients and controls.

TABLE 41

Follow-up electromyograms. Deltoid
Table showing the deviation of the observed mean action potential duration from the predicted.

Case No.	Age	Observed mean action potential duration m sec	Predicted mean action potential duration m sec	Deviation of observed from predicted m sec	Statistical significance of deviation	
					t	P
1	42	9.7	12.0	-2.3	4.862	P< 0.001
4	47	11.9	12.2	-0.3	0.636	0.6>P>0.5
10	38	11.1	11.8	-0.7	1.486	0.2>P>0.1
11	50	12.4	12.4	0	0	0
12	48	12.6	12.3	+0.3	0.632	0.6>P>0.5
13	32	12.3	11.5	+0.8	1.687	0.2>P>0.1
14	26	10.7	11.2	-0.5	1.046	0.4>P>0.3
17	69	11.6	13.3	-1.7	3.462	0.005>P>0.001
18	64	11.2	13.1	-1.9	3.925	P< 0.001
19	66	12.3	13.2	-0.9	1.848	0.1>P>0.05
20	39	12.2	11.9	+0.3	0.636	0.6>P>0.5
22	38	13.0	11.8	+1.2	2.547	0.02>P>0.01
25	55	13.4	12.6	+0.8	1.684	0.2>P>0.1
29	53	11.6	12.5	-0.9	1.898	0.1>P>0.05
30	49	11.6	12.3	- 0.7	1.521	0.2>P>0.1
31	50	12.1	12.4	-0.3	0.635	0.6>P>0.5
32	52	11.3	12.5	-1.2	2.531	0.025>P>0.02
37	36	11.7	11.7	0	0	0
38	58	9.8	12.8	-3.0	6.276	P<0.001
45	55	11.6	12.6	-1.0	2.100	0.05>P>0.025

Action Potential Amplitude. The mean amplitude in the follow-up EMG's done on the deltoid showed no significant difference from that of the controls (Table 42). However, there had been a statistically significant increase in amplitude (137.8 μV) in the EMG's (Table 43) compared with those done before the start of treatment (95.8 μV).

Polyphasic Potentials. The mean percentage of polyphasic potentials in the follow-up EMG's was not markedly different from that of the controls (Table 44) and showed a highly significant reduction compared with the records taken previously (Table 45).

Spontaneous Activity. One fibrillation potential was found in the EMG of Case No. 37.

Electromyogram on Maximal Volition. An interference pattern was found in all the cases and the voltage was not significantly different from that of the controls (Table 46 and Appendix Tables 4 and 7).

Rectus Femoris

Action Potential Duration. Of the 15 electromyograms done on euthyroid patients, all had action potential durations which were normal (86.7%), except for one which was significantly below the predicted and another which was just above the upper limit of normal (Table 47 and Fig. 28).

Action Potential Amplitude. Comparison of the mean amplitude of the follow-up EMG's showed no significant increase on the pre-treatment values (Table 48). In fact, there was a slight

Table 42

Follow-up electromyograms. Deltoid.

Comparison of the mean action potential amplitude of the patients with that of controls (see Appendix Tables 4 and 5).

	Mean amplitude μv.	Standard error of difference	t	Degrees of freedom	P
Controls n = 21	112.0 ± 32.8	14.769	1.724	39	0.1 > P > 0.05 Not significant at P = 0.05
Patients n = 20	137.8 ± 58.7				

Table 43

Follow-up electromyograms. Deltoid.

Comparison of the mean action potential amplitude of the patients four months after becoming euthyroid with the amplitude before the start of treatment (see Appendix Table 4).

Patients	Mean amplitude μv.	Standard error of difference	t	Degrees of freedom	P
Before treatment n = 29	95.8 ± 48.7	17.242	2.430	47	0.02 > P > 0.01 Significant at P = 0.05
After treatment n = 20	137.8 ± 58.7				

Table 44

Follow-up electromyograms: Deltoid.

Comparison of the mean percentage of polyphasic potentials between the patients and the controls (see Appendix Tables 4 and 5).

	Mean % polyphasic potentials	Standard error of difference	t	Degrees of freedom	P
Controls n = 21	9.6 ± 4.3	1.816	1.613	39	0.2 > P > 0.1 Not significant at P = 0.05
Patients n = 20	12.5 ± 7.1				

Table 45

Follow-up electromyograms: Deltoid.

Comparison of the mean percentage of polyphasic potentials in the patients four months after becoming euthyroid with the percentage before the start of treatment (see Appendix Table 4).

Patients	Mean % polyphasic potentials	Standard error of difference	t	Degrees of Freedom	P
Before treatment n = 29	19.8 ± 8.2	2.253	3.215	47	0.005 > P > 0.001 Highly siginficant at P = 0.05
After treatment n = 20	12.5 ± 7.1				

Table 46

Follow-up electromyograms. Deltoid.

Amplitude of the interference pattern in euthyroid patients and in controls.
(see Appendix Table 4).

	Mean amplitude mv.	Standard error of difference	t	Degrees of freedom	P
Euthyroid patients n = 16	4.3 ± 1.5	0.597	0.944	30	0.4 > P > 0.3 Not significant at P = 0.05
Controls n = 16	4.9 ± 1.9				

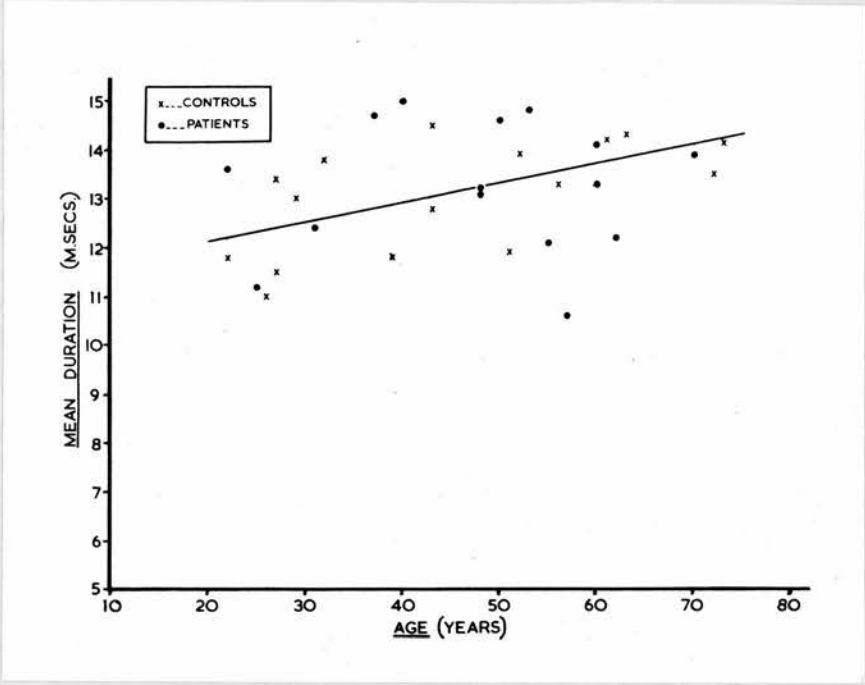

Fig. 28. Rectus femoris. Follow-up electromyograms. Graph showing the relationship between age and mean action potential duration in patients and controls.

TABLE 47

Follow-up electromyograms. Rectus femoris. Table showing the deviation of the observed mean action potential duration from the predicted.

Case No.	Age	Observed mean action potential duration m.sec.	Predicted mean action potential duration m.sec.	Deviation of observed from predicted m.sec.	Statistical significance of deviation	
					t	P
2	48	13.2	13.2	0	0	0
5	60	13.3	13.7	-0.4	0.422	0.7 >P > 0.6
6	22	13.6	12.2	-0.6	0.612	0.6> P > 0.5
7	57	10.6	13.6	-3.0	3.100	0.01 > P > 0.005
8	37	14.7	12.8	+1.9	2.108	0.1>P>0.05
9	53	14.8	13.4	+1.4	1.470	0.2 > P >0.1
16	50	14.6	13.3	+1.3	1.371	0.2 > P>0.1
21	70	13.9	14.1	-0.2	0.199	0.9>P >0.8
27	55	12.1	13.5	-1.4	1.459	0.2>P >0.1
34	31	12.4	12.5	-0.1	0.103	0.95>P>0.90
39	25	11.2	12.3	-1.1	1.113	0.3>P >0.2
41	48	13.1	13.2	-0.1	0.105	0.95>P>0.90
43	60	14.1	13.7	+0.4	0.414	0.7>P>0.6
44	62	12.2	13.8	-1.6	1.646	0.2>P>0.1
47	40	15.0	12.9	+2.1	2.212	0.05>P >0.025

Table 48

Follow-up electromyograms: Rectus femoris

Comparison of the mean action potential amplitude of the patients four months after becoming euthyroid with the amplitude before the start of treatment (see Appendix Table 4)

Patients	Mean Amplitude μv.	Standard error of difference	t	Degrees of freedom	P
Before treatment n = 24	151.5 ± 85.8	23.144	1.166	37	0.3 > P > 0.2 Not significant at P = 0.05
After treatment n = 15	124.53 ± 31.3				

reduction, and the amplitude was not statistically different from that of the controls (Table 49).

Polyphasic Potentials. Following successful treatment of the thyrotoxicosis, the EMG's done on the rectus femoris revealed no significant reduction in the percentage polyphasicity, compared with the previous values (Table 50), and there remained a difference between the patients and the controls in this respect (Table 51).

Spontaneous Activity. No fibrillation potentials or fasciculations were seen in the EMG's done on the rectus femoris of euthyroid patients.

Electromyogram on Maximal Volition (Appendix Table 7). An interference pattern was obtained in all cases with a voltage which did not differ significantly from that of the controls (Table 52).

Triceps

A comparison of Table 53 with Table 21 will show that the action potential duration returned to a level similar to that of the two controls, as did the degree of polyphasicity. Although the mean amplitude rose from 113 μV to 130 μV, it is not known whether or not this is significant.

Table 49

Follow-up electromyograms: Rectus femoris.

Comparison of the mean action potential amplitude of the patients with that of controls (see Appendix Tables 4 and 6).

	Mean Amplitude uv	Standard error of difference	t	Degree of freedom	P
Controls n = 17	158.8 ± 66.2	18.706	1.836	30	0.1 > P > 0.5 Not significant at P = 0.05
Patients n = 24	124.5 ± 85.8				

Table 50

Follow-up electromyograms: Rectus femoris.

Comparison of the mean percentage of polyphasic potentials in the patients four months after becoming euthyroid with the percentage before the start of treatment (see Appendix Table 4).

Patients	Mean % polyphasic potentials	Standard error of difference	t	Degree of freedom	P
Before treatment n = 24	14.8 ± 4.5	1.220	2.215	37	0.1 > P > 0.5 Not significant at P = 0.05
After treatment n = 15	12.6 ± 1.8				

Table 51

Follow-up electromyograms: Rectus femoris.

Comparison of the mean percentage of polyphasic potentials between the patients and the controls (see Appendix Tables 4 and 6).

	Mean % polyphasic potentials	Standard error of difference	t	Degrees of freedom	P
Controls n = 17	8.2 ± 4.3	1.177	3.696	30	P < 0.001 Highly significant at P = 0.05
Patients n = 15	12.6 ± 1.7				

Table 52

Follow-up electromyograms: Rectus femoris

Mean amplitude of the interference pattern in the patients after treatment and in the controls.

	Mean Amplitude mv.	Standard error of difference	t	Degrees of freedom	P
Controls n = 15	4.5 ± 2.0	0.707	0.745	28	0.5 > P > 0.4 Not significant at P = 0.05
Euthyroid patients n = 15	3.9 ± 1.9				

Table 53

Follow-up electromyograms on Triceps in one patient compared with two controls.

	Age	Sex	Action Potential Duration m. sec.			Action Potential Amplitude m. sec.			% Polyphasics	
			Total	No.	Mean	Total	No.	Mean	No.	%
Patient Case No. 3	25	F	424	40	10.6	5070	39	130	5	11.1
Control 1	24	F	248	25	9.9	3540	25	141	3	10.7
Control 2	26	F	261	23	11.3	6700	34	279	4	16.0

SUMMARY OF RESULTS

The Patients:

(1) The average age of onset of thyrotoxicosis was the same for men as for women.

(2) Fifty per cent of the patients had some complaint of weakness, and there was no sex difference in this respect.

(3) 3.7% had weakness as a presenting symptom.

(4) Proximal muscles alone were affected in 63.0% of the patients. Proximal and distal muscles together were involved in a further 18.5%.

(5) In no case were distal muscles solely affected. No cases of bulbar muscle weakness were seen.

(6) Extensor muscles were involved twice as commonly as flexor muscles.

(7) No significant increase in strength developed following the intravenous injection of edrophonium (Tensilon).

Biochemistry:

(1) No consistent abnormalities were found in the serum levels of calcium or potassium.

(2) The mean two hour post-prandial glucose level was raised, indicating a generally diminished tolerance to ingested glucose.

(3) There was usually an increase in urinary creatine excretion and a reduction in creatinine, compared with normal.

Electromyography:

(1) Fifty out of the fifty-four patients (92.6%) showed a reduction in the mean action potential duration in the proximal muscle sampled.

(2) There was no significant change in mean action potential amplitude.

(3) A general increase in the percentage of polyphasic potentials was noted in all three muscles sampled.

(4) Spontaneous activity was inconspicuous, fibrillation and fasciculation being found only once.

(5) Full effort almost always produced a normal interference pattern, though a mixed pattern was seen in three patients. A reduced mean voltage was seen in the EMG's of the rectus femoris.

(6) 42.9% of the 21 patients tested had an abnormal electromyogram of the abductor digiti quinti, and all of these had a gross abnormality of the proximal muscle sampled. Fasciculation and fibrillation was seen in three patients each.

(7) The deviation of the action potential duration was greater in those patients who had clinical weakness of the deltoid muscle than in those without. This relationship was not apparent in the rectus femoris.

(8) The severity of the EMG changes correlated well with the extent of the muscle involvement.

Nerve Conduction Velocities and Latencies:

No abnormality was seen.

Muscle Biopsy:

(1) There was a general reduction in fibre diameter in the thyrotoxic patients, accompanied by an increase in the number of fibres per unit area.

(2) Abnormal histology was found in 23.3% of the biopsies.

Follow-up:

(1) The time taken for normal strength to return and for the euthyroid state to be achieved was the same. Muscle atrophy took a little longer to recover.

(2) Creatine and creatinine excretion returned to normal in nearly all patients.

(3) Only 19% of the EMG's done on the euthyroid patients had an action potential duration which was significantly different from the predicted. There was a significant increase in amplitude in the deltoid muscle, but the mean was still within the normal range. The percentage of polyphasic potentials had returned to normal in the deltoid and triceps muscles, but remained elevated in the EMG's done on rectus femoris.

DISCUSSION

The findings of this study of 54 unselected thyrotoxic patients suggest that a muscular lesion, either apparent or subclinical, is almost a constant feature of hyperthyroidism. The evidence for this rests mainly on the clinical investigation and on the results of electromyography. The histological examination of muscle tissue, while suggestive, did not provide quite such conclusive evidence.

Clinical Aspects

The clinical findings in these patients were strikingly similar to those found by an analysis of the 73 cases of chronic thyrotoxic myopathy described in the literature (compare Tables 1 and 3).

The mean age of patients with myopathy was not significantly different from that of the present unselected thyrotoxics and provided no foundation for the popularly held belief that the muscular lesion of hyperthyroidism is more common in the older age groups (Thorn and Eder 1946, Grob 1963a). No sex difference was discernible in the age of onset of thyrotoxicosis, either in the reported cases or in the present series.

From the frequency with which cases of chronic thyrotoxic myopathy have been reported, it would appear that the condition is more common in males than females. Thirty eight cases have been described in males as compared with 35 in females. This gives an almost 1:1 ratio, in contrast to the usual preponderance of four female patients to one male (Williams 1962, p. 170). In this study the women outnumbered the men by 2.9:1. There are several possible explanations for the relatively more frequent occurrence

of male cases of thyrotoxic myopathy in the literature. The first is that the muscles of men may differ in some way from those of women, but there is no histological or biochemical evidence to support this. The second is that females have proportionately more fat and less muscle in their bodies than men (Staffurth 1962). Consequently it might be expected that, following the onset of thyrotoxicosis, there would be a greater protein sparing effect in women than in men. A third is that men are more usually engaged in heavy physical exertion than are women and hence their weakness would tend to make them seek medical attention rather more than women. That this might be a factor is suggested by the much longer history of the illness in the female patients described in the literature.

The mean weight loss in the reported cases was twice that found in the present study and could be accounted for by the much greater duration of thyrotoxicosis.

Distal muscles and bulbar involvement were seen more often in the cases described in the literature (42.3% and 16.4%) than in the unselected patients (18.5% and 0%), but this too may be merely a reflection of the longer history of the condition.

A goitre was present in 87% of the reported cases of chronic thyrotoxic myopathy which is not significantly different from the incidence of 92.6% found in the patients studied, nor was there any real variation in the incidence of ophthalmoplegia in the two groups of patients, being 5.5% in the reported cases and 7.4% in the present series. Glucose tolerance was equally diminished in both groups, though only a small number of the patients in the literature had had specific investigations for this carried out. No

striking abnormalities in the serum levels of calcium and potassium were noted in the present study.

There were increased amounts of creatine and decreased amounts of creatinine in the urine of both groups of patients. The changes in the quantity of creatine excreted were slightly less marked in the reported cases of myopathy, in some cases of which creatinuria was very low or totally absent (Zierler 1951). Grob (1963a) has already pointed out this tendency for creatinuria to diminish as the muscle involvement becomes more manifest and Hoch (1962) has suggested that it is probably due to a failure of synthesis of creatine.

Though the muscles were, obviously, not so frequently involved as in the cases cited in the literature, 50% of the patients in this study had some complaint of muscle weakness and in 3.7% it was, in fact, the presenting symptom. The most characteristic complaints were those of difficulty in going upstairs or lifting the arms above the head as had been described before in cases of thyrotoxic myopathy (Parsons and Twort 1939, Thorn and Eder 1946, Millikan and Haines 1953, Hoffenburg and Eales 1956, Hed, Kirstein and Lundmark 1958, Whitfield and Hudson 1961). Some of the patients had also noticed weakness and aching in the thighs, even when walking along the level.

On examination no fewer than 81.5% of the patients were found to have some involvement of their muscles. Usually this was a combination of both wasting and weakness, but in a few there was mild atrophy without demonstrable loss of strength and in a larger number there was weakness without any diminution in muscle bulk.

Recently two surveys on the same subject as this thesis have been published by workers in London and Tokyo (Havard, Campbell, Ross and Spence 1963, Satoyoshi et al 1963) and their conclusions correspond quite well with those of articles written a few years before about smaller numbers of patients (Pipberger et al 1955, Hed et al 1958, Gimlette 1959). The results, together with those of the present survey are summarised in the table below:-

Authors	No. of patients	Weakness as a presenting complaint	Weakness as a symptom	Weakness clinically
Pipberger et al 1955	13	-	61.5%	69.2%
Hed et al 1958	20	15%	-	55%
Gimlette 1959	40	-	32.5%	60%
Havard et al 1963	50	6%	34%	80%
Satoyoshi et al 1963	240	-	-	61%
Present series	54	3.7%	50%	81.5%

Considering that the patients are drawn from so far afield as Sweden, Switzerland, Britain and Japan, and taking into account variation in the criteria for clinical weakness, there is a remarkable uniformity in the figures and, on this evidence, that there is loss of muscle power in a majority of patients with hyperthyroidism must be accepted.

A striking feature in both the cases recorded as "chronic thyrotoxic myopathy" and in the survey of Havard et al (1963), as well as the present one, has been the predilection for proximal muscles. Havard and his colleagues found that the deltoid, supraspinatus and the quadriceps were the most commonly involved muscles. In this series the muscles most often affected were those of the shoulder girdle and upper arm, the pelvic girdle and thigh muscles being less frequently involved as can be seen from Table 6. In order of incidence, the most severely affected muscles were the supraspinatus, triceps, deltoid, infraspinatus, biceps brachii, iliopsoas and the glutei . Extensor muscles were twice as commonly affected as flexor muscles.

In 18.5% of the patients distal muscles, always of the forearm and hand, and never of the leg or foot, were wasted and weak in addition to the involvement of the proximal muscles and in no case was a distal muscle involved alone. This situation was also noted in the 73 cases summarised in Table 1, but was more marked. In the cases cited in the literature a moderate incidence of bulbar symptoms occurred. This was not found in the present series.

This march of events - first proximal, then distal, then bulbar muscle - suggests a difference in susceptibility of each type of muscle to the thyrotoxic process. Muscles which are used most for prolonged effort and the maintenance of posture have a higher proportion of red fibres than those which have as their function short bursts of activity. Moreover "the more rapidly contracting flexor muscles in most mammals tend to be more pale than the extensors" (Adams et al 1962, p. 99). Red muscle is known to have a much

greater number of mitochondria than white muscle (Lawrie 1953), a fact which is of great significance, since mitochondria contain the mechanism for the production of energy by oxidative phosphorylation. The muscles more capable of quick movement, that is flexor muscles, with proportionately more white fibres and fewer mitochondria, obtain their energy from anaerobic glycolysis to a greater extent. The connection between mitochondria, muscle weakness and thyrotoxicosis will be discussed later.

Electromyography

Previous reports of electromyography in thyrotoxic patients and the results of the present series are summarised below:

Authors	No. of patients	EMG evidence of myopathy	Characteristic features
Pipberger et al 1955	13	92.3%	Shortening of action potentials, increase in polyphasicity, decrease in amplitude. Normal interference pattern.
Hed et al 1958	17	100%	In areas sampled 75 to 100% of potentials of short duration or polyphasic. "Dense" or "scanty" interference pattern.
Gimlette 1959	40	-	"Myopathic pattern" in the majority.
Yates 1962	10	70%	Shortened action potential duration.
Havard et al 1963	50	88%	Motor units either polyphasic or of a shorter duration than normal.
Satoyoshi, Murakami and Torii 1963	39	61.5%	Unspecified
Present series	**54**	**92.6%**	**Statistically significant reduction in action potential duration.**

All the articles in the literature to date have been about qualitative estimations of the electromyographic findings in thyrotoxicosis and any difference in the results so obtained could be due to observer error. However, apart from the results of Satoyoshi et al (1963), four previous reports are remarkably similar (Pipberger et al 1955, Hed et al 1958, Yates 1962, Havard et al 1963). Presumably the finding by Millikan and Haines (1953) of normal electromyograms in several cases of thyrotoxic myopathy must be explained by the different criteria employed by workers in the past for the visual interpretation of the electromyogram.

The results of the present series show that nearly all thyrotoxic patients, whatever the severity or duration of their illness and no matter what their age, have some evidence of myopathy in their proximal muscles, as defined by a significant reduction in the mean action potential duration on minimal effort. This criterion for the diagnosis of a myopathy, first described by Kugelberg (1947, 1949), has been confirmed by several authors (Pinelli and Buchthal 1953, Buththal and Pinelli 1953, Eaton and Lambert 1957). It must be emphasized, however, that this reduction is in no way specific for thyrotoxicosis, for it occurs in any primary lesion of muscle such as muscular dystrophy, polymyositis or dystrophia myotonica (Pinelli and Buchthal 1953, Buchthal and Pinelli 1953). It has not been noted in patients with disuse atrophy resulting from one to six months' immobilisation (Buchthal 1957).

Although the voltage of the potentials on minimal effort in the present series was generally diminished, a statistical analysis of the results did not reveal that they were significantly lower

than the control values. This finding is not in accord with that of Buchthal (1957) who found a decrease in amplitude of the potentials on minimal contraction. This discrepancy may however be explained by differences in the severity of the muscle lesion, for his examination was performed on patients labelled as "chronic thyrotoxic myopathy", while the present study was on consecutive patients suffering from thyrotoxicosis. Buchthal has himself pointed out (1957) that the mean amplitude must deviate from the normal by more than 50% in order to become statistically significant.

Taking all the patients as a whole the mean percentage of polyphasic potentials was higher than in the control subjects, but, as can be seen from Fig. 5 there was a considerable overlap in results. This increase in polyphasic potentials is a characteristic feature of a myopathy (Kugelberg 1949).

The pattern on maximal effort was nearly always of the interference variety, though a mixed pattern was seen on three occasions. The voltage of the interference pattern was generally reduced, compared with controls, though this relationship was only shown to be significant in the electromyograms done on the rectus femoris. A reduction in the peak to peak voltage of the interference pattern has been found in myopathies in general (Kugelberg 1947, 1949) and in thyrotoxicosis in particular (Hed et al 1958).

Spontaneous activity, in the form of fibrillation potentials and fasciculation was rarely seen, each being found in the proximal muscles sampled in only one patient. This is in agreement with the findings of Hed et al (1958) and of Havard and his colleagues (1963). Relatively more fasciculation and fibrillation was seen

in abductor digiti quinti. The comparative absence of spontaneous activity in the thyrotoxic patients reflects the paucity of similar reports in the literature on thyrotoxic myopathy.

Less than half of the patients tested (42.9%) had a significantly reduced mean action potential duration in their abductor digiti quinti and all of these had evidence of proximal muscular involvement. This tendency for the proximal muscles to be more severely affected electromyographically than the distal muscles has also been noted by Pipberger et al (1955). Thus the electromyographic findings reflected the clinical picture, the proximal muscles being involved in the majority and the distal muscles being affected to a lesser extent and in a smaller number of patients.

There is still no completely adequate explanation of the factors which determine the action potential duration in myopathies. Buchthal and Rosenfalck (1955) pointed out that in normal muscle the longer duration of the motor unit potential compared with that of the individual fibre was due to a temporal dispersion in the summation of the fibres of the motor unit and they suggested that differences in temporal dispersion could be explained by variations in the size of the end plate region. Feinstein, Lindegård, Nyman and Wohlfart (1954) had earlier come to the conclusion that the degree of scatter of fibres of a motor unit could be expected to play a large part in determining the action potential duration recorded on the electromyograph. The short durations recorded in muscles such as the abductor digiti quinti, compared with biceps brachii (Sacco, Buchthal and Rosenfalck 1962), could probably be explained on this basis. Sacco et al postulated that the progressive increase in action potential with age after the age of 20

in most muscles was due to a decrease in muscle volume with advancing years, leading to a closer crowding together of muscle fibres. This would cause the voltage of the initial and terminal components of the motor unit potential, normally picked up from fibres of subunits lying more than 0.5 mm. from the electrode, to be greater and thus more easily recorded. However, they were unable to explain why this increase in duration with age did not occur in the abductor digiti quinti.

The shorter action potential duration in myopathies has been attributed to the decrease in the number of fibres in each subunit (Buchthal and Rosenfalck 1963). This might have the effect of rendering those potentials emanating from distant subunits undetectable to the recording electrode. Theoretically, atrophy of muscle fibres and a resultant higher density per unit area would be expected to reverse this effect. In the present study there was an almost constant reduction in fibre population, yet the action potential duration was shortened in all cases. Assuming that the tendency for the voltage to be lowered both on minimal and maximal effort was true, since Håkansson (1956, 1957) has shown that the voltage of single muscle fibres varies as the square of their diameter, then the reduced action potential found in the present study must have been due to a decrease in the number of <u>functioning</u> fibres.

The increased number of polyphasic potentials, a well-known feature in myopathies, could be due to one of two causes, or both. A motor unit, which in the healthy patient gave rise to a long action potential duration, owing to the large temporal dispersion of subunit potentials, would be expected to show a polyphasic outline

if the number of fibres in each subunit was reduced in an irregular fashion (Buchthal and Rosenfalck 1963). Sprouting of the terminal nerve fibres in the thyrotoxic myopathy described by Coers and Woolf (1959, p. 118), and not yet confirmed, might also give rise to a raised incidence of polyphasic potentials by causing greater temporal dispersion, due to slower conduction through immature nerve fibres (Buchthal and Rosenfalck 1963).

When the presence or absence of clinical weakness in the muscle sampled was compared with the magnitude of the reduction in mean action potential duration, it was found that those patients with loss of muscle power in the deltoid had significantly greater EMG changes than those without. The same relationship could not be shown to be statistically significant in the rectus femoris muscle, probably because of the small number of persons with weakness of the quadriceps group.

The reduction in action potential duration was greatest in those patients with the widest extent of muscular involvement (proximal and distal). Patients with weakness and wasting of proximal muscles only had a smaller reduction. Compared with those with clinically normal muscles, the EMG changes in the first two groups were statistically significant, being more so in the group more extensively affected.

Nerve Conduction

No abnormalities were found of conduction velocity in the ulnar nerve or of latency at the wrist, despite the report by Havard et al. (1963) of swelling and beading in the terminal nerve fibres and clubbing of the motor end plates.

Muscle Biopsy

The results of biopsy show that there was an almost constant reduction (23%) in the diameter of the muscle fibre with a mean of

12 microns, and a consequent higher density per unit area. This finding has not been reported before, although numerous authors have described patchy atrophy of fibres (Morgan and Williams 1940, Bartels and Pizer 1944, Thorn and Eder 1946, Hoffenburg and Eales 1956, Bostrom and Hed 1958, Hed et al 1958, Whitfield and Hudson 1961, Havard 1962, Satoyoshi et al 1963). It is possible that in many of the reports in the literature the increase in sarcolemmal nuclei was more apparent than real, due to the higher density of muscle fibres. In the present series no patients appeared to have an absolute increase of more than 8 nuclei per fibre on cross section (Adams et al 1962, p. 19).

Muscle histology has been variable in the cases of chronic thyrotoxic myopathy reported in the literature. Thus normal biopsies have been reported by Morgan and Williams (1940), Sanderson and Adey (1949), Millikan and Haines (1953), Kite et al (1954), Collings and Lienhard (1957) and Melville (1959), whereas there have been a rather greater number of descriptions of pathological changes in muscle (Morgan and Williams 1940, Bartels and Pizer 1944, Thorn and Eder 1946, Devic et al 1947, Quinn and Worcester 1951, Whitfield and Hudson 1961, Havard 1962). These changes have been variable but have usually included, in addition to increase in sarcolemmal nuclei, fatty infiltration between the muscle fibres, fibrous replacement of muscle tissue, aggregations of lymphocytes (lymphorrhages), vacuolisation and degeneration of isolated muscle fibres with phagocytosis. In addition, Devic et al (1947) found changes in the structure of mitochondria in the region of the motor end plate. Although Havard et al (1963) reported no histopathology in 48 biopsies done on unselected thyrotoxic patients, Hed et al (1958) found abnormalities in 17 out of 18 cases and Satoyoshi and his colleagues (1963) noted scattered pathological changes of varying degree in 68% of their biopsies. Apart from a reduction in

the diameter of muscle fibres, histological abnormalities were found in 23.3% of the 30 biopsies in the present series. The changes included degeneration of isolated fibres with macrophage and lymphocyte infiltration, infiltration of fat between muscle fibres, connective tissue proliferation and focal perivascular collections of lymphocytes (lymphorrages).

The pathology observed by Dudgeon and Urquhart (1926) in the eye muscles of patients suffering from malignant exophthalmos was also found in various skeletal muscles and was very similar to that described in thyrotoxic myopathy. It is possible that the histological lesions are produced by excess thyrotropin or "exophthalmos-producing substance" (Kinderen et al 1960). Some evidence that these changes can be produced by antuitrin T in the absence of thyroxine was provided by Paulson (1939) using thyroidectomised guinea-pigs. This work was confirmed later by Dobyns (1946). Of the 7 patients each with abnormal histology in the present series, 2 had marked bilateral exophthalmos, 3 had unilateral exophthalmos, one had moderate ophthalmoplegia without proptosis and only one had no eye involvement.

If an anterior pituitary factor does produce these histological changes, it seems unlikely that the lesions are the cause of thyrotoxic myopathy, since as soon as the level of circulating thyroxine is reduced to a normal level, by whatever form of treatment, the patient's strength returns and atrophy disappears, despite the general increase in proptosis (see Results) and the rarer development of ophthalmoplegia, sometimes accompanied by pretibial myxoedema and achropachy, all effects attributed to thyrotropin or exophthalmos-producing substance.

Follow-up

The time taken for the patient to regain normal strength was the same as that for the achievement of euthyroidism. This suggests that the weakness was closely related to the presence of excess thyroxine and not to anterior pituitary factors. Muscle bulk took a little longer to return to normal. This might indicate that the muscle atrophy was not the direct cause of the weakness, but was secondary to some biochemical malfunction of the muscle fibres. The association of weakness without wasting was often seen in the patients, while the converse was rare.

Within a period of four months following euthyroidism, nearly all patients had normal creatine and creatinine metabolism as evidenced by their levels of excretion in the urine.

In parallel with the clinical recovery of the patients, the follow-up studies showed that 81% of the patients had a return to normal of their mean action potential duration, and of those whose duration was still significantly reduced all showed considerable improvement. Sanderson and Adey (1949) also noticed the gradual return of short potentials to a normal duration during a period of several months following treatment.

The percentage of polyphasic potentials found in the EMG's of the deltoid done four months after the achievement of the euthyroid state showed a general return to the values found in the control subjects. The persistence of an abnormal percentage of polyphasic potentials in the records taken from the rectus femoris may indicate a slower recovery of that muscle from the effects of thyrotoxicosis, or permanent damage to fibres in large motor units or might even be due to the effects of the sprouting of terminal nerves which was

seen by Cöers and Woolf (1959). Sanderson and Adey (1949) have also noticed this persistence of polyphasic potentials, despite a return of the other features of the electromyogram to normal.

The voltage increase of the interference pattern found in the follow-up EMG's of the rectus femoris suggests that there had been an increase in the number of functioning fibres following the control of the thyrotoxicosis.

The Role of Thyroxine in Myopathy

An analysis of the cases of chronic thyrotoxic myopathy in the literature and the results of the present investigation reveal that on average the symptoms of weakness became apparent one to two months after the onset of thyrotoxicosis and receded as soon as the disease was brought under control. That there is a close relationship between thyroid hormone excess and the production of a myopathy has been seen in experimental animals (Havard et al 1963).

Several authors have shown that mitochondria contain the mechanisms for oxidative phosphorylation and the production of the high energy phosphate bonds of adenosine triphosphate (Green, Loomis and Auerbach 1948, Kennedy and Lehninger 1949, Harman 1950, Lehninger 1959, Green and Hatefi 1961). The transformation of oxidative to phosphorylative bond energy has been called "coupling" by Loomis and Lipmann (1948). Hoch, in a recent article (1962), has made a comprehensive review of the evidence that excess thyroxine produces uncoupling of oxidative phosphorylation and increases the rate of oxygen consumption. He also noted the connection between the swelling of normal mitochondria, when in the presence of an uncoupling substance, and the swelling of mitochondria in thyrotoxic tissue. Hoch (1962) postulated that the net effect of thyroxine on oxidative

phosphorylation was the decreased production of high energy bonds and the dispersion of energy as heat, a feature characteristic of hyperthyroidism.

It is known that muscular contraction results from the interaction of actin, myosin and adenosine triphosphate (A.T.P.) in the muscle fibrils (Mommaerts 1963). Consequently, if the amount of A.T.P. available were diminished, muscular contraction would be expected to be less effective. This loss of mechanical efficiency in thyrotoxicosis has already been shown by Plummer and Boothby (1923) and by Smith and Whalen (1960). Recently Shinosaki et al (1963) discovered a direct correlation between loss of muscular strength and the decreased A.T.P. content of thyrotoxic muscle obtained by biopsy.

Phosphocreatine is necessary for normal muscle contraction. Its probable role is in the immediate resynthesis of A.T.P., acting as the donor of a phosphoryl group to adenosine diphosphate (Thomas 1963, p. 307). A reduction in phosphocreatine was found in thyrotoxic muscle by Shinosaki and his co-workers (1963). This decrease probably is mediated by the direct inhibiting action of excess thyroxine on creatine phosphokinase (Askonas 1951). The inability of the cell to resynthesize phosphocreatine is reflected in the raised serum levels (Shinosaki et al 1963) and the increased urinary excretion of creatine, as well as in the decrease tolerance of thyrotoxic patients to ingested creatine (Thorn and Eder 1946, Wilkins and Fleischmann 1946). An adequate amount of intracellular potassium may also be a necessary factor for the formation of phosphocreatine (Grob, Liljestrand and Johns 1957, Shinosaki et al 1963).

Since creatinine is a breakdown product of phosphocreatine, it is not surprising that its excretion is reduced in thyrotoxic patients. The finding of a low or absent excretion of creatine in some patients with myopathy (Zierler 1951) has been attributed by Hoch (1963) to the failure of synthesis of creatine in the liver and kidneys. This requires A.T.P. for the transfer of a methyl group from methionine.

The role of pyridoxine (Wohl, Levy, Szutka and Maldia 1960) and thiamine deficiency (Williams, Egana, Robinson, Asper and du Toit 1943, Shinosaki et al 1963) in muscle metabolism have not yet been elucidated,nor is it clear whether the atrophy of muscle fibres contributes to the muscle weakness of hyperthyroidism, or is a phenomenon which is secondary to the biochemical dysfunction. One thing is certain, and that is that the rate of protein synthesis is decreased in thyrotoxicosis (Hoch 1962).

Intracellular fluid is normally hypertonic with respect to the extracellular fluid (Keele, Neil and Jepson 1961), and maintains a high concentration of potassium and a low sodium compared with the latter. Energy is necessary for the extrusion of water against an osmotic gradient and for the maintenance of normal concentrations of potassium and sodium against high diffusion gradients. If the amount of energy available were diminished by the action of excess thyroxine, according to Hoch's hypothesis (1962), the selective permeability of the cell membrane might be expected to break down to some extent. Green and Matty (1962) have shown that increased permeability to water is produced by thyroxine. That this also occurs for other substances may be inferred from the finding in thyrotoxic muscle fibres of a reduction in potassium of 21% and a

doubling of the sodium content, as well as a decrease in aldolase and lactic dehydrogenase (Shinosaki et al 1963). No information is available about the intracellular content of chloride in thyrotoxic muscle. Total body water has been found to be abnormally large in some cases of hyperthyroidism (Staffurth 1962), which would be expected to occur if water diffused across cell membranes. However, Shinosaki et al (1963) found a slight decrease in intracellular water in thyrotoxic muscle and further work needs to be done to clear up this point.

The presence in thyrotoxicosis of a low muscle potassium and a high sodium concentration might explain the connection between this disease and the hypokalaemic type of periodic paralysis. McArdle and Merton (1952) and Conn and Streeton (1960) have found similar abnormalities in the muscle of patients between attacks of paralysis. A reduced total exchangeable body potassium also has been noted in both conditions (Conn and Streeton 1960, Staffurth 1962). It is tempting to suggest that the changes produced in thyrotoxic muscle initiate attacks of periodic paralysis in those who have a latent disposition to it. This also would explain why the attacks usually cease once the hyperthyroidism is treated.

No speculation can be made about what effect the ionic changes in thyrotoxic muscle should have upon the resting membrane potential, since the full facts about the intracellular content of water, chloride and several other ions are not yet known. It should be possible to measure the resting membrane potential in vivo, as this already has been done in patients with hypokalaemic periodic paralysis by Shy, Wanko, Rowley and Engel (1961) and by Creutzfeldt, Abbott, Fowler and Pearson (1963).

If any alteration in membrane potential does exist, it also would affect the motor end plates and thus interrupt neuromuscular transmission sufficiently to render overt those patients who had a predisposition to myasthenia gravis. Additional factors linking myasthenia gravis and thyrotoxicosis depend on the auto-immune theory first put forward by Simpson (1960). If there was damage to or alteration in motor end plate structure, as has been described in thyrotoxicosis (Havard et al 1963), it is conceivable that antibodies to end-plate receptor protein would be produced by the thymus. The frequency with which the thymus is enlarged in both myasthenia gravis and thyrotoxicosis has already been remarked upon in the Introduction to this thesis, and there is some tentative evidence that antibodies to motor end plate do exist in myasthenia gravis (Strauss, Seegal, Han, Burkholder, Nastuk and Osserman 1960, Beutner, Witebsky, Ricken and Adler 1962).

SUMMARY AND CONCLUSIONS

A comparison of 73 cases of chronic thyrotoxic myopathy recorded in the literature with 54 consecutive, unselected thyrotoxic patients investigated clinically, electromyographically and by muscle biopsy suggests that no real differences are apparent between the two groups other than those of degree. Fifty per cent of the patients had some complaint of muscle weakness and, on examination, 81.5% had evidence of loss of power, usually accompanied by wasting. There was a marked predeliction for proximal muscles, especially extensors, distal muscles being involved in only 18.5% of the patients. The distal weakness always occurred in association with involvement of proximal muscles.

92.6% of the patients showed a significant abnormality in electromyograms done on proximal muscles. Of the examinations performed on a distal muscle, abductor digiti quinti, only 42.9% were abnormal. The criteria employed were a statistically significant reduction in mean action potential duration, compared with the predicted for any given age. The mean percentage of polyphasic potentials in thyrotoxic patients was significantly higher than in the controls. The amplitude of potentials obtained on minimal effort was normal, but there was some evidence of a reduction on maximal effort, when an interference pattern was obtained in all but 3 cases. These 3 showed a mixed pattern. Spontaneous activity was an inconspicuous feature of the electromyogram in thyrotoxicosis. There was a good correlation between the severity of the electromyographic changes and the extent of the muscular involvement. No abnormality of nerve function was revealed by conduction studies.

Creatine excretion was usually increased and that of creatinine diminished. Serum potassium and calcium estimations were unremarkable and did not add anything to the investigation.

Muscle biopsies, performed on 30 of the patients, revealed an almost constant reduction in the size of the muscle fibre. The mean diameter (41 microns) was 12 microns less in thyrotoxic patients than in the controls (53 microns) and the fibre population per square millimetre was raised. Muscle histology was abnormal in only 23.3% of the biopsies and the changes were similar to those already described in the literature.

Full strength returned as soon as the patients became euthyroid, emphasizing the close relationship between excess thyroid hormone output and muscular weakness. Electromyograms showed a complete return to normal in 81% of the patients and the rest had improved considerably, although there was a persistently increased number of polyphasic potentials in some patients. Creatine and creatinine excretion returned to normal in nearly all cases.

The findings in this study fit in well with the concept of thyrotoxicosis as a disease of mitochondria, in which there is a reduction in available adenosine triphosphate, owing to the uncoupling of oxidative phosphorylation by excess thyroxine. The muscles which are richest in mitochondria are those which contain a preponderance of red muscle fibres and are used for sustained effort, and it is these muscles, particularly the extensors, which are the most commonly affected in thyrotoxicosis. The distal muscles, containing largely white fibres and more concerned with quick, infrequent movements, are less richly supplied with mitochondria and rely largely on anaerobic glycolysis as a source of energy. These

muscles were shown to be less frequently involved by weakness and wasting and to have a much lower incidence of electromyographic change.

It is suggested that myopathy occurs in virtually all thyrotoxic patients, its recognition depending largely on the thoroughness with which muscle weakness is looked for, and on the availability of analytical electromyography. The constant nature of the muscle lesion in thyrotoxicosis and the recently discovered abnormalities of cell chemistry may explain why both hypokalaemic periodic paralysis and myasthenia gravis are more common in this condition than would normally be expected.

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Appendix Table 1

The patients history and examination.

Name	Case No.	Age yrs.	Sex	Occupation	Duration of thyro-toxic symptoms months	Symptoms of weakness	Duration of weakness months	Muscle atrophy	Muscle weakness	Fasci-cula-tion	Weight lbs.	Weight loss lbs.	Reflexes	Goitre	Proptosis mm. R.	Proptosis mm. L.	Other pathology and comments
M.B.	1	42	F	Housewife	3	0	0	0	0	0	107	7.5	Brisk	Diffuse	8	8	
I.M.	2	48	F	Cleaner	4	Legs weak when going up stairs	11	Quadriceps ++	Infraspinatus ++ Quadriceps ++	0	122.5	18	Normal	Diffuse	18	17	
M.L.	3	25	F	Housewife	7.5	Weakness of thigh muscles while going up stairs	8	Triceps ++	Iliopsoas +++ Triceps ++	0	133	7	Brisk	Diffuse	10	10	
E.C.	4	47	M	Petrol checker	1.75	0	0	0	0	0	146	3	Normal	Diffuse	15	15	
E.K.	5	60	F	Dressmaker	2	0	0	0	0	0	126	14	Brisk	Slight enlarge-ment R. lobe			Partial thyroidectomy 27 years previously.
F.R.	6	22	F	Tobacco worker	12	0	0	Supraspinatus ++ Infraspinatus ++ Deltoid ++ Quadriceps +	Supraspinatus + Infraspinatus ++ Deltoid + Biceps br. ++ Triceps ++ Iliopsoas ++ Quadriceps ++	0	94	18	Brisk	Diffuse	15	15	
M.McM.	7	57	F	Farm and housework	20	Aching and weakness of shoulders and upper arms	4	Supraspinatus +++ Infraspinatus +++ Deltoid +++ Biceps br. ++ Triceps ++	Supraspinatus ++ Infraspinatus ++ Deltoid ++ Pectoralis major ++	0	93	19	Normal	Nodular	18	18	
J.H.	8	37	M	Stores clerk	12	Generalised weakness	5	0	0	0	182	35	Brisk	Diffuse	16	13	
R.S.	9	53	M	Bus conductor	3	0	0	0	0	0	132	9	Normal	Diffuse	18	6	
P.C.	10	38	F	Shop assistant	8	Generalised weakness	4	Supraspinatus +++ Infraspinatus +++ Deltoid +++ Triceps ++	Supraspinatus ++ Infraspinatus ++ Deltoid ++ Triceps ++	0	100	20	Brisk	Diffuse	14	14	
M.D.	11	50	F	Housewife	6	0	0	Supraspinatus ++ Infraspinatus ++ Deltoid ++	Supraspinatus + Infraspinatus + Deltoid +	0	147	14	Normal	Diffuse	16	16	

Appendix Table 1 continued.

Name	Case No.	Age Yrs.	Sex	Occupation	Duration of thyrotoxic symptoms months	Symptoms of weakness	Duration of weakness months	Muscle atrophy	Muscle weakness	Fasciculation	Weight lbs.	Weight loss lbs.	Reflexes	Goitre	Proptosis mm. R.	Proptosis mm. L.	Other Pathology and comments
M.A.	12	48	F	Housewife	6	Difficulty lifting with arms and keeping arms above head.	2	Supraspinatus+ Deltoid+ Triceps+	Supraspinatus++ Deltoid++ Triceps++ Biceps br.++	0	115	12.5	Brisk	Diffuse	13	13	
S.McK.	13	32	M	Barman	8	0	0	Supraspinatus++ R. Deltoid+		0	126	20	Normal	Diffuse	21	20	
E.T.	14	26	F	Tobacco Worker	11	Weakness of arms when brushing hair.	11	0	0	0	116	20	Normal	Diffuse	14	13	
T.C.	15	64	M	Boilerman	2.5	Weakness of arms and hands first, then generalised.	2.5	Supraspinatus+++ Infraspinatus+++ Pectorals++ Deltoid+++ Biceps br.+++ Thenar muscles++ Interosseous muscles of hands++ Glutei+++ Quadriceps+++	Supraspinatus++ Infraspinatus++ Pectorals++ Serratus anterior+ Deltoid++ Biceps br.++ Triceps++ Flexors of wrist+ Extensors of wrist+ Thenar muscles+ Interosseous muscles of hand+ Glutei++ Quadriceps+ Hamstrings+	0	100.5	19	K.J. normal A.J. absent	Diffuse	14	13	
M.S.	16	50	F	Housewife	8	Weakness of thighs. Unable to go upstairs.	8	Supraspinatus+++ Infraspinatus+++ Deltoid+++ Biceps br.++ Triceps++ Quadriceps++	Supraspinatus++ Infraspinatus++ Serratus anterior++ Deltoid++ Biceps br.+ Triceps+ Iliopsoas+ Quadriceps+	0	131.5	23	Normal	Diffuse	15	15	
M.D.	17	69	F	Housewife	2	Legs tired when walking, especially thighs.	1	Supraspinatus+ Infraspinatus+ Biceps br.+ Triceps+	Supraspinatus+ Deltoid+ Biceps br.+ Triceps+ Iliopsoas	0	116	16.0	Diminished	Only just palpable	14	14	

Appendix Table 1 continued.

Name	Case No.	Age Yrs.	Sex	Occupation	Duration of thyro-toxic symptoms Months	Symptoms of weakness	Duration of weakness Months	Muscle atrophy	Muscle weakness	Fascic-ulation	Weight lbs.	Weight loss lbs.	Reflexes	Goitre	Proptosis mm. R.	Proptosis mm. L.	Other pathology and comments
S.A.	18	64	M	Shopkeeper	3	0	0	0	Supraspinatus+ Deltoid+ Biceps br.+ Triceps+ Iliopsoas+	0	202	13	Brisk	Mainly L.Lobe	16	16	Jacksonian epilepsy.
M.B.	19	66	F	Housewife	4	Arms tired, difficulty putting things on shelves. Legs weak going upstairs.	4	Supraspinatus+++ Infraspinatus+++ Deltoid++ Biceps br.++ Triceps+++ Hypothenar m.++ Thenar m.++ Glutei+++	Supraspinatus+ Infraspinatus++ Deltoid+ Triceps++ Iliopsoas++	0	116.5	46	Normal	Diffuse	14	12	Simultaneous onset of Diabetes Mellitus Ophthalmoplegia.
P.M.	20	39	F	Civil Servant	8	Unable to lift weights as easily as before.	1.5	0	Biceps br.+ Triceps+	0	144	21	Normal	Diffuse	13	13	
D.P.	21	70	F	Retired	3	Legs weak Arms tired	0.75	Supraspinatus+++ Infraspinatus+++ L. Quadriceps++	Supraspinatus++ Infraspinatus++ Deltoid+ Triceps+ Quadriceps++	0	112	14	Dimin-ished				
E.K.	22	38	M	Factory Supervisor	5	Weakness of arms while lifting weights	4	Supraspinatus+++ Infraspinatus++ Deltoid++ Triceps++ Glutei+++	Supraspinatus++ Triceps++ Glutei+ Iliopsoas+ Quadriceps+	0	136	28	Brisk	Diffuse	17	16	
I.McC.	23	53	F	Housewife	4	0	0	0	0	0	132	6	Normal	Just pal-pable	11	11	
S.M.	24	56	M	Fitter	3	Aching of thighs General tiredness	2	Supraspinatus+++ Infraspinatus+++ Deltoid+++ Biceps br.++ Triceps++ Glutei++ Quadriceps++	Supraspinatus++ Infraspinatus++ Deltoid++ Biceps br.+ Triceps++ Flexors of wrist+ Extensors of wrist+ Iliopsoas+ Quadriceps+	0	118	21	Normal	Diffuse	13	13	

Appendix Table 1 continued.

Name	Case No.	Age Yrs.	Sex	Occupation	Duration of thyrotoxic symptoms Months	Symptoms of weakness	Duration of weakness Months	Muscle atrophy	Muscle weakness	Fasciculation	Weight lbs.	Weight loss lbs.	Reflexes	Goitre	Proptosis mm. R.	Proptosis mm. L.	Other pathology and comments
G.S.	25	55	M	Railway platelayer	12	Weakness of arms while working	12	0	Infraspinatus++ Biceps br.+ Triceps++ Iliopsoas++	0	149	0	Normal	Just palpable	21	22	Ophthalmoplegia
V.W.	26	52	F	Housewife	1.5	General fatigue	1.5	Supraspinatus++ Infraspinatus++ Triceps+	Supraspinatus+ Infraspinatus+ Biceps br.+ Triceps+ Iliopsoas+	0	108	18	Normal	Diffuse	12	12	
F.C.	27	55	M	Farmer	5	0	0	0	Triceps+	0	154	6	Normal	Just palpable	11	11	Radioactive iodine treatment 15 months before Concurrent Diabetes.
M.H.	28	35	F	Housewife	3	Diplopia, ptosis	0.5	Temporalis+++ Supraspinatus+++ Infraspinatus+++ Deltoid++ Biceps br.+++ Triceps+++ Glutei+++	Supraspinatus++ Infraspinatus++ Deltoid+ Biceps br.+ Triceps++ Extensors of wrist+ Glutei+ Iliopsoas+	0	82	32	Brisk	Diffuse	13	12	Concurrent Myasthenia gravis and Ophthalmoplegia
M.L.	29	53	F	Shop Assistant	1.75	Legs weak and painful	1.23	Supraspinatus++ Infraspinatus++ Serratus anterior++ Deltoid++ Biceps br.++ Triceps++	Supraspinatus+ Infraspinatus+ Serratus anterior+ Deltoid+ Biceps br.+ Triceps+ Iliopsoas+	0	112	18	Normal	"Adenoma" L. lobe	14	13	
W.S.	30	49	M	Draughtsman	4	Weakness of thighs, most noticeable on stairs.	2	Supraspinatus++ Infraspinatus++ Deltoid++	Supraspinatus+ Deltoid+	0	147	21	Normal	Just palpable	14	16	Right-sided Parkinsonism for 10 years.
M.L.	31	50	F	Housewife	6	0	0	0	0	0	122	18	Normal	Just palpable	13	15	Pernicious anaemia. Diabetic for 11 yrs. On Insulin. Ophthalmoplegia.
M.S.	32	52	F	Housewife	4	0	0	0	Triceps+	0	105	16	Normal	Diffuse	15	15	
E.L.	33	28	F	Sausage linker	1.25	0	0	0	Supraspinatus+++ Infraspinatus+++ Deltoid+++ Biceps+++ Triceps+++	0	136.5	6	Brisk	Diffuse	13	13	

Appendix Table 1 continued.

Name	Case No.	Age Yrs.	Sex	Occupation	Duration of thyro-toxic symptoms Months	Symptoms of weakness	Duration of weakness Months	Muscle atrophy	Muscle weakness	Fascic-ulation	Weight lbs.	Weight loss lbs.	Reflexes	Goitre	Proptosis mm. R.	Proptosis mm. L.	Other pathology and comments
J.T.	34	31	F	Weaver	8	0	0	0	Left Deltoid+ L.Supraspinatus+ Iliopsoas+	0	128	17	Brisk	Diffuse	14	14	
C.D.	35	15	F	Unem-ployed	0.5	0	0	0	0	0	135.5	3	Normal	Diffuse	18	16	
M.McL	36	48	F	Housewife	4	0	0	0	Iliopsoas+	0	121	5	Brisk	Irregu-lar enlar-gement of both lobes			Partial thyroid-ectomy for toxic goitre 11 years before.
J.L.	37	36	M	Shipping Agent	1.25	0	0	0	Left Triceps+	0	138	21	Brisk	Diffuse	16	14	Ankylosing spondylitis.
H.T.	38	58	F	Housewife	4	0	0	Supraspinatus++ Infraspinatus++ Deltoid++	Supraspinatus++ Infraspinatus+ Deltoid++ Biceps br.+ Triceps+ Iliopsoas+	0	118	17	Brisk	Diffuse	13	12	Radical mas-tectomy for carcinoma 11 years before.
M.J.	39	25	F	House-keeper	9	0	0	0	0	0	146	8	Normal	Diffuse	17	15	
D.C.	40	65	F	Housewife	4	0	0	Supraspinatus+ Infraspinatus+ Deltoid+ Biceps br.+ Triceps+	Supraspinatus+ Infraspinatus+ Deltoid+ Biceps br.+ Triceps+ Iliopsoas+	0	132	35	Normal	Ir-regular	11	10	Partial thyroid-ectomy for toxic goitre 10 years before.
E.W.	41	48	F	Rayon worker	3	0	0	0	Supraspinatus+	0	105	18	Brisk	Diffuse	16	16	
E.H.	42	53	F	Shop Asst.	6	Legs weak while going upstairs. Difficulty lifting heavy objects.	2	Supraspinatus+++ Infraspinatus+++ Deltoid++ Triceps++	Supraspinatus+ Infraspinatus+ Deltoid+ Biceps br.+ Triceps+ Iliopsoas+	0	98	27	Brisk	Diffuse	14	14	
S.L.	43	60	F	Retired	5	Tiredness of upper arms, especially when hanging curtains.	3	Supraspinatus+++ Infraspinatus+++ Pectorals+++ Deltoid+++	Supraspinatus++ Infraspinatus+ Pectorals+ Deltoid++	0	82	29	Normal	Diffuse	14	13	

Appendix Table 1 continued.

Name	Case No.	Age Yrs.	Sex	Occupation	Duration of thyro-toxic symptoms Months	Symptoms of weakness	Duration of weakness Months	Muscle atrophy	Muscle weakness	Fascic-ulation	Weight lbs.	Weight loss lbs.	Reflexes	Goitre	Proptosis mm. R.	Proptosis mm. L.	Other pathology and comments
S.L. contd.	43							Biceps br.+++ Triceps+++ Thenar m.+++ Hypothenar m.+++ Glutei+++	Biceps br.++ Triceps++ Flexors of wrist+ Extensors of wrist+ Thenar m.+ Hypothenar m.+ Glutei+ Iliopsoas++ Quadriceps++								
A.C.	44	62	F	Housewife	7	Generalised	7	Supraspinatus+++ Infraspinatus+++ Serratus anterior+++ Deltoid+++ Biceps br.++ Triceps+++ Thenar m.+++ Quadriceps++	Supraspinatus++ Infraspinatus++ Serratus anterior++ Deltoid++ Biceps br.++ Triceps++ Flexors of fingers+ Thenar m.+ Iliopsoas+	0	92	9	Brisk	L.Lobe	23	22	R.Lobectomy for toxic goitre 25 years before. Mitral stenosis.
M.B.	45	55	F	Housewife	11	0	0	Deltoid++	Supraspinatus++ Infraspinatus+ Pectorals+ Deltoid++ Biceps+ Triceps++ Iliopsoas++	0	111	9	Normal	Diffuse	16	15	
H.W.	46	67	F	Housewife	3	0	0	Supraspinatus+ Infraspinatus+	0	0	141	35	Normal	Diffuse	12	11	
I.M.	47	40	F	Housewife	12	Tired, aching legs while walking. Unable to brush hair.	18	Temporalis+++ Sternomastoids+++ Supraspinatus+++ Infraspinatus+++ Deltoid++ Biceps++ Triceps+++ Thenar m.+++ Hypothenar m.++	Sternomastoids+ Supraspinatus+++ Infraspinatus+++ Serratus anterior+ Deltoid+++ Triceps+++ Extensors of wrist+ Thenar m.+ Iliopsoas+++	0	119	21	Brisk	Diffuse	11	9	
B.B.	48	27	M	Fitter	4	Loss of strength in arms and legs.	4	Supraspinatus+++ Infraspinatus+++ Deltoid++ Biceps br.++ Triceps++ Quadriceps++	Supraspinatus++ Infraspinatus++ Biceps+ Triceps++	0	163	42	Brisk	Diffuse	17	17	

Appendix Table 1 Continued.

Name	Case No.	Age Yrs.	Sex	Occupation	Duration of thyro-toxic symptoms Months	Symptoms of weakness	Duration of weakness Months	Muscle atrophy	Muscle weakness	Fascic-ulation	Weight lbs.	Weight loss lbs.	Reflexes	Goitre	Proptosis mm. R.	Proptosis mm. L.	Other pathology and comments
H.S.	49	42	M	Timber Checker	24	Legs and arms tired. Unable to lift arms above head.	2	Temporalis+++ Sternomastoid+++ Supraspinatus+++ Infraspinatus+++ Deltoid+++ Biceps br.+++ Triceps+++ Extensors of wrist++ Thenar m.++ Hypothenar m.++ Interossei++ Glutei+++ Quadriceps+++	Sternomastoid+++ Supraspinatus+++ Deltoid+++ (unable to lift right arm above shoulder). Biceps br.++ Triceps+++ Extensors of wrist+ Glutei+	0	104.5	7.5	Normal	Diffuse	16	15	Gynaecomastia.
E.H.	50	69	F	Housewife	24	0	0	Supraspinatus++ Infraspinatus++ Deltoid++ Biceps br.++ Triceps++ Glutei++	Supraspinatus+ Infraspinatus+ Deltoid+ Biceps br.+ Triceps+ Iliopsoas++ R.Quadriceps+	0	96	21	Brisk	Nodular	10	10	
M.G.	51	39	F	Barmaid	9	Weakness of legs going upstairs.	1.5	0	Supraspinatus+ Infraspinatus+ Deltoid+ Biceps br.+ Triceps+ Iliopsoas+ Hamstrings+	0	155	8	Normal	Diffuse	12	12	
R.S.	52	41	F	Housewife	9	0	0	0	Supraspinatus+ Deltoid+ L.Iliopsoas++	0	136	11	Brisk	Diffuse	13	13	
J.W.	53	64	F	School-teacher	3	0	0	0	Biceps br.+ Iliopsoas+	0	145	9	Normal	Nodular	12	12	Pernicious anaemia for 6 years.
M.McG.	54	60	F	Housewife	24	Tiredness of thighs.	12	Supraspinatus++ Infraspinatus++ Deltoid++ Biceps++ Triceps++	Supraspinatus++ Infraspinatus++ Deltoid++ Biceps br.++ Triceps++ Iliopsoas++	0	108	32	Brisk	Diffuse	13	12	

APPENDIX TABLE 2

The Patients: General Investigations

Case No.	^{131}I Studies: Thyroid Uptake % 4 hr.	24 hr.	48 hr.	T index	48 hr. P.B.I. ^{131}I% dose/litre plasma	^{132}I Thyroid Uptake 2 hrs.	B.M.R. %	Serum P.B.I. mg. %	Electrocardiogram	2 hr. Post Prandial Blood Glucose mg. %	Serum Calcium mg. %	Serum Potassium m.eq/l.	Urinary Creatine mg./24hr.	Urinary Creatinine mg./24hr.
1	50.0	67.5	67.1	23.4					Sinus tachycardia. Left ventricular hypertrophy.	112	9.6		140	720
2	64.7	76.2	71.1	45.3	0.9				Sinus tachycardia	90	10.1		230	1260
3	76.9	67.9	51.6	8.5	2.8				Sinus tachycardia. Left ventricular hypertrophy.	94	10.3	4.4	360	730
4	43.4	58.8	57.2	20.6	0.5				Sinus tachycardia. Left ventricular hypertrophy.	93	10.5	4.5	640	1440
5	47.5	59.5	45.3	9.7	2.0			10.8	Atrial fibrillation. Left ventricular hypertrophy.	94	10.0	4.6		
6	70.9	77.5	64.1	58.0	1.86				Sinus tachycardia	108	9.7	3.7	840	1140
7							+22		Atrial fibrillation	113	10.3	3.0	335	445
8	70.0	79.0	81.2	42.0	0.3			13.4	Sinus tachycardia		10.5	4.6	230	1070
9	73.5	88.7	72.0					10.6		115	9.5	4.4	530	1370
10						70.2		15.0	Sinus tachycardia	90	9.7	4.9	800	860
11	86.0	78.0	68.0	24.5	0.48			9.7	Sinus tachycardia. Q3 ? flat I, aVL and chest leads.	104	10.5	3.0		
12	75.0	77.5	74.1	51.2				13.1			9.7	4.4	431	504
13	90.6	84.4	77.6	71.2	1.0				Sinus tachycardia	108	10.6	4.0	70	930
14	54.9	77.8	80.0	38.8	0.46			9.5		124	10.2	4.1	190	1095
15	95.0	86.5	85.0		1.27			13.3	Sinus tachycardia	90	10.0	3.8		
16	94.4	67.9	50.4	44.7	4.32				Sinus tachycardia. Left ventricular hypertrophy.	130	10.5	4.4	70	800
17	52.0	62.0	66.0	147.0	1.3			12.1		117	11.9	4.3		
18							+ 48		Atrial fibrillation	170	10.6	4.2	80	1340

Appendix Table 2 continued.

Case No.	I^{131} Studies: Thyroid Uptake % 4 hr.	24 hr.	48 hr.	T index	48 hr. P.B.I.^{131}% dose/litre plasma	I^{132} Thyroid Uptake 2 hrs.	B.M.R. %	Serum P.B.I. mg. %	Electrocardiogram	2 hr. Post Prandial Blood Glucose mg. %	Serum Calcium mg. %	Serum Potassium m.eq/l.	Urinary Creatine mg./24hr.	Urinary Creatinine mg./24hr.
19	70.9	78.5	68.8	46.5				11.3	Sinus tachycardia	18.6 (Diabetic)	9.5	4.5	160	560
20	86.6	88.1	81.0	115.0	1.35				Sinus tachycardia Atrial ectopics	100		4.4	240	880
21	76.1	83.1	75.0		1.7		+36		Sinus tachycardia. Left ventricular hypertrophy.		9.0	4.5	300	860
22	79.0	40.5	31.8	14.5	3.05								260	1420
23	44.5	64.0	63.0	16.8	0.15			12.6	Sinus tachycardia	95		3.7	380	1030
24	84.0	75.0	63.0	21.8	2.1			10.7	Atrial fibrillation Left ventricular hypertrophy.	78	9.4	4.5	110	1120
25	68.0	78.0	74.0	99.0	0.3			10.4	Sinus tachycardia	88	9.0		540	1760
26	68.4	92.0	88.0	33.0	0.65			9.5	Sinus tachycardia. Left ventricular hypertrophy.		9.6	4.5		
27						33.6	+28	9.9	Sinus rhythm. Slight left ventricular hypertrophy.	Diabetic	10.0			
28								13.2	Sinus tachycardia. Left ventricular hypertrophy.	94	9.3	4.9	330	770
29	79.0	82.0	74.0	53.0	1.8			11.6	Sinus tachycardia. T aVL flat.	102	9.9	5.4	120	760
30	39.0	58.0	66.0	32.4	0.6	29.7		15.0	Atrial flutter	94	10.0	4.5	960	50
31	46.0	63.0	65.0		0.65		+67	7.2	Sinus tachycardia	Diabetic	10.6	5.0	590	1010
32	57.0	64.5	53.8	11.8					Q$_3$, aVL	110	10.4	5.4		
33	53.9	70.5	69.5	38.5	0.46				Sinus tachycardia	106	10.0	3.9	270	640
34	87.5	87.5	79.5	55.7	1.19				Sinus tachycardia. Left ventricular hypertrophy.	136	9.9	4.1	200	470
35						67.1		13.0	Sinus tachycardia	110	10.3	4.2	120	300

Appendix Table 2 continued.

Case No.	I^{131} Studies					I^{132} Thyroid Uptake 2 hrs.	B.M.R. %	Serum P.B.I. mg.%	Electrocardiogram	2 hr. Post Prandial Blood Glucose mg.%	Serum Calcium mg.%	Serum Potassium mg.%	Urinary Creatine mg/24hr.	Urinary Creatinine mg./24hr.
	Thyroid Uptake %			T index	48 hr. P.B.I. I^{131}% dose/litre plasma									
	4 hr.	24 hr.	48 hr.											
36						57.6	+64	8.9	Sinus tachycardia. Left ventricular hypertrophy.	176	9.7	3.7	110	1060
37	46.0	61.0	54.0	12.4	0.3			13.0	Sinus tachycardia. Slight left ventricular hypertrophy.	125	10.5	4.5	180	1200
38	87.0	71.0						11.4	Sinus tachycardia. Left ventricular hypertrophy.	128	10.6	4.0	35	990
39						84.1			Sinus tachycardia. Left ventricular hypertrophy.	90	9.9	4.8	50	940
40	59.0	78.0	75.0	45.5	1.16			11.0	Sinus tachycardia. Left ventricular hypertrophy.	118	9.9	3.7	8	1000
41	84.8	71.0	62.0	40.5	4.2			6.4	Sinus tachycardia. Left ventricular hypertrophy.	84	9.7	4.8	150	810
42	72.0	78.0	72.0	8.2	2.01			13.8	Left ventricular hypertrophy.		9.9	3.9		
43	90.0	84.5	77.0	31.5	2.0			15.0	Sinus tachycardia	126	9.8	4.7	146	650
44	75.0	80.0	82.0	64.0	3.2			7.7	Atrial fibrillation. S.T. segment depression.	110	9.9	4.0		
45	70.0	83.0						11.0	Sinus rhythm. S.T. depression in II, III, aVF		11.6	4.7	180	920
46	55.0	72.0	68.0	16.6					Sinus tachycardia. Left ventricular hypertrophy.	112	10.2	4.2		
47	68.5	81.5	75.5		6.65				Sinus tachycardia	114	9.6	3.4	170	760
48	94.0	76.0	70.0	298.0	1.9				Sinus rhythm Q aVL, flat T	130	10.1	4.2	90	680
49	66.0	40.0	21.4	21.3	3.8				Sinus tachycardia	80	9.4	3.3	50	1210

Appendix Table 2 continued.

Case No.	I^{131} Studies					I^{132} Thyroid Uptake 2 hrs.	B.M.R. %	Serum P.B.I. mg.%	Electrocardiogram	2 hr. Post Prandial Blood Glucose mg.%	Serum Calcium mg.%	Serum Potassium mg.%	Urinary Creatine mg/24hr.	Urinary Creatinine mg./24hr.
	Thyroid Uptake %			T index	48 hr. P.B.I. ^{131}% dose/litre plasma									
	4 hr.	24 hr.	48 hr.											
50	41.5	56.0	57.0	12.0			+23	8.8	Atrial fibrillation. Ventricular ectopics.	120	10.3	4.3	35	890
51	74.9	86.2	83.3		0.62		+37		Sinus tachycardia	108	9.5	4.0	510	1280
52	63.5	71.0	62.0	65.0	0.67				Sinus rhythm	100	10.0	4.5	40	1220
53	70.5	76.8	74.0	19.4	0.5			14.0	Atrial fibrillation	122	9.4	4.0	40	1270
54	64.0	84.0	76.0	228.0	0.9			14.6	Sinus tachycardia (with bouts of paroxysmal atrial fibrillation).	110	10.3	4.6	315	945

APPENDIX TABLE 3

Time legs could be maintained in elevation by thyrotoxic patients before and after edrophonium (Tensilon).

Leg raising (average of both legs) secs.		
Case No.	Before edrophonium	After edrophonium
30	62.5	85
31	75	120
32	90	130
33	60	60
34	40	20
36	52.5	50
37	77.5	72.5
38	57.5	60
39	57.5	52.5
40	37.5	52.5
42	52.5	80
43	32.5	30
44	77.5	85
45	97.5	150
46	70	75
47	10	22.5
48	65	47.5
51	62.5	47.5
53	42.5	82.5

APPENDIX TABLE 4

The patients Electromyography before and after treatment

			Electromyogram while Thyrotoxic											Electromyogram 4 months after becoming euthyroid									
			Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort	Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort
Case No.	Age	Muscle Sampled	Total m.sec.	No. of Potls.	Mean m.sec.	Total µv.	No. of Potls.	Mean µv.	No.	%					Total m.sec.	No. of Potls.	Mean m.sec.	Total µv.	No. of Potls.	Mean µv.	No.	%				
1	42	R. Delt.	208	24	8.7	4220	24	175	6	20.0	0	0	0	I.P.	244	25	9.7	3290	24	137	1	3.8	0	0	0	
2	48	R. Rect. Fem.	267	33	8.1	4880	33	148	5	13.2	0	0	0	I.P.	489	37	13.2	5570	37	150	5	11.9	0	0	0	I.P.
3	25	R.Triceps	156	20	7.8	2270	20	113	8	28.6	0	0	0	I.P.	424	40	10.6	5070	39	130	5	11.1	0	0	0	I.P.
4	47	R. Delt.	175	20	8.8	3100	20	155	6	23.1	0	0	0	I.P.	418	35	11.9	4370	35	125	5	12.5	0	0	0	I.P.
5	60	R.Rect.Fem.	222	26	8.5	4160	26	160	3	10.3	0	0	0	I.P.	585	44	13.3	6610	44	150	9	16.9	0	0	0	I.P.
6	22	R.Rect.Fem.	192	22	8.7	4350	21	207	7	24.1	0	0	0	I.P.	529	39	13.6	4330	37	117	6	13.3	0	0	0	I.P.
7	57	R.Rect.Fem.	222	22	10.1	2630	22	119	4	15.4	0	0	0	I.P.	381	36	10.6	4860	36	135	1	2.7	0	0	0	I.P.
8	37	R.Rect.Fem.	370	31	11.9	8060	29	278	3	8.8	0	0	0	I.P.	501	34	14.7	5520	34	162	0	0	0	0	0	I.P.
9	53	R.Rect.Fem.	278	26	10.7	17720	36	492	5	16.1	0	0	0	I.P.	682	46	14.8	5560	46	123	4	8.0	0	0	0	I.P.
10	38	R. Delt.	163	22	7.4	1990	21	95	6	21.4	0	0	0	I.P.	355	32	11.1	3420	31	110	6	15.8	0	0	0	I.P.
11	50	R. Delt.	261	33	7.9	4520	33	137	3	8.3	0	0	0	I.P.	285	23	12.4	2780	23	121	12	34.3	0	0	0	I.P.
12	48	R. Delt.	190	25	7.6	6370	26	245	10	28.6	0	0	0	I.P.	466	37	12.6	5860	36	162	9	19.6	0	0	0	I.P.
13	32	R. Delt.	196	27	7.3	5580	35	159	5	15.6	0	Fib.x1	0	I.P.	629	51	12.3	5290	51	104	4	7.3	0	0	0	I.P.
14	26	L. Delt.	183	22	8.3	3960	20	198	5	18.5	0	0	0	I.P.	342	32	10.7	8500	29	293	3	8.6	0	0	0	I.P.
15	64	R. Delt.	221	23	9.6	2050	23	89	17	42.5	0	0	0	I.P.												
16	50	L.Rect.Fem.	206	21	9.8	2310	21	110	7	22.2	0	0	0	I.P.	510	35	14.6	5430	35	155	2	5.4	0	0	0	I.P.
17	69	L. Delt.	307	40	7.5	4900	40	122	10	20.0	0	Fascicx1	0	I.P.	650	56	11.6	17060	56	305	6	9.7	0	0	0	I.P.
18	64	R. Delt.	302	35	8.6	4330	34	127	6	14.6	0	0	0	I.P.	449	40	11.2	4070	40	102	4	9.1	0	0	0	I.P.
		R.Ab.Dig.V	246	35	7.0	2980	35	85	2	5.4	0	0	0	I.P.												
19	66	R. Delt.	187	25	7.5	2730	25	109	11	30.6	0	0	0	I.P.	405	33	12.3	3540	33	107	5	13.2	0	0	0	I.P.
20	39	R. Delt.	212	30	7.1	4850	30	162	4	11.8	0	0	0	I.P.	281	23	12.2	2540	23	110	6	20.7	0	0	0	I.P.

Appendix Table 4 continued.

Case No.	Age	Muscle Sampled	Electromyogram while Thyrotoxic: Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort	Electromyogram 4 months after becoming Euthyroid: Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort
			Total m.sec.	No. of Potls.	Mean m.sec.	Total µv.	No. of Potls.	Mean µv.	No.	%					Total m.sec.	No. of Potls.	Mean m.sec.	Total µv.	No. of Potls.	Mean µv.	No.	%				
21	70	L.Rect. Fem.	263	30	8.8	4550	29	157	7	18.9	0	0	0	I.P.	502	36	13.9	4980	36	138	5	12.2	0	0	0	I.P.
22	38	R. Delt.	268	32	8.4	6250	32	195	4	11.1	0	0	0	I.P.	534	41	13.0	6100	40	152	8	16.3	0	0	0	I.P.
23	53	L.Rect. Fem.	367	35	10.5	5950	35	170	7	16.7	0	0	0	I.P.												
		R.Ab.Dig.V	463	42	11.0	5580	41	137	4	8.7	0	0	0	I.P.												
24	56	R. Delt.	210	27	7.8	2510	27	100	6	18.2	0	0	0	I.P.												
		R.Ab.Dig.V	215	25	8.6	2340	25	94	7	21.9	0	Fascic. x 7	0	I.P.												
25	55	R. Delt.	293	31	9.5	2850	30	95	5	13.9	0	0	0	I.P.	321	24	13.4	3470	24	145	1	4.0	0	0	0	I.P.
		R.Ab.Dig.V	326	54	6.0	7940	49	162	6	10.0	0	Fascic. x 1	0	I.P.												
26	52	R. Delt.	321	41	7.8	3080	40	77	9	18.0	0	0	0	I.P.												
		R.Ab.Dig.V	221	33	6.7	4970	32	155	5	13.2	0	0	0	I.P.												
27	55	R.Rect.Fem.	284	26	10.9	3360	26	129	3	10.4	0	0	0	I.P.	386	32	12.1	4460	31	144	4	11.1	0	0	0	I.P.
28	35	R. Delt.	141	21	6.7	2696	21	128	8	27.6	0	0	0	I.P.												
29	53	R. Delt.	183	23	7.9	1990	23	86	11	32.3	0	0	0	I.P.	372	32	11.6	3870	32	121	6	15.8	0	0	0	I.P.
		R.Abd.Dig.V	195	33	5.9	5510	31	178	6	15.4	0	Fib.x1	0	I.P.												
30	49	L. Delt.	227	25	9.1	2280	25	115	3	10.7	0	0	0	I.P.	388	33	11.6	4450	33	135	2	5.7	0	0	0	I.P.
		L.Ab.Dig.V	331	39	8.5	4490	36	125	10	20.4	0	Fib.x1	0	I.P.												
31	50	R. Delt.	272	25	10.9	3810	25	152	7	21.9	0	0	0	I.P.	435	36	12.1	4240	36	118	4	10.0	0	0	0	I.P.
		R.Ab.Dig.V	481	46	10.5	5900	46	128	8	14.8	0	Fascic. x 1	0	I.P.												
32	52	R. Delt.	253	24	10.5	2900	24	120	8	25.0	0	0	0	I.P.	408	36	11.3	4470	35	128	6	14.3	0	0	0	I.P.
		R.Ab.Dig.V	279	30	9.3	3860	30	129	7	18.9	0	0	0	I.P.												
33	28	L.Rect.Fem.	138	20	6.9	2060	20	103	4	16.7	0	0	0	I.P.												

Appendix Table 4 continued.

Case No.	Age	Muscle Sampled	Electromyogram while Thyrotoxic: Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort	Electromyogram 4 months after becoming Euthyroid: Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort
			Total m.sec.	No. of Potls.	Mean m.sec.	Total µv.	No. of Potls.	Mean µv.	No.	%					Total m.sec.	No. of Potls.	Mean m.sec.	Total µv.	No. of Potls.	Mean µv.	No.	%				
34	31	R.Rect.Fem.	426	43	9.9	2280	41	70	8	16.3	0	0	0	I.P.	298	24	12.4	2160	24	90	8	25.0	0	0	0	I.P.
		R.Ab.Dig.V	274	38	7.2	3550	36	99	6	13.6	0	0	0	I.P.												
35	15	R. Delt.	352	45	7.4	5290	45	117	9	16.7	0	0	0	I.P.												
36	48	R.Rect.Fem.	357	36	9.9	3010	34	88	5	12.2	0	0	0	I.P.												
		R.Ab.Dig.V	178	24	7.4	2070	24	86	7	33.3	0	0	0	I.P.												
37	36	R. Delt.	323	32	10.1	2180	32	68	13	28.9	0	0	0	I.P.	411	35	11.7	2860	35	82	2	5.4	0	Fib.x1	0	I.P.
		R.Ab.Dig.V	267	39	6.8	5610	39	144	4	9.3	0	0	0	I.P.												
38	58	L. Delt.	178	31	5.7	3550	30	118	2	6.1	0	0	0	I.P.	412	42	9.8	3520	42	83	6	12.5	0	0	0	I.P.
39	25	R.Rect.Fem.	225	22	10.2	2980	21	142	5	18.5	0	0	0	I.P.	370	33	11.2	3190	33	97	1	2.9	0	0	0	I.P.
40	65	R.Rect.Fem.	639	59	10.8	8140	56	145	7	10.6	0	0	0	I.P.												
		R.Ab.Dig.V	694	80	7.4	14370	78	184	8	9.1	0	0	0	I.P.												
41	48	R.Rect.Fem.	391	47	8.3	5320	47	113	4	7.8	0	0	0	I.P.	499	38	13.1	4010	38	105	3	7.3	0	0	0	I.P.
		R.Ab.Dig.V	366	58	6.3	6910	56	123	6	9.4	0	0	0	I.P.												
42	53	R.Rect.Fem.	480	59	8.1	6370	58	110	9	13.2	0	0	0	I.P.												
		R.Ab.Dig.V	336	46	7.3	4410	46	96	4	8.0	0	0	0	I.P.												
43	60	R.Rect.Fem.	357	45	7.9	3690	44	84	11	19.6	0	0	0	M.P.	382	27	14.1	2070	27	77	7	20.6	0	0	0	I.P.
44	62	R.Rect.Fem.	304	34	8.9	3320	34	95	8	19.0	0	0	0	M.P.	389	32	12.2	2110	32	66	5	13.5	0	0	0	I.P.
		R.Ab.Dig.V	282	43	8.9	6550	41	160	4	8.5	0	0	0	I.P.												
45	55	L. Delt.	570	49	11.6	10190	49	208	8	14.0	0	0	0	I.P.	349	30	11.6	3520	30	117	4	11.8	0	0	0	I.P.
		R.Ab.Dig.V	432	49	8.8	4050	49	83	13	20.9	0	0	0	I.P.												

Appendix Table 4 continued.

Case No.	Age	Muscle Sampled	Electromyogram while Thyrotoxic: Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort	Electromyogram 4 months after becoming Euthyroid: Action Potential Duration			Action Potential Amplitude			Polyphasic Potls.		Insertional Activity	Denervation	Silent Areas	Maximum effort
			Total m.sec.	No. of Potls.	Mean m.sec.	Total μv.	No. of Potls.	Mean μv.	No.	%					Total m.sec.	No. of Potls.	Mean m.sec.	Total μv.	No. of Potls.	Mean μv.	No.	%				
46	67	R.Rect.Fem.	553	52	10.6	7690	51	151	8	13.3	0	0	0	I.P.												
		R.Ab.Dig.V	492	67	7.3	6710	64	105	9	11.5	0	Fib.x1	0	I.P.												
47	40	R.Rect.Fem.	517	46	11.2	8720	44	198	7	13.2	0	0	0	I.P.	375	25	15.0	3970	25	159	1	3.8	0	0	0	
48	27	R. Delt.	398	52	7.6	5580	52	107	10	16.1	0	0	0	I.P.												
		R.Ab.Dig.V	239	33	7.2	5080	32	159	3	8.3	0	0	0	I.P.												
49	42	R. Delt.	264	32	8.2	2650	31	85	4	11.1	0	0	0	I.P.												
		R.Ab.Dig.V	286	36	7.9	4430	35	127	4	10.0	0	0	0	I.P.												
50	69	R. Delt.	188	21	8.9	2010	21	96	8	27.6	0	0	0	I.P.												
51	39	R.Rect.Fem.	497	46	10.8	6910	46	150	3	6.1	0	0	0	I.P.												
52	41	R.Rect.Fem.	438	40	10.9	4870	38	128	7	14.9	0	0	0													
53	64	R. Delt.	399	44	9.1	4210	44	96	10	18.5	0	0	0	I.P.												
		R.Ab.Dig.V	325	58	5.6	7190	56	128	4	6.4	0	0	0	I.P.												
54	60	R.Rect.Fem.	394	46	8.6	4060	45	90	10	17.9	0	0	0	I.P.												

I.P. = Interference pattern
M.P. = Mixed pattern
Ind. volt. = Induced voltage.

Appendix Table 5

Control electromyograms: Deltoid.

No.	Age	Sex	Condition	Action Potential Duration			Action Potential Amptitude			Polyphasic potentials		Insertional Activity	Denervation	Silent areas	Maximum effort.
				Total m.sec.	No. of potls.	Mean m.sec.	Total µv.	No. of potls.	Mean µv.	No.	%				
1	27	M	Normal	335	31	10.8	2380	31	77	4	11.4	0	0	0	I.P.*
2	49	F	Myocardial infarct	404	34	11.9	3260	34	96	4	10.5	0	0	0	I.P.
3	43	M	Normal	492	37	13.3	1930	24	80	2	5.1	0	0	0	I.P.
4	43	M	Normal	259	20	12.9	1930	20	96	3	13.0	0	0	0	I.P.
5	67	F	Hiatus hernia	433	34	12.7	2970	34	87	7	17.1	0	0	0	I.P.
6	71	M	Myocardial infarct	261	30	12.0	2850	30	95	7	18.9	0	0	0	I.P.
7	35	F	Thyroid cyst	487	45	10.8	5570	45	124	1	2.2	0	0	0	I.P.
8	32	M	Normal	360	33	11.0	5190	33	157	4	10.8	0	0	0	I.P.
9	38	M	Renal glycosuria	428	36	11.9	3110	36	86	3	7.7	0	0	0	I.P.
10	72	F	Myocardial infarct	461	37	12.5	4590	37	124	4	9.8	Fib. x 2	0	0	I.P.
11	60	M	Cholecystitis	488	35	13.9	4110	35	117	2	5.4	Fib. x 1	0	0	I.P.
12	74	M	Myocardial infarct	506	38	13.3	3470	36	96	6	13.6	0	0	0	I.P.
13	54	F	Stokes Adams attacks	561	42	13.4	3360	42	80	5	10.6	0	0	0	I.P.
14	21	F	Normal	376	30	12.5	2530	30	84	1	3.2	0	0	0	I.P.
15	66	M	Normal	576	47	12.3	5820	47	124	4	7.8	0	0	0	I.P.
16	20	F	Normal	430	35	12.3	3520	35	100	4	10.3	0	0	0	I.P.
17	23	M	Normal	322	28	11.5	2940	28	105	4	12.5	0	0	0	I.P.
18	22	M	Normal	336	29	11.6	5010	27	186	1	3.3	0	0	0	I.P.
19	19	M	Normal	242	23	10.5	4310	23	187	2	8.0	0	0	0	I.P.
20	27	M	Normal	325	31	10.5	4620	31	149	3	8.8	0	0	0	I.P.
21	21	M	Normal	409	39	10.5	4250	39	110	5	11.4	0	0	0	I.P.

*I.P. = Interference pattern.

APPENDIX TABLE 6

Control Electromyograms: Rectus femoris

No.	Age	Sex	Condition	Action potential duration			Action potential amplitude			Polyphasic potentials		Insertional activity	Denervation	Silent areas	Maximum effort
				Total m.sec.	No. of potls.	Mean m.sec.	Total uv.	No. of potls.	Mean uv.	No.	%				
1	22	M	Strep. pharyngitis	342	29	11.8	2690	29	93	2	6.5	0	0	0	I.P.*
2	56	F	Myocardial infarct	385	29	13.3	4930	28	176	1	3.3	0	0	0	I.P.
3	61	M	Myocardial infarct	397	28	14.2	8820	27	327	2	6.7	0	0	0	I.P.
4	72	F	Myocardial infarct	352	26	13.5	2510	26	93	3	10.3	0	0	0	I.P.
5	60	F	Paroxysmal arrhythmia	422	30	14.1	8480	30	283	3	9.0	0	0	0	I.P.
6	43	M	Myocardial infarct	320	25	12.8	4870	25	195	1	3.8	0	0	0	I.P.
7	63	M	Chronic bronchitis	357	25	14.3	2000	23	87	2	7.4	0	0	0	I.P.
8	52	M	Duodenal ulcer	665	48	13.9	6810	48	142	6	11.1	0	0	0	I.P.
9	73	M	Myocardial infarct	282	20	14.1	3190	20	159	1	4.8	0	0	0	I.P.
10	43	M	Normal	581	40	14.5	2670	30	89	5	11.1	0	0	0	I.P.
11	39	F	Normal	236	20	11.8	1970	17	116	3	13.0	0	0	0	I.P.
12	51	F	Normal	430	36	11.9	4850	34	143	3	7.7	0	0	0	I.P.
13	27	M	Normal	482	36	13.4	5040	36	140	5	12.2	0	0	0	I.P.
14	32	M	Normal	429	31	13.8	4580	30	153	4	11.4	0	0	0	I.P.
15	29	M	Normal	481	37	13.0	7640	37	206	0	0	0	0	0	I.P.
16	26	M	Normal	274	25	11.0	4950	29	171	6	17.1	0	0	0	I.P.
17	27	M	Normal	241	21	11.5	2690	21	128	1	4.5	0	0	0	I.P.

*I.P. = Interference pattern.

APPENDIX TABLE 7

Electromyograms: Peak to peak voltage of the interference pattern on maximal effort.

Deltoid						Rectus Femoris					
Thyrotoxic		Euthyroid		Controls		Thyrotoxic		Euthyroid		Controls	
Case No.	Voltage mv.	Case No.	Voltage mv.	No.	Voltage mv.	Case No.	Voltage mv.	Case No.	Voltage mv.	No.	Voltage mv.
11	2.4	11	3.8	1	3.8	2	0.9	2	2.8	1	7.0
30	2.6	12	3.8	2	3.7	5	1.6	4	7.3	2	3.5
35	2.1	13	1.0	5	3.8	7	2.1	5	2.7	3	6.5
37	3.7	14	8.2	6	5.7	16	1.6	6	3.3	4	6.0
45	3.4	17	4.0	8	5.8	34	2.4	7	2.9	5	5.3
48	4.1	18	5.0	9	7.5	36	3.3	8	7.8	6	6.0
49	5.3	19	4.0	10	3.2	39	3.8	10	6.7	7	4.3
50	4.0	20	5.3	11	3.8	40	3.1	16	4.0	8	4.3
53	5.3	22	3.5	12	3.0	41	4.3	21	2.5	9	2.5
		29	3.5	13	4.0	42	2.4	27	3.2	11	1.7
		30	3.8	14	7.7	43	1.7	34	3.5	12	1.9
		31	5.2	15	4.8	44	3.3	39	2.5	13	4.7
		32	5.0	16	4.7	46	2.3	41	4.0	14	3.0
		37	4.8	17	6.0	47	3.0	43	3.8	15	8.3
		38	2.7	19	2.7	51	4.5	44	2.0	16	1.9
		45	4.7			54	1.1				

APPENDIX TABLE 8

Control Electromyograms: Abductor digiti quinti

No.	Age	Sex	Condition	Action Potential Duration			Action Potential Amplitude			Polyphasic Potentials		Insertional Activity	Denervation	Silent Areas	Maximum Effort
				Total m.sec.	No. of Potls.	Mean m.sec.	Total μv.	No. of Potls.	Mean μv.	No.	%				
1	32	F	Pneumonia	326	32	10.2	4,960	32	155	5	13.5	0	0	0	I.P.*
2	43	M	Normal	288	38	7.6	4,050	37	109	6	13.6	0	0	0	I.P.
3	21	F	Normal	377	38	9.9	4,170	38	110	4	9.5	0	0	0	I.P.
4	23	M	Normal	325	41	7.9	6,320	38	166	8	16.3	0	0	0	I.P.
5	22	M	Normal	271	30	9.0	3,920	29	135	4	11.7	0	0	0	I.P.
6	71	M	Myocardial infarct	378	39	9.7	3,774	37	102	7	15.9	0	0	0	I.P.
7	68	M	Myocardial infarct	305	27	11.3	3,861	27	143	3	10.0	0	0	0	I.P.
8	57	F	Peptic ulcer	273	29	9.4	6,757	29	233	2	6.5	0	0	0	I.P.
9	55	M	Myocardial infarct	266	28	9.5	2,800	28	100	3	9.7	0	0	0	I.P.
10	42	F	Cholecystitis	409	47	8.7	16,200	45	360	3	6.2	0	0	0	I.P.
11	43	M	Myocardial infarct	286	34	8.4	5,066	34	149	1	2.9	0	0	0	I.P.
12	26	M	Normal	535	50	10.7	6,600	50	132	4	7.4	0	0	0	I.P.
13	65	F	Myocardial infarct	331	38	8.7	4,484	38	118	4	9.5	0	0	0	I.P.
14	27	F	Normal	336	40	8.4	6,840	40	171	5	11.1	0	0	0	I.P.
15	55	F	Cholecystitis	515	56	9.2	6,490	55	118	9	14.1	0	0	0	I.P.
16	29	F	Normal	353	42	8.4	10,500	42	250	4	8.7	0	0	0	I.P.
17	64	M	Myocardial infarct	270	27	10.0	2,970	27	110	2	6.9	0	0	0	I.P.
18	37	F	Urinary tract infection	391	38	10.3	4,826	38	127	2	5.1	0	0	0	I.P.

*I.P. = Interference Pattern.

APPENDIX TABLE 9

Ulnar Nerve: Latencies and Conduction Velocities in Controls and Thyrotoxic Patients.

Controls					Thyrotoxic Patients			
No.	Age	Condition	Latency Wrist - Abd.Dig. Quinti. m.sec.	Conduction velocity, elbow-wrist. m/sec.	Case No.	Age	Latency Wrist - Abd.Dig. Quinti. m.sec.	Conduction velocity, elbow-wrist. m/sec.
1	32	Pneumonia	3.2	52.1	41	48	2.25	96.5
2	43	Normal	2.8	64.1	42	53	3.8	79.4
3	21	Normal	3.4	64.3	43	60	2.5	47.3
4	23	Normal	2.8	65.2	44	62	2.4	63.9
5	22	Normal	2.5	47.6	45	55	2.7	67.7
6	71	Myocardial infaret	2.3	67.8	46	67	2.3	50.9
7	26	Normal	2.3	72.6	47	40	2.25	51.2
8	68	Myocardial infaret	2.9	58.7	48	27	2.8	59.7
9	65	Myocardial infaret	3.2	42.3	49	42	2.3	58.1
10	57	Peptic Ulcer	2.4	55.8	51	39	2.9	65.9
11	43	Myocardial infaret	2.3	69.7	53	64	2.3	58.7
12	55	Cholecystitis	3.1	59.4	54	60	2.4	45.4
13	37	Urinary infection	2.6	49.5				
14	38	Normal	2.6	57.5				
15	29	Normal	3.4	53.3				

APPENDIX TABLE 10

The Patients: treatment and follow-up

Case No.	Age	Sex	Treatment	Time taken to become Euthyroid Months	Time for Muscular power to return to normal Months	Time for atrophy to disappear Months	Weight increase lb.	Urinary Creatine mg./24hr.	Urinary Creatinine mg./24hr.	Proptosis mm.		Net increase or decrease in Proptosis mm.
										R.	L.	
1	42	F	Carbimazole, iodine and thyroidectomy	2	0	0	8.0	95	880	10	10	+ 2.0
2	48	F	Radioactive iodine	4	1	4	12.5	30	960	21	19	+ 2.5
3	25	F	Carbimazole and l-thyroxine	2	1	1	12.0	270	1230	12	11	+ 1.5
4	47	M	Radioactive iodine	5.5	0	0	13.0	18	820	15	14	- 0.5
5	60	F	Two doses of radioactive iodine, one month's Carbimazole after each.	6	0	0	12.0	129	771	15	15	0
6	22	F	Carbimazole and l-thyroxine	1.0	1.0	4	12.0	90	875	14	13	- 1.5
7	57	F	Carbimazole, guanethidine, iodine and thyroidectomy.	0.5	2	5	6.5			16	16	- 2.0
8	37	M	Carbimazole, then Pot. perchlorate, thyroidectomy.	3	0	0	28.0	50	1000	16	14	+ 0.5
9	53	M	Radioactive iodine	4	0	0	13.0	60	1420	19	17	+ 1.0
10	38	F	Carbimazole, l-thyroxine, iodine and thyroidectomy.	2.5	2.5	4.75		120	1130	14	14	0
11	50	F	Radioactive iodine	4		4	17.0	60	1410	17	16	+ 0.5
12	48	F	Radioactive iodine	3.25	3.25	3.25	0	232	1088	14	14	+ 1.0
13	32	M	Carbimazole, l-thyroxine, iodine and thyroidectomy.	1	0	1	10.0			20	17	- 2.0
14	26	F	Carbimazole and l-thyroxine	3	0	0	5.0	40	1125	16	14	+ 1.5
15	64	M	One dose of radioactive iodine, followed by Carbimazole for one month. Remission for 3 months, then relapse, treated insimilar fashion.	3	3	3	41.5			14	14	+ 0.5
16	50	F	Radioactive iodine and Carbimazole for one month.	1	3	3	16.5	20	1210	15	14	- 0.5
17	69	F	Radioactive iodine and Carbimazole for 6 weeks.	2.5	2.5	2.5	12.0	24	762	15	16	+ 1.5

Appendix Table 10 continued.

Case No.	Age	Sex	Treatment	Time taken to become Euthyroid Months	Time for Muscular power to return to normal Months	Time for atrophy to disappear Months	Weight increase lb.	Urinary Creatine mg./24hr.	Urinary Creatinine mg./24hr.	Proptosis mm. R.	Proptosis mm. L.	Net increase or decrease in Proptosis mm.
18	64	M	Carbimazole, l-thyroxine, iodine and thyroidectomy.	1.5	1.5	0	41.0	100	1720	17	17	+ 1.0
19	66	F	Radioactive iodine	3	3	3		248	821	16	13	+ 1.5
20	39	F	Carbimazole, l-thyroxine, iodine, thyroidectomy.	2	2	0	31.0	50	1430	14	13	+ 0.5
21	70	F	Carbimazole, l-thyroxine	1.75	1.75	1.75	15.0	114	775	15	12	+ 1.5
22	38	M	Carbimazole, l-thyroxine, iodine, thyroidectomy.	3	1	6	18.5			17	16	0
23	53	F	Radioactive iodine	4	0	0	18.0			14	12	+ 2.0
24	56	M	Two doses of radioactive iodine	1.5 (after 1st dose)	1.5	1.5	18.0			18	18	+ 5.0
25	55	M	Carbimazole, l-thyroxine	1.75	0.75	0	12.0	20	1726	22	23	+ 1.0
26	52	F	Radioactive iodine	2	2	2						
27	55	M	Radioactive iodine			0	21.0	60	1640	13	12	+ 1.5
28	35	F	Carbimazole, l-thyroxine, iodine, thyroidectomy.	3	1	3						
29	53	F	Radioactive iodine and Carbimazole for 7 weeks.	0.75	3	0.75	36.0	57	1040	13	13	- 0.5
30	49	M	Radioactive iodine and Carbimazole for 2 months.	2	2	2	21.0	40	1430	14	16	0
31	50	F	Carbimazole, l-thyroxine	0.75	0	0	20.0	38	946	16	18	+ 3.0
32	52	F	Radioactive iodine, carbimazole for one month.	1	1	0	17.0	24	1008	15	15	0
33	28	F	Carbimazole, l-thyroxine	4	4	0	7.5			15	15	+ 2.0
34	31	F	Carbimazole, l-thyroxine	1.5	1.5	0	6.0			12	12	- 2.0
35	15	F	Carbimazole, l-thyroxine	1	0	0	15.0			19	18	+ 1.5
36	48	F	Radioactive iodine	2.75	5	0				11	11	- 0.5

Appendix Table 10 continued.

Case No.	Age	Sex	Treatment	Time taken to become Euthyroid Months	Time for Muscular power to return to normal Months	Time for atrophy to disappear Months	Weight increase lb.	Urinary Creatine mg./24hr.	Urinary Creatinine mg./24hr.	Proptosis mm.		Net increase or decrease in Proptosis mm.
										R.	L.	
37	36	M	Carbimazole, l-thyroxine, iodine, thyroidectomy.	3.75	3.75	0	17.0	40	1190	17	16	+ 1.5
38	58	F	Radioactive iodine and carbimazole for one month	1	3.5	3.5	10.0	66	1067	16	13	+ 2.0
39	25	F	Carbimazole, l-thyroxine	1	0	0	11.0	36	964	17	15	+ 1.0
40	65	F	Radioactive iodine and carbimazole for one month.	2.25	2.25	2.25	11.0					
41	48	F	Radioactive iodine and carbimazole for six weeks	1	1	0	19.0	310	1420	17	16	+ 0.5
42	53	F	Radioactive iodine and carbimazole for six weeks. Relapse one month later.	1	1	2						
43	60	F	Radioactive iodine and carbimazole for one month.	1	4.25	2	19.0	64	783	15	14	+ 1.0
44	62	F	Radioactive iodine and carbimazole for one month.	1.5	3	3	13.0			23	22	0
45	55	F	Radioactive iodine and carbimazole for one month.	1.25	1.25	5	16.5	90	1230	18	16	+ 1.5
46	67	F	Radioactive iodine and carbimazole for one month.	1	0	1	20.0			14	14	+ 2.5
47	40	F	Carbimazole, l-thyroxine, iodine and thyroidectomy.	1.25	2.25	1.25	21.0	50	1130	12	11	+ 1.5
48	27	M	Carbimazole, l-thyroxine, iodine and thyroidectomy.	2	2	2	37.0			16	16	- 1.0
49	42	M	Carbimazole	Being treated privately.								
50	69	F	Carbimazole, iodine, thyroidectomy. Atrial fibrillation removed with D.C. de-fibrillator.	1.25	4	4	6.0			12	10	+ 1.0
51	39	F	Carbimazole, l-thyroxine	1.5	1.5	0						
52	41	F	Carbimazole, l-thyroxine	1	1	0				15	15	+ 2.0
53	64	F	Radioactive iodine, carbimazole for 7 weeks. Atrial fibrillation converted with D.C. de-fibrillator.	2	1	0						
54	60	F	Radioactive iodine	3	3	3						

APPENDIX TABLE 11

Data on the extent of muscle involvement in thyrotoxicosis, weight loss and the deviation of the observed mean action potential duration from the predicted.

Atrophy and/or weakness								
Proximal and distal muscles			Proximal muscles only			None		
Case No.	Wt. loss lb.	Deviation m.sec.	Case No.	Wt. loss lb.	Deviation m.sec.	Case No.	Wt. loss lb.	Deviation m.sec.
6	18	3.5	2	18	5.1	1	7.5	3.3
7	19	3.5	3	7	2.8	4	3	3.4
15	19	3.5	10	20	4.4	5	14	5.2
19	46	5.7	11	14	4.5	8	35	0.9
24	21	4.9	12	12.5	4.7	9	9	2.7
28	32	5.0	13	20	4.2	14	20	2.9
43	29	5.8	16	23	3.5	23	6	2.9
44	9	4.9	17	16	5.8	31	18	1.5
47	21	1.7	18	13	4.5	35	3	3.3
49	7.5	3.8	20	21	4.8	39	8	2.1
			21	14	5.3			
			22	28	3.4			
			25	0	3.1			
			26	18	4.7			
			27	6	2.6			
			29	18	4.6			
			30	21	3.2			
			32	16	2.0			
			33	6	5.5			
			34	17	2.6			
			36	5	3.3			
			37	21	1.6			
			38	17	7.1			
			40	35	3.1			
			41	18	4.9			
			42	27	5.3			
			45	9	1.0			
			46	35	3.4			
			48	42	3.7			
			50	21	4.4			
			51	8	2.0			
			52	11	2.0			
			53	9	4.0			
			54	32	5.1			

APPENDIX TABLE 15

Deltoid and Rectus femoris

Deviations of the observed mean action potential duration from the predicted in thyrotoxic patients with and without clinical weakness of the sampled musele.

Deltoid				Rectus femoris			
Deviation m. sec.				Deviation m. sec.			
Case No.	Weakness present	Case No.	Weakness absent	Case No.	Weakness present	Case No.	Weakness absent
10	4.4	1	3.3	2	5.1	5	5.2
11	4.5	4	3.4	6	3.5	8	0.9
12	4.7	13	4.2	7	3.5	9	2.7
15	3.5	14	2.9	21	5.3	23	2.9
17	5.8	20	4.8	43	5.8	27	2.6
18	4.5	22	3.4			28	5.5
19	5.7	25	3.1			34	2.6
24	4.9	26	4.7			36	3.3
28	5.0	31	1.5			39	2.1
29	4.6	32	2.0			40	3.1
30	3.2	35	3.3			41	4.9
38	7.1	37	1.6			42	5.3
45	1.0	48	3.7			46	3.4
49	3.8	53	4.0			47	1.7
50	4.4					51	2.0
						52	2.0
						54	5.1

APPENDIX TABLE 14

Relationship between serum protein bound iodine and the deviation of the observed mean action potential duration from the predicted. (m.sec.)

Case No.	Serum P.B.I. µg. %	Deviation of observed from predicted
5	10.8	5.2
8	13.4	0.9
9	10.6	2.7
10	15.0	4.4
11	9.7	4.5
12	13.1	4.7
14	9.5	2.9
15	13.1	3.5
17	12.1	5.8
19	11.3	5.7
23	12.6	2.9
24	10.7	4.9
25	10.4	3.1
26	9.5	4.7
27	9.9	2.6
29	11.6	4.6
30	15.0	3.2
31	7.2	1.5
35	13.0	3.3
36	8.9	3.3
37	13.0	1.6
38	11.4	7.1
40	11.0	3.1
41	6.4	4.9
42	13.8	5.3
43	15.0	5.8
44	7.7	4.9
45	11.0	1.0
50	8.8	4.4
53	14.0	4.0
54	14.6	5.1

APPENDIX TABLE 13

Rectus femoris: Thyrotoxic patients

Data on duration of thyrotoxicosis, weight loss and the deviation of the observed mean action potential duration from the predicted.

No.	Age Years	Duration of thyro-toxicosis Months	Weight loss lb.	Deviation of action potential duration m. sec.
2	48	4.0	18	5.1
5	60	2.0	14	5.2
6	22	12.0	18	3.5
7	57	20.0	19	3.5
8	37	12.0	35	0.9
9	53	3.0	9	2.7
16	50	8.0	23	3.5
21	70	3.0	14	5.3
23	53	4.0	6	2.9
27	55	5.0	6	2.6
33	28	1.25	6	5.5
34	31	8.0	17	2.6
36	48	4.0	5	3.3
39	25	9.0	8	2.1
40	65	4.0	35	3.1
41	48	3.0	18	4.9
42	53	6.0	27	5.3
43	60	5.0	29	5.8
44	62	7.0	9	4.9
46	67	3.0	35	3.4
47	40	12.0	21	1.7
51	39	9.0	8	2.0
52	41	9.0	11	2.0
54	60	24.0	32	5.1

APPENDIX TABLE 12

Deltoid: Thyrotoxic Patients

Data on duration of thyrotoxicosis, weight loss and the deviation of the observed mean action potential duration from the predicted.

No.	Age Years	Duration of thyro-toxicosis Months	Weight loss lb.	Deviation of action potential duration m. sec.
1	42	3	7.5	3.3
4	47	1.75	3	3.4
10	38	8	20	4.4
11	50	6	14	4.5
12	48	6	12.5	4.7
13	32	8	20	4.2
14	26	11	20	2.9
15	64	2.5	19	3.5
17	69	2	16	5.8
18	64	3	13	4.5
19	66	4	46	5.7
20	39	8	21	4.8
22	38	5	28	3.4
24	56	3	21	4.9
25	55	12	0	3.1
26	52	1.5	18	4.7
28	35	3	32	5.0
29	53	1.75	18	4.6
30	49	4	21	3.2
31	50	6	18	1.5
32	52	4	16	2.0
35	15	0.5	3	3.3
37	36	1.25	21	1.6
38	58	4	17	7.1
45	55	11	9	1.0
48	27	4	42	3.7
49	42	24	7.5	3.8
50	69	24	21	4.4
53	64	3	9	4.0