

Thyrotoxic muscle disease

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Summary

Evidence suggests that most hyperthyroid patients have a proximal myopathy. The more severe this is the more frequently are distal muscles, and ultimately, bulbar muscles involved. Probably acute thyrotoxic myopathy or encephalopathy supervenes on a previous chronic background or occurs concurrently with skeletal muscle involvement. Using careful electromyographic techniques evidence of myopathy may be found in most thyrotoxics; it disappears with adequate treatment of the primary disease.

Myasthenia gravis and periodic paralysis are also associated with thyrotoxicosis and their differentiation is discussed. Infiltrative ophthalmopathy is not related to the effects of excess thyroid hormone, but is possibly due to EPS working in conjunction with LATS.

Introduction

Although muscular weakness was recognized by both Graves (1835) and Basedow (1840) as a symptom of hyperthyroidism and the first case of thyrotoxic muscular atrophy was described in 1885 by Du Cazal (Sattler, 1952), the syndrome of thyrotoxic myopathy was thought to be extremely rare (Waldenström, 1945; Whitfield & Hudson, 1961). Only seventy-three cases could be found in the literature between 1895 and 1962 (Ramsay, 1964). Recent work, however, suggests that muscular involvement may be present in the majority of thyrotoxic patients (Havard *et al.*, 1963; Satoyoshi *et al.*, 1963a; Ramsay, 1966).

In 1945 Waldenström reviewed a group of patients who had presented with acute muscular weakness involving particularly the bulbar muscles. Since then there has been argument as to whether these patients had acute thyrotoxic myopathy or encephalopathy or whether they had myasthenia gravis (Millikan & Haines, 1953). An attempt will be made in this review to show that there is probably one primary muscle disorder of hyperthyroidism, of varying severity, to which occasionally the effects of other diseases such as

myasthenia gravis and periodic paralysis may be added.

Chronic thyrotoxic myopathy

Seventy-three cases of marked muscular atrophy and weakness associated with hyperthyroidism which were reported in the literature between 1895 and 1962 have been analysed (Ramsay, 1964).

Clinical features

The mean age of presentation of cases of chronic thyrotoxic myopathy was 47.7 years with no significant sex difference. The age range was 20-69 years for males and 11-70 for females. The women had longer histories of thyrotoxicosis than the men, an average of 25.3 months compared with 11.3 months, and they had also noticed myopathic symptoms for a longer period of time (22.5 months and 11.1 months). The mean weight loss was rather similar, being 16.6 kg for males and 15.1 kg for females.

Proximal muscles alone were affected by weakness and/or wasting in 49.3% of the cases. In 34.3% proximal and distal muscles were involved, and in the remaining 16.4% there was generalized muscle disease involving also bulbar muscles. There was no significant difference between the sexes as to the groups of muscles picked out by the myopathic process.

In 23% of the patients the muscle lesion was the presenting complaint. In most of the rest, however, the onset of muscle symptoms was concurrent with those of hyperthyroidism. 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 experienced great fatigue even while walking along the level, while a few just experienced generalized weakness.

Two patients (Sanderson & Adey, 1952; Millikan & Haines, 1953) had had cramps in their legs, while Hoffenburg & Eales (1956) described a man with pain and stiffness in his muscles and contractures, and muscular aching was a feature noted by Whitfield & Hudson

(1961) in one patient. In the patients with bulbar involvement difficulty in speaking was the most common symptom and consisted of dysphonia, hoarseness and weakness of speech or an alteration in the quality of the voice. Dysphagia was the second commonest source of trouble 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 were unlikely to have been seen since fibrillation consists of the contraction of individual muscle fibres and cannot be seen through the skin (Thomas, 1963). McEachern & Ross (1942) and Kite, McLintock & Graves (1954) postulated that the 'fasciculations' in the thyrotoxics were due to an undue sensitivity of the motor end-plate in a state of abnormal metabolism. Harman & Richardson (1954) considered that in many of these patients the phenomenon observed was, in fact, myokymia, a type of movement which may occur in normal people, especially under conditions of fatigue. It is seen 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. Electromyographic studies show that nerve excitability is increased, but that there is no evidence of a lower motor neurone lesion.

However, if these findings in cases recorded as 'chronic thyrotoxic myopathy' are compared (Table 1) with the findings in unselected thyro-

TABLE 1

A comparison between seventy-three patients with chronic thyrotoxic myopathy and fifty-four unselected thyrotoxics (Ramsay, 1964)

	Seventy-three 'chronic thyrotoxic myopathy' patients	Fifty-four unselected thyrotoxics
Mean age (years)	47.7	47.9
Male/female ratio	38 : 35	14 : 40
Mean duration of thyrotoxic symptoms (months)	18.5	6.6
Mean duration of weakness (months)	16.4	5.0
Mean weight loss (kg)	15.9	8.0
Ophthalmoplegia (%)	6.2	7.4
Muscles affected:		
Proximal alone (%)	49.3	63
Proximal and distal (%)	34.3	18.5
Generalized and bulbar (%)	16.4	0

toxics (Ramsay, 1966) it can be seen that the differences are ones of degree only. The mean age at presentation is virtually the same. The pro-

portion of men in the reported cases is higher than would normally be expected in an unselected group of thyrotoxics, but this can probably be explained by the importance of normal muscle-power in enabling a man to perform his job. Half of the patients in the author's series (Ramsay, 1966) had a history of some muscle weakness. The majority complained of difficulty in walking upstairs, while the remainder had noticed principally arm weakness. The women among them had noticed great fatigue in trying to comb their hair. The men who were engaged in manual labour had noticed a decline in their ability to lift heavy objects and often required assistance for tasks they had previously been able to manage alone. There were no symptoms suggestive of bulbar muscle weakness.

The onset of typical thyrotoxic symptoms was the presenting feature in 79.6% of the author's patients. In 3.7% weakness was the first symptom noted and in 16.7% this was concurrent with thyrotoxic symptoms. No sex differences were discernible in any of the three groups and in the patients with weakness, the duration of this symptom was much the same as that of the general features of thyrotoxicosis.

As can be seen in Table 1, 63% had proximal muscle involvement, usually weakness and wasting, occasionally weakness without atrophy, rarely atrophy without weakness (two patients). Distal muscles in addition to the proximal ones were affected in 18.5%. No bulbar weakness was detected and in 18.5% the skeletal were judged to be clinically normal. There was no variation in the findings between the two sexes, nor was there any age difference between those who had and those who had not muscle involvement. An analysis of the muscles involved showed that muscles of the shoulder girdle were more often affected than those of the pelvic girdle and that extensors were involved twice as commonly as flexors. Havard *et al.* (1963) noted in their fifty thyrotoxic patients that the muscles most commonly involved were the deltoid, the supraspinatus and the quadriceps.

Table 2 compares the incidence of weakness in the seventy-three patients reported as 'chronic myopathy' with six series of hyperthyroid patients. It can be seen that even in unselected thyrotoxic patients weakness may be the presenting feature, that it is a symptom in about a third to a half of cases and that it may be detected clinically in 60-80%. The figures are remarkably uniform in the unselected groups considering that the patients are drawn from Switzerland, Britain and Japan.

Tendon reflexes were unremarkable in the

TABLE 2

A comparison of the symptoms and signs of weakness in seventy-three patients with chronic thyrotoxic myopathy and in several series of unselected thyrotoxic patients

Series	No. of patients	Weakness as the presenting complaint (%)	Weakness as a symptom (%)	Weakness clinically (%)
Recorded cases of myopathy (see above)	73	23	100	100
Pipberger, Kålin & Wegmann (1955)	13		61.5	69.2
Gimlette (1959)	40		32.5	60
Havard <i>et al.</i> (1963)	50	6	34	80
Satoyoshi <i>et al.</i> (1963a)	240			61
Ramsay (1965, 1966)	54	3.7	50	81.5

thyrotoxic myopathy patients. As nearly an equal number were hyperactive as were diminished and in a small number of cases they were absent. In a series of ordinary thyrotoxic patients (Ramsay, 1966) the reflexes were considered to be normal in 53.7%, brisk in 42.6% and reduced in 3.7%. Sensory abnormalities have not been described.

Prostigmine or edrophonium testing

Prostigmine or edrophonium (Tensilon) was given to twenty-seven of the cases of chronic myopathy described in the literature. No increase in power was noticed in twenty-four instances and it produced a good response in only one patient (McEachern & Ross, 1942) and a slight response in a further two (Sanderson & Adey, 1949; Melville, 1959). Havard *et al.* (1963) assessed muscular strength in forty-nine thyrotoxics before and 30 min after 1.5 mg of intramuscular neostigmine. Forty-three patients showed no increase in power, though six were thought to be stronger. Ramsay (1966) found no significant difference in the length of time for which thyrotoxic subjects could maintain their legs at an angle of 45 degrees to the horizontal before and after the intravenous injection of edrophonium chloride.

Biochemistry

Apart from the usual indices of hyperthyroidism there have been no constant biochemical features either in patients reported on as having myopathy or in unselected thyrotoxics. Generally speaking there is normocalcaemia, though a few have slightly elevated values, and normal levels of serum potassium, sodium and chloride (Satoyoshi *et al.*, 1963a, b; Ramsay, 1964). Satoyoshi and his colleagues (1963a, b) found that muscle cell potassium was reduced and sodium increased and noted a strong positive correlation between intracellular potassium levels and muscle strength.

Other workers, however, have denied a decrease in muscle cell potassium and the matter is not yet resolved (Staffurth & Thompson, 1965; Shishiba *et al.*, 1966).

Creatine and creatinine metabolism

Creatine is synthesized in the liver from glycoylamine which originates in the kidneys. It is then taken up by the muscles and converted by phosphocreatine kinase into phosphocreatine. Phosphocreatine is necessary for normal muscle contraction, its probable role being in the immediate resynthesis of adenosine triphosphate (ATP) by the transfer of a phosphoryl group to adenosine diphosphate. Satoyoshi and his co-workers (1963a, b) found significantly reduced muscle creatine, phosphocreatine and ATP in thyrotoxics and showed that there was a correlation between muscle ATP concentrations and muscular strength. Phosphocreatine in muscle may be lowered because of the inhibiting effect of thyroxine on phosphocreatine kinase (Askonas, 1951) or because a normal intracellular potassium may be necessary for its formation (Grob, Liljestrand & Johns, 1957).

Because the degenerating muscle is unable to store the creatine the serum level rises (Kuhlback, 1957; Satoyoshi *et al.*, 1963a), the renal threshold is exceeded and urinary excretion increases. It follows from this that thyrotoxic patients have a reduced tolerance to ingested creatine (Thorn & Eder, 1946; Wilkins & Fleischmann, 1946). Urinary creatine is virtually absent in normal adult males, though values of up to 50 mg/day may be found in women (*Documenta Geigy*, 1962). In thyrotoxics with and without obvious myopathy the excretion is generally raised, though the high levels in serum and urine may be reduced, usually within one day, by the administration of potassium chloride (Satoyoshi *et al.*, 1963a, b).

Creatine is broken down to creatinine by an-

hydration, so it is not surprising that the amount of creatinine found in the urine of hyperthyroid patients is usually diminished. It must be emphasized, however, that the increased urinary excretion of creatine and the diminished excretion of creatinine are not specific for thyrotoxicosis, but occur in other sorts of muscular dystrophies and myopathies and are found in normal old age (Zierler, 1951). Moreover, in some patients with thyrotoxic myopathy there is no significant creatinuria (Zierler, 1951). This has been explained by Hoch (1962) as being due to a failure of synthesis. In the liver ATP is required for the transfer of a methyl group from methionine to glycocyamine in order to form creatine (Kuhl-bäck, 1957).

Muscle enzymes

Aldolase, lactic dehydrogenase and total thiamine were found to be decreased in thyrotoxic muscle (Satoyoshi *et al.*, 1963a). Phosphocreatine kinase also tended to be lower than in controls and to be significantly increased in the serum. The amounts of free thiamine and glutamic oxaloacetic transaminase were normal.

Electromyography

Sanderson & Adey (1949, 1952) were the first to describe electromyographic abnormalities in chronic thyrotoxic myopathy, namely a significant reduction in mean action potential duration, low voltage of the motor unit potentials and an increased incidence of polyphasic potentials. Millikan & Haines (1953) found normal electro-

myograms (EMGs), though since their report Boström & Hed (1958), Hed, Kirstein & Lundmark (1958), Whitfield & Hudson (1961) and Havard (1962) have all reported typical myopathic patterns in their patients with clinical thyrotoxic myopathy.

Since 1955 seven series of thyrotoxic patients have been studied electromyographically and the results are summarized in Table 3. Most of the previously published papers have given quantitative estimations of the electromyographic findings in thyrotoxicosis, and so the results are subject to observer error. This may explain the normal EMGs in the patients of Millikan & Haines (1953). If, however, a quantitative method of electromyography is used (Ramsay, 1965; Yates, 1965) in which twenty to twenty-seven different areas in each muscle are sampled and the mean action-potential duration is compared to the normal for that patient's age, then a higher degree of accuracy may be achieved. By this method 92.6% of Ramsay's (1965) patients were shown to have evidence of a myopathy in proximal muscles and 42.9% in distal muscles also.

Fig. 1(a) and (b) show the shortened mean action potential duration in thyrotoxic patients compared to controls and the return towards normality on re-testing 4 months after the patients had become euthyroid. In addition the thyrotoxic patients had a significantly higher percentage of polyphasic potentials than the controls, with again a return to normality after treatment had been effective. Havard *et al.* (1963)

TABLE 3
Reports of electromyograms (EMGs) done on thyrotoxic patients

	No. of patients	EMG evidence of myopathy (%)	Characteristic EMG features
Pipberger <i>et al.</i> (1955)	13	92.3	Shortening of action potentials, increase in polyphasicity, decrease in amplitude. Normal interference pattern.
Hed <i>et al.</i> (1958)	17	100	In areas sampled 75–100% of potentials were of short duration or polyphasic. 'Dense' or 'scanty' interference pattern.
Gimlette (1959)	40		'Myopathic' pattern in the majority.
Havard <i>et al.</i> (1963)	50	88	Motor units either polyphasic or shorter than normal.
Satoyoshi <i>et al.</i> (1963b)	39	61.5	Unspecified.
Yates (1963, 1965)	10	70	Shortened action potential duration.
Ramsay (1965)	54	92.6	Statistically significant reduction in action potential duration and increase in percentage polyphasicity.

and Yates (1965) noted normal EMGs in their patients following clinical recovery. Fibrillation was very rarely, and fasciculation never, found (Havard *et al.*, 1963; Ramsay, 1966). Both the patients with fibrillation potentials reported by Hed *et al.* (1958) probably had a lower motor neurone lesion.

severity of the thyrotoxicosis and the degree of EMG change.

Nerve conduction

No abnormalities in nerve conduction were found in thyrotoxics (Ramsay, 1965), though demyelination and vacuolization of minor nerves (Hed *et al.*, 1958), terminal sprouting of nerve fibres (Coërs & Wolf, 1959), and swelling and beading of terminal nerve fibres (Havard *et al.*, 1963) have been described histologically.

Muscle pathology

Askanazy (1898) was the first to describe changes in the muscles of thyrotoxic patients. 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 & Urquhart, 1926; Morgan & Williams, 1940; Bartels & Pizer, 1944; Quinn & Worcester, 1951; Boström & Hed, 1958; Havard, 1962; Satoyoshi *et al.*, 1963a), but in addition aggregations of lymphocytes, or lymphorrhages, have been noted (Dudgeon & Urquhart, 1926; Liechti, 1938; Thorn & Eder, 1946; Hed *et al.*, 1958; Whitfield & Hudson, 1961). Devic *et al.* (1947) described an alteration of the mitochondria in the region of the motor end-plates and degeneration of muscle mitochondria has recently been observed by Engel (1966) who also noted alterations of the cell surface and of the transverse tubular system.

Coërs & Wolf (1959), using an intravital staining technique, found changes in the terminal nerve fibres, mainly profuse distal sprouting, often with the formation of multiple end-plates on single muscle fibres. Havard *et al.* (1963) described diffuse axonal swelling with multiple beading, rounded or oval swellings of the terminal axon and clubbing of the end-plate. However, since neither Coërs & Wolf (1959) nor Havard *et al.* (1963) published adequate control data, it is difficult to assess the significance of their findings.

Hed *et al.* (1958) noticed the presence in the muscle tissue of iron-loaded phagocytes. The subsarcolemmal semilunar accumulations of metachromatic substance observed by Asboe-Hansen, Iversen & Wichmann (1953) in thyrotoxics, but most markedly in those with progressive exophthalmos, have been confirmed by Kirchheiner (1962). This phenomenon can only be seen in

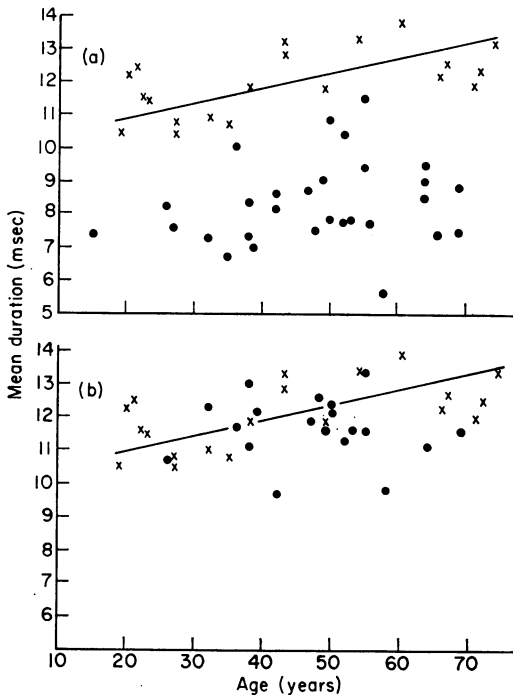


FIG. 1. (a) Deltoid EMGs. Graph showing the relationship between age and mean action potential duration in control subjects (X) and the shortening of the mean action potential duration in thyrotoxic patients (●). (b) Deltoid follow-up EMGs. Graph showing a return to a normal action potential duration in the majority of the euthyroid patients (●). (Reproduced by kind permission of the Editors of the *Quarterly Journal of Medicine*.)

The shorter action potential duration in myopathies does not occur in disuse atrophy (Buchthal, 1957) and has been attributed to a decrease in the number of fibres in each sub-unit (Buchthal & Rosenfalck, 1963). Since the EMGs return to normal in thyrotoxicosis after treatment it seems likely that the myopathy is due to a reversible decrease in *functioning* muscle fibres. Havard *et al.* (1963) found a reasonable correlation between muscle weakness and electromyographic findings and this was confirmed quantitatively by Ramsay (1964, 1965) who also found no relationship between the duration or

muscles which have been fixed in basic lead acetate; this precipitates acid mucopolysaccharides (Iverson, Asboe-Hansen & Carlsen, 1953).

There have also been quite frequent reports of normal histological findings in patients with thyrotoxic myopathy (Morgan & Williams, 1940; Sanderson & Adey, 1949; Millikan & Haines, 1953; Kite *et al.*, 1954; Collings & Lienhard, 1957) and this has been confirmed in a recent series of thyrotoxic patients by Havard *et al.* (1963), though some abnormalities were found in 23.3% and 68% of their cases, respectively, by Ramsay (1966) and by Satoyoshi *et al.* (1963a, b). The Japanese workers found that when thyrotoxic symptoms were present for less than a year abnormalities were present in 50% of cases, but rose to 85% if the patients had been ill for longer than 1 year. There was, however, no correlation between the muscle biopsy findings and the severity of the thyrotoxicosis.

Ramsay (1964) used a muscle-biopsy technique designed to prevent distortion of the muscle architecture (Buchthal, Guld & Rosenfalck, 1955). Muscle-fibre diameters were measured with a micrometer gauge and it was found that the mean diameter was 12 μ smaller than in the controls. The apparent increase in the number of sarcolemmal nuclei, described by many authors, was attributed to the reduction in diameter of the fibres and their closer crowding together, for, on cross-section a normal number of nuclei was seen (Ramsay, 1966).

Muscle pathology similar to that described in thyrotoxic myopathy has been found by Dudgeon & Urquhart (1926) in the extrinsic eye muscles of patients suffering from malignant exophthalmos and it has been observed that these changes could be produced by an anterior pituitary extract in thyroidectomized guinea-pigs (Paulson, 1939; Dobyons, 1946). Recent work (Kinderen, 1967) has isolated this pituitary factor and it has been called exophthalmos producing substance (EPS). The role of long-acting thyroid stimulator (LATS) in the eye changes of thyrotoxicosis is not yet clear (Pimstone, Hoffenberg & Black, 1964), though Kinderen (1967) thinks that it may act as a facilitator in the presence of EPS. It may well be that the histological changes seen in thyrotoxicosis are nothing to do with the myopathy *per se*, but are caused by either EPS or LATS, for whereas the myopathy remits with the achievement of euthyroidism, the concentration of the latter two substances may remain elevated in the serum.

Prognosis

Two of the earlier cases in the literature

(McEachern & Ross, 1942; Morgan & Williams, 1940) died of respiratory paralysis, but it is likely that their patients had myasthenia gravis (Millikan & Haines, 1953). A patient of Thorn & Eder (1946) with some evidence of bulbar involvement succumbed. Three of Devic *et al.*'s (1947) patients died following thyroidectomy, but apart from one patient (Hed *et al.*, 1958) who died of an unrelated disease, not a single death in a patient with chronic thyrotoxic myopathy has been reported since 1947. This reflects the introduction of more effective treatment for hyperthyroidism in the last 25 years. Full recovery of muscle strength was noted in fifty-three of the reports in the literature and full power returned in 100% of thyrotoxic patients in recent series (Havard *et al.*, 1963; Satoyoshi *et al.*, 1963a; Ramsay, 1964, 1966). Muscle power became normal in about the same time as it took for the patients to become euthyroid after the start of treatment although atrophy took significantly longer to disappear (Ramsay, 1966). Creatine and creatinine excretion returned to normal (Ramsay, 1966) as did electromyograms (Havard *et al.*, 1963; Coomes, 1965; Ramsay, 1965; Yates, 1965).

Aetiology of myopathy

Three factors have to be considered as possible causes of thyrotoxic muscle dysfunction. They are thyroid stimulating hormone (TSH), LATS and the thyroid hormones (triiodothyronine and thyroxine). Although TSH stimulates the normal thyroid to produce hormone, its production by the anterior pituitary is usually suppressed in thyrotoxicosis (Lemarchand-Béraud, Vanotti & Scazziga, 1967; Blum *et al.*, 1967). LATS has been shown to be present in up to 90% of thyrotoxic patients (Blum *et al.*, 1967), and it seems likely, in at least the majority of instances of Graves' disease, that this γ -globulin is responsible for the excessive thyroid stimulation. Since LATS may persist after the successful control of thyrotoxicosis, though the myopathy always remits, one is left with the conclusion that thyroid hormone is responsible for the muscle lesion.

The mode and site of action of thyroid hormone has recently been reviewed (Hoch, 1962, 1968; Tapley, 1964; Parsons & Ramsay, 1968). Most of the evidence points to the mitochondrial membrane as being primarily involved, for experimentally physiological concentrations of thyroxine can be shown to cause mitochondrial swelling (Tapley, 1964). Mitochondrial alteration (Devic *et al.*, 1947) and degeneration (Engel, 1966) have been seen in muscle from thyrotoxic patients. Mitochondria are important in muscle

metabolism because they contain the mechanisms of oxidative phosphorylation and the production of the high-energy phosphate bonds of adenosine triphosphate (ATP). The muscles most affected by weakness in thyrotoxicosis are the proximal ones, particularly the extensors; these rely to a much greater extent on mitochondrial mechanisms as a source of energy than do the distal muscles, served largely by anaerobic glycolysis (Ramsay, 1966). Hoch (1962) has summarized the evidence that thyroxine produces 'uncoupling' of the reaction which transforms oxidative to phosphorylative bond energy, the net result being a decrease in the production of high-energy bonds and the dispersion of energy as heat. Chappell & Greville (1958) have shown that thyroxine-induced swelling of mitochondria can be reversed by the addition of ATP. Satoyoshi and his colleagues (1963a) found a decreased amount of ATP in thyrotoxic muscles and demonstrated a relationship between this and the muscular strength of their patients.

Other factors probably play a part in the decreased production of ATP. Phosphocreatine kinase is inhibited by excess thyroxine (Askonas, 1951) and thus phosphocreatine, which normally donates a phosphoryl group to adenosine diphosphate, is synthesized in diminished amounts. Cell potassium depletion also adversely affects the manufacture of phosphocreatine (Grob *et al.*, 1957; Satoyoshi *et al.*, 1963a).

Another result of ATP-lack is a breakdown in the energy-dependent control of membrane permeability. As a result water and sodium may enter the muscle cell and potassium and enzymes may leave it (Satoyoshi *et al.*, 1963a, b). Certainly Green & Matty (1962), using thyroxine, were able to demonstrate an increase in membrane permeability to water. Staffurth & Thompson have recently (1965) found an increase in muscle cell water in patients with thyrotoxic myopathy, but were unable to demonstrate a drop in the potassium content. Although the effect of thyroxine on mitochondria seems to be important in producing the weakness, other mechanisms may play a part. For instance, Engel (1966), in electron-microscopic studies, has shown that there are alterations of the muscle-cell surface and of the transverse tubular system which may be important in the local activation of striated muscle fibre (Huxley & Taylor, 1958).

The metabolically inefficient muscle fibres are not capable of proper contraction and they atrophy. This leads to a decrease in the number of *functioning* fibres in each motor unit and probably explains the reduction in mean action potential duration and the increased number of

disintegrated or polyphasic potentials seen in the EMGs of thyrotoxic patients (Ramsay, 1965). The fact that muscle strength returns so quickly following treatment and that the EMGs become normal suggests that the myopathy is essentially metabolic in nature rather than structural.

Acute thyrotoxic myopathy

Acute thyrotoxic myopathy will be considered together with encephalopathy, because both titles seem to be ascribed to the same clinical situation by different authors. The first papers in English on the acute paresis of thyrotoxicosis were by Laurent (1944), Waldenström (1945), Sheldon & Walker (1946) and Strong (1949). However, Waldenström, in addition to describing his own ten cases, quoted a large number of patients with similar features which had been gathered 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 also been described in subsequent case-reports (Chapman & Maloof, 1956; Gimlette, 1959; Heinrich *et al.*, 1962). Eight out of Waldenström's ten patients had atrial fibrillation compared with 14% in an unselected thyrotoxic population (Ramsay, 1964), and this possibly reflects the severity of the disease. Other features which have been noted are aching in the limbs and paraesthesiae (Gimlette, 1959). In most of the articles written since 1945 the authors have noted that in addition to the symptoms of ptosis, difficulty with speech, dysphagia and the nasal regurgitation of fluids, there was also generalized muscle weakness. Ophthalmoplegia does not appear to be a particularly common feature, occurring in only two cases (Waldenström, 1945; Strong, 1949) out of fifty-five (3.6%). 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).

Fasciculation was seen in the patient of Heinrich *et al.* (1962) and fibrillation was reported in Strong's (1949) case, though, for reasons which are discussed above, it was probably fasciculation or myokymia.

Pathological reports are scanty, but in Waldenström's review an enlarged thymus was noted in three patients and degeneration and haemorrhage into the cranial nerve nuclei in three cases. Microscopic examination of the brain in Chap-

man & Maloof's (1956) second patient revealed slight to moderate swelling of oligodendroglia in the sub-cortical white matter. There have been two reports on muscle histology. 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.

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 & Maloof, 1956; Gimlette, 1959; Heinrich *et al.*, 1962).

It is difficult to decide whether this condition should be called acute thyrotoxic myopathy or encephalopathy. In favour of the lesion being a myopathy, it has been noted that the patients did have skeletal muscle weakness as well as bulbar symptoms and it has already been remarked upon that 16.4% of the patients described as having chronic thyrotoxic myopathy also had bulbar weakness. The evidence for encephalopathy rests on three cases (Waldenström, 1945) with haemorrhage into cranial nerve nuclei and slight to moderate swelling of oligodendroglia in another patient (Chapman & Maloof, 1956). It is of course known that patients may die of thyrotoxic crisis or in coma without any preceding bulbar paralysis and the same non-specific pathological changes are found at autopsy. The proposition is therefore made that 'acute thyrotoxic myopathy' may represent the stage at which bulbar weakness complicates a chronic myopathy. However, if the thyrotoxic process is severe enough the phase of generalized muscle weakness may be short and the bulbar involvement, with its dramatic symptoms, becomes the most pronounced feature. It must not be forgotten, however, that the patient could have myasthenia gravis in addition to thyrotoxic myopathy. Millikan & Haines (1953) thought that many of the earlier cases described in the literature probably had coincident myasthenia gravis and thyrotoxicosis, and neostigmine gave dramatic relief from the bulbar symptoms in three of the more recent cases (Laurent, 1944; Sheldon & Walker, 1946).

Infiltrative ophthalmopathy

This condition is probably connected only

incidentally with overactivity of the thyroid gland for it may also occur in Cushing's syndrome, acromegaly, hypothyroidism and in apparently euthyroid individuals. It is characterized by progressive exophthalmos, oedema of the lids and conjunctivae, weakness of the extraocular muscles, particularly those showing elevation (Hall, Ford & Manson, 1967), convergence and lateral movement, and occasionally papilloedema and corneal ulceration.

The administration of thyroid extract or thyroxine to experimental animals does not, by and large, produce exophthalmos, but the latter can be initiated by the administration of anterior pituitary extracts, particularly post-thyroidectomy (Brain, 1959). This tallies closely with clinical experience, for severe involvement of the eye occurs more frequently following successful treatment of the thyrotoxicosis than during the course of the disease itself (Asboe-Hansen, Iversen & Wichmann, 1952; Brain, 1959). The thyroid hormones thus do not seem to be the culprits.

Asboe-Hansen *et al.* (1952, 1953) found raised serum levels of thyrotropin in nine out of ten patients with progressive exophthalmos. Kinderen Houtstra-Lanz & Schwarz (1960) and Dobyns, Wright & Wilson (1961) have isolated a substance which they call 'exophthalmos producing substance' (EPS) and which they believe to be an entity quite separate from thyrotropin. They also found a good correlation between the presence or absence of exophthalmos and of EPS in the serum of thyrotoxic patients (Schwarz, Kinderen & Houtstra-Lanz, 1966). Improvement in some patients' exophthalmos following pituitary-stalk section or hypophysectomy (McCullagh, Clamen & Gardner, 1957) seemed to indicate the pituitary origin of ophthalmopathy and recently workers in Utrecht have shown EPS activity in the pituitaries of exophthalmic patients (Kinderen, 1967). Moreover, they found that the activity of EPS in serum dropped markedly following hypophysectomy or pituitary irradiation. EPS has also been demonstrated in the serum of exophthalmic patients with Cushing's syndrome and acromegaly so there is good evidence for it being the causative factor. LATS is usually present in addition to EPS in patients with infiltrative ophthalmopathy and thyrotoxicosis and Kinderen (1967) has suggested that it may act as a facilitatory factor.

It is interesting to compare the pathological changes described in the extrinsic eye muscles with those found in muscle tissue elsewhere. Askanazy (1898) found similar changes in both (see above). Dudgeon & Urquhart (1926) ob-

served lymphorrhages, which were sometimes perivascular, proliferation of interstitial cells and atrophy of muscle fibres. These abnormalities were most marked in the eye muscles, less so in the deltoid and biceps and least in the myocardium; the changes were similar to those found in the muscles of thyroidectomized guinea-pigs injected with thyrotrophic anterior pituitary extracts (Paulson, 1939; Dobyns, 1946).

The semi-lunar accumulations of mucopolysaccharides situated under the sarcolemmal covering of skeletal muscle fibres of patients with progressive exophthalmos (Asboe-Hansen *et al.*, 1952) were also found in the extra-ocular muscles (Wegelius, Asboe-Hansen & Lamberg, 1957). Mucopolysaccharides, particularly hyaluronic acid, were present in the orbital tissue of these patients (Ludwig, Boas & Soffer, 1950; Asboe-Hansen & Iverson, 1951) and have been produced in both intact and thyroidectomized animals by the injection of thyrotropin.

It is therefore proposed that the histological features described in thyrotoxic myopathy, apart from muscle atrophy, are probably due to the effect of a pituitary factor. Thyrotropin itself cannot be implicated since its concentration in the blood of thyrotoxics is either normal or low (Lemarchand-Béraud *et al.*, 1967; Blum *et al.*, 1967) and it is possible that the changes are produced by a synergistic action of EPS and LATS.

The mechanism whereby the eyes are protruded in exophthalmos has been explained by Iverson & Asboe-Hansen (1952) as being the result of the water-binding qualities of the mucopolysaccharides in the orbital tissues. The muscle paralysis could be secondary to stretching and venous occlusion caused by the proptosis and retro-orbital oedema, but it is more likely to be due to a primary muscle disease, since ophthalmoplegia may occur without any demonstrable exophthalmos (Naffziger, 1932; Dobyns, 1950; Logothetis, 1961).

Treatment is unsatisfactory, though the condition usually either regresses or stabilizes within a few months or years. Prednisone in large doses (30–100 mg/day) may be successful in diminishing the severity of the ocular changes, but it is difficult to continue with this because of the occurrence of steroid side-effects. Tarsorrhaphy may be performed in order to prevent corneal ulceration and orbital decompression or hypophysectomy is sometimes done as a last resort. A recent report of the beneficial effects of metronidazole in the treatment of exophthalmos (Harden, Chisholm & Cant, 1967) sounds promising, but further work is needed for evaluation.

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 fifty cases (Adams, Denny-Brown & Pearson, 1962).

It has been estimated that during the course of their disease 1% of thyrotoxics will develop myasthenia gravis (Grob, 1963) and that the incidence of thyrotoxicosis preceding, accompanying or following the clinical onset of myasthenia gravis is 5% (Millikan & Haines, 1953). Osserman & Silver (1961) tested ninety of their myasthenic patients and diagnosed thyrotoxicosis in eight. Millikan & Haines (1953) found that 80% of the patients with this combination of two diseases were women and that the type of myasthenia was the same as that in patients without thyrotoxicosis. The diplopia, ptosis, facial weakness, bulbar palsy, etc., respond well to anticholinesterase drugs (Millikan & Haines, 1953), but the myopathy of thyrotoxicosis remains unaltered (Havard *et al.*, 1963; Ramsay, 1964). Fig. 2 shows a patient (Ramsay, 1964) who presented with the simultaneous onset of thyrotoxicosis and myasthenia gravis. Her diplopia and ptosis responded dramatically to edrophonium chloride intravenously, but produced no change in her myopathic proximal limb muscles.

Some authors have tried to find factors which are common to both myasthenia gravis and thyrotoxicosis. Cohen & King (1932) commented on the hypertrophy of lymphatic tissue, the occasional lymphocytosis and the finding of lymphorrhages in muscle tissue. An enlarged thymus is found in half the thyrotoxic patients who come to post-mortem examination (Williams, 1962) and thymic abnormalities are found in about 60% of myasthenics (Castleman & Norris, 1949; Rowland, Aranow & Hoefer, 1957; Grob, 1961). In 15–33% of patients there is a thymoma; in 25–35% the thymus is hyperplastic. The thyrotoxicosis appears first in about half the patients. Myasthenia gravis precedes the thyroid disease in a third to just under a half and in 9–20% the onset of both is simultaneous (Millikan & Haines, 1953; Grob, 1963). Although McEachern & Parnell (1948) described a 'see-saw' relationship between the diseases, the myasthenia increasing as the thyrotoxicosis diminishes and vice-versa, only three reports have supported this concept (Thorner, 1939; Cohen, 1946; Maclean & Wilson, 1954). The majority of opinion concludes that both diseases move in parallel or show no obvious pattern of interaction (Thorn & Tierney, 1941; Kowallis, Haines & Pemberton, 1942; Flynn, 1944; Greene, 1949; Millikan &

Haines, 1953; Engel, 1961b, Osserman & Silver, 1961). Adams *et al.* (1962) take the view that whatever the factors are which link the two diseases, the thyrotoxicosis does not make the myasthenia gravis worse *per se*, but merely adds the weakness of thyrotoxicosis to that of the latter. In support of this is Grob's (1961) experience that myasthenia gravis may be precipitated, or be aggravated, by the treatment of other diseases with thyroid extract.

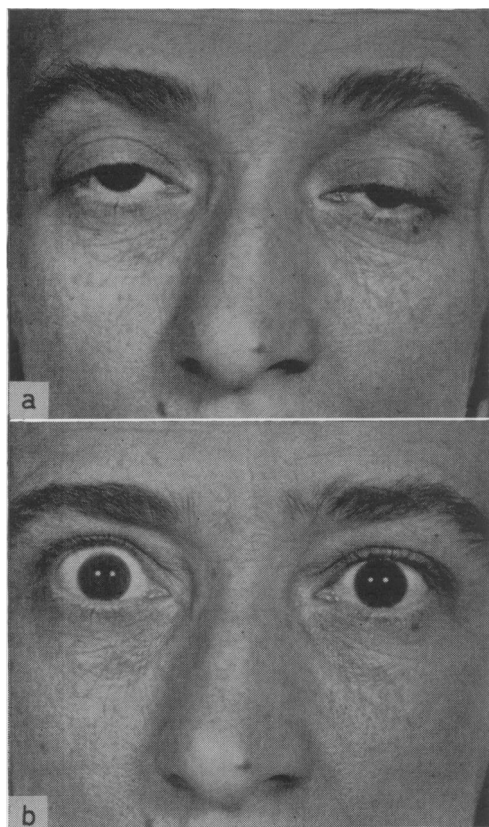


FIG. 2. Female aged 35 with concurrent thyrotoxicosis and myasthenia gravis: (a) showing ptosis, (b) following the intravenous injection of edrophonium.

The suggestion has been made that both myasthenia gravis (Simpson, 1960, 1966) and thyrotoxicosis (Anderson *et al.*, 1964) are autoimmune diseases. Simpson (1966) believes that the relationship, which is similar to that between thyroiditis and idiopathic Addison's disease (Blizzard, Chee & Davis, 1967; Irvine, Stewart & Scarth, 1967), may be the result of a genetic defect in immunological control.

Clinically the differentiation between myasthenia gravis with hyperthyroidism and pure thyro-

toxic myopathy is fairly straightforward. The most prominent symptoms of the patient with myasthenia gravis will be ptosis, diplopia, dysarthria and dysphagia and there will be a variation in the degree of weakness throughout the day, whereas the patient with myopathy will have complaints associated mainly with proximal muscle weakness. Only rarely will bulbar muscles be involved and when they are the possibility of myasthenia gravis must be carefully considered. The simplest test to perform is to inject 10 mg of edrophonium chloride (Tensilon) intravenously, having given the first milligram as a test dose. Within a minute the muscles involved by myasthenia gravis will have become stronger in 95% of cases (Osserman & Silver, 1961). The muscles affected by thyrotoxic myopathy remain just as weak. If the results are equivocal, further tests are available (Osserman & Silver, 1961; Simpson, 1964). Patients with myasthenia gravis become much weaker after receiving one-fifth to one-tenth of a normal curating dose of D-tubocurarine, but this has no effect on thyrotoxics. In normal subjects and in hyperthyroid patients electromyographic potentials do not decrease in amplitude following repetitive nerve stimulation, but they do in myasthenics and this decrease can be reversed by giving edrophonium.

Periodic paralysis

More than 200 cases of concurrent thyrotoxicosis and periodic paralysis were reviewed by Engel in 1961 (Engel, 1961a) Okinaka and his colleagues (1957) in Japan found a 1.9% incidence of periodic paralysis in their thyrotoxic patients with a relatively higher incidence for male patients (8.2%) than for females (0.4%), giving a male-female ratio of 20.5:1 compared with a ratio of 3:1 in uncomplicated periodic paralysis. They found a family history of periodic paralysis in only one out of 119 subjects and discovered that the major incidence of periodic paralysis associated with thyrotoxicosis was in the third and fourth decades compared with the first and second for the uncomplicated disease. Seventy-five patients were followed up and all but three of them remitted after effective treatment of hyperthyroidism. The Japanese workers felt that the simultaneous occurrence of the two diseases was probably due to pre-existing latent periodic paralysis becoming unmasked by the development of thyrotoxicosis (Okinaka *et al.*, 1957). They have, in fact, recently shown that the mechanism of the paralysis is the same in patients with and without thyrotoxicosis, namely an influx of potassium into the cells from the extracellular space

(Shizume *et al.*, 1966). It is known that the administration of adrenaline causes the movement of potassium from the extracellular fluid into muscle cells (Grob *et al.*, 1957). Since an effect of excess thyroid hormone is to sensitize body tissues to normal circulating amounts of adrenaline (Brodie *et al.*, 1966) this may explain the linkage between the two diseases. Certainly attacks of paralysis in uncomplicated periodic paralysis can be initiated by the administration of thyroid hormone (Shinosaki, quoted by Okinaka *et al.*, 1957).

The weakness of periodic paralysis can be distinguished from that of myasthenia gravis in that it tends to occur in the morning or after a large carbohydrate meal. The weakness involves the legs, then the arms, trunk and face. Swallowing, movement of the eyes and respiration are preserved until the last.

Conclusions

Most patients who have thyrotoxicosis suffer from some degree of myopathy, whether or not it is obvious clinically. Occasionally, and especially in the elderly patients who have Plummer's disease and therefore no exophthalmos, the myopathy may be the presenting feature. Thyrotoxicosis, therefore, should be always high up on the differential diagnosis of myopathy. If adequate treatment is given for the hyperthyroidism the myopathy will remit completely in just about the same time as it takes for the patient to become clinically euthyroid.

Bulbar myopathy ('acute thyrotoxic myopathy') is an indication of the severe nature of the patient's hyperthyroidism and may be either the end-stage of chronic thyrotoxic myopathy or part of a more acute involvement of most of the muscles in the body. The situation is serious and treatment must be instituted immediately to control the hypermetabolic state with iodine, carbimazole, propranolol and cooling. Maintenance of a good airway, the administration of oxygen and the prevention of aspiration of food are important measures. In addition it is advisable to give supplementary cortisol intravenously, especially if the blood pressure is low.

Finally it is important to remember that a patient with gross chronic thyrotoxic myopathy who also has bulbar symptoms may have myasthenia gravis, and the appropriate investigations must therefore be carried out.

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