rate at which this occurs on the smooth skin of the trunk and limbs is uncertain, but, arguing from the above findings, it would appear that the infected layer is shed in approximately 10 to 14 days. Desquamation in palms and soles takes much longer, probably between four and six weeks.

Nail infection presents a different problem, since here keratin does not desquamate: hence it is necessary to wait for the nail to grow sufficiently for infection to be carried beyond the free edge. Rates of nail growth differ greatly, the fingernails growing approximately four times as fast as toenails (Le Gros Clark, 1958). An average rate of growth for the normal thumbnail is 3 mm. a month (Le Gros Clark and Buxton, 1938), so at least four months must be allowed for infection of fingernails to grow out, while well over a year would be required for infection to be eliminated from the nail of the big toe.

Whether it would therefore be necessary to administer griseofulvin continuously or intermittently over such a long period can be proved only by trial and error. Since the action is one of fungistasis, any temporary fall below the concentration necessary to inhibit fungal growth would allow reinvasion to take place, either from mycelium itself or from the germination of spores which are unaffected. This effect has already been observed in the hair root (J. M. Beare, 1959, personal communication), and it would seem reasonable to suppose that a similar effect could take place in the nail. Long-continued administration of the drug would in addition raise the question of resistance developing in the fungus. This has not yet been observed in the dermatophytes, but adaptation to fungicides has been observed among plant fungi (Parry and Wood, 1958).

Increasing use of griseofulvin will clarify the position about toxicity. In our series three patients were unable to tolerate the drug, but in spite of noting some variation in the differential blood count we have insufficient evidence to say that it has a toxic effect on the bone-marrow. Further patients, not included in this series, have also shown no significant haematological change. It would, however, appear important that this possibility is borne in mind, particularly in view of the report of Paget and Walpole (1958), who showed that it had a colchicine-like action on mitoses when given intravenously in large doses.

In our present state of knowledge it would seem that a combination of surgical removal of nails, with griseofulvin systemically and possibly the subsequent use of topical fungicides, would offer the patient suffering from chronic nail infection by *T. rubrum* the best chance of cure.

Summary

Thirty-four patients with fungal infections of the skin have been treated with oral griseofulvin in a dosage of 1–2 g. daily.

Two children with candidiasis and one man with tinea versicolor showed no improvement.

Two patients infected with *T. verrucosum* derived no significant benefit.

Infection by *T. mentagrophytes* in one patient cleared after four weeks' treatment.

Two cases of *T. rubrum* infection of the smooth skin were treated for three weeks; one cleared completely and the other improved.

Twenty-six patients with long-standing *T. rubrum* infection with nail involvement were treated for periods of 3–20 weeks. The majority improved, but in only one instance was the infection eradicated.

Toxic reactions are recorded and possible reasons for the wide variations in clinical response discussed.

Some of these cases were under the clinical care of Professor J. T. Ingram, Dr. F. F. Hellier, and Dr. S. T. Anning, and we would like to thank them for their co-operation and advice. We also thank the staff of the pathological department at both hospitals, and Dr. J. F. Wilkinson for his advice on haematology, Dr. Jacqueline Walker for kindly co-operating in the mycology, and Messrs. Glaxo Limited for generous supplies of griseofulvin.

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THE MUSCULAR LESION IN HYPERTHYROIDISM

BY

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The occurrence of muscular weakness in hyperthyroidism is well recognized, but it is difficult to state exactly the incidence of muscular involvement, since normal function is hardly possible to define and mild degrees of impairment are most common. Evidence of a muscular lesion can probably be demonstrated in most hyperthyroid patients, and in some it may be the most important part of the disease. Twenty-six cases of hyperthyroidism with a varying degree of muscular involvement are described (See Table). The first two patients were seen a year before the rest of the series, and are included as examples of the rare severe form of muscle lesion (Cases 1 and 2). The remaining 24 were those of some 40 unselected hyperthyroid patients in whom evidence of a muscle lesion was particularly looked for clinically, and in many cases electromyographically, and whose progress was then followed for between one and two years.

The Muscular Lesion

In three patients (Cases 1, 2, and 3) severe muscular weakness developed acutely over the course of a few days, each patient having been hyperthyroid for a few weeks. Two of these three (Cases 1 and 2) had aching in the muscles, and one (Case 2) also had paraesthesia in the legs. Two (Cases 2 and 3) had mental confusion combined with an appearance of apathy—not real, but imposed by the profound weakness; also, the facial muscles were weak and speech became faint and indistinct, and all the voluntary muscles of the trunk and limbs were involved. Swallowing and respiration remained adequate in these patients, but deaths have been reported in similar cases, probably from respiratory insufficiency. In Cases 1 and 2 the diagnosis of hyperthyroidism was not at first considered. Both these patients responded rapidly to antithyroid treatment when

it was begun some two months after the onset of the muscular symptoms. These patients resembled certain cases described either as thyrotoxic coma, as distinct from crisis, or as apathetic hyperthyroidism (Lahey, 1932). The condition is probably not very rare, but is not always obviously of thyroid origin and if undiagnosed may be fatal.

In most patients there was a less severe, more chronic muscle lesion accompanied by obvious signs of hyperthyroidism. Some patients (Cases 4–16) complained of muscular symptoms, and weakness and wasting were easily confirmed clinically. Others (Cases 17–26) had no very definite complaints suggesting a muscle lesion, but this was nearly always demonstrable clinically as well as electromyographically, and it improved after treatment of the hyperthyroidism.

The muscle lesion was assessed clinically by simple tests; precise quantitative testing was not undertaken, and allowance was made for variations in age and physique of the various patients. Patients were asked to step from the ground up on to a chair; even those not complaining of muscular weakness often found great difficulty in doing so unaided. Some with little or no dyspnoea were obliged to crawl upstairs. Nearly all were unable to maintain abduction of the arms against the examiner's downward pressure. Other muscle groups were tested similarly. The weakness was much more pronounced in the shoulder and pelvic girdles than in the distal or bulbar muscles. One patient presented with backache due to weakness of his back muscles which responded to thiouracil and twice recurred when the drug was withdrawn. Pain was exceptional, however. Testing the strength of grip by maintaining pressure through a sphygmomanometer bulb was an unsatisfactory indication of hyperthyroid muscular weakness; the use of the hand was seldom demonstrably affected.

Muscular wasting was generally in proportion to weakness, but in many of the less severely affected patients it was not obvious. Wasting was usually most apparent in the scapular muscles, particularly in the supraspinatus and the posterior part of the deltoid, sometimes in the glutei or the quadriceps. The triceps, the most satisfactory muscle for electromyographic testing, showed gross wasting less clearly. Wasting which extended peripherally to include the small muscles of the hand was occasionally seen (Cases 1 and 2), but only when there was gross wasting elsewhere. Some patients with quite mild hyperthyroidism, but with rather severe muscle involvement, had lost much weight (over 20% of their body weight), probably owing to loss of muscle rather than fat. The smooth firm skin usually preserved in thyrotoxicosis suggests that the subcutaneous fat may be largely intact; creatine studies suggest that functioning mass, if not actual mass, of muscle is reduced.

In most of the patients studied the tendon reflexes showed characteristic quick but weak muscle contraction and quick relaxation. Exceptions were found occasionally in very severely affected muscles where the tendon reflexes were diminished or absent. The muscles in hyperthyroidism show fatigability, which has led to confusion with myasthenia gravis. However, the fatigability in thyrotoxicosis is less pronounced, and there is not the characteristic increase in myasthenic weakness as the day goes on. The two conditions are also distinguished by the failure of hyperthyroid weakness to respond to anticholinesterase. Normal responses to edrophonium chloride and to curare were shown in six patients thus tested.

Electromyography was done before treatment in all but two patients in the series, and in most of them it was repeated at least once after treatment had taken effect. In the majority of hyperthyroid patients tested the electromyogram was abnormal in a characteristic way, termed the "myopathic pattern" (Bauwens, 1955). Action potentials on volition were of high frequency and low voltage, and there was no evidence of

Summary of Cases

Case No.	Age and Sex	Muscle Involvement Clinically	External Ophthalmoplegia	Weight Loss (% of Normal)	B.M.R.	Radio-iodine Test	Serum Creatine (mg./100 ml.)	Creatine Excretion (mg./24 Hours)	Creatinine Excretion (mg./24 Hours)	Myopathic Pattern in Electromyogram	Treatment	Assessment After Treatment: Muscle Involvement Clinically	Assessment After Treatment: Serum Creatine (mg./100 ml.)	Assessment After Treatment: Myopathic Pattern in Electromyogram
1	M 21	Ac.+++	–	15	+37		1·30	124	1,090		Iodine. Surgery	–	0·45	
2	M 19	Ac.+++	–	20		+				+	Thiouracil	–		–
3	M 52	Ac.+++	–	20			0·78			+	Iodine. Thiouracil. Surgery	–		±
4	M 18	++	+	25	+15	+	0·55			+	Thiouracil. Surgery	–	0·45	–
5	F 20	++	+	24	+51		0·61	110	770	+	Iodine. Thiouracil. Surgery	–		–
6	F 33	++	–	25		+	0·93			+	Iodine. Surgery	±	0·50	±
7	F 63	++	+	25	+45		1·30				Thiouracil	±	0·56	
8	F 27	++	+	15	+49	+	0·95			+	Iodine. Thiouracil. Surgery	–		–
9	F 24	++	–	25	+51	+	0·74			+	Iodine. Surgery	–		–
10	F 45	++	+	20	+51	+	0·70			+	Iodine. Thiouracil. Surgery	±	0·40	±
11	F 58	++	–	20		+	1·18	226	654	+	Radio-iodine	–	0·45	–
12	F 51	++	+	24	+40		0·70		900	+	,,	±		±
13	F 36	++	–	8		+	0·95	237	680	+	Thiouracil. Surgery	–	0·35	–
14	M 67	++	–	20		+	0·77	Nil	1,039	+	Radio-iodine			
15	M 46	++	–	25	+38	+	1·1	58		+	,,	±		+
16	M 47	++	+	15	+45		1·1			–	Thiouracil. Radio-iodine	+		
17	F 47	+	–	12	+33	+	0·80	71	684	+	Radio-iodine	±	0·40	–
18	M 47	±	+	6	+41		0·88	Nil		+	Iodine. Surgery	–	0·28	–
19	F 48	+	–	10		+	0·37			+	Thiouracil	–	0·20	–
20	F 41	±	–	10			0·71			+	Iodine. Thiouracil. Surgery	–	0·51	–
21	F 34	+	–	15			1·13	168	756	+	,, ,,	±	0·35	±
22	F 60	+	–	25		+	0·91			+	Radio-iodine	±	0·53	–
23	F 42	±	–	8	+40		0·93	319	1,084	+	Thiouracil	±		–
24	M 30	+	–	15	+41	+	0·73	Nil	1,410	+	Thyroidectomy			
25	F 45	+	+	20	+40	+	0·70			+	Iodine. Surgery	–		–
26	F 59	+	+	10	+20		0·70			+	,, ,,	±	0·53	±

denervation or myelopathy. These findings were most readily obtained from the triceps, and this muscle was generally used for testing. An abnormal electromyogram, improving after treatment, was obtained from several patients with only minimal symptoms of the muscular lesion; a normal electromyogram was obtained from one patient with muscular involvement which clinically seemed quite pronounced (Case 16).

Electromyography in four other patients, not included in this series, with clinically doubtful muscle involvement showed no abnormality. The electromyogram returned towards normal after antithyroid treatment. The rate of return and its completeness varied and were independent of the type of treatment. In some patients the electromyogram was normal within two weeks of starting treatment; in others it was still abnormal, though improved after three months. The abnormal electromyogram provided supporting evidence that a disorder of muscle function was often present, and the invariable improvement after treatment suggested that the disorder was due to hyperthyroidism. The electromyographic findings were not quantitative, nor were they specific for hyperthyroidism.

Other Features

The diagnosis of hyperthyroidism was evident in most of the patients. Cases 1 and 2 were unusual in that the muscular weakness was profound and the diagnosis was not apparent at first. All the patients had a resting pulse rate of over 100, two had atrial fibrillation, several had mild heart failure—in Case 3 severe. Tremor, nervousness, irritability, and increased sweating were present, and either the B.M.R. or a radio-iodine test confirmed the diagnosis in most instances. Very high basal metabolic rates were not encountered, and some of the patients with much muscular involvement had only a moderate increase; sometimes other hyperthyroid symptoms appear mild, or perhaps are masked by weakness. Evidence of disordered creatine metabolism was found in most of the patients. The serum creatine was 0.7 mg./100 ml. or over in 22 out of 25 patients, and it invariably fell after treatment. The 24-hour excretion of creatine and creatinine was estimated in 11 patients: in 6 creatine excretion was excessive, in 5 creatinine excretion was probably subnormal. No other significant biochemical abnormalities were noted. The serum potassium was normal in those patients tested. No patient showed evidence of renal disease.

Other Types of Muscular Disorder

In the present study thyrotoxicosis associated with a true myopathy was not seen. A diagnosis of myasthenia gravis was occasionally considered but was dismissed on clinical grounds and after testing with edrophonium chloride or neostigmine. None of the patients showed the features of periodic paralysis or of Parkinsonism.

External ophthalmoplegia was not outstandingly severe in the patients in this series with thyrotoxic muscular weakness. Ophthalmoplegia in a mild form was observed in nine of the patients. The degree of ophthalmoplegia and its incidence was unrelated to the severity of muscular weakness elsewhere; it was absent in some of the patients with the most severe generalized muscular weakness, and it did not respond consistently to antithyroid treatment.

Treatment

Treatment of the muscular lesion in thyrotoxicosis was found to be equally effective by all forms of antithyroid therapy. Generally the muscular lesion did not demand urgent treatment in itself, and improvement was quite rapid after all forms of therapy. When the weakness is unusually severe iodine is probably the method of choice, being the most quick-acting; in Case 3 rapid recovery occurred after 10 days. Relapse of thyrotoxicosis sometimes, but not invariably, resulted in a return of the muscular weakness.

Case Histories

Case 1.—A man aged 21 became ill with fever, heart failure, and tachycardia not responding to digitalis. There were no eye signs or thyroid enlargement. After four months there was a rapid onset of muscular weakness, at first with aching, in all four limbs and also the bulbar muscles, with loss of reflexes but no sensory involvement. B.M.R. was +37%. Muscle biopsy showed widespread degeneration of muscle fibres with foci of lymphocytes. Treatment with iodine was begun two months after the onset of muscle weakness, during which time there had been little change. After a month there was considerable recovery; he could walk again and the reflexes returned; B.M.R. +16%. After nine months he relapsed and thyroidectomy was carried out, followed by rapid and apparently complete recovery of both heart and muscles. Two years later he developed heart failure again, with little recurrence of muscle weakness, and died. At necropsy the only positive finding was cardiac enlargement.

Case 2.—A youth aged 19 presented with an illness of rapid onset, the main features of which were psychotic disturbance, extreme muscular weakness with pain in the legs and paraesthesia, loss of tendon reflexes, unimpaired swallowing and respiration, and loss of 28 lb. (12.7 kg.) in weight. There was diffuse enlargement of the thyroid, but eye signs were absent. The electromyograph was characteristic of myopathy. Treatment with thiouracil was begun after the situation had remained unchanged for two months; improvement started after 10 days and was rapid. Three months later the symptoms and signs had almost disappeared and the electromyograph was nearly normal. Treatment was continued for a year; two years later he was well and had no muscular weakness.

Case 3.—A man aged 52 had increasingly severe cardiac failure for a few weeks; he lost 28 lb. (12.7 kg.) in weight and had exophthalmos and lid-lag but no external ophthalmoplegia. He was admitted to hospital, and after a few days his muscular weakness, slight on admission, rapidly increased and wasting became apparent. The face and bulbar muscles were involved, but there was no serious difficulty in swallowing or respiration. The tendon reflexes were quick. The electromyograph showed a myopathic pattern. He was treated with iodine and thiouracil concurrently; the muscular weakness showed a dramatic improvement, starting after about 10 days and rapidly recovering. Thyroidectomy was carried out later.

Discussion

A lesion of the skeletal muscles, mainly centripetal in distribution, often accompanies hyperthyroidism, sometimes being a very severe feature of the disease. The lesion has been called thyrotoxic myopathy, and the fully developed chronic form somewhat resembles true myopathy clinically as well as electromyographically, but it is reversible, being closely linked with the state of hyperthyroidism.

Besides the general muscular lesion described, various other locomotor disorders occur in thyrotoxicosis.

External ophthalmoplegia is common, but in the present study there was no correlation between this and the general muscular weakness, suggesting that the two have a different mechanism. Myasthenia gravis occurs more often than by chance in thyrotoxicosis, but a causal relationship between the two has always been difficult to demonstrate (Millikan and Haines, 1953), and the muscular weakness and fatigability in hyperthyroidism have been confused with myasthenia gravis. Periodic paralysis has been described, fluctuating with hyperthyroidism (Millikan and Haines, 1953), but the relationship is not clear and periodic symptoms were not observed in the present series. Nor was any relationship between Parkinsonism and hyperthyroidism (Chapman and Maloof, 1956) observed. Generalized myokymia, without gross weakness or wasting, has been described in hyperthyroidism (Harman and Richardson, 1954).

Muscle biopsy was done in Case 1; widespread degeneration with loss of striation in the fibres and foci of lymphocytes were found. Such changes are unspecific, and a variety of findings, including normality, have been reported since Askanazy, in 1898, described atrophy of the muscle fibres with rows of fat cells in between and abnormal nuclei resembling those of giant cells (Adams, Denny-Brown, and Pearson, 1953). Electron microscopy has shown a deposit of homogeneous material containing mucopolysaccharide within the sarcolemma (Iversen, Asboe-Hansen, and Carlsen, 1953), but this change seems unspecific and of doubtful significance. Coërs and Wolff (1959) have described profuse sprouting of subterminal motor-nerve fibres. Electromyography is a useful method of demonstrating the muscle lesion and distinguishing it from the effects of neuropathy and myelopathy, also in assessing the response to injected edrophonium chloride and curare. However, neither histology nor electromyography defines the exact site of mechanism of the muscle lesion. The changes shown are not specific except in their reversibility by antithyroid treatment.

It is likely that the muscle disorder in hyperthyroidism is essentially one of muscle-fibre metabolism, structural and other changes being secondary. The exact nature of this disorder is unknown, but there are some biochemical findings of possible relevance. Zondek (1944) suggested that in hyperthyroidism muscular work was uneconomical in oxygen consumption and was associated with a rise in blood lactic acid due to a failure of glycogen resynthesis. Abnormalities of creatine and creatinine metabolism have been attributed to disordered muscle metabolism.

Creatine is synthesized by the liver, largely taken up by the muscles, and later excreted in the urine as creatinine. If muscle mass is reduced, excess creatine is excreted in the urine and the serum creatine exceeds about 0.6 mg./100 ml.; creatinine excretion is diminished (Milhorat, 1953). Probably this excess creatine excretion is not an indication of the site of the chemical disorder of muscle metabolism, at the stage of phosphocreatine synthesis, but results simply from decreased muscle mass, because similar changes in creatine metabolism are found in normal old age as well as a variety of other conditions with wasted muscles (Zierler, 1951). It has not been found that the change in creatine metabolism accurately reflects the severity of the muscle lesion. Muscle lesions attributed to tocopherol deficiency and potentiated by thyroid have been described in experimental animals, and the possibility that tocopherol deficiency or depletion in clinical hyperthyroidism is related to the muscle lesion has to be considered. Postel (1956) found that there was a close association between a reduced serum tocopherol level and severe hyperthyroidism, but no correlation with the degree of muscle involvement. The results of tocopherol therapy in hyperthyroidism have been indifferent.

The severer muscular lesion in hyperthyroidism is of some importance and should be recognized. Severe muscular weakness of acute onset may be the first symptom of hyperthyroidism, or it may develop rapidly in a patient already hyperthyroid, and the usual symptoms of hyperthyroidism can be partly masked by muscle-weakness. Thyrotoxic myopathy should always be considered as a possible cause when dealing with a patient with muscular weakness, because this dangerous condition is curable. In patients who have the commoner chronic mild muscle lesion with hyperthyroidism a separate cause for the weakness and wasting need seldom be sought and a good prognosis can be given. The muscle lesion is of some value as a confirmatory sign in the diagnosis of hyperthyroidism.

Summary

Twenty-six cases with evidence of a muscular lesion with hyperthyroidism are described.

The muscle lesion occurs in an acute generalized form, which is rare and may not be easily recognized, and in a chronic, more localized form which is probably present to some extent in most patients with hyperthyroidism.

Clinical and electromyographic features of a myopathy are present. The lesion is cured by all forms of antithyroid treatment. It is probably a biochemical one, but its exact nature is not known.

I am indebted to the physicians of St. Thomas's Hospital for permission to describe cases under their care; to Dr. H. J. Anderson for helpful advice and criticism; and to Dr. P. Bauwens for the electromyographic findings.

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New activities and research in the field of cancer, heart disease, atomic energy, and rehabilitation of the physically and mentally handicapped were approved by the 28-nation Regional Committee for Europe at its ninth session in Bucharest, under the chairmanship of Professor V. MARINESCU, Minister of Health and Social Welfare for Rumania. The Committee also adopted a co-ordinated plan establishing priority for the eradication of malaria in continental Europe, in order that total eradication be attained at the latest in 1962. (W.H.O. Euro/104.)