which the great majority of patients were cared for at home. Given the lack of trained personnel, it was felt expedient not to concentrate upon training an inevitably small number of specialists, but to guide the future physicians in understanding and forwarding the mental health programme and to instruct them to treat mild psychiatric problems competently.

To this end the teaching of psychiatry in the Medical School was intensified; a total of 330 hours, of which 300 consist of clinical clerkship training both in out- and in-patient departments, with direct contact with patients, case-conferences, seminars, etc., was devoted to it for all students, with, moreover, half the students spending six to seven weeks as interns in the final year. Psychiatry was taught: (*a*) as a specialty of medicine in treating mentally sick persons; (*b*) as an introduction to psychosomatic medicine and the psychology of the physically ill; (*c*) as a part of the basic philosophy of medical education in presenting the concepts of man as a bio-psycho-social unit and of sound doctor–patient relationships; and (*d*) from the point of view of its part in community health programmes.

Possible criteria for evaluating the success of this teaching programme are discussed.

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PRETIBIAL MYXOEDEMA

BY

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Pretibial myxoedema is a condition in which there is local thickening of the skin by a mucin-like deposit; it is nearly always associated with exophthalmos and with past or present hyperthyroidism. Pretibial myxoedema is not rare, but most papers and textbooks dealing with the subject do not convey this, probably because only extreme examples are usually recognized. In a recent comprehensive review Graciansky, Leclercq, and Youénou (1957) collected 151 case reports, many of which were of single severe cases; some descriptions were purely dermatological, and exophthalmos and the endocrine state were unrecorded.

Present Investigation

Between April, 1956, and September, 1958, 280 patients with thyrotoxicosis were admitted to the medical wards of St. Thomas's Hospital; 12 of these (Table, Cases 1–12) had pretibial myxoedema or developed it later, an incidence of 4.3%. Transient lesions may well have been overlooked, and the true incidence was probably over 5%. Some findings in 23 patients (4 men, 19 women) with pretibial myxoedema are described, the lesions having been observed for more than a year in every case. The condition produced severe swelling of the feet and legs, causing some disablement in four patients; these four and two others also had thyroid acropachy (Gimlette, 1960) (see Table). The changes

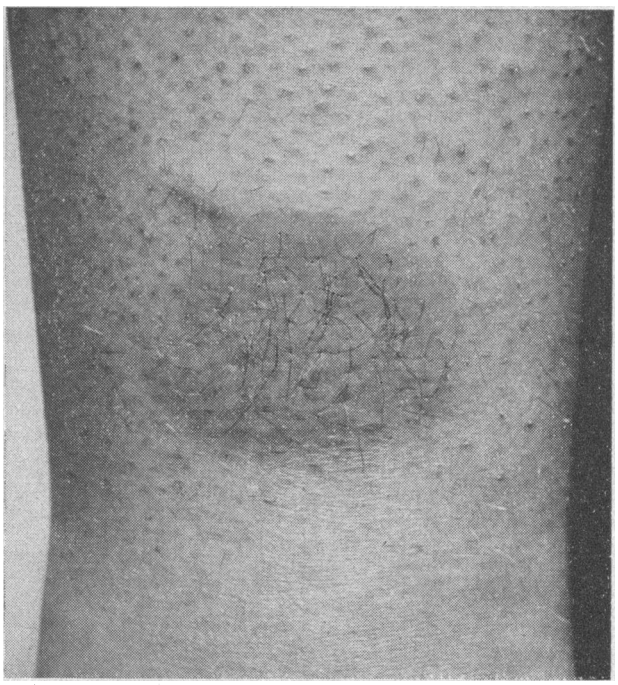

FIG. 1.—Case 2*Y*. Early lesion (actual size 4 cm. across) showing thickening of skin and coarse hair, and involvement of minute scar at upper left edge of lesion.

in the other patients were milder and in some cases rather insignificant. The age at onset of pretibial myxoedema ranged from 31 to 64 years.

The earliest stage of pretibial myxoedema was a shiny red plaque a few millimetres in diameter, usually on the anterolateral side of the lower half of the leg. Several separate lesions often appeared simultaneously, sometimes first on one leg, sometimes quite symmetrically; they might progress no further, or regress, or the plaques might enlarge and grow together. The condition was seen unilaterally only in the early stage. The area of the lesion was usually quite bright red, particularly when warm, or it might appear cyanotic; when bloodless the lesions were yellowish. Often notably coarse hair grows, and excessive sweating occurs, in the area of the lesions (Fig. 1).

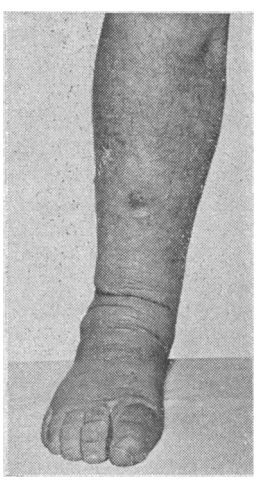

FIG. 2.—Case 4. Two years after onset of pretibial myxoedema. Changes in skin of foot resembling elephantiasis; earlier there had been pitting oedema. Biopsy scar on outer side of leg.

About half the patients complained of irritation, and the lesions occasionally became modified by lichenification and scaling. In the four most severe cases the lesion spread to involve most of the skin of the legs up to the knees; the ankles and feet were also involved, and in these latter parts there was hyperkeratosis; deep folds appeared in the thickened skin, and the appearance of the feet resembled that of elephantiasis (Fig. 2). In one such patient (Case 4) lymphangiography (Professor J. B. Kinmonth) showed normal lymphatics at the early stage, when there was pitting oedema of the feet; this later changed to hard

woody oedema. Lymphangiography has not been repeated since. There seems to be no particular tendency to infection despite the fissures and hyperidrosis in the affected skin. In one patient pretibial myxoedema developed on the dorsum of the foot after the original lesion had been excised and Thiersch-grafted, and also on the donor area on the thigh (Figs. 3 and 4); at the latter site particularly it had regressed after five years. The formation of tissue resembling keloid in appearance, where an area of pretibial myxoedema has been excised for biopsy (Fig. 2) or other reason, or after trauma, is very characteristic and is a contraindication to surgical intervention. There was also a definite tendency for developing pretibial myxoedema to be accentuated at the site of old scars. In Case 15 a small area of pretibial myxoedema appeared over the sternum. Localized lesions occurring above the knee, which are rare, are to be distinguished from lichen myxoedematosus or tuberous myxoedema.

It was thought unnecessary and undesirable to do a biopsy in most cases. The histological appearance in pretibial myxoedema is that of oedema of the corium, which contains a substance, staining like mucin, separating the collagen fibres. Chemical analysis has shown the mucopolysaccharide content to be increased greatly in the affected skin and to a less extent in the patient's unaffected skin elsewhere (Beierwaltes and Bollet, 1959), and hyaluronidase is certainly capable of softening this tissue. Possibly some of the orbital changes in severe exophthalmos are the same. The hyalase test (Kellgren, Ball, and Tutton, 1952) in the normal forearm skin of two patients with severe pretibial myxoedema was negative.

Of the 23 patients with pretibial myxoedema, all except one presented with hyperthyroidism; the exception (Case 15) was never hyperthyroid and presented with exophthalmos. In all the hyperthyroid patients except one exophthalmos developed at the same time as hyperthyroidism, or soon after, and before the hyperthyroidism was treated. Pretibial myxoedema was noticed at the time of onset of the other symptoms or soon after, and before any treatment, in 10 out of 21 patients.

In 22 hyperthyroid patients thyroidectomy was done, or some other form of treatment given, generally within a year of the onset of symptoms. The hyperthyroidism was apparently permanently controlled by the initial treatment in 14 patients; six were considered to have become hypothyroid after initial treatment and were thereafter given thyroid extract. Two of these patients developed severe exophthalmos, five developed severe or moderately severe pretibial myxoedema, and four eventually developed acropachy. On the other hand, in eight there was unsatisfactory control or relapse needing different or repeated treatment; these patients showed rather less tendency to severe progressive exophthalmos and pretibial myxoedema than the others (see Table overleaf).

Pretibial myxoedema was already present before hyperthyroidism was treated in nine patients: it increased in none, remained the same in five (two moderately severe), and decreased in four (one moderately severe). Pretibial myxoedema developed after treatment of hyperthyroidism in 13 patients; in four of them it became severe, and in three moderately severe. In these latter seven patients there was nothing, in retrospect, to show that severe pretibial myxoedema could have been anticipated. Severe pretibial myxoedema was associated with the later development of thyroid acropachy in six patients.

The above findings are summarized in the Table.

Treatment

Many different treatments for pretibial myxoedema have been advocated; the results are confusing, and it is clear only that there is no satisfactory answer. Mild lesions in hyperthyroid patients tend to resolve or to get

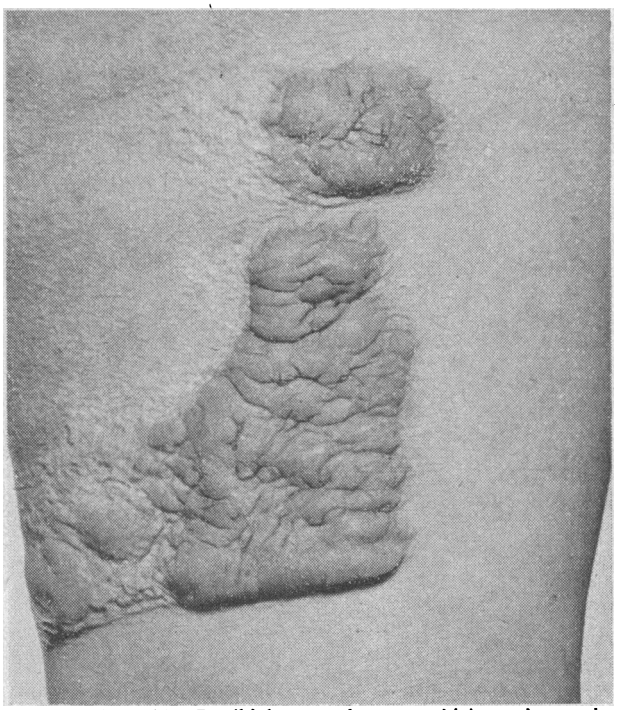

FIG. 3.—Case 14. Pretibial myxoedema on thigh at donor site two years after skin graft.

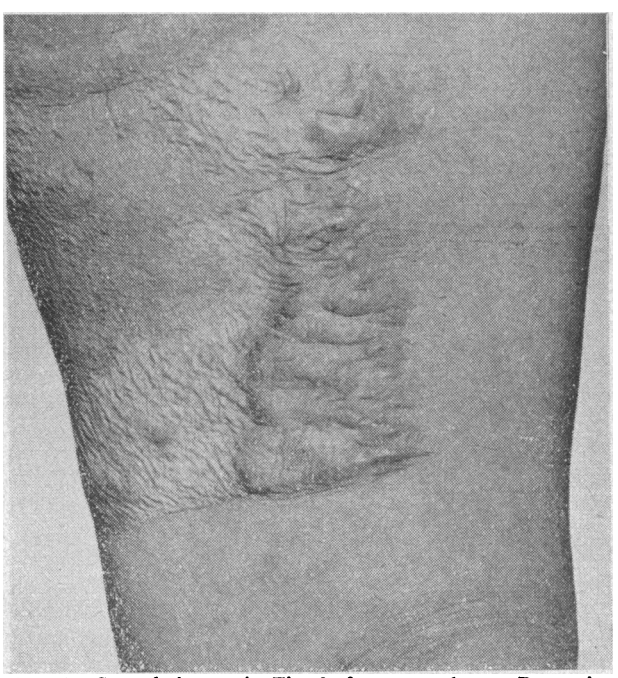

FIG. 4.—Same lesion as in Fig. 3, four years later. Regression has taken place, probably not attributable to treatment; changes of thyroid acropachy had recently developed.

no worse when the hyperthyroidism is cured, and no treatment seems to be indicated. The prognosis in severe pretibial myxoedema appears to be unaffected by treatment. In two patients with severe lesions, these had receded a little after 12 and 7 years after their onset (Cases 14 and 19). In any case, the treatment of hyperthyroidism or severe exophthalmos must take priority.

Treatment was attempted in some patients with progressing pretibial myxoedema. Thyroid given orally failed to produce any convincing change. Injections of triiodothyronine into the affected skin produced no local change, though doses of 200 and 400 μg. caused easily detectable general metabolic effects. Treatment with large doses of prednisone orally produced transient softening and recession of the lesions, but after two or three weeks on continued high dosage they returned to the previous state. Local injection of hydrocortisone was followed after two or three weeks by resolution, usually permanent, of some small lesions. This treatment left an area of slightly wrinkled skin, which was not noted after slower spontaneous resolution in other patients, in whom the lesions left no trace. Parts of larger lesions were affected in the same way by intensive local injection with hydrocortisone, but after about six months the treated areas tended to relapse. Local hydrocortisone injections produced little or no objective change in the elephantiasis-like areas around the ankle and on the toes. Local injection of hyalase (1,500 units in 1 ml.) produced a transient area of softening lasting up to two weeks in the lesions; attempts to infuse larger quantities in more dilute solution by subcutaneous drip were painful and ineffective. The combination of hyalase with hydrocortisone seemed to have no advantage.

Surgical excision and grafting were followed by recurrence in the grafted area and the donor site within a few months (Fig. 3) (Patterson, 1958). Local radiotherapy to the lesions had no effect, nor did radiotherapy to the pituitary. The generalized leg-swelling of extensive pretibial myxoedema was reduced very little by prolonged firm bandaging of the feet and legs, with massage of the skin and galvanism to the calf muscles.

Details of Cases

Case No.	Age and Sex	Hyperthyroid	Treatment of Hyperthyroidism	Exophthalmos		Pretibial Myxoedema			Acropachy
				Before Treatment of Hyperthyroidism	After Treatment of Hyperthyroidism	Before Treatment of Hyperthyroidism	After Treatment of Hyperthyroidism	Time of Onset Before or After 1st Treatment of Hyperthyroidism	
1	42 F	+	^{131}I*	+++	++	++	+	6/12 before	–
2	51 F	+	Carbimazole. ^{131}I*	++	+	–	+	3/12 after	–
3	56 F	+	^{131}I	++	++	+	–	3/12 before	–
4	47 F	+	Surgery†	++	+++	–	+++	1/12 after	+
5	40 F	+	^{131}I	+	++	++	++	3/12 before	–
6	57 F	+	^{131}I	++	++	+	–	3/12 ,,	–
7	43 F	+	^{131}I	+	+	–	+	4/12 after	–
8	45 F	+	Surgery. ^{131}I*	+	+	–	+	6/12 ,,	–
9	51 F	+	^{131}I	+	+	+	+	1/12 before	–
10	31 F	+	Surgery	+	+	+	–	8/12 ,,	–
11	45 F	+	Surgery	+	++	–	+–	3/12 after	–
12	47 F	+	^{131}I†	+	+	–	++	4/12 ,,	+
13	35 F	+	Thiouracil. ^{131}I*	+	+	+	+	6/12 before	–
14	56 M	+	Surgery†	+	+++	–	+++	1 yr. after	+
15	42 M	–		+++		+			–
16	39 F	+	Surgery	+	++	–	+++	1/12 ,,	+
17	50 F	+	Surgery. ^{131}I*	+	+	–	++	1/12 ,,	+
18	50 F	+	Thiouracil*	+	+	+	+	8 yrs. before	–
19	36 M	+	Thiouracil†	+	++	–	+	1/12 after	–
20	50 F	+	Thiouracil. ^{131}I*	+	++	–	+	6 yrs. after	–
21	64 F	+	Surgery†	–	+	–	+++	8/12 ,,	+
22	63 M	+	^{131}I†	+	+	++	++	?/12 before	–
23	33 F	+	Surgery. ^{131}I*	++	++	–	++	3/12 after	+

* Relapse after treatment.
† Rendered hypothyroid.

+ Mild exophthalmos.
++ Moderate exophthalmos with some external ophthalmoplegia.
+++ Severe exophthalmos with loss of vision or requiring decompression.

+ Mild pretibial myxoedema.
++ Moderate pretibial myxoedema exceeding 100 sq. cm. in total area.
+++ Severe pretibial myxoedema resembling elephantiasis.

Discussion

The usual order of onset of symptoms is hyperthyroidism, exophthalmos, pretibial myxoedema, and in some patients acropachy. Mild pretibial myxoedema is not uncommon, either before or after treatment of hyperthyroidism, and it tends to resolve spontaneously. Severe pretibial myxoedema usually but not invariably occurs in patients with severe exophthalmos, and only in a minority of these. Sometimes thyroid acropachy develops later. In the present series severe pretibial myxoedema tended to occur in patients who did not have it at all before treatment of their hyperthyroidism, and in whom treatment induced hypothyroidism. The cause of pretibial myxoedema is obscure, and, while it is very doubtful that the lesion is caused by overtreatment of hyperthyroidism, its occurrence in a severe form in patients in whom hyperthyroidism was easily reversed may be significant.

The development of exophthalmos, pretibial myxoedema, and thyroid acropachy may be so far apart in time that it is not obvious that they have an identical cause. These conditions may each appear, progress up to a certain point, and then progress no further or even regress, while another in turn appears and progresses (Fig. 4). However, the almost invariable order in which the symptoms develop and the nearly constant association with hyperthyroidism has suggested a single stimulus responsible for all. This stimulus evidently can take a long time to produce its full effect, but all the tissue changes it produces may be essentially the same. The likeliest nature of the stimulus appears to be a hormone from the anterior pituitary; there have been various and conflicting views about this which cannot be considered in detail.

In pretibial myxoedema there is usually no evidence of dysfunction of the pituitary or of other endocrine glands apart from the thyroid. There have been reports of eosinophil adenoma (Freeman, 1958) and eosinophil hyperplasia (Levitt, 1954), each in a patient with pretibial myxoedema. In the present series there were no deaths and no radiological evidence of pituitary enlargement in the patients with severe pretibial myxoedema, nor was there evidence of any other endocrine disorder, and none of the patients was diabetic.

The theory that thyroid-stimulating hormone (T.S.H.) also caused exophthalmos has not been confirmed (Gilliland and Strudwick, 1956; Querido and Lameyer,

1956), and it has been suggested that there is a separate exophthalmos-producing substance (E.P.S.). The physiological role of this substance is puzzling and its assay is difficult. It has been claimed that E.P.S. can be separated chemically from T.S.H. (Dobyns and Steelman, 1953), that it can produce exophthalmos experimentally, and that excess of it in the serum of patients is correlated with exophthalmos (Dobyns and Wilson, 1954; Brunish, 1958). It has yet to be established that E.P.S. or any other substance is present in excess in the serum of patients who develop pretibial myxoedema and later acropachy. The concept that excess of a pituitary hormone produces change in certain parts of a target organ, the skin, is not yet proved and is unhelpful as a basis for therapy. At present one can only say that pretibial myxoedema in the skin is one of several localized disorders, perhaps essentially similar, which may appear in Graves's disease under certain circumstances as yet obscure.

Summary

In 23 patients with pretibial myxoedema the appearance and behaviour of the lesions, and their relationship with hyperthyroidism, are described.

Minor pretibial lesions are not uncommon; they usually soon resolve after hyperthyroidism has been controlled.

Severe pretibial myxoedema, when it develops, tends to do so after cure of hyperthyroidism and in association with severe exophthalmos. When the lesions become extensive they persist and are resistant to treatment.

I thank the physicians of St. Thomas's Hospital who have allowed me to describe patients under their care.

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"Roughly the same is true about the theory either of contraceptive measures or of treatment of sub-fertility. Although each of them contains some new elements each can be developed from the basic physiological and anatomical knowledge common to all doctors. The situation is utterly different with regard to the therapy of marital problems. First, our knowledge of the natural history of marriages is most rudimentary, it does not bear comparison with physiology and still less with anatomy. Since pathology and therapy of marriage is not part of the medical curriculum it follows then that the mere fact that someone has obtained a medical qualification does not mean that he or she will possess the skill required for this kind of work. Should a doctor want to treat marital problems he must be prepared, as in any other special branch of medicine, to learn a good deal, theoretically and practically." ("The Marital Problem Clinic," Dr. M. Balint, *Family Planning*, April, 1960.)

RETINITIS PIGMENTOSA, HYPERTENSION, AND URAEMIA IN WERNER'S SYNDROME

REPORT OF A CASE, WITH NECROPSY FINDINGS

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In 1904 Werner described a peculiar disorder termed "cataract in connexion with scleroderma" occurring in four brothers and sisters. Oppenheimer and Kugel (1934) distinguished this condition from its related Rothmund (1868) syndrome and established the eponym "Werner's syndrome." In 1941 they reported the first post-mortem findings on such a case. In a comprehensive review of the condition Thannhauser (1945) emphasized that the skin changes were not true scleroderma. By 1953 Irwin and Ward listed 55 cases, and up to the time of writing the present article approximately 62 cases have been placed on record, with only one additional post-mortem description (Perloff and Phelps, 1958).

The manifestations of the fully developed syndrome may be summarized as follows: (1) Habitus: short stature, stocky trunk, and slender extremities. (2) Premature senility: appearance in the third or fourth decade of juvenile cataracts, grey hair, baldness, and arteriosclerosis. (3) Scleroderma-like changes: atrophy of skin and subcutaneous tissue, circumscribed hyperkeratosis, trophic ulcers about ankles and feet, and beaked nose. (4) Endocrine: tendency to diabetes mellitus, hypogonadism, thyroid-gland dysfunction, osteoporosis.

Only one manifestation may be prominent in the clinical picture, so that cases may be overlooked and regarded as juvenile cataracts, primary hypogonadism, scleroderma, or generalized arteriosclerosis. Our present case, the third with necropsy findings, is unusual as its presenting symptoms were uraemia and hypertension.

Case Report

A Persian Jew aged 39 was admitted to the Rambam Government Hospital on January 9, 1958, complaining of shortness of breath, persistent severe headaches, and frequent vomiting of five days' duration.

His past history revealed that as a child he was healthy. Between the ages of 18 and 19 he rapidly lost most of the hair on the top of his head without any apparent disease or illness. He had never married, as he was always poor and could not afford a wife, but he also admitted that he had never had a sexual urge or libido.

At the age of 30 his vision began to fail, gradually getting worse and worse until six years later he could only distinguish finger movements in front of his eyes. It was about this time, in December, 1954, that he was admitted to the eye department of the Rambam Government Hospital with bilateral posterior pole juvenile cataracts. After operation on the left eye his sight improved slightly, and on examination of the eyeground retinitis pigmentosa was