is particularly suitable as maintenance treatment in a scheme of indefinitely prolonged chemotherapy, and can be conveniently prescribed in the form of cachets containing both drugs. Primary or induced resistance to any of the three standard antituberculosis drugs, and especially to P.A.S. or isoniazid, naturally introduces problems in maintenance therapy. One patient (Case 6) whose maintenance treatment required a daily injection exemplifies this. Joiner *et al.* (1954) found P.A.S., 10 g. daily, along with isoniazid, 250 mg. daily, disappointing in the treatment *ab initio* of a small series of cases with chronic fibrocaseous pulmonary tuberculosis because of the emergence of resistant strains of the organism. Such findings, however, if substantiated, do not necessarily invalidate the use of P.A.S. plus isoniazid in maintenance treatment of such cases after the preliminary use of streptomycin along with P.A.S. or isoniazid for a sufficient period to reduce the bacterial population to a low level. In the cases described in this report sputum negativity is being successfully maintained in spite of the presence of gross radiological change with open cavitation by the daily administration of P.A.S. in 12-g. or 20-g. dosage along with 200 mg. of isoniazid.

It is still too early to assess the long-term results in the cases described. The likelihood of maintaining sputum negativity, however, seems promising.

Other major potential hazards in this type of case include haemoptysis and the development of secondary pulmonary infection. Haemoptysis, initially present in all cases, has not occurred in any after the first month of treatment. Auerbach (1955), in a study of pulmonary lesions after chemotherapy, mentions greatly decreased tendency to pulmonary haemorrhage as one of the most dramatic effects resulting from prolonged chemotherapy and suggests reasons for this phenomenon.

Grossly destroyed pulmonary tissue provides a *locus minoris resistentiae* for the establishment of secondary infection which must be regarded as a particular hazard for the type of case under discussion. With this in mind, patients were advised on leaving hospital to seek medical advice early should upper respiratory infection occur. It is interesting to note, however, that only one patient has so far required specific treatment for secondary respiratory infection, and that on one occasion only. The possible development of amyloid disease and late cor pulmonale are problems for future assessment.

One further important problem remains. How long must chemotherapy be maintained; and, indeed, is it ever possible to sterilize tuberculous lesions by drug treatment? Myers (1955) expresses doubt that this can be achieved with the drugs at present available, and it may be that certain cases will require chemotherapy which is literally indefinitely prolonged. Numerous reports have been published on this aspect of the problem, and further study is required before this crucial aspect of the problem of long-term chemotherapy can be elucidated. The fact that a positive culture was isolated in one of the above cases after fourteen months' treatment suggests that in this type of case treatment for so short a time is inadequate.

Summary

Six cases of advanced pulmonary tuberculosis are described. All had gross cavitation and were treated by long-term chemotherapy alone because of the extent of the disease, respiratory insufficiency, or advanced years. The patients have been rendered sputum-negative for periods of 16 to 35 months and enabled to take their place in the community once more.

The chemotherapy used is described and the problems of long-term chemotherapy in such cases are discussed.

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CLINICAL APPLICATION OF AN ASSAY OF THYROID-STIMULATING HORMONE IN RELATION TO EXOPHTHALMOS

BY

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The aetiology of the exophthalmos that frequently occurs in relation to thyroid disorders has not yet been elucidated and treatment is consequently unsatisfactory and largely empirical. The exophthalmos is commonly held to be the result of an excessive secretion of thyroid-stimulating hormone (T.S.H.) by the pituitary gland. This was first suggested by the experimental work of Marine and Rosen (1934) on rabbits, and of Smelser (1937) on guinea-pigs. They showed that it was possible to produce both thyroid overactivity and exophthalmos in animals by injection of a pituitary extract rich in T.S.H. The similarity of these experimental findings to the clinical conditions encountered in man suggested that both the thyroid overactivity and the exophthalmos were caused by the one factor, the T.S.H. of the pituitary. Conflicting results, however, have been obtained by numerous observers using different assay procedures to estimate the T.S.H. in the blood and urine of patients suffering from thyroid and ophthalmopathic disorders. Many of these procedures were difficult or were complicated by the fact that excess thyroxine in the serum might affect the test animals. For this reason a new method for clinical assay has been developed which would not be affected by the presence of excess thyroid hormone, and this report is based upon the results obtained.

Method

The method has been described in detail elsewhere (Gilliland and Strudwick, 1953). It is based on the discharge of

iodine from the thyroids of day-old chicks by T.S.H. and is similar to that of Piotrowski *et al.* (1953). ^{131}I is used for convenience of estimation and because it allows *in vivo* measurements of the chicks' thyroids before and after the T.S.H. administration. The neck count before administration of T.S.H. enables the chicks to be placed into groups matched according to their count, and thus to help to lessen the effect of the considerable biological variation in the chicks. After the administration of 20 μc. of carrier-free ^{131}I, the chicks are given 8 μg. of L-thyroxine daily to suppress endogenous T.S.H. activity. This has an additional advantage, as there is little difference in the suppression over a range of between 8 and 30 μg. of L-thyroxine, and so the presence of further thyroxine in the serum to be tested can be disregarded.

The method was adapted to a standard "four-point" assay. For an individual assay we use four groups with 10 chicks to each group. Two groups are given T.S.H. and two groups the serum to be tested. T.S.H. of known potency* is used, and the ^{131}I discharged from the chick's neck is measured at one dose level in one T.S.H. group and at twice this dose level in the second T.S.H. group. Thus we derive the amount of ^{131}I discharge occasioned by known amounts of T.S.H. at two points on a linear regression line (Gilliland and Strudwick, 1953). The two serum groups are treated similarly. One group is given a dose of serum and the second group is given twice that dose. Thus we derive a second two points of ^{131}I discharge occasioned by an unknown amount of T.S.H. present in the serum. Computations are then made of the validity of the assay and the amount of T.S.H. present in the unknown sample, together with some estimate of the limits of error involved.

Clinical Cases

The patients on whom T.S.H. serum levels were estimated were untreated at the time of their first assay. The majority were deliberately selected because both clinical and laboratory data made the diagnosis clear. Subsequent follow-up over a period of at least six months, and in most cases longer, has confirmed the diagnosis.

The following cases were studied :

Normals (5) (Cases 1–5).—These were volunteer healthy hospital workers without evidence of endocrine disorder.

Simmonds's Disease (3) (Cases 6–8).—These patients gave a history of post-partum haemorrhage, with subsequent failure of lactation and menstruation. Their urine contained less than 4 mouse units of follicle-stimulating hormone in 24 hours. Evidence of hypothyroidism was shown by low B.M.R.s, E.C.G.s with low voltage and flat T waves, and hypothyroid urinary ^{131}I tests (Fraser *et al.*, 1953). In addition, they had evidence of adrenal failure with low urinary 17-ketosteroids, abnormal water diuresis, corrected by cortisone, and hypoglycaemic unresponsiveness to insulin-tolerance tests.

Spontaneous Myxoedema (10) (Cases 9–18).—Most of these were chosen as characteristic on clinical grounds, with unequivocal confirmatory data—that is, low B.M.R.s, high plasma cholesterol concentration, and ^{131}I excretion tests confirming myxoedema. In addition, they showed no significant failure to excrete F.S.H. in their urine and no significant failure of diuretic response when subjected to a water load. Two of the cases (Nos. 14 and 16) differed from the others in that they were unusually severe and of particularly long duration. One of these had been previously reported as Case 3 by Garrod and Gilliland (1954). Long-term follow-up treatment on thyroxine alone has confirmed the diagnosis.

Induced Myxoedema (2) (Cases 19 and 20).—The myxoedema of these patients was the result of thyroidectomy performed for malignancy and heart failure respectively, and was of approximately three months' duration. T.S.H. was estimated before thyroid therapy was begun.

Cretins (2) (Cases 21 and 22).—These were diagnosed by the same testing procedures coupled with *x*-ray evidence of delayed bone age and epiphysial dysplasia and confirmed by subsequent progress on thyroid therapy alone.

Thyrotoxicosis (14) (Cases 23–36).—Cases with hyperthyroidism were, with one exception, characteristic on clinical grounds and confirmed by radioactive iodine tests, raised B.M.R.s, and subsequent response to antithyroid treatment: A further subdivision was made of those with thyrotoxicosis.

(*a*) *Thyrotoxicosis with Minimal Eye Signs* (2) (Cases 23 and 24).—These two patients had no more than an equivocal lid-lag.

(*b*) *Thyrotoxicosis with Moderate Eye Signs* (3) (Cases 25–27).—Those who had, or developed, lid-lag, but no gross exophthalmos or ophthalmoplegia, have been classified as showing moderate eye signs common to many cases of Graves's disease.

(*c*) *Thyrotoxicosis with Severe Eye Signs* (8) (Cases 28–35).—These patients were specially chosen as having severe eye signs showing both exophthalmos and ophthalmoplegia. Three of them had pretibial myxoedema as well.

(*d*) *Severe Eye Signs with Minimal Thyrotoxicosis* (1) (Case 36).—This patient was a youth who showed severe eye signs and who was not obviously thyrotoxic on clinical grounds, but on whom repeated tests with ^{131}I showed a hyperactive state.

Severe Eye Signs without Thyrotoxicosis (3) (Cases 37–39).—These patients showed no evidence of thyroid disorder on clinical grounds or on any of our tests. They had normal B.M.R.s, ^{131}I test, and protein-bound iodine levels. One subsequently required decompression of the orbit to save her sight.

Results

Normals.—The Table gives the results in the normal. Difficulties were met with in estimating T.S.H. in the serum of normal people owing to the amount of serum required by

Table of Results

	Case No.	Age	Sex	Estimate in μg./100 ml.	Upper 95%	Lower 95%
Normals	1*	25–35	M and F	29	43	18
	2	30	M	31		
	3	58	F	54	70	40
	4	28	M	No measurable response		
	5	19	M	,, ,,	,,	
Simmonds's disease	6	42	F	No measurable response		
	7	58	F	,, ,,	,,	
	8	48	F	,, ,,	,,	
Spontaneous myxoedema	9	50	M	219	499	103
	10	62	M	259		
	11	56	F	276	922	88
	12	48	F	202	356	115
	13	53	F	166	385	72
	14	62	F	No measurable response		
	15	63	F	183	334	100
	16 (before)	63	F	No measurable response		
	16 (after)	63	F	228	342	90
	17	53	F	180	294	98
	18	45	F	292	500	161
Induced myxoedema	19	42	F	592		
	20	38	M	399	516	308
Cretins	21 (before)	17	M	651	1,040	407
	21 (after)	17	M	No measurable response		
	22	12	F	370	515	266
Thyrotoxicosis with minimal eye signs	23	25	F	No measurable response		
	24	32	F	84	128	55
Thyrotoxicosis with moderate eye signs	25	50	F	No measurable response		
	26	42	M	,,	,,	,,
	27	45	M	109	269	44
Thyrotoxicosis with severe eye signs	28	49	F	141	218	91
	29	60	M	172		
	30	43	M	235	428	131
	31	58	F	122	225	66
	32	39	M	123	318	47
	33	65	M	138	295	60
	34	52	M	8	†	†
	35	48	M	124	192	78
Severe eye signs with minimal thyrotoxicosis	36	17	M	200	396	101
Severe eye signs with no thyrotoxicosis	37	58	F	19	153	8
	38	60	F	No measurable response		
	39	31	F	,, ,,	,,	

* This case is represented by the pooled serums of 6 normal volunteers.
† Poor assay with limits about twenty times greater than the others.

*Armour, T.S.H., R377158.

this method. The most satisfactory response (Case 1) was obtained by pooling the serum of six normal volunteers and giving one test group of chicks 5 ml. each and the second group 10 ml. Injections of such large volumes are difficult, and it might be better to extract the serum if low values are to be estimated. As some normals gave no response by this method, it is unsuitable for differentiating between normal and subnormal states.

Simmonds's Disease.—No response could be obtained in three patients with this disease.

Spontaneous Myxoedema.—A high level of circulating T.S.H. was found in the serum, except in the particularly severe and long-established cases (Nos. 14 and 16). Case 16 was retested a year later, when she was again admitted in relapse, having neglected to take her thyroxine for at least seven weeks. After 14 days on L-thyroxine, 0.1 mg. a day, retesting showed the response to be once more comparable to the other cases of myxoedema.

Induced Myxoedema.—These showed even greater amounts of T.S.H. circulating.

Cretins.—These showed high levels. Case 21 was retested six weeks later, when on a dose of L-thyroxine, 0.3 mg. a day, which was the margin of toleration; at this point no T.S.H. was demonstrated in the serum.

Hyperthyroidism.—(*a*) *Thyrotoxicosis with minimal eye signs:*—T.S.H. could be estimated in one case and not in the other. (*b*) *Thyrotoxicosis with moderate eye signs:*—T.S.H. could be measured in one, but not in the other two. (*c*) *Thyrotoxicosis with severe eye signs:*—T.S.H. was measurable in all these patients. Case 34 was a poor assay with very wide limits of error, but was not negative. The others showed a considerable amount of T.S.H. circulating. (*d*) *Severe eye signs with minimal thyrotoxicosis:*—This youth (Case 36) showed considerable T.S.H. circulating in the serum.

Severe Eye Signs without Thyrotoxicosis.—The three patients with ophthalmopathy without thyrotoxicosis did not differ from the normal group.

The significant difference (1%) between the value of groups was assessed. Each assay gave the logarithm of the estimate of circulating T.S.H. and hence the estimate itself. In comparing the various groups of patients in whom a response was obtained, the logarithms of the estimates were therefore examined by means of the analysis of variance, and the significance of the differences was found by the method of Scheffé (1953). This showed that the spontaneous myxoedema group was not significantly different from the thyrotoxicosis group with severe eye signs, but was significantly lower than those of induced myxoedema and cretinism. The two cases with minimal and moderate eye signs in which a raised level was found were significantly lower than the cases of spontaneous myxoedema. For comparison with the normal cases, the logarithm of the estimate could not be used, as two normal cases showed no measurable response. The arithmetic means were used to test approximately the differences of certain groups from the normal group. The group with spontaneous myxoedema showed a significant (1%) increase over the normals. The group with thyrotoxicosis and severe eye signs was significantly greater than normal at the 5% level.

Discussion

It has been generally agreed that the amount of T.S.H. circulating in the serum of normal healthy people is so small that its measurement is difficult (De Robertis, 1948; D'Angelo *et al.*, 1951). D'Angelo *et al.* were able to discriminate between the normal level and the low level of T.S.H. in Simmonds's disease. Our method is not sensitive enough to allow this distinction, and we can only record the fact that no T.S.H. was measurable in three cases of Simmonds's disease.

A raised level of T.S.H. in spontaneous myxoedema has been observed by others in the serum (Hertz and Oastler, 1936; De Robertis, 1948; Purves and Griesbach, 1949; D'Angelo *et al.*, 1951; Asboe-Hansen *et al.*, 1952) and in the urine (Hertz and Oastler, 1936; Cope, 1938; Jones, 1939). It has been found to be particularly high in induced myxoedema (Rawson and Starr, 1938), especially after thyroidectomy. On the other hand, some of the same observers (D'Angelo and De Robertis) have also reported cases of low levels in myxoedema. Starr *et al.* (1939) suggested that in profound myxoedema the pituitary itself might be affected and fail to release T.S.H. They showed that the administration of small doses of thyroxine to one such case caused T.S.H. to reappear in the urine; this later disappeared when the myxoedema was under complete control. Our Case 16 is in many ways similar. Initially, this patient showed no measurable T.S.H. in the plasma. Her myxoedema was controlled until seven weeks before her second admission, when she again relapsed from failure to take thyroid. Her pituitary had evidently recovered its ability to secrete T.S.H. in the interval. We were not able to make further observations in Case 14, but we feel that the profundity of her myxoedema, rather than a selective pituitary failure of T.S.H. secretion, such as Cope (1938) and Shuman (1953) have suggested, could also explain our negative assay in this case. The occurrence of even higher levels in myxoedema of recent origin induced by thyroidectomy lends support to the idea that pituitary activity is greater in the early stages of myxoedema and may fail with prolonged lack of treatment.

The occurrence of high levels of T.S.H. in cretinism may be related to the youth of these patients, and is of particular interest since exophthalmos is not a feature of cretinism.

Our findings in cases of thyrotoxicosis without eye signs are similar to those of several other observers, though there is no general agreement. Some (Krogh and Okkels, 1933; Cope, 1938; Rawson and Starr, 1938; Galli-Mainini, 1942; De Robertis, 1948; Purves and Griesbach, 1949; D'Angelo *et al.*, 1951) found no measurable serum T.S.H. in cases without eye signs. The raised level of serum T.S.H. in the ophthalmic type has been found by De Robertis (1948), Asboe-Hansen *et al.* (1952), and Purves and Griesbach (1949), although the last have also found none present in some acutely advancing cases of malignant exophthalmos. It is possible that the distinction is more emphatic in our cases because the present method of assay is not significantly affected by the presence of excess thyroxine in the serum.

The interpretation of the variable results is difficult. De Robertis, whose results closely approximate to ours, suggested that there might be two types of thyrotoxicosis—one primarily of the thyroid itself, causing depression of pituitary activity, and the second primarily at a higher level with pituitary overactivity as the cause of the thyroid disorder. Our method is not suitable for detecting ranges of T.S.H. lower than normal, and consequently for showing pituitary depression in some cases. However, our findings show the association of severe exophthalmos with pituitary overactivity. It is possible that pituitary activity is of a lesser degree in those patients with minimal or moderate eye signs, and hence not easily measured. It is also possible that pituitary overactivity is not constant but variable, and that it is more spasmodic in ordinary cases, becoming more continuous in the cases with severe exophthalmos. It would therefore be more likely that high levels of serum T.S.H. would be found in random samplings from the latter cases. In either interpretation it is not likely that the T.S.H. itself is the cause of the exophthalmos, because equal and even greater amounts are found in hypothyroidism without eye signs. Some other factor must be involved.

Our findings in the three cases with severe ophthalmopathy in whom there was no evidence of thyroid disorder are also interesting. It is commonly believed that these cases are examples of the same type of disorder, the eyes only being affected. On this assumption the results could show that in these cases the other factor involved was operating alone. However, this is only an assumption, and it is equally possible that they are examples of some other unrelated disorders of which we have personal experience and which are well known to ophthalmologists (Duke-Elder, 1952).

It is, however, clear that a high level of serum T.S.H. can be found in cases without ophthalmopathy. If these cases of ophthalmopathy without thyroid disorder are accepted as the same disease, then ophthalmopathy can also exist without a high level of circulating T.S.H.

Thus our assay results could best be explained by assuming that there were two factors involved—one which produces exophthalmos and one which produces thyrotoxicosis. Although both appear to be present in thyrotoxicosis with severe eye signs, they need not necessarily be combined or produce both effects in the one patient. This suggestion has already been made as a result of experimental work in animals, which also implies that the other factor may be derived from the pituitary.

Brown Dobyns (1946) observed that highly purified T.S.H. had relatively little effect in producing exophthalmos in animals. Jefferies (1949) showed that iodination of pituitary extracts inactivated the T.S.H. principle but left some exophthalmos-producing reaction. Dobyns and Steelman (1953) extended the previous observations and were able, by repeated extracting, to produce two substances from the pituitary. In testing these two substances on animals they showed that one contained a T.S.H. free from exophthalmos-producing substance and the other an exophthalmos-producing substance virtually free from T.S.H. These observations, combined with our findings, permit us to support the contentions of De Robertis (1948) and Purves and Griesbach (1949) that T.S.H. alone is not the cause of the development of exophthalmos, and would suggest that the pituitary is also the source of a separate factor, capable of producing exophthalmos.

Summary

A method of assay of T.S.H. has been applied to clinical cases.

So small an amount of T.S.H. circulates in the serum of the normal person that estimation is difficult.

Patients with myxoedema of recent origin and young cretins showed a high level of serum T.S.H., as did most patients with spontaneous myxoedema. The pituitary may ultimately fail to secrete T.S.H. in myxoedema, but this may be reversed by treatment. The high level of T.S.H. in one cretin disappeared with substitution therapy.

Two out of five patients with thyrotoxicosis without severe eye signs showed a raised serum T.S.H., but not to the same level as those with severe eye signs.

Eight patients with thyrotoxicosis with severe eye signs all showed a raised serum T.S.H. level comparable to that of spontaneous myxoedema.

Three patients with severe eye signs without thyrotoxicosis showed levels not differing from those found in normal people.

We conclude that T.S.H. alone is not the cause of exophthalmos, but that some other factor which may also be of pituitary origin is involved.

We thank Dr. Russell Fraser for allowing us access to the patients, most of whom were under his care, and for his constant help and encouragement. Our thanks are also due to Mr. N. W. Please for his help with the statistical analysis, and to Armour Laboratories for their generous provision of the T.S.H. used.

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CONTINUOUS "NISENTIL" AND SUXAMETHONIUM IN ANAESTHESIA

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Continuous suxamethonium drip is proving a beneficial method of obtaining relaxation during anaesthesia for abdominal surgery. Though the method initially proved cumbersome, Green (1953) standardized a useful technique for its use in conjunction with nitrous oxide.

Its chief advantage is that after the drip is stopped full respiratory excursions return within one to five minutes. There is no residual paralysis as occurs when employing the long-acting muscle relaxants. In the light of present-day experience, partial curarization predisposes not only to anoxia but to the danger of undetected carbon dioxide accumulation, and in a very ill patient this may lead to a fatality shortly after leaving the operating theatre (Pask, 1955). The use of neostigmine to antagonize the muscle relaxants introduces undesirable muscarinic side-effects on the myocardium and the bronchial tree. In addition there is difficulty in defining its indication or contraindication in the individual case (Nosworthy, 1953).

The problem of prolonged apnoea which occurs with a single dose of 50 to 100 mg. of suxamethonium is largely eliminated. For by continuous drip administration the anaesthetist is readily able to observe the degree of individual sensitivity and regulate the dosage accordingly.

However, reflex activity, as a result of operative stimuli, may prove difficult to suppress when continuous suxamethonium is supplemented solely by nitrous oxide. The rate of flow of suxamethonium is regulated to produce respiratory arrest to an "end-point." This end-point is respiratory movement just short of diaphragmatic paralysis. It is our experience that the margin of flexibility between the end-point and a degree of paralysis where reflex movement of limbs or spasmodic, jerky contractions of the diaphragm occur is very narrow. Moreover, after discontinuance of the suxamethonium drip the patient regains consciousness too rapidly and may become restless and unmanageable. In some cases psychic trauma may well be a consequence.

Herington and James (1953) employed intermittent doses of pethidine to remedy some of these difficulties.