The following case of hypopituitarism illustrates the danger if the underlying cause of apparent myxoedema is unrecognised, and emphasises the risks of thyroid therapy under such circumstances. Some of the hormonal, haematological, electrocardiographic and renal functional changes are discussed.

**Case Report**

Mrs A. W., aged 46, a widow, was admitted to hospital on 15.10.48 complaining of pain in, and swelling of the eyelids, with purulent discharge from her eyes and nose for the preceding three days. She had had a cough and some tightness of her chest for the previous three months, and had been forced to curtail her household activities because of general weakness and shortness of breath. She thought her weight had remained constant for some years; for three years she had been taking iron tablets for “bloodlessness,” and during this time she had noticed her hair had been steadily falling out.

**Past History.**—She had had 11 pregnancies, the last eleven years previously, when she was delivered of a stillborn male child by breech presentation, and the placenta had been retained. The day following delivery she became febrile and was sent to a fever hospital where she remained for twenty-seven days. She failed to lactate, but this may well have been due to absence of suckling apart from pituitary insufficiency. Menstruation had not occurred subsequently.

**Examination.**—Temperature 97.6° F., pulse rate 82/mt., respiration 22/mt., height 54½ ins., weight 113 lbs. (3.12.48). Mentally she was markedly retarded, and appeared apathetic and listless. Her speech was slow, in keeping with her general demeanour. She was pale and obese, with gross palpebral oedema and a purulent discharge from the eyes and nose, from both of which a culture of staph. albus was later grown. Her hair was very thin, short, and brittle. Apart from some short “downy” hair the occiput was bare (Fig. 1). The eyebrows were thin, particularly laterally. Axillary and pubic hair was completely absent. The breasts appeared normal (Fig. 2). Her skin was dry and felt unusually soft in texture. Subcutaneous fat was normal in amount and consistency. The forearms and dorsum of the proximal phalanges showed a sparse growth of short fair hair.

**Systems.**

**Alimentary.**—Edentulous apart from two carious roots. Abdomen showed nothing abnormal.

**Cardiovascular.**—Nothing abnormal. B.P. 140/100.

**Respiratory.**—Some fine crepitations at both lung bases.

**Nervous.**—Myopic crescents in the optic fundi. Nil else abnormal.

**Genito-urinary.**—Urine. Acid. S.G. 1016. No albumin or reducing substance. Deposit—n.a.d. microscopically.
**Progress.**—The conjunctival and nasal infection cleared rapidly on systemic penicillin and sulphacetamide locally. In view of the tentative diagnosis of myxœdemà made at her initial examination she was given tab. thyroid sicc. gr. 1 daily from 19.12.48 for the following week, when the dose was increased to gr. 2 daily. After one week on this increased dosage, when about 20 gr. had been given, she began to feel nauseated, complained of epigastric discomfort and vomited frequently. B.P. was 120/80. General examination showed no change in her condition and no apparent cause for the vomiting, but the thyroid was stopped. The vomiting, however, continued intermittently for ten days, she became febrile (T. 09-100°F.) and her blood pressure fell to 80/50. She gradually recovered, and sixteen days after stopping thyroid in order to confirm that there was an association between thyroid medication and her vomiting, fever and hypotension, thyroid gr. 1 was given on two successive days. On the third day she became febrile (T. 09-4°F.), vomited and her blood pressure dropped from 110/85 to 85/55, so thyroid was again stopped. Although no further thyroid was given she continued to vomit at intervals, but her blood pressure remained between 115/70 and 100/60. On the numerous occasions when urinary chlorides were estimated they were found to vary between 3-9 g. per litre (Fantus’ method).

**Investigations.**—(Those which were made frequently are shown in the accompanying chart).

| Test                     | Result                        |
|--------------------------|-------------------------------|
| Hb. (Haldane)            | 75 per cent.                 |
| R.B.C.                   | 3,910,000/mm.³               |
| C.I.                     | 0.96.                         |
| P.C.V.                   | 36 per cent.                 |
| W.B.C.                   | 7000/mm.³                    |
| B.S.R. (Westergren)      | 19 mm. in 1 hr.              |
| Film                     | showed some anisocytosis with a fairly high proportion of macrocytes. Sternal marrow—normoblastic reaction. X-ray of chest normal. Cardiac size and outline normal. X-ray skull normal sella turcica. Histamine-fast achlorhydria (0.5 mg. histamine acid phosphate subcutaneously). Wassermann reaction negative. |
| 8.12.48 Glucose tolerance. Fasting blood sugar 67 mg. per cent. After 50 g. glucose orally, venous blood sugars were: ½ hr. 80 mg. per cent.; 1 hr. 100; 1½ hr. 92; 2 hr. 87; 2½ hr. 92. |
| 9.12.48 Insulin sensitivity. Fasting blood sugar 67 mg. per cent. Given 5 units sol. insulin intravenously. Venous blood sugar after 10 min. 60 mg. per cent.; 20 mins. 39; 30 mins. 42; 45 mins. 44; 60 min. 46. The test was terminated after one hour by giving glucose orally as the patient was flushed and stuporous but could be roused to drink; it was considered injudicious to proceed further, insulin hypersensitivity having been convincingly demonstrated though blood sugar was unknown at the time. |
| 15.12.48 B.M.R.          | –42 per cent.                |
| 16.12.48 B.M.R.          | –42 per cent.                |
| 28.12.48 Urinary gonadotrophin assay. Rat Uterine "units" per 24 hours 2.2 Rat Ovarian "units" *20. |
(These results were obtained by interpolation on previously constructed dose-response curves for the rat uterus and ovaries, using menopausal urine. Normally in a patient of this age significant increases in the weights of uterus and ovary will be obtained by the administration of the equivalent of 50 ml. of urine per rat, the gonadotropin in urine being extracted by the kaolin-acetone-ether method (Loraine, 1950). In this case, however, a slight response only was obtained with the equivalent of 300 ml. of urine, i.e. six times the quantity one would expect to produce a response at this age. These results are therefore expressed in terms of animal "units," as international standards for pituitary follicle stimulating and luteinising hormones are not available at present.)

Treatment was as shown on the chart. During the time that the higher dosage of testosterone was maintained thyroid was also given in doses of gr. 2 daily, but when the dose of testosterone was reduced that of thyroid was stopped, and almost immediately her weight began to increase steadily, and the vomiting
which had recurred from time to time, stopped. The packed cell volume
(P.C.V.) which had previously remained constant at about 35 per cent. rose
on testosterone therapy and was later maintained at 43.5 per cent.

19.3.49. Blood volume 2670 ml. (Evans Blue). Predicted normal blood
volume was 3400 ml. (Gibson and Evans, 1937). Urea clearance
(Van Slyke) 38 per cent. of normal. At this time she still retained
her myxedematous appearance and on 30.3.49 thyroid gr. 1
daily was recommenced in addition to the testosterone. Her
weight increased while on testosterone therapy by 14 lbs. in
ten weeks.

29.4.49. Blood urea nitrogen 24 mg. per cent. Water diuresis. Excreted
1050 ml. of 1130 ml. ingested within three hours. Maximum
spec. grav. 1013, minimum 1004.

3.5.49. Water diuresis repeated. Excreted 907 ml. of 1130 ingested within
three hours. Maximum spec. grav. 1011, minimum 1003.

These figures for water excretion are unusually high, as considerable water
retention usually occurs in response to ingestion of such amounts (Pickford
and Watt, 1950).

1.6.49. Urea clearance (Van Slyke) 49 per cent. of normal.

17.6.49. Gastric analysis: histamine-fast achlorhydria.

The deoxycortone injections were then stopped, and an attempt was made
to replace them by oral sodium chloride. This was given in cachets containing
a total of 10 g. daily and later 5 g. daily, but administration was invariably
followed by vomiting. After eighteen days, salt medication was stopped without
appreciable effect other than cessation of vomiting. Thyroid gr. 1 daily was
continued.

In November 1949, the patient was re-admitted to hospital to examine the
effects of ACTH, insulin and adrenalin on adrenal cortical function. These
have been reported separately (Duthie, 1950).

17.11.49. Thiocyanate space. 9.8 litres (21.3 per cent. of body weight).

This can be regarded as normal, and suggests that no undue
basal water retention was occurring. Insulin sensitivity (4 units
insulin intravenously).—Fasting capillary blood sugar 92 mg.
per cent.; 20 min. 56; 40 min. 46; 60 min. 58; 90 min. 75;
120 min. 58.

24.11.49. Urea clearance (Van Slyke) 32 per cent.

28.11.49. B.M.R. —11 per cent.

29.11.49. B.M.R. — 9 per cent.

1.12.49. Urinary gonadotrophins—No effect was obtained on either rat
ovary or uterus with a total dose equivalent to 400 ml. of urine.

9.12.49. 25 mg. ACTH (Organon) I.M. During the succeeding 24 hours
the output of urinary 17-ketosteroids was approximately doubled.

April 1950. Subsequently the patient's general condition remained
stationary. Physically and mentally she remained active if not agile, and was
able to do a full day's housework. Her appearance remained unchanged
while on thyroid, though hair growth, while much improved on the head,
was still almost absent in the axillae and on the pubis. Facial pallor remained
striking, though on 10.3.50 her haemoglobin was 102 per cent., P.C.V. 45 per
cent, and R.B.C. 5.29 million/mm.3 During routine out-patient visits her
blood pressure on occasions has been noted as high as 180/115.

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Discussion

The conception of "pituitary myxoedema" in which hypothyroidism develops as a sequel to failure of thyrotrophic hormone production, following destruction of the anterior pituitary, was firmly established by Means, Hertz and Lerman in 1940. Simpson (1948) condemns the term as confusing, but if it serves to draw attention to hypothyroidism as secondary to hypopituitarism, then it is useful, particularly as the latter has more important implications than the former.

Since 1940 and tentatively before then, many such cases have been described, and as in Means' patients so in this case, the unusual response to thyroid aroused the suspicion that the disorder was not primarily thyroid in origin. The vomiting, weakness, fever and hypotension, with continuing urinary chloride excretion, suggested that something closely resembling an Addisonian crisis had been precipitated, and this with myxoedema indicated a common origin in hypopituitarism. Further evidence was provided in the history of amenorrhoea persisting since the last confinement. Sheehan (1939, 1949) has provided detailed reviews of hypopituitarism, and shows that by far the commonest cause is post-partum collapse due to hæmorrhage. In this patient full records of the last confinement were not traceable, but it was noted that the sepsis resulted from retained placenta, and it is likely that removing the placenta produced a sufficient degree of shock to account for necrosis of the anterior pituitary by infarction.

The diagnosis of hypopituitarism in this patient was based therefore on the following points:

1. The history of a difficult confinement with retained placenta and post-partum sepsis, followed by failure of lactation and amenorrhœa.
2. The clinical appearance of myxoedema, with a low B.M.R. and high blood cholesterol.
3. The presence of generalised skin pallor, with complete absence of axillary and pubic hair.
4. The precipitation of an Addisonian crisis by giving thyroid in small doses.
5. The low urinary excretion of follicle stimulating hormone at an age when it would normally be high.

It was considered that the patient's condition warranted treatment with thyroid, but when given in doses which would be sub-optimal in primary hypothyroidism, and in a fraction of the dose which could be tolerated by a normal individual, an Addisonian crisis was precipitated. Subsequent experience showed that if the dose was increased very slowly, or if D.C.A. or testosterone propionate was administered simultaneously, thyroid could be given in therapeutic doses.
Fig. 1.—Shows the marked thinning of the hair over the occiput. Some months later it appeared normal.

Fig. 2.—Illustrating the normal nutritional status of the patient and the absence of pubic and axillary hair.
It has generally been advised that caution be exercised in giving thyroid to patients suffering from Simmonds' disease. Means (1949) mentions a case of "full-blown classic myxœdema" admitted to hospital, who on treatment with thyroid lost all semblance of myxœdema but went into a mysterious state of shock and died. Autopsy disclosed atrophy of most endocrines including the anterior pituitary and adrenals. Crooke (1948) discussing the treatment of Simmonds' disease, writes "Thyroid extract is dangerous until the patient is under control with testosterone and desoxycorticosterone, and its administration has resulted in death." Selye (1949) states: "thyroid therapy (to compensate for the secondary hypothyroidism) is dangerous, since hypopituitary patients are extremely sensitive to thyroid-hormone overdosage." Sayers and Sayers (1948) also drew attention to this extreme sensitivity to thyroid hormone of patients with Addison's disease and panhypopituitarism. Long and Miles (1950) described the opposite actions of thyroid and adrenal hormones in allergic hypersensitivity in guinea-pigs and produced evidence that administration of thyroid at first depresses adrenal cortical function and later, if continued, induces hypertrophy with presumably but not necessarily increased hormonal output. The doses of thyroxine used, however, were far from physiological, the animals were not hypophysectomised, and the striking feature of the effect of thyroid in hypopituitarism is the small dose required to precipitate a crisis.

Whether thyroid acts by further depressing already inactive adrenals or simply creates a relative insufficiency at the tissue cell level is of more than academic interest, as these cases require thyroid for restoration of normal activity. Although deoxycortone or testosterone may be required to counter adrenal insufficiency, if there was a possibility of inducing adrenal cortical hyperplasia by giving thyroid, it would obviously be undesirable that any further treatment should be given which might interfere with an increase of adrenal function. In this patient almost one year of treatment with thyroid was associated with an increase of urinary 17-ketosteroid excretion from less than 1 mgm. per diem to 1.6 and 1.2 mgm. per diem, *i.e.* from not measurable to measurable amounts. The evidence in animals for an effect of exogenous thyroid on the adrenals is that this is not exerted directly, but rather through the medium of the anterior pituitary (Tepperman, Engel and Long, 1943). Lack of this pathway in hypopituitarism would explain the different response to treatment from that in simple myxœdema, in which the adrenals are capable of responding to increased cellular metabolism by an increased output of cortical hormone.

**Electrocardiographic Findings**

Evans (1949) considered that such changes as occur in the heart in Simmonds' disease are the outcome of adrenal deficiency, but does not mention the influence of hypothyroidism or the effect of thyroid
extract under such circumstances. The E.C.G. reproduced (Fig. 3) was taken twelve days after finishing an initial course of 25 grains of thyroid extract given over sixteen days, when the adrenal crisis apparently so precipitated was subsiding, and the blood pressure was 110/70. The B.M.R. four weeks subsequently was —42 per cent. on two occasions.

Fig. 4 was taken seven months later when the patient had been on treatment with 1 grain thyroid daily for several months, and had been receiving DCA 5 mgm. I.M. daily for six weeks without extra salt. It shows striking changes in the shortening of the PR interval from 0·20 to 0·18 sec., increased amplitude of the QRS complexes which have been narrowed from 0·10 to 0·06 sec., while the T waves retain and have increased their positive charges very considerably except in lead III. The blood pressure at this time was 190/110, but the blood volume (2650 ml.) was less than when the patient was having testosterone (2950 ml.), so that the changes in the E.C.G. were probably not due to blood volume changes. Fig. 5 was taken a further five months later, during which interval the patient had been taking thyroid gr. 1 daily only, and shows little change except that the PR interval has shortened once more to 0·18 sec. The B.M.R. at this time was —11 and —9 per cent. on successive days, and the blood volume unchanged at 2630 ml.

It is unfortunate that no record is available of the E.C.G. before any specific treatment had been given. However, it seems probable that such changes as occurred were in fact the result of correction of adrenal insufficiency rather than of hypothyroidism, as when the
first record was taken there had been clear evidence of adrenal insufficiency, and sufficient thyroid had been given to precipitate it. The cardiac outline on X-ray at that time did not suggest myxœdematous changes and consequent alteration of the E.C.G. due to hypothyroidism.

![ECG tracings](image)

Fig. 4.—E.C.G. 6.6.49 after several months on thyroid and six weeks on DCA 5 mg. daily intramuscularly. The QRS complexes are narrower and of higher voltage, while the T waves are considerably more positive in limb leads I and II. QTc is now 0.437 sec.

Hæmatological Changes

Initially the patient showed a normocytic normochromic anaemia with the packed cell volume (P.C.V.) constantly about 35 per cent., and a normal sternal marrow. After several weeks on oral iron therapy the anaemia remained, even after two weeks’ treatment with testosterone propionate 50 mgm. daily and thyroid gr. 2 daily. A
further four weeks later on 25 mgm. testosterone propionate daily with oral iron but without thyroid the P.C.V. has increased to 43.5 per cent. and remained between 42.5 and 44.5 per cent. during the subsequent nine months without further testosterone therapy. The anaemia had failed to respond to two months' treatment with iron and thyroid gr. ½ to 2 daily, but having responded to testosterone remained normal subsequently without further androgen therapy. The total blood volume remained low throughout the nine months of observation (2670 ml., 2650 ml., 2630 ml.) except after prolonged testosterone therapy when it increased to 2950 ml. These observations, however, were all made after treatment with testosterone had been started. Watkinson, McMenemey and Evans (1947) discussed the
use of testosterone in the treatment of the anaemia associated with hypopituitarism and hypogonadism and concluded that the administration of male sex hormone in the two cases described enabled the marrow to utilise haematinic principles which it had previously been unable to do. Naish and Foss (1947) reported a similar case.

The behaviour of the anaemia in the patient now described would support this view, iron and thyroid had been given in adequate amounts, but liver extract had not been given as the appearance of a normoblastic marrow indicated that it was unnecessary.

**Gastric Function**

Examination of gastric juice following the injection of histamine showed achlorhydria before and after treatment with thyroid, testosterone and DCA, so that none of these measures apparently affected acid secretion. The position of the tube, however, was not checked radiologically.

Watkinson et al. (loc. cit.) reported the reappearance of free acid in the gastric juice and adduced this as evidence that pituitary function had improved in response to testosterone. In general such replacement therapy tends to diminish pituitary activity, and a test meal without the use of histamine forms the basis of this opinion. Sheehan and Summers (1949) remarked that of 21 accepted cases of hypopituitarism in whom gastric analysis was carried out, 5 patients had a small amount of free hydrochloric acid and 3 showed normal curves. They added that there was no constant relation between the degree of anaemia and the failure to secrete hydrochloric acid.

**Renal Function**

It has long been recognised that this is impaired in adrenal insufficiency, in hypopituitarism, and in myxoedema.

In this patient, concentrating power was constantly impaired, and although no measurements of renal blood flow were made there was no evidence that the therapeutic measures employed made any difference to concentrating power as measured by concentration—dilution, and urea clearance tests.

Luft and Sjögren (1949) reported a case of panhypoadenopituitarism with marked improvement in renal blood flow following thyroxin with testosterone propionate, and in whom the addition of deoxycortone increased the glomerular filtration while the renal blood flow remained constant. Beaumont and Robertson (1943) and Miller (1946) reported similar cases showing impaired renal function. Pickford and Watt (1950) reported on the changes in renal function in man due to disease of the anterior lobe of the pituitary, and found that the absence of an intact anterior lobe leads to an inability to excrete a suddenly increased load of water, and even to water
intoxication with fits. This depression of renal function is associated with a low filtration rate and a low rate of blood flow through the kidney, with a normal filtration fraction. White, Heinbecker and Rolf (1949a) have observed a marked enhancing effect of growth hormone on renal function in both normal and hypophysectomised dogs, having concluded from earlier experiments (1947, 1949b) that the depressing effects of hypophysectomy on renal function were not due to a lowering of thyroid, of gonadal, or of adrenal cortical function, and they suggest that pituitary growth hormone may be identical with "renotrophic factor."

It seems probable, therefore, that in these patients, depression of renal function is commensurate with the degree of destruction of the anterior lobe of the pituitary, which as Sheehan (1937) has shown, may be incomplete. In any case, the renal disability resulting is a minor handicap.

TREATMENT

In order to restore these patients to normal activity the fullest possible replacement therapy is required. While no satisfactory and complete anterior pituitary replacement is at present feasible, it is possible to substitute for "end-organ" hormonal lack by giving thyroid, deoxycortone, and the appropriate sex hormone. Thyroid, as is well recognised, is dangerous unless the patient is protected against acute adrenal insufficiency by deoxycortone. Cortisone, if more generally available, particularly in a delayed absorption form such as implantation pellets or an oral preparation, would be most valuable in correcting the faulty glucose metabolism. These patients and those with Addison's disease, frequently die in coma associated with hypoglycaemia; cortisone should be most effective in protecting against this complication. Meanwhile, this drug is in short supply and is unsuitable in its present form for prolonged treatment. In this connection it is possible that one less well recognised effect of testosterone may be responsible for its satisfactory reputation in the treatment of this condition. In general testosterone produces water and electrolyte retention with protein anabolism, and induces a feeling of well being. Its virilising effect follows with prolonged large doses. Eisenberg, Gordon and Elliott (1949) have shown that testosterone under certain conditions is capable of inhibiting the uptake of oxygen and glucose by rat brain, and in this way testosterone may correct the metabolic defect associated with hypoglycaemia which is responsible for the death of so many of these patients in coma.

SUMMARY

1. A case of hypopituitarism is described which presented clinically as myxœdema.
2. The danger of administering thyroid to such patients without
the addition of DCA or testosterone is illustrated, and the mechanism of this hypersensitivity to thyroid is examined.

3. The changes in the blood, in renal and gastric function, and in the electrocardiogram are discussed.

4. Treatment of such cases is satisfactory, but requires constant supervision.

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REFERENCES

Ashman, R., and Hull, E. (1941), Essentials of Electrocardiography, second edition. New York.

Beaumont, G. E., and Robertson, J. D. (1943), Brit. Med. Journ., 2, 356.

Crooke, A. C. (1948), Practitioner, 161, 298.

Duthie, J. J. R. (1950), Edin. Med. Journ., 57, 341.

Eisenberg, E., Gordon, G. S., and Elliott, H. W. (1949), Endocrinol., 45, 113.

Evans, W. (1949), Proc. Roy. Soc. Med., 42, 331.

Gibson, J. G., and Evans, W. A. (1937), Journ. Clin. Invest., 16, 317.

Graybiel, A., and White, P. D. (1949), Electrocardiography in Practice. London: W. B. Saunders Company.

Long, D. A., and Miles, A. A. (1950), Lancet, 1, 492.

Loraine, J. A. (1950), Journ. Endocrinol., 6, 319.

Luft, R., and Sjögren, B. (1949), Acta Endocrinologica, 2, 44.

Means, J. H. (1949), Journ. Clin. Endocrinol., 9, 659.

Means, J. H., Hertz, S., and Lerman, J. (1940), Trans. Assoc. Amer. Phys., 55, 32.

Miller, R. A. (1946), Brit. Med. Journ., 2, 650.

Naish, J., and Foss, G. L. (1947), Lancet, 2, 35.

Pickford, M., and Watt, J. A. (1950), Journ. Endocrinol., 6, 398.

Sayers, G., and Sayers, M. A. (1948), Rec. Progress Hormone Research, 2, 81.

Schweizer, M., Ehrenberg, A., and Gaunt, R. (1943), Proc. Soc. Exper. Biol. and Med., 52, 349.

Selye, H. (1949), Textbook of Endocrinology, second edition, p. 288. Montreal.

Sheehan, H. L. (1937), Journ. Path, and Bact., 45, 189.

Sheehan, H. L. (1939), Quart. Journ. Med., 32, 277.

Sheehan, H. L., and Summers, V. K. (1949), Quart. Journ. Med., 42, 319.

Simpson, S. L. (1948), Major Endocrine Disorders, second edition, p. 81. London.

Tepperman, J., Engel, F. L., and Long, C. N. H. (1943), Endocrinology, 32, 373.

Watkinson, G., McMenemey, W. H., and Evans, G. (1947), Lancet, 1, 631.

White, H. L., Heinbecker, P., and Rolf, D. (1947), Amer. Journ. Physiol., 149, 404.

White, H. L., Heinbecker, P., and Rolf (1949b), Amer. Journ. Physiol., 157, 47.

White, H. L., Heinbecker, P., and Rolf (1949b), Amer. Journ. Physiol., 156, 67.