A synopsis of

ENDOCRINOLOGY AND METABOLISM

IAN RAMSAY

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PREFACE TO SECOND EDITION

When asked by Dr Ferriman to undertake the revision of 'A Synopsis of Endocrinology and Metabolism' for its second edition, I willingly accepted, thinking that it would just be a question of introducing a new test here and a new drug there. In fact the whole subject has moved at such a great pace over the past 10 years, since the first edition was published, that the book has been almost totally rewritten, although the original format has largely been adhered to.

One of the biggest difficulties has been to decide what was outmoded and should be left out of this edition. Critics may find some antediluvian tests retained in the book. This has been done deliberately since many of the people in the less technologically developed areas of the world who will (hopefully) buy the book may not have access to sophisticated methods for measuring hormones.

Purists may also complain that, in a book which contains the word 'metabolism' in its title, there is no mention of subjects such as porphyria, Gilbert's disease or gout. These omissions are deliberate; it was decided to include only those areas of metabolism which are normally regarded as the province of the practising clinical endocrinologist.

I hope that this book will be of use to senior medical students, junior doctors, general practitioners and those in other specialities who need a synopsis of what has become to them a 'terra incognita'.

Since the medical world is now divided between those who use conventional units of measurement and those who have discovered the magic of SI, normal values are given in both. The normal values are given only as a guide and will not necessarily coincide absolutely with those of the reader's local laboratory.

My thanks are due to Mrs Maureen Reynolds for deciphering my handwriting and typing the manuscript and to Miss Siew Bazany and Miss B. Whiteley for the illustrations.

London, January, 1979 *Ian Ramsay*

FOREWORD

By Sir Richard Bayliss, KCVO MD FRCP
Physician to HM The Queen and Head of HM's Medical Household
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Inevitably any textbook is a compromise; a compromise between brevity and length, between what to put in and what to leave out, between the old and the new and between the superficial and the deep. Dr Ian Ramsay has evolved his own compromise, a personal one which his publishers are likely to accept readily because in small compass he has written a textbook likely to have wide appeal. The mode of presentation has a particular attraction.

None of this would have been to much avail were it not for Dr Ramsay's profound knowledge of his subject and his prodigious industry. Within his professional life-time endocrinology and the important metabolic disorders, that he writes about, have undergone such major advances that this simply has to be a new book. It is; and it is also a great credit to British medicine and to a single physician; for few have the breadth to write single-handed such a text which by virtue of its single-handedness has balance and uniformity of style.

CONTENTS

DISEASES OF THE HYPOTHALAMUS AND ANTERIOR LOBE OF THE PITUITARY

The pituitary and hypothalamus are so closely related that their anatomy and physiology will be considered together.

HYPOTHALAMUS

Anatomy. The hypothalamus is that part of the cerebral cortex which makes up the floor and part of the lateral walls of the third ventricle (*Fig.* 1). It lies above and behind the pituitary and extends from the optic chiasma anteriorly to the mamillary bodies posteriorly. The lowest part of the hypothalamus is called the tuber cinereum. From this a process extends anteriorly and inferiorly to form the infundibulum or pituitary stalk and the posterior lobe of the pituitary. The hypothalamus contains a large number of nerve cells, some of which, on anatomical and functional grounds, have been identified as nuclei. The main ones are the supraoptic and paraventricular nuclei and the mamillary bodies (*Fig.* 1).

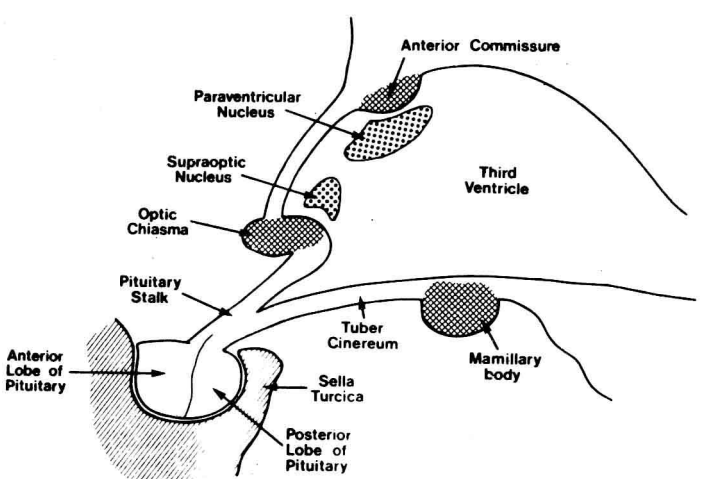

Fig. 1. Longitudinal, vertical, midline section of the hypothalamus and pituitary. Anterior is to the left.

The blood supply of the hypothalamus is from small vessels arising from the Circle of Willis and also from branches of the middle cerebral artery. The blood supply of the pituitary stalk is from the paired superior hypophysial arteries arising from the internal carotids just above the dura mater.

The main neural connections between the hypothalamus and pituitary are tracts carrying fibres from the supraoptic and paraventricular nuclei to the posterior lobe and fibres which transmit release or inhibiting factors from the medial and basal parts of the hypothalamus to the capillaries of the portal veins, whence they are passed to the anterior pituitary.

Neural connections are known to exist between the hypothalamus and the frontal lobes, the thalamus and brain stem.

Physiology. The hypothalamus contains a number of important centres which control various body functions.

1. Centres affecting activities under the control of the autonomic nervous system including circulatory, respiratory and gastrointestinal behaviour, appetite and food intake, temperature regulation, carbohydrate and fat metabolism.
2. Centres in the tuber cinereum concerned with the regulation of secretion of anterior pituitary hormones. Substances are released which pass down the portal system of veins into the anterior pituitary. The structures of some of them are known. Most have a stimulatory role and the secretion of some of them may be regulated either by the level of anterior pituitary hormones reaching the hypothalamus (short feedback loop) or by the concentration of target gland hormones (e.g. of thyroid, adrenal or gonad) in the hypothalamus (long feedback loop).

Stimulatory hormones:

Thyrotrophin-releasing hormone (TRH)
Gonadotrophin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH)
Growth hormone-releasing hormone (GRH)
Corticotrophin-releasing factor (CRF)
Prolactin-releasing factor (PRF)

Hypothalamic inhibiting hormones also exist and pass down the portal system.

Inhibitory hormones:

Prolactin release-inhibiting factor (PIF)
Growth hormone-release inhibiting hormone (GH-RIH or Somatostatin)
Melanocyte-stimulating hormone inhibitory factor (MIF)

It should be noted that corticotrophin-releasing factor is probably also responsible for the release of 'β-melanocyte-stimulating hormone', now known to be β-lipotrophin. TRH also releases prolactin

from the pituitary. Somatostatin, which has also been found in the stomach, small intestine and pancreas has, in addition to its effect on growth hormone, a variety of other inhibitory actions, including suppression of insulin and glucagon secretion from the pancreas, of gastrin from the stomach and duodenum and of cholecystokinin, secretin and enteroglucagon from the small intestine. It also interferes with TSH response to TRH.

The control of anterior pituitary activity by the hypothalamus may be modified by physical and emotional stress and by the action of drugs which alter the concentrations of hypothalamic neurotransmitters.

Brief mention must be made of the endorphins and enkephalins since, although their role in endocrinology is not at all clear, new data are being rapidly accumulated. They are closely related groups of peptides and represent fragments of the anterior pituitary hormone β-lipotrophin. Although β-endorphin can be released from the anterior pituitary it seems clear that β-lipotrophin and its derivatives are synthesized mainly in the brain. Their prime effect is on opiate receptors in the brain, where they have a morphine-like action, but they have also been shown to stimulate the secretion of growth hormone and prolactin by the anterior pituitary. Since these are 'stress' hormones, and since the parent molecule β-lipotrophin is also secreted by the anterior pituitary in stressful situations, much speculation has arisen about the role of endorphins and enkephalins in integrating the hormonal and opiate responses to noxious stimuli.

3. The onset of puberty is determined in the hypothalamus. The mechanisms are complex. Prepubertally there seems to be a highly sensitive inhibitory feedback by gonadal steroids on the release of gonadotrophins. During late prepuberty a rise in the threshold occurs and this initiates gonadotrophin secretion. Destructive lesions of the posterior hypothalamus lead to precocious puberty and of the anterior hypothalamus to testicular atrophy in the male and amenorrhoea in the female.

   Melatonin produced by the pineal gland may inhibit puberty physiologically. Tumours of the pineal can cause precocious puberty.

4. The supraoptic and paraventricular nuclei are concerned with the release of:
   a. Arginine vasopressin (antidiuretic hormone) (*see* Chapter 2).
   b. Oxytocin which is concerned with the maintenance of established labour, the contraction of the uterus postpartum and the ejection of milk during breast feeding.

   Arginine vasopressin and oxytocin pass down nerve fibres in neurosecretory granules bound to neurophysins into the posterior pituitary, where, after being stored, they are released into the bloodstream. In the event of damage to the posterior pituitary the

hormones can be released from higher up the stalk and such damage does not therefore always lead to diabetes insipidus (*see* Chapter 2).

5. The hypothalamus is concerned with emotional behaviour, though this is an activity which is shared with other parts of the central nervous system. Strong emotion, stress signals, etc., emanating from the cerebral cortex spread through the limbic system to the hypothalamus. This results in the increased release from the pituitary of such hormones as ACTH, growth hormone, prolactin and arginine vasopressin.

PITUITARY GLAND

Embryology. The pituitary is formed by the fusion of two separate structures:

1. An upgrowth from the primitive buccal cavity forms a closed sac called Rathke's pouch. This becomes the anterior lobe of the pituitary. The residual lumen of Rathke's pouch obliterates or may remain as a small cyst or cysts.
2. A neural downgrowth from the floor of the third ventricle which forms the pituitary stalk and the posterior lobe.

Anatomy. The pituitary consists of anterior and posterior lobes. The main blood supply of the anterior lobe is from the portal veins which run from the junction of the pituitary stalk with the hypothalamus to sinusoids in the anterior lobe. Additional blood supply may be derived from branches (the arteries of the trabecula) of the superior hypophysial arteries and from the inferior hypophysial arteries which come off the internal carotid arteries in the cavernous sinuses. The posterior lobe of the pituitary is supplied by the inferior hypophysial arteries. The venous drainage of the pituitary is to the cavernous sinuses.

ANTERIOR LOBE (PARS DISTALIS)

Histology. The anterior lobe contains several cell types. The original classification was based on the colour produced by staining with haematoxylin and eosin. More information has been added by the development of various periodic acid-Schiff histochemical methods and recently immunological methods have identified specific cells as producing individual hormones. Cell types which are currently recognized are:

Growth hormone acidophils.
Prolactin acidophils.
TSH basophils.
Gonadotrophin basophils.
ACTH and lipotrophin (β MSH) basophils.

Chromophobes, found on conventional staining, usually are seen to contain secretory granules on electron microscopy, and may secrete ACTH and prolactin.

Physiology. The anterior pituitary secretes:

1. Growth hormone (human growth hormone, HGH, somatotrophin).
2. Thyroid-stimulating hormone (TSH, thyrotrophin).
3. Adrenocorticotrophin (ACTH, corticotrophin).
4. Follicle-stimulating hormone (FSH).
5. Luteinizing hormone (LH) in the female, known previously as interstitial-cell-stimulating hormone (ICSH) in the male.
6. Prolactin (mammotrophin).
7. Lipotrophin (LPH, melanocyte-stimulating hormone, MSH).

1. GROWTH HORMONE (HGH). HGH is a single-chain polypeptide. The anterior pituitary contains abundant growth hormone throughout life and the hormone can resist post-mortem autolysis. The secretion per 24 hours is about 4 mg, but the rate increases under the stimuli of fasting, sleep, muscular exercise, hypoglycaemia, stress and following the administration of arginine. The secretion is very labile and a rise in serum levels can be demonstrated within a few minutes of insulin-induced hypoglycaemia.

   The effects of HGH are:

   a. Protein anabolism, with nitrogen retention.
   b. Acceleration of epiphysial bone growth and thus an increase in height.
   c. Inhibition of fat synthesis and the release of free fatty acids (FFA, non-esterified fatty acids, NEFA) from fat stores. The mobilization of fat for energy purposes may spare amino acids needed for anabolic purposes.
   d. Uptake of glucose by cells diminishes and there is increased resistance to the hypoglycaemic action of insulin. Excess HGH leads to hyperglycaemia. Deficiency of HGH leads to hypoglycaemia and undue sensitivity to insulin.
   e. Calcium, phosphorus, sodium, potassium, chloride and magnesium balances become positive following HGH administration, probably secondarily to its effect upon growth.

   It is likely that certain of the above effects are not produced by HGH itself but by substances produced by the liver called somatomedins. Their production is stimulated by HGH and is potentiated by good nutrition and by the action of insulin. Cirrhosis, malnutrition, glucocorticoids and oestrogens seem to have an inhibitory effect on somatomedin production. Tissue response to the action of somatomedins is genetically determined.

2. THYROID-STIMULATING HORMONE (TSH, THYROTROPHIN). TSH is a double-chain glycoprotein produced by specific polyhedral

basophils, which can be shown to become hyperplastic in patients with primary hypothyroidism. Radioimmunoassay shows undetectable levels (< 2 μU/ml) of TSH in 20 per cent of the normal population and concentrations in the remainder ranging up to about 4 μU/ml (4 mU/l). Mean values in young and middle-aged adults measured by the more sensitive cytochemical bioassay are approx. 1 μU/ml. The secretion of TSH is controlled by two mechanisms. The first is by the hypothalamic secretion of the tripeptide thyrotrophin-releasing hormone (TRH). This may have a circadian rhythm with low levels of stimulation during the late afternoon and high levels in the early hours of the morning. TRH may be stimulated by exposure to a cold environment. It is possible that thyroid hormones have an inhibitory negative feedback effect on TRH as does growth hormone-release inhibiting hormone (GH-RIH, somatostatin). The second and probably the more important means of controlling TSH secretion is by a negative feedback of thyroid hormones on the anterior pituitary, which modifies the response of the thyrotrophs to TRH. Low levels of thyroid hormone stimulate the thyrotrophic response to TRH and high levels inhibit it (*Fig.* 2). Thus in hypothyroidism the TSH concentration in serum is high, whereas in hyperthyroidism it is suppressed.

TSH stimulates the thyroid by activating adenyl cyclase in cell membranes. It causes:

a. An increase in mass of the thyroid.
b. An increase in acinar cell height.
c. An acceleration in synthesis and secretion of thyroid hormones. All steps in the synthesis are affected (*see* Chapter 3) and are reflected by an increase in iodine uptake by the thyroid.

3. ADRENOCORTICOTROPHIN (ACTH, CORTICOTROPHIN). ACTH is a single-chain polypeptide consisting of 39 amino acids. The 24 amino acid sequence at the N-terminal end is responsible for its biological activity and has been synthesized (Synacthen, Ciba). ACTH stimulates the production and secretion of cortisol and other hormones from the adrenal cortex. It increases adrenal blood flow, raises the cholesterol content of the adrenal, leads to ascorbic acid depletion in the cortex and, if the stimulation is long continued, causes adrenal hyperplasia. The production of aldosterone by the adrenal cortex is largely determined by the renin-angiotensin system (*see* Chapter 4).

ACTH secretion is stimulated by corticotrophin-releasing factor (CRF), produced in the hypothalamus and secreted into the portal veins whence it passes to the anterior pituitary. The control of CRF seems to be by means of a negative feedback of cortisol on the hypothalamus, high levels inhibiting CRF and low levels stimu-

lating it. However, there is an apparent change in the level at which the feedback control is set since there is a circadian rhythm of ACTH secretion. Low levels are found at midnight, but increasing amounts are secreted between 2.00 a.m. and 8.00 a.m. Levels then gradually fall. ACTH concentrations at 10.00 a.m. are between 10 and 80 ng/l and are below 10 ng/l at midnight. ACTH secretion can be stimulated by physical and emotional stress and can be inhibited by the administration of glucocorticoids.

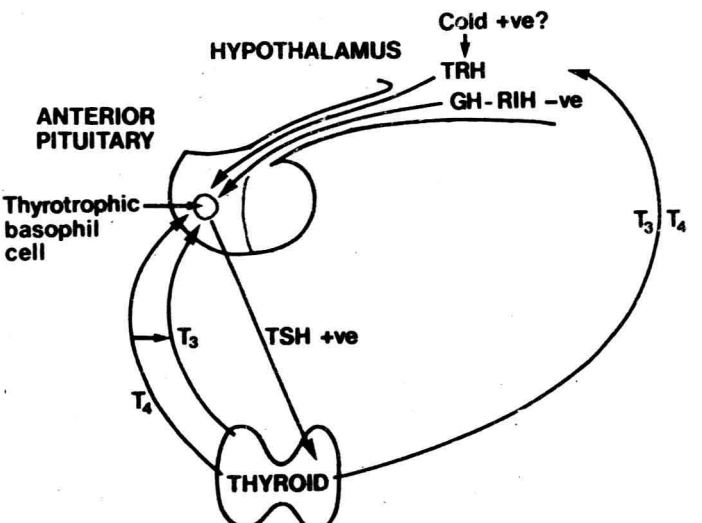

Fig. 2. Control of the secretion of TSH by the anterior pituitary. T_4 = thyroxine, T_3 = tri-iodothyronine, GH-RIH = growth hormone release inhibiting hormone (somatostatin), +ve = stimulatory, –ve = inhibitory.

In primary hypoadrenalism (Addison's disease) the increased skin pigmentation may be due to the excessive production of ACTH or β-lipotrophin, or both, since they have a common heptapeptide core (Met-Glu-His-Phe-Arg-Trp-Gly) which causes pigmentation in amphibian bioassays. Contrariwise, the pale skin of hypopituitarism is due to deficiency of ACTH and/or lipotrophin.

4. FOLLICLE-STIMULATING HORMONE (FSH). FSH is a double-chain glycoprotein. The concentration is low in infancy, but rises

with the onset of puberty, more so in boys than girls. In adult males FSH is secreted in a pulsatile manner, but the oscillations in the level are of low amplitude. The normal range is from 2 to 6 U/l. FSH stimulates growth of the seminiferous tubules and the production of spermatozoa. The secretion of FSH is stimulated by the hypothalamic peptide hormone gonadotrophin-releasing hormone (GnRH). The feedback control is probably via a substance produced during the process of normal spermatogenesis called 'inhibin'. FSH levels are raised in disease involving the seminiferous tubules and in 50 per cent of males after the age of 50.

In women FSH causes the development of follicles in the ovary. The follicle produces increasing amounts of oestrogen, with a rapid rise in the four days before the 14th day of the cycle. The peak level of oestrogens is followed within 24 hours by a surge in LH and, to a lesser extent, in FSH and ovulation takes place. FSH secretion is governed by GnRH, but the feedback control is complex, oestrogens inhibiting one 'centre' (negative feedback), but stimulating another at the midpoint of the cycle (positive feedback). Normal plasma values for women are:

Follicular phase	1–6 U/l
Mid-cycle peak	4–15 U/l
Luteal phase	1–5 U/l

After the menopause, in patients with ovarian dysgenesis or agenesis and following gonadal destruction or removal the FSH levels are higher than 20 U/l.

5. LUTEINIZING HORMONE (LH). LH is a double-chain glycoprotein. In women it plays a part in stimulating oestrogen production by the ovary, it is responsible for the release of the ovum from the follicle and for the development and maintenance of the corpus luteum and its production of progesterone. The secretion of LH is controlled by GnRH and the feedback mechanism is as described above. Normal levels in a female are:

Follicular phase	1–10 U/l
Mid-cycle peak	8–60 U/l
Luteal phase	2–14 U/l

In males LH (or interstitial cell-stimulating hormone, ICSH, as it is more properly but more cumbersomely known) stimulates the production of testosterone by the interstitial cells (Leydig cells). Normal plasma levels of LH in males are 4–14 U/l.

6. PROLACTIN (MAMMOTROPHIN). Prolactin is a single-chain polypeptide. It is secreted in a pulsatile manner and blood levels are higher at night and during sleep which is not associated with rapid eye movements. Normal levels during the morning are less than 360 mU/l. Levels rise with physical and emotional stress. Its release is mainly controlled by prolactin release-inhibiting factor (PIF). It

seems likely that PIF is, in fact, dopamine. Drugs which block dopamine receptors, e.g. chlorpromazine, haloperidol and metoclopramide, or which deplete neural tissues of dopamine, e.g. α-methyldopa and reserpine, elevate prolactin levels. Thyrotrophin-releasing hormone (TRH) and vasopressin act as prolactin-releasing factors, but their effect may not be physiological. The existence of an additional prolactin-releasing factor has been suggested. The presence of high levels of oestrogens seems to have a facilitative effect on prolactin synthesis and release. Levels are high in pregnancy, when the pituitary enlarges due to hypertrophy of the prolactin-secreting acidophils. Suckling, mammary stimulation and coitus also raise prolactin levels, possibly by a hypothalamic serotonin mechanism.

Prolactin seems to have many effects on animal physiology but in man it has only been shown to be important in the initiation and continuation of breast feeding and in inhibiting fertility while breast feeding continues.

7. LIPOTROPHIN (LPH, MSH). β-Lipotrophin release from the anterior pituitary seems to be controlled in the same way as that of ACTH. Its only biological effect seems to be pigmentation of the skin. This effect was previously attributed to β-MSH but this hormone is not in fact found in man, though its 22 amino acid sequence does form part of the structure of β-lipotrophin.

DISEASES OF THE HYPOTHALAMUS

Aetiology

1. Tumours – craniopharyngioma, hamartoma, ectopic pinealoma, neurofibroma, ganglioglioma.
2. Infections – basal meningitis, tuberculosis, syphilis, encephalitis.
3. Encephalopathy.
4. Sarcoidosis and other granulomas.
5. Reticuloses.
6. Collagenoses.
7. Genetic conditions – tuberous sclerosis, releasing factor deficiencies.
8. Mechanical factors – hydrocephalus, injuries involving the base of the brain.
9. Arteritis and arteriosclerosis.

Signs and Symptoms. They are many and varied owing to the presence of so many centres in a small area. They may be classified as follows:

1. VEGETATIVE DISTURBANCES, such as somnolence, hypothermia or hyperthermia.
2. METABOLIC DISTURBANCES, such as increased appetite and

obesity or decreased appetite and emaciation, hyperglycaemia and glycosuria, the latter usually being transient.

3. DISTURBANCE OF ANTERIOR LOBE HORMONE PRODUCTION from involvement of centres controlling the release or inhibition of hormones. There may be:
   a. Galactorrhoea and hypogonadism due to lack of PIF and consequent excessive secretion of prolactin.
   b. Retarded growth due to reduction in HGH.
   c. Testicular atrophy with loss of libido, potency and body hair in men, oligomenorrhoea or amenorrhoea in women and delayed puberty in children due to gonadotrophin deficiency. Precocious puberty may be due to premature release of gonadotrophins.
   d. Signs indicative of diminished ACTH such as lassitude and hypotension or signs of increased activity such as hypertension, hirsuties and impaired glucose tolerance.
   e. Signs of diminished thyroid function due to lack of TSH.
4. DISTURBANCE OF ARGININE VASOPRESSIN (ANTIDIURETIC HORMONE) PRODUCTION with polyuria and polydipsia. (*See* Diabetes Insipidus, Chapter 2.)
5. PSYCHIC AND EMOTIONAL DISTURBANCES – diencephalic epilepsy, change in personality, dementia.

METHODS OF INVESTIGATING THE HYPOTHALAMUS

1. GROWTH HORMONE. The most commonly used test is stress induced by insulin hypoglycaemia. Soluble insulin 0·1–0·15 unit/kg body weight (0·05 unit/kg if hypoadrenalism also seems likely) is injected after a fasting blood sample has been obtained for basal HGH. Bloods are sampled for HGH and glucose every half hour for 3 hours. The blood glucose should fall below 2·2 mmol/l (40 mg/100 ml) at about 30–45 minutes and there should be symptoms of hypoglycaemia (sweating, palpitations, feelings of unreality, etc.). If there is inadequate hypoglycaemia give a repeat dose or half a dose at 45 minutes. If the patient gets severe hypoglycaemia during the test, blood should be taken for glucose and HGH (and cortisol where appropriate) and 15–25 g of glucose should be given i.v. Sampling of blood should continue till the end of the test as the stress response will be apparent if the patient is normal, or absent if the patient is abnormal.

   The test should not be performed in patients with hypokalaemia or epilepsy and only in patients with ischaemic heart disease or cerebrovascular disease if absolutely essential to diagnosis and management.

   Basal fasting HGH is usually 0–10 μU/ml (0–10 ng/ml) and a normal response to hypoglycaemia is a rise to more than 20 μU/ml.

However in some laboratories a rise to between 10 and 20 μU/ml is regarded as normal. Note that the rise will be impaired not only in hypothalamic disease but also in anterior pituitary disease.

Less commonly used tests are performed by the injection of lysine vasopressin or of bacterial pyrogen. Their side effects are unpleasant and the results not as reliable as those produced by insulin hypoglycaemia.

Paediatricians may prefer not to perform an insulin hypoglycaemia test. The alternatives are exercise, subcutaneous glucagon and the oral administration of Bovril or arginine. If the HGH rises to above 20 μU/ml the response is normal. If the rise is less than this an insulin test should be carried out.

2. THYROID-STIMULATING HORMONE. It is not possible to define a lower range of normality for TSH measured by radioimmunoassay. Patients with low thyroxine and tri-iodothyronine levels in blood who also have low or unrecordable TSH levels may have either hypothalamic or pituitary disease. The injection of TRH 200 μg i.v. may show a rise of TSH in patients with hypothalamic disease, the 60-min value exceeding that at 20 minutes. Although an absent rise may indicate pituitary disease, this response can also happen in elderly euthyroid persons. Patients with hypopituitary hypothyroidism may sometimes show a TSH response to TRH. Conversely, euthyroid acromegalic patients may show no response. The test is thus difficult to interpret.
3. ADRENOCORTICOTROPHIN. In most situations measurement of plasma cortisol gives accurate information about the secretion of ACTH. The most commonly used stimulatory test is the insulin hypoglycaemia test (*see* p. 15). Other less commonly used tests are the lysine vasopressin and bacterial pyrogen tests (*see above*). Providing that the adrenal has been shown to be capable of responding to exogenous ACTH (*see* p. 15) a failure of the cortisol to rise by 200 nmol/l (7·2 μg/100 ml) above the basal level or fail to reach 550 nmol/l (20 μg/100 ml) implies either hypothalamic or pituitary disease but does not distinguish between them. The figures given for cortisol are as measured by the Mattingly fluorometric method.
4. FOLLICLE-STIMULATING HORMONE
5. LUTEINIZING HORMONE

these will be considered together.

In hypothalamic or pituitary disease gonadotrophins are at the lower limit of the normal range or subnormal. In pituitary disease the injection of gonadotrophin-releasing hormone (GnRH or LHRH) 100 μg fails to cause a rise of FSH or LH, whereas in hypothalamic disease there may sometimes be a response. Solitary hypothalamic deficiency of GnRH may be associated with anosmia (Kallman's syndrome) so the sense of smell should also be tested.