# Assessment of hypothalamic pituitary function in endocrine disease[1]

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SYNOPSIS  The insulin test carried out with adequate safeguards under standardized conditions yields valuable information regarding hypothalamic and pituitary function when plasma levels of sugar, cortisol, and growth hormone are determined. The use of a test based on the plasma cortisol response to the infusion of lysine-vasopressin, a polypeptide with a corticotrophin-releasing action, is also of value as a test of pituitary function. Used in conjunction with the insulin test it enables pituitary disorders to be differentiated from those involving the hypothalamus.

The three anatomical components of the pituitary are each concerned with the secretion of peptide hormones which are essential to a variety of metabolic processes. Thus the anterior pituitary of man synthesizes and releases growth hormone, follicle-stimulating hormone, luteinizing hormone, thyrotrophic hormone (TSH), corticotrophin (ACTH), and possibly prolactin; the pars intermedia secretes $\alpha$ and $\beta$ melanocyte-stimulating hormone (MSH) and the posterior pituitary is concerned with the storage and release of antidiuretic hormone (ADH) and oxytocin. It is axiomatic that the assessment of endocrine function in patients suspected of having pituitary disorders should be based upon a careful clinical examination and on investigations which determine the functional status of the pituitary and of the endocrine glands under its control. The procedures used in our laboratories are summarized in Table I. The scope of the present paper has been confined to two of the pituitary hormones, namely, growth hormone and ACTH.

An important advance in assessing pituitary function has been the introduction of radioimmunoassay for growth hormone (Glick, Roth, Yalow, and Berson, 1963; Hunter and Greenwood, 1964a) since it has allowed the routine determination of circulating levels of a pituitary hormone using small volumes of plasma. It is also possible by similar techniques to determine plasma ACTH levels (Yalow, Glick, Roth, and Berson, 1964). In the present study, however, the ability of the pituitary

## TABLE I

PROCEDURES USED IN THE ASSESSMENT OF PITUITARY FUNCTION

| Pituitary Hormone | Diagnostic Procedures Employed |
| --- | --- |
| Growth hormone | Fasting plasma growth hormone values and their response to insulin-induced hypoglycaemia and to orally or intravenously administered glucose |
| ACTH | Ability to excrete a water load. Basal plasma cortisol values and their response to ACTH, lysine-vasopressin, and to insulin-induced hypoglycaemia. Basal urinary 17-hydroxy-corticosteroid values and their response to the oral administration of metyrapone[1] |
| TSH | Determination of the basal metabolic and sleeping pulse rates. Electrocardiogram and electroencephalogram tracings. Plasma protein-bound iodine values. The determination of the neck uptake of $^{131}I$ with and without the prior administration of TSH |
| Gonadotrophins | Basal urinary gonadotrophin values |
| ADH | Ability to respond to fluid deprivation |

[1]Metyrapone (2-methyl-1, 2-bis (3-pyridyl)-propan-1-one)

to secrete this hormone has been assessed indirectly by investigations of adrenal function.

The determination of resting growth hormone levels is of limited diagnostic value except in acromegaly. Basal plasma and urinary steroid levels are likewise of limited diagnostic value. Normal levels have been found in patients with hypothalamic or pituitary dysfunction, who, nonetheless, developed acute adrenal insufficiency when subjected to the stress of an air encephalogram (Landon, Greenwood, Stamp, and Wynn, 1966b). Increasing attention has consequently been paid to the design of safe and rapid 'dynamic' procedures which test specifically the ability of the pituitary to increase its

rate of hormone secretion in response to a controlled stimulus. These procedures are based upon the mechanisms known to control growth hormone and ACTH release.

FACTORS CONCERNED IN THE SECRETION OF CORTISOL

There is extensive evidence, recently reviewed by Yates and Urquart (1962), that secretion of ACTH is controlled normally by means of a negative feedback mechanism, whereby the rate of ACTH secretion from the pituitary is inversely related to the level of plasma corticosteroids. There is also evidence that another control mechanism operates during a variety of stressful situations, such as surgery or infection. This stress mechanism overrides feedback control and results in increased release of ACTH and raised plasma cortisol levels (Liddle, Island, and Meador, 1962). The hypothalamus, by means of a low molecular weight polypeptide (Schally, Saffran, and Zimmerman, 1958), termed corticotrophin-releasing factor (CRF), plays an essential role in controlling the secretion of ACTH from the anterior pituitary (Green and Harris, 1947; Harris, 1951). Both the stress and the feedback control mechanisms are mediated by the secretion of this neurohormone into an hypothalamic-hypophyseal portal vascular system. In addition the pituitary response to stress involves neural pathways in the central nervous system. The pathways leading to the secretion of plasma cortisol following various stimuli are illustrated in Fig. 1. The procedures used to test the functional integrity of the component paths are also shown.



FIG. 1. *Diagram of the tests for the mechanisms controlling the secretion of cortisol.*

Tests based on the administration of exogenous ACTH or its synthetic analogues have been discussed previously (Landon, Wynn, James, and Wood, 1965). Although affected indirectly by hypothalamic or pituitary dysfunction they assess adrenocortical function. The use of lysine-vasopressin, a polypeptide with a corticotrophin-releasing action (MCann and Brobeck, 1954), tests the ability of the pituitary to release ACTH (Gwinup, 1965). The administration of metyrapone tests hypothalamic as well as pituitary and adrenal function and assesses the integrity of the feedback mechanism (Liddle, Estep, Kendall, Williams, and Townes, 1959; Landon, James, and Stoker, 1965). Finally the use of pyrogen (Melby, 1959) or insulin (Landon, Wynn, and James, 1963) tests the function of the entire cerebro-hypothalamo-pituitary-adrenal axis and assesses its ability to respond to stress. The present paper is concerned mainly with tests based on the use of insulin and of lysine-vasopressin.

FACTORS CONCERNED IN THE SECRETION OF GROWTH
HORMONE

Some of the factors known to stimulate or inhibit growth hormone secretion are shown in Fig. 2. The pathway is known only from the hypothalamus to the pituitary and a growth hormone-releasing factor appears to be involved (Abrams, Parker, Blanco, Reichlin, and Daughaday, 1964; Roth, Glick, Yalow, and Berson, 1963b). The pathways over which the stimulations or inhibitions are transmitted to the hypothalamus are not known. Stimulation of growth hormone secretion has been shown to follow fasting, exercise, and insulin or tolbutamide-induced hypoglycaemia (Roth *et al.*, 1963a and b; Hunter and Greenwood, 1964b). The higher levels of plasma growth hormone in children than in adults (Greenwood, Hunter, and Marrian, 1964) have been interpreted as reflecting a difference in total demands for energy substrates between growth plus activity in children and activity alone in adults (Greenwood, 1965). These stimuli represent demands for energy substrates which are met by the lipid mobilized by growth hormone (Raben and Hollenberg, 1959). It has recently been shown that the intravenous infusion of single amino-acids in the fasted adult is followed in many instances by a marked secretion of growth hormone (Knopf, Conn, Fajans, Floyd, Guntsche, and Rull, 1965). The results may be interpreted as showing that the clearance of plasma amino-acids is an energy-requiring process which is met in the fasted adult by growth hormone secretion. However, secretion was not always associated with a previous hypoglycaemia and the results may demonstrate that growth
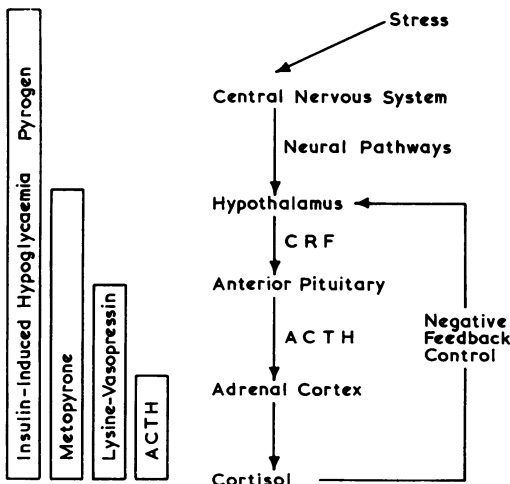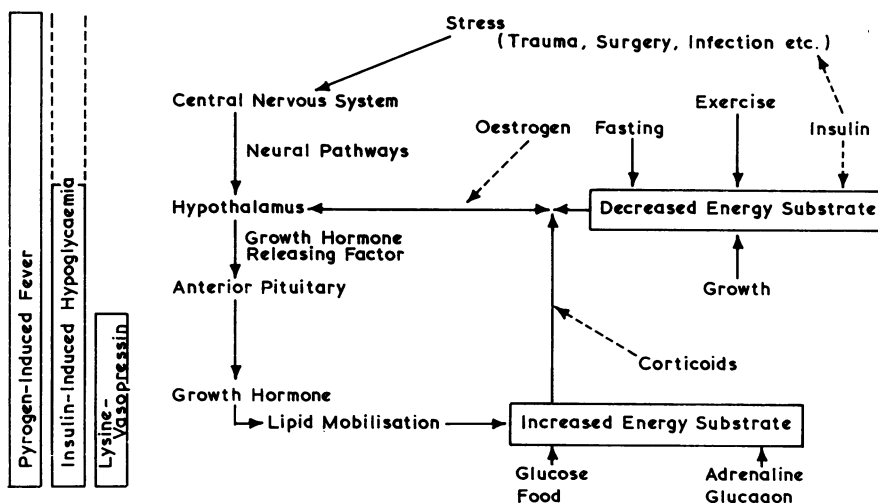
FIG. 2.    Diagram of the tests for the mechanisms controlling the secretion of growth hormone.
The stimulation by oestrogen and the inhibition by corticoid of growth hormone secretion is
assumed to be at the level of the hypothalamus. Stimulation by insulin-induced hypoglycaemia is
represented as a metabolic and stress effect. The stimulation of secretion which follows intravenous
amino acids has been omitted since the mechanism has not been clarified.

hormone has a direct role in the regulation of amino-acid metabolism.

Secretion of growth hormone is abolished or not invoked when glucose is supplied or mobilized by other hormones. Thus the negative feedback between growth hormone and the available pool of energy substrates contributes to glucose homeostasis by providing lipid substrates when glucose is not freely available. Mobilization of energy substrates before they are required and irrespective of the size of the available pool is suggested by the rises in plasma growth hormone in response to emotional (Fig. 3) or to pyrogen (Fig. 4) stress (Greenwood and Landon, 1966) unaccompanied by changes in the plasma sugar. A separate pathway for these stimuli is suggested by analogy with control mechanisms for ACTH and by the finding that a rise in growth hormone after a pyrogen stress is not suppressed by glucose. High plasma levels of corticoids suppress the normal response of growth hormone to insulin (Frantz and Rabkin, 1964; Hartog, Gaafar, and Fraser, 1964) but the point of inhibition is not known. Conversely endogenous or exogenous oestrogen sensitizes the subject to the stimulating effects of fasting and exercise on growth hormone secretion (Frantz and Rabkin, 1965) and this effect has been assumed to take place at the hypothalamic level. The first effect of glucose is to inhibit secretion. The relative hypoglycaemia two to three hours after glucose causes a subsequent rise in plasma growth hormone (Roth et al., 1963b).

The tests for the pathways leading to the secretion of growth hormone are shown in Fig. 2. Pyrogen stimulation is shown to test hypothalamic and pituitary function and higher nervous centres involved in the transmission of stress stimuli. Insulin-induced hypoglycaemia is represented as a metabolic stimulus to the feed-back mechanism and assumed to act at the level of the hypothalamus. Insulin is also shown (dotted line), by analogy with Fig. 1, as a stressor. In either event the pathways to the hypothalamus are not known. It is postulated that lysine vasopressin acts directly at the pituitary level although it does not invariably cause release of growth hormone.

USE OF INSULIN-INDUCED HYPOGLYCAEMIA AS A TEST
OF PITUITARY AND HYPOTHALAMIC FUNCTION

The determination of plasma cortisol and plasma growth hormone levels before and 20, 30, 60, 90, and 120 minutes after the intravenous injection of insulin has proved a valuable means of assessing hypothalamic and pituitary function. Some clinicians have reservations concerning the safety of giving insulin to patients suspected of having endocrine hypofunction (Ross, 1961) because of their increased sensitivity to its hypoglycaemic effects (Fraser, Albright, and Smith, 1941). In our experience the value of this procedure far outweighs any possible risks, provided adequate safeguards are employed. These include the presence of a physician through-
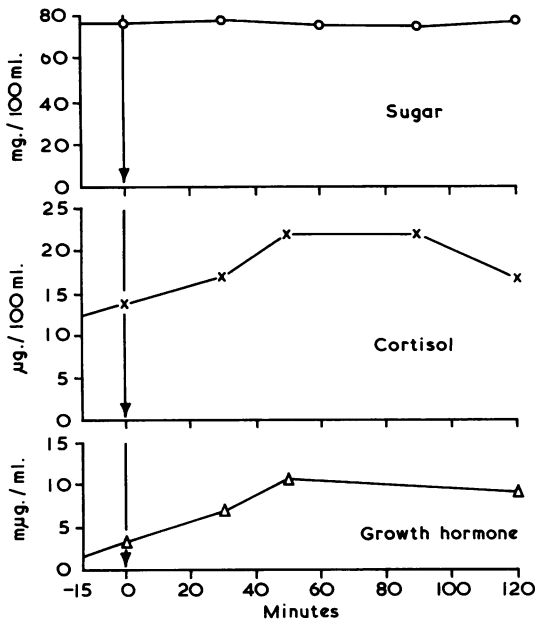
FIG. 3. *The effect of an emotional stress on plasma cortisol and growth hormone. Saline was injected (vertical arrow) into a volunteer member of the medical staff expecting a 'massive dose' of insulin and subsequent hypoglycaemic symptoms. Significant rises in the levels of plasma cortisol and of plasma growth hormone followed injection without changes in the level of plasma sugar.*

out the test, the immediate availability of glucose for intravenous injection, and the use of an amount of insulin related to the tentative diagnosis. We have never found it necessary to use a dose of less than 0·10 units/kg. body weight even in patients with hypopituitarism. Employing these safeguards no severe side effects have been experienced and termination of the procedure by glucose has been required on only four occasions in more than 400 tests. Larger doses of insulin, up to 0·3 units/kg., are needed for patients with insulin resistance.

The validity of the test rests eventually on the precision, sensitivity, and specificity of the methods we have used for the determinations of the hormones in plasma. These criteria have been discussed previously and are satisfactory for growth hormone (Hunter and Greenwood, 1964b) and cortisol (Mattingly, 1962). Plasma sugar values were determined by the ferricyanide method of Hoffman (1937) modified for use with an AutoAnalyser (Technicon). Although this method gives values which are 5 to 10 mg./100 ml. above those found using a more specific glucose oxidase method (Marks and Lloyd, 1963), its precision was adequate to check that the
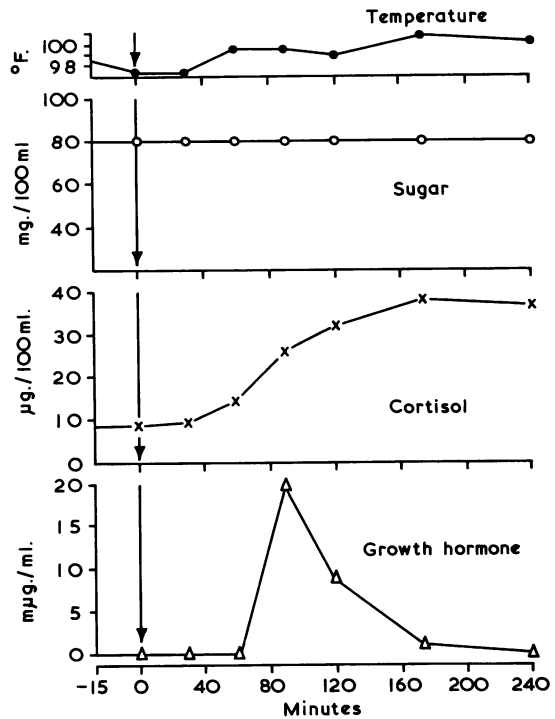


FIG. 4. *Responses to the injection of a bacterial pyrogen in a normal subject. A bacterial pyrogen (0·005 µg./kg. body weight: Organon) was injected into a normal woman, aged 36 yr. as shown by the vertical arrow. The subsequent fever was not accompanied by changes in the plasma sugar but the stressor produced marked rises in both plasma cortisol and plasma growth hormone.*

degree and duration of the insulin-induced hypoglycaemia was of the necessary order to stimulate secretion of cortisol and growth hormone.

NORMAL RESPONSES    The range and time sequence of the plasma sugar, free fatty acid, cortisol, and growth hormone response has been determined in 54 insulin tests on 38 control subjects (Greenwood, Landon, and Stamp, 1966). Typical responses are shown in Fig. 5. In order to compare responses between individuals the maximum levels of plasma cortisol and growth hormone observed are used, together with their maximum increment above the resting value. The minimum of the plasma sugar and its recovery index provided indices of the extent and duration of the hypoglycaemic response. (The recovery index is defined as the sum of the 60, 90, and 120 minute values expressed as a percentage of the resting value.) The data obtained in a group of 28 control subjects given 0·15 units of soluble insulin/kg.

## TABLE II

SUMMARY OF THE RESPONSES TO THE INTRAVENOUS INJECTION OF 0·15 UNITS/KG. OF INSULIN IN 28 CONTROLS[1]

|  |  | Mean | S.D. | Range |
|---|---|---|---|---|
| Plasma sugar | Minimum[2] (mg./100 ml.) | 31 | 9 | 18 - 53 |
|  | Recovery index[3] | 211 | 36 | 161 -292 |
| Plasma FFA | Minimum[2] (mEq./l.) | 330 | 90 | 140 -480 |
|  | Recovery index[3] | 286 | 67 | 188 -403 |
| Plasma cortisol | Maximum (μg./100 ml.)[4] | 28·1 | 5·0 | 21·7- 37·6 |
|  | Maximum increment (μg./100 ml.)[5] | 15·4 | 4·8 | 7·7- 24·2 |
| Plasma growth hormone | Maximum (mμg./ml.)[4] | 37·4 | 25·2 | 15·1-121·1 |
|  | Maximum increment (mμg./ml.)[5] | 35·0 | 24·9 | 13·7-118·6 |

[1]Data from Greenwood, Landon, and Stamp (1966).
[2]Mean ± SD of the minimum values 0-120 min. after injection.
[3]Mean ± SD of the recovery indices; the sum of the values at 60, 90, and 120 min. after injection as a percentage of the control value.
[4]Mean ± SD of the maximum values 0-120 min. after injection.
[5]Mean ± SD of the maximum increment; the maximum value 0-120 min. after injection less value of control sample.

body weight are summarized in Table II. Other control subjects received insulin doses over the range 0·025 to 0·10 units/kg. By statistical analysis the plasma responses were shown to be related to the dose of insulin over the dose range 0 to 0·15 units/kg. Further analysis based upon the more usual logarithmic dose/response relationship was not attempted, since on retesting control subjects at the same dose, wide variation of the growth hormone response

was obtained although the plasma sugar and cortisol responses were reproducible (Fig. 6).

RESPONSES IN PATIENTS WITH ENDOCRINE DYSFUNCTION    Increased or decreased insulin sensitivity is frequently associated with endocrine dysfunction. Comparison between control subjects and patients has consequently been based on tests employing amounts of insulin causing a comparable hypo-
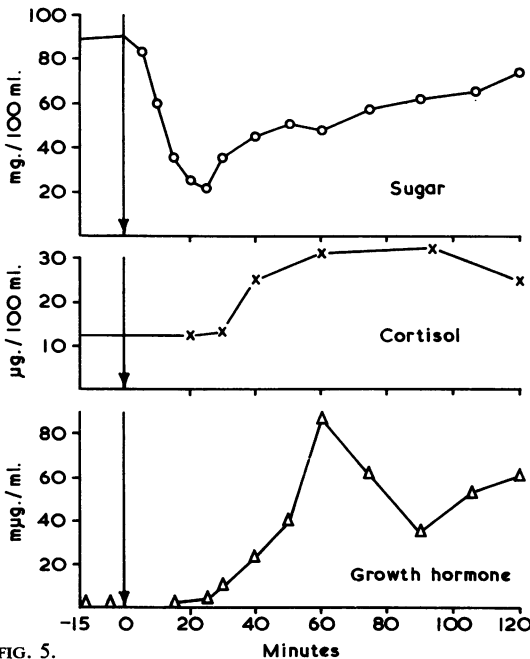
FIG. 5.    Minutes

FIG. 6.    Minutes

FIG. 5.    *Typical responses to intravenous insulin in a normal subject. Responses in plasma sugar, plasma cortisol (×) and plasma growth hormone to the injection of insulin (0·15 units/kg. body weight), shown by the vertical arrow.*
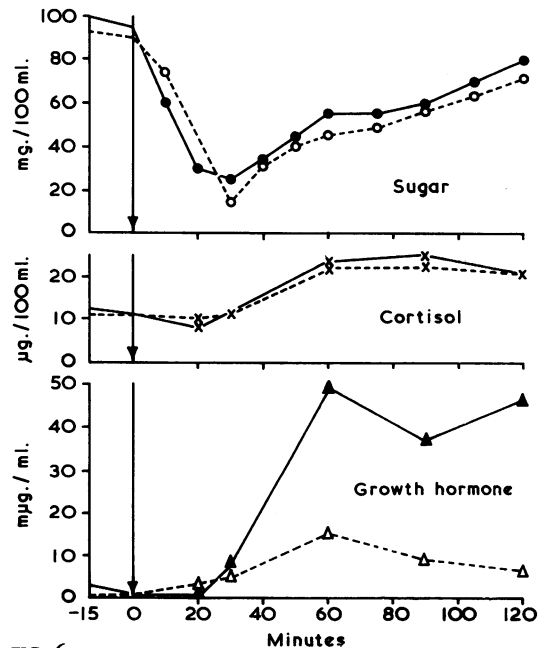
FIG. 6.    *The reproducibility of the responses to intravenous insulin. Insulin (0·15 units/kg. body weight) was injected (vertical arrow) into a 19-year-old control subject (——) and again two weeks later (- - -). Responses in plasma sugar and in plasma cortisol were reproducible, the responses in plasma growth hormone were not.*
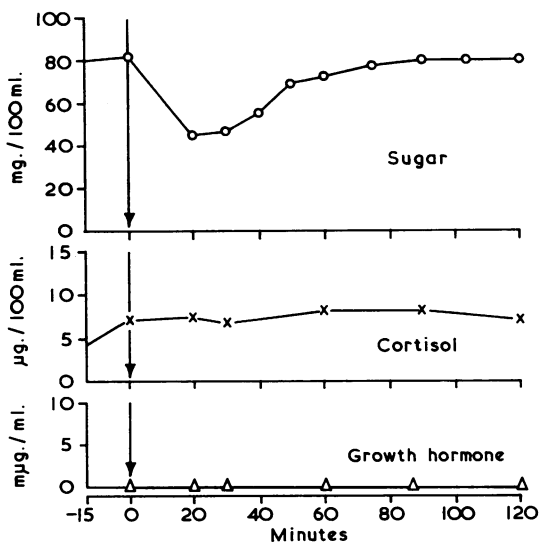
FIG. 7. *Responses to intravenous insulin during long-term corticoid therapy. A 12-year-old boy was tested with insulin (0·15 units/kg. body weight) after 20 months of corticoid therapy (25 mg. prednisolone per day). Responses in plasma cortisol and plasma growth hormone were essentially absent although the response in plasma sugar was not abnormal.*

FIG. 8. *Responses to intravenous insulin in patients with chromophobe adenomas. Insulin (0·10 units/kg. body weight) was injected (vertical arrow) into a 73-year-old man (——) and a 16-year-old boy (- - -) with pituitary chromophobe adenomas. Insulin sensitivity shown by the marked hypoglycaemia was not accompanied by responses in plasma growth hormone but one of the subjects (——) showed a response in plasma cortisol.*

glycaemic response. The results can be graded as 'normal', 'reduced', or 'absent', based on the range of responses found in control subjects. Typical responses to insulin in patients with endocrine dysfunction are shown in Figs. 7-11 selected from a series of more than 100 cases (Landon *et al.*, 1966a; James, Greenwood, Landon, and Wynn, 1966).

Prolonged glucocorticoid therapy with daily doses of 10 mg. or more of prednisolone (or its steroid equivalent) impairs both the plasma cortisol and growth hormone response to insulin, as illustrated in Fig. 7 by a study on a 12-year-old boy with non-specific uveitis who had not grown since prednisolone treatment (25 mg. daily) was instituted 20 months previously. Similar findings have been reported by Frantz and Rabkin (1964) and by Hartog *et al.* (1964) and raise the question as to whether steroid-induced dwarfism is related to the suppression of growth hormone secretion. The suppression of the plasma cortisol and growth hormone response to insulin is only temporary since normal responses were found at varying times after the cessation of therapy. For example a patient tested 30 days after the completion of a prolonged course of prednisolone (30 mg. daily for five years) gave normal responses. Patients with Cushing's syndrome associated with bilateral adrenal hyperplasia also show an impaired growth hormone
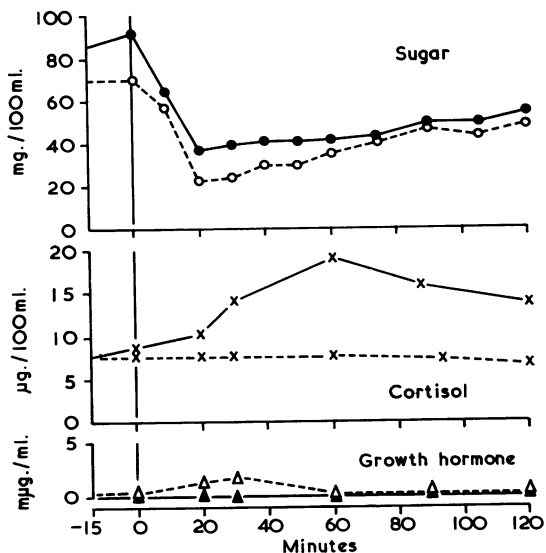
response. This abnormality frequently persists following total bilateral adrenalectomy, whereas it remains normal in patients adrenalectomized for other reasons, such as carcinoma of the breast. Consequently it seems possible that the impaired growth hormone response in patients with Cushing's syndrome represents a more fundamental defect of the hypothalamic-pituitary axis than that produced by the administration of exogenous steroids.

Three patients with primary hypothalamic dysfunction, nine patients with non-secreting pituitary tumours, two patients with Sheehan's syndrome, and 13 patients who had had a partial or complete hypophysectomy have been studied. In none of these was there a normal growth hormone response and this abnormality frequently preceded evidence of any other pituitary hormonal defect. As illustrated (Fig. 8), the plasma cortisol response to insulin in patients with chromophobe adenomas may or may not be impaired. Although the determination of plasma cortisol values has proved of less diagnostic value in these patients, it has the considerable merit of indicating whether they require maintenance steroid therapy. The test has also proved of value in the differential diagnosis of hypopituitarism and anorexia nervosa in that, although both groups show increased sensitivity to the hypoglycaemic effects of
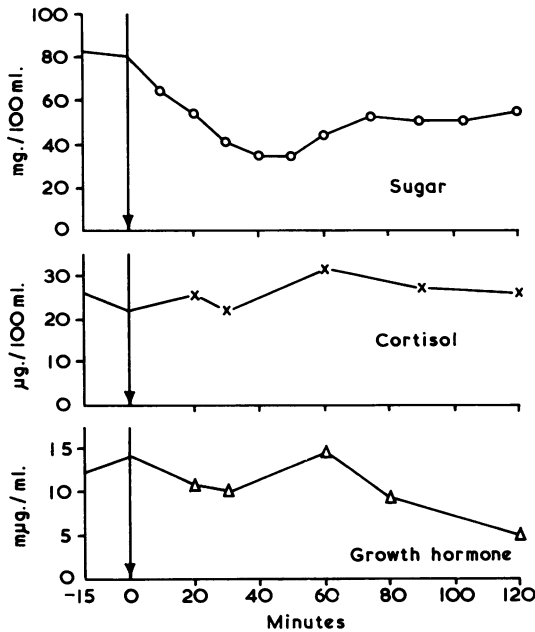
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FIG. 9. *Responses to intravenous insulin in a patient with anorexia nervosa. Responses to 0·10 units insulin/kg. body weight in a 19-year-old woman. Despite a marked hypoglycaemia no stimulation of the high control levels of plasma cortisol and of plasma growth hormone was obtained.*
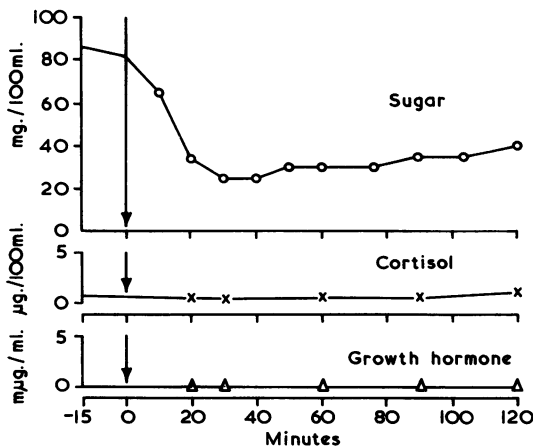


FIG. 10. *Responses to intravenous insulin in a patient with hypopituitarism. Insulin (0·10 units/kg. body weight) was injected (vertical arrow) into a 27-year-old woman with hypopituitarism. Despite a marked and prolonged hypoglycaemia, plasma cortisol and plasma growth hormone were not measurable either before or after insulin.*

insulin, the resting levels of growth hormone and cortisol are raised in patients with anorexia nervosa (Fig. 9). Although the endocrine axes are intact in this condition the continuous stimulation induced by the lowered fasting plasma sugar frequently found in these patients may lower pituitary reserves of growth hormone and possibly ACTH (Marks, Greenwood, and Howarth, 1966). The absence of plasma cortisol and growth hormone in resting samples from hypopituitary subjects readily excludes anorexia nervosa but is not diagnostic for hypo-pituitarism. The increased insulin sensitivity unaccompanied by rises in plasma growth hormone and cortisol (Fig. 10) demonstrates an hypothalamic-pituitary dysfunction.

Tests based on the use of insulin are of limited value in the diagnosis of acromegaly. Thus the growth hormone response to insulin in patients with this condition is variable and plasma values may, or may not (as illustrated in Fig. 11), increase above their high initial levels. Provided large enough amounts of insulin (0·30 units/kg.) are given to induce adequate hypoglycaemia the determination of
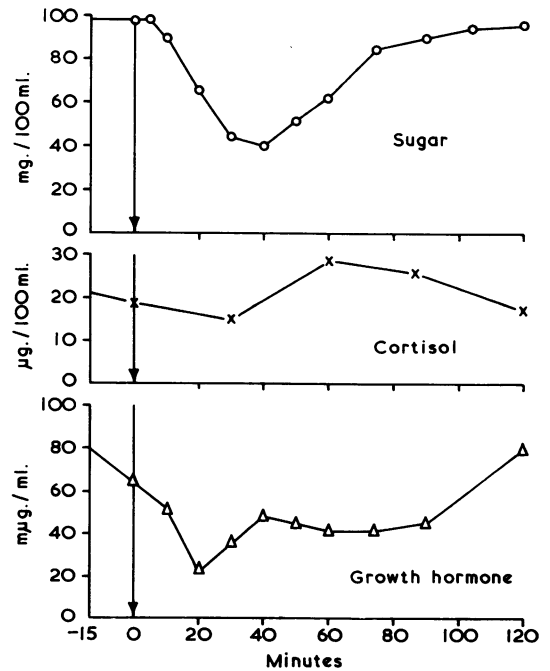


FIG. 11. *Response to intravenous insulin in an acromegalic subject. Insulin at a high dose level (0·30 units/kg. body weight—vertical arrow) produced hypoglycaemia in a 40-year-old male subject with acromegaly. A normal rise in plasma cortisol was observed but the high control levels of plasma growth hormone were decreased rather than increased by hypoglycaemia.*
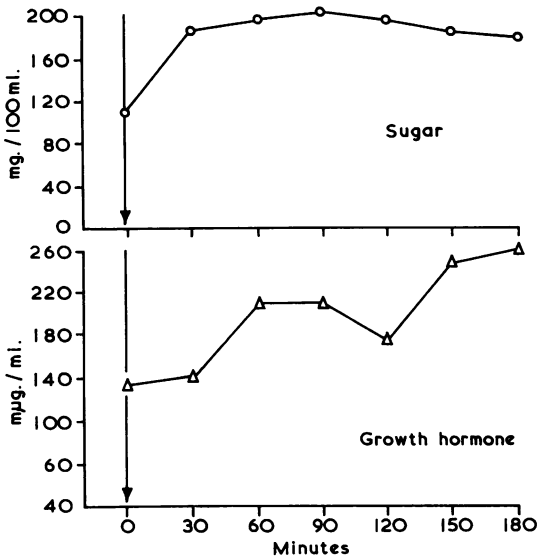
FIG. 12. *Responses to oral glucose in an acromegalic subject. Oral glucose (g./kg. body weight) was given to a 47-year-old acromegalic subject at 0 min. A diabetic response in plasma sugar was observed. Despite the hypoglycaemia the high control levels of plasma growth hormone were not decreased but increased.*

plasma cortisol levels is of value in assessing the integrity of the hypothalamic-pituitary-adrenal axis. A more valuable diagnostic procedure is one based on the administration of food or glucose. Whereas this suppresses growth hormone levels in normal subjects, acromegalic patients are unresponsive (Fig. 12). Such procedures have proved of value in assessing the results of treatment in these patients (Greenwood, Stewart, Forrest, and Wood, 1965; Linfoot and Greenwood, 1965).

### USE OF LYSINE-VASOPRESSIN AS A TEST OF PITUITARY FUNCTION

It is often impossible to distinguish hypothalamic and pituitary abnormalities on clinical grounds and there are no laboratory tests at present which are of value for this purpose. Although metyrapone has been used extensively for the evaluation of pituitary-adrenal function (Liddle *et al.*, 1959) it is not clear to what extent hypothalamic function is involved. Similarly, tests based on the administration of a pyrogen or insulin do not differentiate hypothalamic and pituitary disorders since they are impaired in both conditions. Such a distinction would, however, be possible using specific releasing factors for growth hormone and corticotrophin which are normally secreted by the hypothalamus. Thus an impaired

response to these two factors would indicate pituitary dysfunction, while a normal response, together with an impaired response to insulin-induced hypoglycaemia, would indicate that the lesion was proximal to the pituitary in the cerebro-hypothalamic-pituitary axis.

Neither growth hormone-releasing factor nor corticotrophin-releasing factor are available for clinical use. Vasopressin, however, has corticotrophin-releasing factor activity in the rat (McCann and Brobeck, 1954) and in man (McDonald and Weise, 1956; Clayton, Librik, Gardner, and Guillemin, 1963).

The plasma cortisol response to the infusion of lysine-8-vasopressin at a rate of 5 p.u./hr. for two hours has been studied in 19 control subjects (Landon, James, and Stoker, 1965). The maximum increment in plasma cortisol during the test ranged from 5·6 to 33·5 $\mu$g./100 ml. A response in growth hormone, however, is not found in all control subjects and the presence or absence of a response appears to be un-
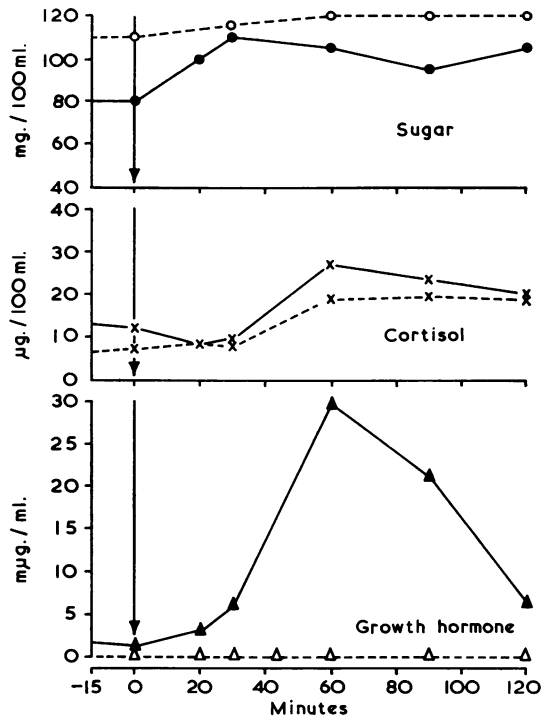


FIG. 13. *Responses to the infusion of lysine-vasopressin in normal subjects. Lysine-8-vasopressin (Sandoz) was infused (vertical arrow) at the rate of 5 pressor units/hr. for 2 hr. into a normal male (- - -) and a normal female (——). Rises in plasma cortisol accompanied infusion in both subjects but a rise in plasma growth hormone was observe only in the female and was unrelated to the effect on plasma sugar.*

## TABLE III

SUMMARY OF THE RESPONSES TO ACTH, LYSINE-VASOPRESSIN, METYRAPONE, AND INSULIN-INDUCED
HYPOGLYCAEMIA IN PATIENTS WITH A VARIETY OF ENDOCRINE DISORDERS

| Category | Response to | | | | |
| --- | --- | --- | --- | --- | --- |
| | ACTH | LVP | Metyrapone | Insulin | |
| | | | | Cortisol | Growth Hormone |
| Normal subjects | + | + | + | + | + |
| Patients with pituitary hypofunction | { + | + | + | + | .. |
| | { + | + | − | − | − |
| | { − | − | .. | − | .. |
| Patients with hypothalamic hypofunction | + | + | ... | − | - |
| Patients with acromegaly | + | + | + | + | ± |
| Patients with anorexia nervosa | + | ± | ± | ± | ± |

related to the changes in plasma cortisol or plasma
sugar levels (Fig. 13).

A summary of the responses to ACTH, lysine-
vasopressin, metyrapone, and insulin-induced hypo-
glycaemia in a variety of endocrine disturbances is
given in Table III.

In three patients with hypothalamic dysfunction
there was a normal plasma cortisol response to
ACTH and to lysine-vasopressin but an impaired
response to insulin. The urinary steroid response to
metyrapone was also impaired in these patients. In
a group of 12 patients with pituitary tumours or post-
partum necrosis the majority either responded
normally, or had an impaired response to all these
tests except ACTH. Two patients with pituitary
tumours were of particular interest in that the results
of their tests were similar to those found in the group
with hypothalamic dysfunction, namely, an impaired
response to insulin and metyrapone and a normal
response to ACTH and lysine-vasopressin. An air
encephalogram showed that the tumour in both
patients had a large suprasellar extension which was
compressing the hypothalamus and causing distor-
tion of the third ventricle. Five patients with
acromegaly produced adequate amounts of cortico-
trophin as evidenced by their normal adrenal
response to all four tests.

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