

## Anterior Pituitary

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**Objective:** To understand the biologic actions, regulation of secretion, and clinical disorders of anterior pituitary hormones, including recognition of pituitary tumors. Main emphasis will be on growth hormone and prolactin; other hormones will be considered in subsequent lectures.

**Background:** Review anatomy of the pituitary and its connections with the hypothalamus. Review chemistry and physiology of individual hormones.

### Hypothalamic Control of Pituitary

Most regulation of pituitary function occurs at the level of the hypothalamus, various cells of which secrete different releasing and inhibiting factors directly into the hypophyseal portal vessels. These vessels reach the pituitary by way of the stalk and furnish some, but not all, of its blood supply.

Most pituitary hormones are regulated predominantly by tonic *stimulation*. An exception is prolactin, which is regulated predominantly by *inhibition*. It is possible that each pituitary hormone has both a releasing and an inhibiting hormone, although not all of the hypothalamic hormones have yet been chemically characterized. Most are peptides, but unlike the pituitary hormones, most are relatively small molecules, 3–44 amino acids long. These hypothalamic substances are present in high concentrations in portal blood, but in peripheral blood they are difficult or impossible to measure because of dilution and rapid enzymic degradation.

The releasing factors are elaborated by the hypothalamus in response to stimuli which impinge on its various nuclei from a number of tracts. These tracts are of various kinds, according to the neurotransmitters they liberate, i.e., dopaminergic, noradrenergic, serotonergic, and others. Hypothalamic neurons may also respond to changes in blood substances, such as glucose, serum osmolality, and target organ hormones (thyroid hormone, cortisol, gonadal steroids), although a large amount of the negative feedback of target organ hormones appears to take place at the level of the pituitary itself. In addition, there is also so-called “short loop” feedback for most pituitary hormones, in which a hormone such as growth

hormone may exert a direct negative feedback on its own secretion via suppression of a releasing factor. Thus, there are multiple pathways of control for each pituitary hormone.

**Table 1. Pituitary Hormones and Their Hypothalamic Regulating Factors**

Pituitary Hormone	Hypothalamic Hormone	
	Releasing	Inhibiting
Growth hormone	GHRH-44aa's	Somatostatin (SRIF)-14aa's
Prolactin	(TRH)	Dopamine
ACTH	CRH-41aa's, Vasopressin	
LH	GnRH	
	} > 10aa's	
FSH	GnRH	
TSH	TRH-3aa's	(Somatostatin)

### Other Hypothalamic Peptides

Besides the releasing and inhibiting factors listed above, plus the posterior pituitary hormones vasopressin and oxytocin (which are entirely synthesized within the hypothalamus), the hypothalamus—in some cases other parts of the brain as well—has recently been shown to contain small amounts of numerous other physiologically active peptides. These include enkephalins and endorphins (which are also present in pituitary; see below under ACTH), neurotensin, substance P, bombesin, gastrin, cholecystokinin, VIP (vasoactive intestinal peptide), and others, all of which have also been found in the gastrointestinal tract and pancreas. In addition to these, small amounts of most anterior pituitary hormones can also be found by sensitive immunocytochemical and radioimmunoassay techniques in different areas of the hypothalamus, although the concentrations are several orders of magnitude lower than in the pituitary. It is still too soon to evaluate the significance of these findings, most of which are very recent. Some of these peptides may have short-range inhibitory or excitatory influences on adjacent neurons, but in most cases their physiological roles, if any, are still unclear.

### Anterior Pituitary Hormones

All anterior pituitary hormones are proteins, mostly of relatively high molecular weight. Progress during the past 30 years has included (1) chemical isolation of hormones and determination of complete amino acid structures; (2) development of sensitive radioimmunoassay techniques to measure hormones in blood; and (3) determination of control mechanisms governing secretion of hormones.

## I. GROWTH HORMONE

Mol. wt. 22,600. 191 amino acids. Unusually high species specificity—only the human (or primate) hormone works in humans.

### ***A. Actions***

The physiological role of growth hormone in adults is still not completely understood. It probably acts in concert with insulin to control deposition and utilization of available energy stores. Some established actions are as follows:

1. Promotes nitrogen retention by facilitating conversion of amino acids into protein
2. Mobilizes lipid; causes hydrolysis of fats and mobilization of FFA's
3. Opposes action of insulin with respect to glucose utilization and incorporation into fats
4. Promotes linear growth in children

There is good evidence to suggest that growth hormone does not exert many of its effects on cells directly but instead causes the generation of several substances which are collectively termed *somatomedins*. The somatomedins are anabolic substances and tissue growth factors which, unlike growth hormone, are active on isolated tissues *in vitro*. Somatomedin- C, also known as Insulin-like Growth Factor 1, or IGF-1, is the principal member of this group. It is a 70-amino-acid protein having a high degree of homology with proinsulin. It is made locally, under the influence of growth hormone, in tissues all over the body; it also circulates in blood, where it can be measured by radioimmunoassay. Circulating IGF-1 is thought to be made largely by the liver. It is high in plasma in states of growth hormone excess (acromegaly) and low in states of growth hormone deficiency. It is also low in states of malnutrition or prolonged fasting, even if growth hormone is normal or high.

Partly because it is tightly bound to a binding protein, IGF-1 has a long half-life in blood and shows little fluctuation during a 24-hour period. In this it contrasts markedly with growth hormone, which is secreted in a pulsatile fashion, has a short half-life in blood, and shows great variation in levels throughout the day.

Measurement of IGF-1 is of clinical value in suspected acromegaly, particularly in cases where growth hormone levels are borderline or only minimally elevated. In these situations IGF-1 affords a sharper distinction than growth hormone itself, since there appears to be essentially no overlap between IGF-1 levels in normal individuals and in patients with acromegaly.

In cases of suspected hypopituitarism, on the other hand, measurement of IGF-1 does not appear to add much useful information beyond that obtained by measurement of growth hormone itself.

### ***B. Secretory pattern***

Growth hormone is secreted in a series of irregular secretory pulses throughout the day. Often it is below the level of detectability by current commercially

available assays (less than 1.0 ng/ml). The major secretory peak occurs at night, soon after falling asleep, and is correlated with deep (stage 3–4) sleep.

### *C. Regulation of secretion*

#### *Stimulated by:*

Sleep  
Stress  
Hypoglycemia or falling  
  blood sugar  
Exercise  
GHRH  
Ghrelin  
L-dopa  
Amino acids (arginine)  
Estrogen (enhances some responses)  
Propranolol ( $\beta$ -adrenergic blockade)

#### *Suppressed by:*

Glucose (transiently)  
Somatostatin  
Octreotide (Sandostatin)  
  —a synthetic somatostatin  
analogue  
Glucocorticoids  
Phentolamine( $\alpha$ -adrenergic  
blockade)

The hormonal regulation of GH by the hypothalamus appears to be predominantly dual, via GHRH (stimulatory) and somatostatin (inhibitory). Very recently a third circulating regulatory factor, **ghrelin**, has been identified. Ghrelin, a 28 amino acid oligopeptide, is made predominantly in the stomach. It reaches specific receptors on the hypothalamus (and some other tissues as well) via the bloodstream. Its main effect appears to be to enhance the growth hormone stimulatory actions of GHRH, by mechanisms which are still unclear. (In this it resembles several small peptide and non-peptide molecules, empirically synthesized by drug companies over the last two decades, whose use is still experimental). Gastric ghrelin production is inhibited by feeding and increased by fasting, and ghrelin may have a role in modulating food intake and utilization as well as growth hormone secretion.

### *D. Normal values*

<1 to 5 ng/ml in A.M. at complete rest.

Many normal adults less than 1.0. May be temporarily higher than 5.0 ng/ml in some subjects, particularly women.

Children after first few weeks of life similar to adults.

### *E. Stimulation and suppression tests*

1. **For suspected acromegaly:** Serum hGH during oral glucose tolerance test - specimens at 0, 1/2, 1 and 2 hours.

**Diagnostic criterion for acromegaly:** Failure to suppress to less than 1.0

ng/ml at some time during test.

2. **For suspected hypopituitarism:** Serum hGH during insulin tolerance test or thorough stimulation with arginine and GHRH, usually used together.

**Diagnostic criterion for hypopituitarism:** Failure to rise to at least 5–7 ng/ml in children, or 7-10 ng/ml in adults, at some time during test.

## ***F. Disorders of secretion***

### ***1. Hypersecretion (acromegaly)***

Growth hormone is hypersecreted in 10–15 percent of pituitary tumors, making it the second most commonly hypersecreted hormone. Tumors are usually chromophobe, less commonly eosinophilic, adenomas. Very rarely acromegaly can be due to overproduction of GHRH by an “ectopic” tumor, such as the pancreas, and the acromegaly may be cured by resection of the tumor. Ectopic production of growth hormone itself by a non-pituitary tumor in amounts sufficient to cause acromegaly has been reported in two cases to date.

*Diagnosis of acromegaly.* The diagnosis of acromegaly is almost always first suggested by changes in the patient’s facial appearance, which typically have occurred slowly over a period of years. It is confirmed by measurements of serum growth hormone and IGF-1. The normal upper limit of hGH is arbitrarily considered to be less than 5 ng/ml (except for occasional secretory spikes), and most acromegalic patients have levels consistently in excess of this value, usually in the range of 6-50 ng/ml, though greater elevations can be seen. Some patients may have levels less than 5 ng/ml and rarely less than 1 ng/ml in patients with small tumors, though never undetectable. To confirm acromegaly when the serum hGH is normal or only slightly elevated (e.g. less than 10 ng/ml), an oral glucose tolerance test may be performed. As indicated above there is resistance to glucose suppression, and serum hGH will not fall to below 1.0 ng/ml, as it will in normals.

Serum IGF-1 should also be measured in all acromegalic patients. Normal levels have to be adjusted both for age and gender, and different laboratories may have different normal values depending on assay methodology. Serum IGF-1 is a better diagnostic indicator than hGH itself, particularly in cases where hGH is in the lower range. IGF-1 is essentially always elevated in active acromegaly, and is very useful in evaluating the effects of surgery or other treatment.

## **SYMPTOMS.**

See Table 2.

**Table 2: Clinical Manifestations of Acromegaly\***

	Frequency (%)
Local ss and sx. of tumor growth	
Enlarged sella turcica	80–93
Headache	75–87
Visual field impairment	<50 (5–62)
Increased growth hormone secretion	
Coarsening of facies; enlargement of hands, feet	ess. 100
Excess sweating	60
Increased body hair	53
Arthritic complaints	common
Visceromegaly	common
Skin tags	common
Weight gain	39
Goiter (usually nontoxic nodular)	25
Impaired CHO tolerance	25–37
Clinical diabetes mellitus	12
Colonic polyps	occ.
Galactorrhea (with or without ↑ prolactin)	4
Other hormonal disturbances	
↓ gonadal function	25 or more
↑ prolactin secretion	ca. 40

\*Taken in part from Daughaday WH: The adenohypophysis. In Williams RH, Ed.: *Textbook of Endocrinology*, ed. 6, 1981.

*Treatment of acromegaly.* Surgical resection of a growth hormone producing tumor, usually by the transsphenoidal route, is in most cases the first line of approach to the treatment of acromegaly. If surgery is deemed inadvisable, or if it fails to correct the growth hormone hypersecretion (as is likely if the tumor is very large or the plasma growth hormone highly elevated), octreotide or some other long-acting analogue of somatostatin may be given. These drugs will usually lower circulating growth hormone and IGF-1, though not always to normal levels. They are expensive and must be given by injection. Modest tumor shrinkage may occur in some patients. Pegvisomant, a selective antagonist of the growth hormone receptor, can reduce IGF-1 levels and improve some symptoms of acromegaly. It is expensive, however, and must be given by injection.

Radiotherapy is another treatment option for pituitary tumors of all kinds, including those that secrete growth hormone. It will arrest the growth of most tumors but has the disadvantage of causing a very delayed reduction of hormone overproduction, and a high rate of late-developing panhypopituitarism. Rarely, it may cause optic nerve damage or other CNS symptoms, although with modern methods of delivery of focused radiation these outcomes are rare.

## **2. Hyposecretion**

Some deficit in hGH secretion can be found in the majority of patients with pituitary disease, whatever its cause. HGH and gonadotropins are the two most commonly reduced functions in patients with pituitary disease (ACTH and TSH less often affected). There is no obvious serious clinical consequence of decreased hGH secretion in the adult, but GH replacement in GH deficient adults may lead to some modest reduction in body fat and cholesterol and increases in bone density. In children it leads to short stature. Whereas in adults the cause is most frequently pituitary tumor, in children decreased hGH secretion is most often hypothalamic, due to defective secretion of GHRH, rather than to intrinsic pituitary causes. Most such cases of short stature are sporadic, but a few are familial. (See section on Growth Disorders.)

## **II. PROLACTIN**

Mol. wt. 23,500. 198 amino acids. Related chemically to growth hormone. Definitively identified as a separate hormone in humans in 1970.

### **A. Actions**

1. Mammotropic
2. Lactogenic
3. Growth hormone-like, to slight degree
4. Parental behavior-stimulating (in birds)
5. 'Antigonadotropic' If present in excess causes decreased gonadal function in women and men.

### **B. Secretory pattern**

The secretory pattern of prolactin is somewhat similar to that of hGH in showing a series of pulses with a night-time secretory peak that is related to sleep. The time of onset (later) of the sleep peak and its duration (more prolonged) are not the same as for hGH, however.

### **C. Regulation of secretion**

*Stimulated by:*

Sleep  
Stress  
Nursing (in postpartum women)  
Breast stimulation (in some nonpostpartum women)  
Pregnancy  
Estrogens

*Stimulated by (cont'd.):*

Hypoglycemia (slightly)

*Suppressed by:*

L-dopa and dopamine  
Bromocriptine (Parlodel),  
and other dopaminergic  
ergot derivatives

Chlorpromazine and other antidopaminergic  
neuroleptics  
TRH  
Primary hypothyroidism (mildly)  
Opiates, including  $\beta$ -endorphin  
Cimetidine  
Metoclopramide  
Renal failure  
Misc. diseases of pituitary and  
hypothalamus, especially  
pituitary tumors

#### ***D. Normal values***

Men: 0–20 ng/ml; mean, 4.8 ng/ml in A.M.

Women: 1–25 ng/ml; mean, 8.0 ng/ml in A.M.

Children: similar to adult men after first few weeks of life

#### ***E. Disorders of secretion***

##### *1. Hypersecretion*

#### **TUMORS.**

Prolactin is hypersecreted by approximately 60 percent of all pituitary tumors, making it the most commonly hypersecreted anterior pituitary hormone. The incidence of such tumors is probably about the same in men as in women, but diagnoses are made more often in women, and at an earlier age, because of the common early symptom of amenorrhea.

Prolactin levels in patients with hypersecreting tumors range all the way from only slightly elevated (more than 25 ng/ml) to grossly elevated (highest, 46,000 ng/ml). Most are in the range of 50–300 ng/ml.

Many tumors start early in life and may go undetected for years. They almost never metastasize and may continue for decades with little or no growth in size. The recent application of prolactin measurements and improved techniques of sella turcica radiography have revealed that small prolactin-secreting pituitary tumors, often referred to as ‘microadenomas’ if they are less than 10 mm in diameter, are much more common than previously thought. Small pituitary tumors (which may or may not have been prolactin-secreting) are a common (20-25%) incidental finding at autopsy. Surgery is currently reserved for prolactin-secreting tumors only when the tumor is acutely threatening visual acuity or when the patient is intolerant of dopaminergic medicines.

In all cases of increased serum PRL for which no other explanation is apparent, a careful radiologic search should be made for a pituitary tumor, including an MRI scan. In those patients with normal sellas, the height of the serum prolactin is directly correlated with the likelihood of a tumor. All patients with prolactin more than 300 ng/ml, and most with prolactins more than 100 ng/ml, have tumors. Some elevated values without obvious radiologic evidence of tumor probably represent microadenomas too small to be visualized.



### **OTHER CAUSES OF INCREASED SERUM PRL.**

Estrogen ingestion, pregnancy, tranquilizing drugs, opiates, cimetidine, metoclopramide, primary hypothyroidism (sometimes), renal failure (reason unknown), any disease of hypothalamus (sarcoidosis, craniopharyngioma, Schüller-Christian, etc.—due to decreased PIF), chest wall trauma or surgery (due to nerve stimulation).

### **SYMPTOMS OF HYPERPROLACTINEMIA.**

#### *Amenorrhea.*

Very common. Measure serum prolactin in any case of unexplained amenorrhea, primary or secondary.

#### *Decreased libido, impotence, infertility in men.*

Common but not invariable, usually associated with low serum testosterone.

#### *Galactorrhea.*

Present in about two-thirds of women with increased PRL but rarely in men with increased PRL, presumably because of inadequate priming of breasts with estrogen and progesterone.

In working up patient with galactorrhea, measure prolactin, think of all possible causes of increased PRL, especially pituitary tumor. In 30–50 percent of women with galactorrhea PRL is *normal*. These women usually have normal menses, no evidence of any definite hormonal disorder. Galactorrhea may be due to increased sensitivity of breast to normal levels of circulating prolactin.

#### *Other symptoms.*

Long-standing amenorrhea due to hyperprolactinemia may predispose a woman to osteoporosis. The mechanism probably involves a relative reduction in estrogen secretion. It thus resembles to some extent the accelerated development of osteoporosis that occurs in normal women after the menopause. Aside from the above, there are essentially *no* symptoms of PRL hypersecretion, even when long continued. There is no evidence to date that most breast disorders, including cancer and gynecomastia, have anything to do with excess PRL.

### **TREATMENT.**

In the treatment of hyperprolactinemia, whether due to tumor or other cause, bromocriptine (Parlodel) has been found to be very effective in lowering serum prolactin, as have some other related ergot derivatives (cabergoline). These drugs are now regarded as first line treatment for most prolactin secreting tumors, if treatment is deemed advisable. They may be given orally for long periods of time. They function essentially as long-acting dopamine agonists and will usually restore normal menses and fertility in cases of amenorrhea due to hyperprolactinemia. They will also shrink most prolactin-secreting pituitary tumors. When dopaminergic agents are withdrawn after prolonged (years) use, some prolactin-secreting tumors will resume their pre-treatment size. Many others, however, remain smaller or even disappear for prolonged periods off medication.

Surgery and radiotherapy are also treatment options for prolactinomas.

## **2. Hyposecretion**

Prolactin is *low* (less than 1.0 ng/ml) in only a small minority of subjects with pituitary disease, usually tumor. These patients will be unresponsive to TRH stimulation and will not have postpartum lactation, should they become pregnant.

## **III. ACTH**

Mol. wt. 4569. 39 amino acids.

ACTH (the first anterior pituitary hormone to be sequenced, in the 1950's) has been identified as one component of a larger intrapituitary precursor molecule, sometimes referred to as "pro-opiomelanocortin." The structure of this molecule also includes the larger peptide  $\beta$ -lipotropin, which has fat-mobilizing properties in experimental animals but is probably not a physiologically important regulator of lipolysis.

$\beta$ -lipotropin includes the sequence of  $\beta$ -MSH, the chief MSH in humans, as well as  $\beta$ -endorphin, a naturally occurring opioid or morphine-like substance. The first 5 a.a.s of  $\beta$ -endorphin are met-enkephalin, another opioid, subject to rapid enzymic degradation, which is widely distributed in nervous tissue and gut. In its extrapituitary locations, enkephalin is probably synthesized independently of  $\beta$ -endorphin, and it may function locally in tissues to modulate neuronal activity.

$\beta$ -endorphin can be measured in peripheral blood, where its secretion, like that of  $\beta$ -lipotropin, seems to parallel the secretion of ACTH. All these peptides are probably released simultaneously following enzymatic cleavage of the precursor molecule at several points. The physiologic role of  $\beta$ -endorphin is still unclear. It can produce typical morphine-like effects if injected intracerebrally or intraventricularly into CSF but is relatively inactive if given intravenously, especially in doses corresponding to physiologic plasma concentrations. Opioids and related peptides are currently under very active investigation.

### ***A. Actions of ACTH***

1. Increases production of cortisol and adrenal androgens by adrenal cortex.
2. Increases size and weight of adrenal cortex.
3. Several extra-adrenal actions, probably of little physiological consequence.

Insert Figure

### **Partial Structure of ACTH precursor model**

#### ***B. Secretory pattern***

There is a true circadian 24-hour pattern, with highest values in early A.M., lowest in evening. The pattern to some degree is independent of sleep.

#### ***C. Regulation of secretion***

Decreased by glucocorticoids, in inverse feedback relationship with adrenal cortex

Increased by stress

Increased by hypoglycemia

#### ***D. Normal values***

Up to 27 pg/ml (depending on the assay method) at 8–10 A.M. in unstressed individual.

#### ***E. Stimulation and suppression tests***

Discussed elsewhere.

#### ***F. Disorders of secretion***

Discussed elsewhere.

#### **IV. MSH**

Two forms,  $\alpha$ - and  $\beta$ -MSH (see under ACTH). Not generally measured. May be hypersecreted, usually together with ACTH, by tumors.

#### **V. GONADOTROPINS**

**FSH** and **LH**. Glycoproteins. Mol. wt. 32,000. Each consists of two pairs of chains,  $\alpha$  and  $\beta$ .  $\alpha$ -chain of FSH is identical to that of LH, TSH, and hCG.  $\beta$ -chains show some homologies but are immunologically and physiologically distinct from one another.

##### ***A. Actions***

FSH acts to mature ovarian follicles in women, seminiferous tubules in men. LH promotes estrogen secretion by ovary, testosterone secretion by testes.

##### ***B & C. Secretory patterns and regulation of secretion***

Hormone levels fluctuate within a relatively constant range in men and women, except for a brief midcycle peak of both hormones in women which triggers ovulation. The mode of regulation is complex and still not completely understood. Estrogens (and to a lesser extent testosterone, probably via conversion to estradiol) cause inhibition of both hormones in a negative feedback system. There is also evidence for positive feedback by estrogen on LH. Serum levels of both hormones rise in women after the menopause.

Recent work indicates that there are short-term fluctuations of gonadotropins in human blood with a period of about 1 hour, sometimes termed a "circoral" rhythm. These are due to corresponding hourly fluctuations in the secretion of GnRH. If one wishes to produce sustained elevation of gonadotropins in humans by giving GnRH (e.g., to treat certain forms of hypogonadism caused by hypothalamic insufficiency), the GnRH must be given in pulsatile fashion with a pulse every hour or so. Continuous administration of GnRH will cause, after an initial increase in gonadotropins, a paradoxical and sustained decrease in gonadotropin secretion due to blockade of the secretory mechanism. Long-term continuous administration of GnRH or its long-acting analogues has been used to turn off gonadotropin secretion and is a form of treatment for precocious puberty. It is also used, as an alternative to surgical castration, to reduce testosterone secretion in men with prostate cancer, and to reduce estrogen secretion in women with endometriosis.

##### ***D. Normal values***

Immunoassay of FSH and LH in plasma is now the standard method. Normal values differ from lab to lab, depending on standards used and other factors. High levels are significant and indicate primary gonadal failure. Low levels are harder to interpret because of the broad normal range but, taken together with evidence of hypogonadism, suggest hypopituitarism.

##### ***E. Stimulation and suppression tests***

Discussed elsewhere.

### ***F. Disorders of secretion***

Clinical syndromes due to hypersecretion of FSH or LH by pituitary tumors are comparatively rare. Hyposecretion may exist as an isolated defect (sometimes associated with increased prolactin) or in association with other pituitary hormone deficiencies; it causes amenorrhea in women, loss of libido and potency in men. The distinction from primary gonadal failure is made on the basis of plasma gonadotropin measurements. Low FSH and LH in postmenopausal women, where they would normally be high, are particularly significant as indicators of pituitary disease.

## **VI. TSH**

Mol wt. 32,000. A glycoprotein, with  $\alpha$ - and  $\beta$ -chains closely related to the gonadotropins with  $\alpha$  chains identical to that in gonadotropins, unique  $\beta$  chains.

### ***A. Actions***

Increases synthesis and release of thyroid hormones by thyroid gland, and causes growth of thyroid tissue.

### ***B. & C. Secretory pattern and regulation of secretion***

Secretion in adults is relatively constant. Negative feedback by thyroid hormones on TSH secretion, interestingly, primarily acts directly on the pituitary itself rather than via the hypothalamus.

### ***D. Normal values***

0.35 to 4.00  $\mu$ U/ml. In older assays, low values were sometimes not easily distinguishable from normal because of sensitivity limitations of assay, but low or low normal values together with clinical hypothyroidism and low  $T_4$  indicate pituitary or hypothalamic failure. High values are seen in primary hypothyroidism; in borderline hypothyroidism, elevated TSH levels are usually an earlier and more sensitive index of early thyroid failure than is a frankly low serum  $T_4$ .

### ***E. Stimulation and suppression tests***

There is a hyper-response of TSH to TRH in primary hypothyroidism, and a hyporesponse in hyperthyroidism of any cause, although these are rarely used.

### ***F. Disorders of secretion***

#### ***1. Hypersecretion***

Extremely rare, but has been reported in a very few patients with TSH-secreting pituitary adenomas as a cause of hyperthyroidism. TSH levels are low in both Graves' disease and toxic nodular goiter, indicating that these are not diseases of pituitary origin.

#### ***2. Hyposecretion***

TSH is reduced less frequently than hGH or gonadotropins by pituitary disease—about as often as decreased ACTH, although not necessarily in association with the latter. Isolated TSH deficiency occurs but is rare. Determination of plasma TSH is the best single test for differentiating primary thyroid failure (where TSH is high) from pituitary hypothyroidism (where it is low or normal in the face of low T<sub>4</sub> levels).

## **Diagnostic Approach to Patients with Pituitary Disease**

### **I. HISTORY**

**A.** In children, a slowing of growth is commonly present. Older children may have failure of puberty.

**B.** In adults, premature loss of sexual function is common, particularly amenorrhea in women.

**C.** Symptoms of decreased thyroid and adrenal function should be asked for but are less common than those due to decreased hGH and gonadotropins.

**D. Symptoms** of *hypo*function are more common than those of *hyper*function. Any combination of deficits, including isolated loss of a single hormone, can occur. Isolated losses of hGH and gonadotropins are more common than isolated losses of TSH or ACTH, which are quite rare.

**E.** Symptoms particularly suggestive of *pituitary tumor* are headache (rare in microadenomas, but present in 50 percent or more of patients with larger tumors); visual field defects, which are even more suggestive, but less common and often unnoticed by patients; other cranial nerve signs, chiefly III, IV, VI, still less common (ca. 5 percent).

**F.** Tumor (most often, chromophobe adenoma) is the most common cause of hypopituitarism in adults. Idiopathic deficiency is the most common cause of hypopituitarism in children. Although craniopharyngioma, an uncommon cause, can occur at any age, it is more frequent in children. Diabetes insipidus usually implies a disease process intrinsic to or compressing the hypothalamus, and is a rare complication of pituitary tumor.

### **II. INITIAL LABORATORY TESTS**

#### **A. RADIOLOGIC IMAGING.**

MRI scans can show small pituitary tumors (microadenomas) not evident as enlargement of the sella turcica on routine x-rays. MRI scans should be ordered on any patient with unexplained elevated prolactin or with other symptoms strongly suggestive of pituitary disease.

#### **B. SERUM PROLACTIN.**

Should be ordered in all patients with suspected pituitary disease, including women whose only complaint is amenorrhea, because of the high incidence of elevated prolactin levels in the presence of a pituitary tumor. Some patients with small tumors will have increased prolactin with normal MRI scans.

#### **C. SERUM TESTOSTERONE IN POST-PUBERTAL MALES.**

#### **D. SERUM FOR FSH AND LH IN NON-MENSTRUATING WOMEN AND IN MALES WITH LOW TESTOSTERONE.**

Serum estradiol levels are not usually helpful as they fluctuate widely with the menstrual cycle. Biologic indices of estrogen function (e.g., menstrual history) are more informative.

**E. SERUM TSH AND THYROXINE.**

**F. A.M. SERUM CORTISOL.**

**G. VISUAL FIELD TEST.**

Done if there is any evidence of pituitary enlargement.

**H. WRIST FILMS FOR BONE AGE IN CHILDREN.**

A reduced bone age in comparison with chronologic age is suggestive of growth failure.

**I.** Other tests can be ordered later for more specific evaluation of individual hormones.

**J.** If the sella turcica is enlarged on a routine film, an MRI scan is indicated. The purpose of this is to define:

1. Nature of the tumor, including possible optic chiasm involvement.
2. Possible “*empty sella syndrome*,” a condition more common than previously recognized, in which much of the sella is occupied by CSF. Except in unusual cases it is not accompanied by any major hormonal abnormalities, has a benign prognosis, and should not be treated.

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