Chapter 35
PITUITARY AND ADRENAL

PITUITARY

Anatomy

MACROSCOPIC ANATOMY

The pituitary gland is surrounded by the *sella turcica,* covered superiorly by the *diaphragma sellae,* through which the pituitary stalk passes. The optic chiasm lies superior and anterior to the stalk. The hypothalamus lies directly above. The cavernous sinuses border the lateral walls of the sella. The pituitary weighs 500 mg in the adult male and 600 mg in the adult female.

The gland is composed of the anterior pituitary, or *adenohypophysis* (*pars distalis,* which is the major portion; *pars intermedia,* which is rudimentary; and *pars tuberalis,* which extends the pars distalis along and around the stalk), and the posterior pituitary, or *neurohypophysis* (median *eminence,* or infundibulum, in the hypothalamus; infundibular stem, which is the neural portion of the stalk; and *neural lobe,* or *infundibular process,* the inferior portion of the neurohypophysis).

MICROSCOPIC ANATOMY

Vascular Anatomy The anterior pituitary has the highest blood flow of any organ (0.8 mL/g/min). The superior hypophyseal arteries from the internal carotid form a portal venous system that carries stimulatory and inhibitory hypothalamic hormones to the anterior pituitary. The posterior pituitary is perfused by short portal veins from the lower infundibular stem. Pituitary hormones are released into the surrounding dural sinuses. Low pressure in the portal system makes the pituitary vulnerable to ischemic injury.

ADENOHYPOPHYSIS

Immunohistochemistry has allowed description of pituitary cells according to their secretory function.

Growth Hormone (GH)–Producing Cells (Somatotropes) These are located in the lateral aspect of the adenohypophysis. GH

effects growth of bone, muscle, and visceral organs. It is released in surges six to eight times daily. Growth hormone-releasing hormone (GHRH) stimulates secretion; somatostatin limits it.

Prolactin-Producing Cells (Mammotropes), Lateral Aspect Prolactin facilitates the development of breast tissue to ensure lactation. Hypothalamic control is maintained through prolactin-inhibiting factor (dopamine) and prolactin-releasing factor (thyrotropin-

releasing hormone, TRH). Pregnancy, lactation, stress, and exercise are associated with high levels.

Adrenocorticotropic Hormone–Producing Cells (Corticotropes), Mediolateral Aspect Adrenocorticotropic hormone (ACTH) promotes growth of the adrenal cortex and synthesis of adrenal steroid hormones and also is melanotropic. Normal secretion is stimulated by corticotropin-releasing hormone (CRH) from the hypothalamus, following the circadian rhythm—highest late in sleep period. Inhibition of release is by negative feedback of cortisol on corticotrope and release of CRH.

Thyroid-Stimulating Hormone (TSH)–Producing Cells (Thyrotropes), Anteromedial Aspect TSH increases thyroid growth and synthesis of thyroid hormones. Hypothalamic control is through thyrotropin-releasing hormone (TRH). Triiodothyronine (T_3) and thyroxine (T_4) inhibit TSH release: cold and stress increase release.

Gonadotrophic Hormone–Producing Cells (Gonadotropes) *Follicle-Stimulating Hormone (FSH)* FSH is responsible for growth and maturation of ovarian follicles or testicular growth and spermatogenesis.

Luteinizing Hormone (LH) LH promotes development of the corpus luteum and enhances ovarian estrogen and progesterone production or stimulates the testes to produce testosterone. Hypothalamic influence is mediated via gonadotropin-releasing hormone (GnRH).

NEUROHYPOPHYSIS

The posterior pituitary has no blood-brain barrier. It consists of hypothalamic neuronal axons and terminals, specialized glial cells, and blood vessels.

Regulation of the Hypothalamic-Pituitary Axis This is mediated by parvocellular and magnocellular neuronal systems.

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Parvocellular Small neurons originate in cell groups that produce the hypothalamic-pituitary hormones and end in the median eminence, where these hormones are released and regulate adenohypophyseal release of hormones via the portal circulation.

Magnocellular Large-body neurones contain oxytocin (uterine contraction) and vasopressin (antidiuretic hormone, ADH) and end in the posterior lobe, where hormones are stored and released. ADH is regulated through osmoreceptors in the hypothalamus and by baroreceptors.

Diagnostic Studies

NEUROENDOCRINE EVALUATION

Anterior Pituitary Patient presents with signs or symptoms of single or multiple hormonal deficits, hyperprolactinemia, hyperthyroidism, diabetes insipidus, a hypothalamic disorder, or any sellar or suprasellar lesion.

TSH Deficiency Measure simultaneous basal serum TSH and thyroid hormone levels; low

T_4 with low TSH suggests central cause. TRH test differentiates hypothalamic from pituitary defect.

ACTH Deficiency Dynamic testing is required (A.M. cortisol level is low only when the ACTH deficiency is very severe). With the CRH test, no ACTH response means corticotrope deficiency. An ACTH stimulation test measures the capacity of the adrenals to secrete cortisol.

Gonadotropin Deficiency Measure simultaneous basal serum FSH and LH levels as well as gonadal steroids (estradiol or testosterone). High FSH and LH levels mean primary gonadal failure. The GnRH stimulation test measures gonadotrope function.

GH Deficiency Plasma level of insulin-like growth factor-1 (IGF-1) reflects 24-h secretion of GH.

Posterior Pituitary *Central Diabetes Insipidus (DI)* This results from the insufficient secretion of vasopressin (not renal DI, in which the kidney fails to respond to elevated vasopressin levels). Diagnosis is made by the water deprivation test with development of abnormally concentrated plasma (osmolality > 300 mOsm/kg) and dilute urine (osmolality < 270 mOsm/kg), which is not reduced in volume as much as expected. Administration of vasopressin will correct these abnormalities (not in renal DI).

RADIOGRAPHIC EVALUATION

Provides information about the bony anatomy of the sella and surroundings and intrasellar contents. Lateral skull radiographs may show enlargement of sella in intrasellar tumors. For a more precise evaluation, use computed tomography (CT) with special “windows” to enhance bony detail.

For soft tissue detail, magnetic resonance imaging (MRI) is the first choice. High-field thin-section MRI appears to be the most sensitive method for preoperative localization of pituitary adenomas. CT may be used if MRI is not available (and may provide supplemental information about bony landmarks and lesion calcification).

Anterior Pituitary Disorders

POSTPARTUM PITUITARY ISCHEMIA

Postpartum Infarction and Necrosis (Sheehan Syndrome) The pathogenesis of this syndrome is debatable but hypovolemic shock and portal venous thrombosis from diffuse intravascular coagulation are suggested. Hypopituitarism may be total or partial, delayed or acute. Clinical features include failure to lactate, amenorrhea, and progressive indications of adrenal and thyroid insufficiency.

PITUITARY ADENOMAS

Benign Tumors These may originate from any of the above-described pituitary cell types. Microadenomas (<10 mm in diameter) may be present in 10–20 percent of the older

population. Macroadenomas (>10 mm) are quite rare. They are classified according to their secretory product, if any.

Null-Cell Adenomas Most common; these are without function, so they are more likely to reach macro size and produce symptoms by displacement or pressure such as headache, visual failure, or hypopituitarism. They may be misdiagnosed as prolactinoma because pressure can lead to stalk compression, causing loss of dopaminergic inhibition of tonic prolactin release.

Therapy Objectives: (1) relief of signs and symptoms from mass effect and (2) correction of endocrine abnormalities. For nonfunctioning tumors, primary prescription is surgical, with radiation therapy second.

Prolactinomas These are the most common functional adenomas, with equal frequency in men and women. Their clinical significance is greater in women, in whom secondary amenorrhea is

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the presenting symptom and only half have galactorrhea. In men, decreased libido and impotence usually are attributed to aging, so the diagnosis is missed until mass effect is present.

Treatment Surgery is the first choice for microadenomas; cure is frequent. Long-term surgical cure is less frequent with large or invasive tumors. Bromocriptine should reduce both the size and prolactin secretion and should be used first; surgery is reserved for patients intolerant of side effects to reduce the required dose. Radiation therapy also can bring residual tumor under control.

Cushing's Disease Cushing's disease is characterized by hypersecretion of ACTH by corticotrope adenomas in 90 percent of patients (or diffuse corticotrope hyperplasia from hypersecretion of hypothalamic CRH in the remainder). Cushing's disease affects women eight times more frequently than men.

Clinical Manifestations (1) Those resulting from glucocorticoid excess: central obesity, “moon” facies, dorsocervical and supraclavicular fat pads, proximal muscle wasting, thin skin with ecchymoses, and violaceous striae, cataracts, osteoporosis, amenorrhea, diabetes mellitus, growth retardation in children, and immunosuppression with fungal infections, and (2) those resulting from peripheral androgen excess: hirsutism and acne.

Diagnosis (1) Increased basal plasma cortisol level with loss of diurnal variation, (2) elevated 24-h urinary free cortisol excretion (>100 mg/24 h), and (3) failure of the serum cortisol to suppress with *low-dose dexamethasone suppression test* (1 mg dexamethasone at 11 P.M.; 8 A.M. plasma cortisol > 4 mg/dL).

Therapy Most patients have microadenomas that can be excised completely. Macroadenomas frequently invade adjacent dura and bone and so defy chemical cure by surgery alone. If medical therapy fails, adrenalectomy will palliate.

Acromegaly and Gigantism Excess GH produces acromegaly. Before epiphyses fuse, it produces gigantism, with growth to more than 7 ft. Soft tissue changes in acromegaly include coarsening of facial features, vocal enlargement, goiter, thick heel pads, acanthosis

nigrans, cardiomegaly, and hepatomegaly. Bony changes include facial prognathism, enlargement of the mandible, and bony enlargements of hands and feet. Metabolic changes include associated hypertension, diabetes mellitus, and cardiomyopathy. These disorders affect males and females with equal frequency.

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Diagnosis Diagnosis is by physical examination and assessment of GH secretion (basal fasting GH level > 10 ng/mL in 90 percent of acromegalics). Confirmation is by the glucose suppression test (100 g of glucose PO fails to suppress GH level to <5 ng/mL at 60 min). Serum IGF-1 levels are elevated in acromegalics. MRI and/or CT demonstrates a pituitary adenoma in more than 90 percent of patients.

Treatment Treatment should be expedient because of associated metabolic problems. Complete surgical removal of pituitary adenomas that secrete GH controls the elevated GH level and may be curative. Lesions that are not completely resectable may be helped by parenteral octreotide or radiation therapy.

Surgery for Pituitary Adenomas *Preoperative Evaluation* An adequate endocrine evaluation is necessary to minimize the potential for catastrophe because of inadequate pituitary reserve. Most important are cortisol and thyroid levels. Cortisol replacement prevents adrenal insufficiency. Reestablishment of euthyroidism requires a week of treatment. Electrolyte status defines marginal DI.

Transsphenoidal Approach Transnasal transsphenoidal approach is the procedure of choice for surgical access to sellar lesions. In microadenomas, the transsphenoidal approach has resulted in greater than 90 percent tumor control. In larger tumors, control has been only 50–85 percent with surgery alone. Operative mortality is less than 1 percent. Morbidity includes DI (1.8–17 percent), postoperative cerebrospinal fluid (CSF) fistulas (1–4.4 percent), stroke, visual loss, vascular injury, meningitis, CSF rhinorrhea, and cranial nerve palsy (3.5 percent). Relative contraindications include extensive lateral tumor, ectatic carotid arteries (*transcranial approach* may be used), or acute sinusitis.

Perioperative Management Glucocorticoids are given to all patients. Serial visual field testing is used to monitor visual and neurologic condition. Any loss of vision postoperatively may indicate hemorrhage. CT scanning further defines this. Urine volume and serum glucose levels are followed along with sodium levels to detect DI. The A.M. fasting cortisol level before discharge determines the need for cortisol replacement. Thyroid function is tested at 3–4 weeks.

Primary Radiation Therapy With radiation therapy, there is a significant risk of worsening preexisting hypopituitarism; it also increases the rate of atherogenesis and can cause visual impairment.

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It should be reserved for patients with major operative risk factors. *Stereotactic radiosurgery* may prove a safer and more effective method for pituitary adenomas. *Postoperative radiotherapy* to reduce the incidence of recurrence is used for large tumors and those with cavernous sinus invasion.

OTHER LESIONS

The differential diagnosis of mass lesions that can affect pituitary function includes *benign cysts, meningiomas, craniopharyngiomas* (characteristic appearance on skull radiograph or CT scan: calcification within or above sella; primary treatment is surgical, but the results are disappointing), *optic chiasm* or *hypothalamic glioma* (associated with neurofibromatosis, but sporadic cases are more frequent and defy surgical cure, so surgery is used to establish the diagnosis), *sellar metastases* (present as progressive hypopituitarism), and *empty sella syndrome* (herniation of arachnoid and subarachnoid space of suprasellar cistern through an incompetent diaphragma sellae; may be primary or follow surgery or radiation therapy).

Trauma

The pituitary stalk is susceptible to transection in basilar skull fracture. Most pituitary and hypothalamic damage results from increased intracranial pressure (ICP).

Posterior Pituitary Disorders

Diabetes insipidus involves impaired H_2O conservation; one-third of cases are idiopathic. Other causes include tumors, granulomatous disease, or trauma that destroys the hypothalamus, pituitary stalk, or posterior pituitary. The *syndrome of inappropriate secretion of antidiuretic hormone* (SIADH), which occurs in 15 percent of hospitalized patients, leads to impaired water excretion.

ADRENAL

Embryology

The cortex and medulla arise separately. The primitive cortex develops from the coelomic mesoderm. The medulla and sympathetic nervous system develop together from primitive neural crest cells. One group migrates along the adrenal vein, invades, and becomes surrounded by cortex. Preganglionic sympathetic fibers synapse directly with these medullary cells. A second group forms the organs

of Zuckerkandl lateral to the aorta near the inferior mesenteric artery. They usually atrophy in childhood but are a frequent location of extraadrenal chromaffin tumors (Fig. 35-1).

FIGURE 35-1 Location of ectopic adrenal tissue. The location of ectopic adrenal medullary tissue is shown in black; cortical tissue is shown in the shaded areas. The incidence of extraadrenal medullary tissue is very high compared to the incidence of extraadrenal cortical tissue, and while functioning extraadrenal medullary tissue occurs in about 1 in 8 cases of medullary hyperfunction, it occurs in fewer than 1 in 1000 cases of adrenocortical hyperfunction.

Anatomy

The adrenal glands are bilateral, located near the upper pole of each kidney, and each weighs 3–5 g and is bright yellow in color. Each is supplied by numerous small arteries from the inferior phrenic artery, the aorta, and the renal artery. The right adrenal vein enters the posterior aspect of the vena cava; the left adrenal vein enters the left renal vein. There are three cortical zones: the outer glomerulosa, (aldosterone), the reticularis (sex steroids), and the fasciculata (cortisol). There is also a central medulla (catecholamines).

Adrenal Cortex

PHYSIOLOGY

Aldosterone This causes sodium retention by renal tubules. It is regulated by the *renin-angiotensis system,* with potassium concentration, atrial natruretic hormone, and dopamine making contributions, to maintain extracellular fluid volume, extracellular potassium concentration, and blood pressure.

Cortisol Glucocorticoids are essential for life. Secretion occurs in a circadian pattern, with the peak before awakening in the morning. Secretion is mediated through ACTH and stimulated by stress, antidiuretic hormone (ADH), and epinephrine. Most important is CRH. Plasma cortisol levels exert negative feedback on ACTH at the pituitary and CRH at the hypothalamus.

Sex Steroids During normal sexual development, *adrenarche* marked by secretion of dehydroepiandrosterone (DHA).

PATHOLOGY

Hyperplasia This is an increased number of cells. In Cushing's disease, hyperplasia is caused by increased pituitary secretion of ACTH.

Adrenal Cortical Adenoma This is a benign neoplasm of the cortex. It may cause symptoms by unregulated production of hormone. Adenomas do not exceed 5 cm in diameter. Cells usually look bland, but pleomorphism and necrosis may be seen.

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Adrenal Cortical Carcinoma This is a malignant neoplasm of cortical cells. It is rare, having a bimodal peak occurrence at less than 5 years and during the fifth decade. These carcinomas are larger than 6 cm. Vascular invasion, desmoplastic bands, and mitoses are suggestive of the diagnosis. Nodal or distant metastasis is the only reliable criterion.

CUSHING'S SYNDROME

Cushing's syndrome is endogenous hypercortisolism caused by secretion of ACTH by a pituitary tumor (Cushing's disease), secretion of cortisol by an adrenal tumor, or ectopic secretion of ACTH by a nonadrenal tumor.

Clinical Manifestations Clinical manifestations include truncal obesity, thinning of the extremities due to muscle wasting, “buffalo hump,” “moon” facies, mildly increased blood pressure, purple striae along the flank, hirsutism with excessive fine hair on the face, upper back, and arms, mild hyperglycemia, muscle weakness, menstrual irregularity, impotence,

ruddy facial appearance, mental changes from mild depression to severe psychosis, impaired immune function leading to opportunistic infections, and arrest of normal growth.

Diagnosis The diagnosis depends on recognizing the different signs and symptoms. Three steps: First, establish the presence of hypercortisolism. The best screen is a 24-h urinary free cortisol test; another is the single-dose dexamethasone suppression test. Normal individuals given 1 mg dexamethasone PO at 11 P.M. have plasma cortisol levels below 5 µg/dL at 8 A.M. In hypercortisolism, the level will be higher. Second, determine if the hypercortisolism is pituitary dependent. The plasma ACTH level is undetectable or low with a primary adrenal tumor, intermediate with a pituitary tumor, and very high with an ectopic ACTH-producing tumor. Third, determine the exact cause. With the CRH test, 1 g/kg CRH increases the plasma ACTH and cortisol levels in pituitary tumor but not in ectopic ACTH syndrome. The dexamethasone suppression test (see above) also can be used. In addition, metyrapone stimulates ACTH release in pituitary disease.

Radiographic Evaluation CT and MRI of the sella turcica detect tumor only in a small percentage of patients. Bilateral petrosal sinus sampling is best for differentiating a pituitary from an ectopic ACTH-secreting tumor. Sampling of blood from both the inferior petrosal sinuses and peripheral veins before and after CRH administration produces a ratio of more than 3:1 in Cushing's disease,

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which helps with lateral localization. An adrenal CT scan can distinguish cortical hyperplasia from tumor with more than 95 percent sensitivity. A T_2-weighted MRI adds specificity and may distinguish adenoma from carcinoma. Pheochromocytoma is particularly bright. Radioisotope imaging with labeled iodocholesterol may differentiate hyperplasia (bilateral) from adenoma (unilateral) or carcinoma (usually cold).

ADRENAL INSUFFICIENCY (ADDISON'S DISEASE)

Primary adrenal insufficiency is caused by autoimmune adrenalitis, tuberculosis, adrenomyeloneuropathy, fungal infections, the acquired immune-deficiency syndrome (AIDS), metastatic carcinoma, adrenal hemorrhage, familial deficiency, or adrenal surgery. Secondary adrenal insufficiency is caused by an abnormality of the pituitary or hypothalamus. Most commonly it is iatrogenic from long-term glucocorticoid administration. It may lead to an adrenal crisis perioperatively.

Clinical Manifestations Clinical manifestations include weakness and fatigue, weight loss and anorexia, and dehydration. In adrenal crisis, poorly defined upper abdominal or flank pain, fever, nausea, lethargy, disorientation and confusion, hypotension, hypoglycemia, hyperkalemia, leukocytosis with eosinophilia, and prerenal azotemia may be seen. These signs with or without cardiovascular collapse in any perioperative or critically ill patient should raise the question of insufficiency.

Diagnostic Testing The plasma cortisol level is often depressed, and the ACTH level is often elevated. The capacity to respond to ACTH stimulation is measured to assess the stress response. Cortisol is measured before and 60 min after administration of 250 µg ACTH. Function is normal if the basal level is 20 µg/dL and there is an increment of more than 7 µg/dL over basal levels at 60 min.

Treatment If the clinical condition is rapidly deteriorating, a blood sample for plasma ACTH and cortisol, glucose, Na, K, blood urea nitrogen (BUN), and creatinine determination and a complete blood count (CBC) should be drawn, and 200 mg of a water-soluble corticosteroid should be administered. After the initial intravenous bolus, 100–200 mg of corticosteroid should be administered over the next 24 h. Fluid and electrolyte imbalances are corrected with intravenous replacement fluids, and the underlying cause is sought. High-dose replacement should be continued for several days and then tapered.

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Perioperative Treatment Patients currently taking steroids or who have taken them within 2 years should be treated perioperatively with hydrocortisone. If there is a question, a cosyntropin stimulation test may be done. The amount of perioperative steroid treatment will depend on the magnitude of the surgical procedure. Patients undergoing major procedures (e.g., Whipple procedure, coronary artery bypass grafting) need 100–150 mg IV on-call to the operating room, 50 mg IV every 8 h for 2 days, 25 mg every 8 h for 3 days, and then maintenance. For smaller operations, lower doses are sufficient. For surgical treatment of endogenous hypercortisolism, glucocorticoid replacement is required after removal of the cause.

PRIMARY HYPERALDOSTERONISM (CONN'S SYNDROME)

Diagnosis This is one of the few surgically curable causes of hypertension. The causes include adrenocortical adenoma (80 percent), hyperplasia of the zona glomerulosa, and (rarely) adrenocortical carcinoma.

Hypertension (predominantly diastolic), spontaneous hypokalemia, high plasma levels of aldosterone, and low plasma levels of renin are characteristic. Patients may be asymptomatic or have weakness, muscle cramps, polyuria, and polydipsia. It is important to rule out essential hypertension treated with potassium-wasting diuretics. Stop all diuretics and measure 24-h excretion of potassium (>30 mEq/24 h is suggestive).

The ratio of plasma aldosterone to renin is usually greater than 30. An inability to reduce the plasma aldosterone level to less than 15 ng/dL and raise plasma renin activity after administration of captopril is confirmatory.

Localization High-resolution CT scanning (75–90 percent accurate) of the contralateral adrenal cortex should show it to be atrophic. Tumors of less than 1 cm may be missed. Radioactive iodocholesterol scanning may be helpful Selective venous sampling for aldosterone is indicated when these tests fail.

Treatment *Adenoma* Laparoscopic adrenalectomy is the treatment of choice.

Hyperplasia Medical management is attempted with spironolactone, nifedipine, and/or amiloride plus other antihypertensive drugs.

HYPOALDOSTERONISM

Hypoaldosteronism may be genetic or autoimmune. It may follow excision of an aldosteronoma. It is treated with fludrocortisone (0.1–0.2 mg/day) for months.

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ADRENOGENITAL SYNDROME

Adrenogenital syndrome is associated with congenital adrenal hyperplasia, a group of inherited diseases caused by defects in one of five enzymes that contribute to synthesis of cortisol from cholesterol resulting in a decrease in cortisol and an increase in precursors. Hyperplasia is driven by ACTH. An associated finding is ambiguous external genitalia as a result of a deficiency or excess of adrenal androgens. Treatment is glucocorticoid replacement and may include surgical correction of genitalia.

Postnatal children and adults may preset with signs or symptoms of excess sex hormone secretion, almost always caused by tumors of the adrenal, usually carcinoma.

ADRENAL MASS

This is an unexpected finding in 0.6 percent of abdominal CT scans. Most are usually benign, nonfunctional adenomas (autopsy incidence 10 percent). The surgeon should obtain a careful history and physical examination, a stool guaiac test, a Pap smear and hematocrit, and determinations of the 24-h urine for free cortisol level (Cushing's syndrome), vanillylmandelic acid (VMA), and catecholamines (pheochromocytoma). Aldosterone and renin should be measured in any patient with hypertension or hypokalemia. Even if nonfunctional, a mass larger than 5 cm may be carcinoma and should be resected. Smaller masses should be remeasured by CT in 6 months and resected if larger or left alone if unchanged. If pheochromocytoma is excluded and metastatic disease is suspected, a fine-needle aspiration (FNA) may be helpful (Fig. 35-2).

FIGURE 35-2 Flow diagram for the management of an incidentaloma.

Treatment of Adrenal Cortical Neoplasms *Adenoma* Treatment involves complete resection of the involved adrenal gland using laparoscopic technique with postoperative glucocorticoid supplementation.

Carcinoma Stage I is a tumor smaller than 5 cm without local invasion. Stage II is the same but larger than 5 cm. Stage III shows local invasion or positive nodes. Stage IV shows distant metastases. CT scan or MRI should include the chest to assess extent of tumor. A venacavagram is necessary if the vena cava appears to be involved. A contrast study is needed to document contralateral function if nephrectomy is needed. En bloc resection of the tumor and involved adjacent organs provides the best chance for cure and may require a thoracoabdominal approach. Even debulking will help by reducing the amount of hormone-secreting tissue. Cure is likely only in stage I or II disease. The 5-year survival is 10–35 percent. Recurrent or metastatic disease is usually treated with mitotane,

which affects steroid metabolism and can reduce symptoms of hypercortisolism.

ECTOPIC ACTH SYNDROME

The diagnosis requires Cushing's syndrome and bilateral adrenal hyperplasia but no evidence of pituitary tumor. Ectopic ACTH-producing tumors include oat cell or small cell lung cancer, bronchial or thymic carcinoid, pancreatic islet cell tumor, medullary thyroid cancer, pheochromocytoma, midgut carcinoid, and others. Workup should screen for and localize these tumors. A suspicious finding is confirmed by FNA and radioimmunoassay for ACTH on aspirate. Treatment is resection or debulking of tumor

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or medical control of metabolic abnormalities. Bilateral adrenalectomy may be indicated.

Adrenal Medulla

PHYSIOLOGY

The sympathoadrenal system consists of a sympathetic neuronal component that uses norepinephrine as the main neurotransmitter and adrenomedullary secretory hormone, epinephrine, the main hormone secreted into the bloodstream. The system influences cardiovascular, metabolic, and visceral activity, and its typical effects are observed during severe stress. Release of norepinephrine at sympathetic nerve endings is critical for maintenance of normal blood pressure, especially during upright posture. Epinephrine metabolites (e.g., normetanephrine, metanephrine, and VMA) are excreted with catecholamines in the urine.

PHEOCHROMOCYTOMA

Pheochromocytomas arise from chromaffin cells that are associated with sympathetic ganglia in fetal life and are concentrated in the adrenal medulla after birth. Between 85 and 90 percent of pheochromocytomas arise in the adrenal medulla, but they can arise wherever there is a sympathetic ganglion, including the carotid body, the heart, along the thoracic or abdominal aorta, and in the renal hilum or urinary bladder. The most common extraadrenal site is the organ of Zuckerkandl near the origin of the inferior mesenteric artery. Pheochromocytomas are usually 3–5 cm in diameter and weigh about 100 g. Ten percent or more are malignant, and these tend to be larger. The only absolute criteria are the presence of secondary tumors where chromaffin cells are not found and identification of visceral metastases.

Associated Syndromes Ten percent of pheochromocytomas occur as part of an inherited condition. Bilateral medullary pheochromocytomas are components of multiple endocrine neoplasia (MEN) types IIA and IIB. They can occur in families without other manifestations of MEN syndromes. They occur in 25 percent of patients with von Hippel–Lindau's disease and in less than 1 percent of patients with neurofibromatosis and von Recklinghausen's disease.

Clinical Manifestations Pheochromocytomas can cause anxiety attacks and episodic or sustained hypertension. Patients classically describes “spells” of paroxysmal headaches, pallor, palpitations, hypertension, and diaphoresis. Some have mild hypertension;

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others suffer sudden death from myocardial infarction or cerebrovascular accident. They

may have chronic hypovolemia or lactic acidosis. Most patients have mild weight loss.

Diagnosis Diagnosis is based on a 24-h urine collection for catecholamine, metanephrine, and VMA determinations. Plasma levels may be measured but are not as sensitive. Elevated levels of norepinephrine occur with extraadrenal pheochromocytomas. The clonidine suppression test may be supplemental. Clonidine suppresses plasma levels in normal individuals, not in those with pheochromocytomas.

Localization Studies CT and MRI detect tumors greater than 1 cm diameter. Each has advantages. Nuclear medicine scanning with ^{131}I-labeled metaiodobenzylguanidine (MIBG) is 78–91 percent sensitive and 98–100 percent specific.

Treatment *Preoperative Preparation* Treatment starts with alpha-adrenergic blockade with phenoxybenzamine, 10–20 mg PO 2–3 times a day, increasing to 20 mg/day until the blood pressure is stabilized. Tachycardia of more than 130 beats per minute is treated with beta-adrenergic blockade (propranolol). Extra volume is required.

Intraoperative Management Right-sided heart catheter monitoring, an arterial catheter, and peripheral intravenous catheters are placed. Manipulation of the tumor causes changes in blood pressure. Nitroprusside and Levophed are used to titrate the blood pressure quickly and effectively. A transabdominal approach with a long midline or bilateral subcostal incision is used. The entire abdomen is visualized and palpated. A laparoscopic approach can be used for precisely localized tumors but is still considered experimental. Family members require yearly physical examinations and screening for elevated catecholamines, calcitonin, and serum calcium.

Malignant Pheochromocytoma Metastases may not develop for years. The basic principle is to resect recurrences of metastases whenever possible and to treat hypertension with appropriate blockade. Painful bony metastases respond to radiotherapy. Chemotherapy with cyclophosphamide, vincristine, and dacarbazine has been beneficial. Five-year survival is 36–60 percent.

NEUROBLASTOMA

This is the fourth most common pediatric malignancy. Median age at diagnosis is 2 years. Neuroblastomas may be associated with genetic diseases, including neurofibromatosis, Beckwith-Weidemann syndrome, and trisomy 18. They may spontaneously differentiate and regress. Neuroblastomas are thought to arise from the embryonic neural crest. They may be difficult to distinguish from other small, round blue cell tumors of childhood. Look for tumor markers in the serum or urine. Elevated 24-h urine levels of homovanillic acid and VMA are detected in 65 and 90 percent, respectively. Neuroblastomas can occur anywhere along the sympathetic nervous system. Metastases (50 percent in infants and 67 percent in older children) usually involve lymph nodes, bone marrow, bone, liver, and subcutaneous tissue.

Clinical Manifestations The most common presenting symptom is an abdominal or flank mass. Thoracic neuroblastoma presents as a posterior mediastinal mass on chest radiograph and may cause respiratory distress or cord compression. Neck tumor presents with a cervical mass. Pelvic tumor usually involves the organ of Zuckerkandl.

Radiology and Staging CT is the best imaging study for patients with neuroblastoma and should be performed to determine the extent of disease. Useful nuclear medicine studies include a technetium bone scan and a ^{131}I-MIBG scan.

Treatment Treatment depends on the stage of disease. Stage I and II tumors can be resected. Most abdominal tumors involve major vessels. Unresectable abdominal tumors are biopsied, treated with radiation or chemotherapy, and then removed if possible. Radiation therapy is useful in nodal disease and in infants with spinal cord compression. Neuroblastomas are highly chemoresponsive.

Adrenalectomy

Adrenalectomy may be done using a posterior approach through the bed of the twelfth rib or laparoscopically using a lateral approach. The laparoscopic approach is suited for small aldosteronomas or cortisol-secreting adenomas or hyperplastic adrenal glands. It is not recommended for pheochromocytoma because of the need for tumor manipulation and because the adrenal vein cannot be controlled early.

For a more detailed discussion, see Couldwell WT, Simard MF, Weiss MH, and Norton JA: Pituitary and Adrenal, chap. 35 in *Principles of Surgery,* 7th ed.