Objectives:
At the end of this presentation the participant will be able to:
1. select the most appropriate tests for distinguishing among the three major causes of endogenous Cushing's syndrome.
2. list the causes of adrenal insufficiency in patients with AIDS.
3. identify the disorders associated with hyporeninemic hypoaldosteronism.
CUSHING'S SYNDROME

Clinical Manifestations:

Lipid Abnormalities: Weight Gain/Obesity (79-97%) - The typical presentation is one of truncal obesity (increased fat in trunk and abdomen, with sparing or even wasting of the extremities), with increased pre-auricular fat (“moon facies”) (75%), increased fat in the temporal fossae (which may prevent eyeglass frames from fitting properly), increased supraclavicular fat pads, increased dorsocervical fat pad (buffalo hump), a prominent upper lip (Cupid bow), and even exophthalmos in 6% (from increased retro-orbital fat). Spinal epidural lipomatosis may cause neurologic deficits. Widening of the mediastinum can be seen due to mediastinal lipomatosis. Generalized obesity can be seen in adults, but only occasionally. In children, however, generalized obesity is the rule rather than the exception. Patients who diet and exercise vigorously may present with little or no weight gain, moon facies or truncal obesity.

There is evidence that the increased visceral fat with normal or low subcutaneous fat in Cushing’s syndrome may be related to the fact that glucocorticoids significantly decrease AMP-activated protein kinase (AMPK) activity in visceral adipose tissue, without effect on subcutaneous adipose tissue. AMPK switches off anabolic pathways such as fatty acid biosynthesis and protein synthesis, and switches on catabolic pathways including fatty acid oxidation. Therefore, inhibition of AMPK activity in visceral adipose tissue would be expected to increase the net synthesis of fatty acids.

Blood levels of VLDL, LDL, HDL, and triglycerides are increased because of increased hepatic synthesis without any change in their clearance rate. Cardiovascular mortality is increased in untreated cases of Cushing’s syndrome, probably from a combination of hyperlipidemia, diabetes, hypertension, and the prothrombotic state seen in the disease.

Muscle and Connective Tissue: Proximal muscle weakness and wasting – one of the most discriminatory features of the syndrome (histologically reflected in profound atrophy of muscle fibers without necrosis) (61%); a protuberant abdomen which is due to both an increased abdominal panniculus and relaxed abdominal muscles; plethora (60%) (plethora is redness of the cheeks, anterior neck and sun-exposed chest – due to thinning of the skin and loss of facial subcutaneous fat); wide (> 1 cm), deep, purplish or reddish stretch marks on the lower flanks and abdomen that can also be seen on the breasts, hips, buttocks, thighs, upper abdomen, shoulders, upper arms and axillae (striae) (66%) (reddish-purple because the skin is so thin that you can see the color of the blood in the underlying dermis) (deep, reddish-purple striae > 1 cm in diameter are virtually pathognomonic for Cushing’s syndrome – they are less common in patients over 50 years old); easy bruising (42%) (a history of spontaneous bruising is more specific than a simple history of bruising easily); thin skin (the skin may peel off with adhesive tape like damp tissue paper) (the skin over the dorsum of the hand may be wrinkled and have a “cigarette paper” appearance – referred to as "Liddle's sign"); poor wound healing; keratosis pilaris (abnormal
accentuation of the follicles).

**Bone and Calcium Abnormalities**: 50% of adults with Cushing’s syndrome have osteoporosis by DEXA. 40% of patients present with back pain, and 16-22% experience compression fractures of the vertebrae and loss of height. A history of fractures, especially of the feet, ribs and vertebrae, may be the presenting manifestation of Cushing’s syndrome – especially in men. Rib fractures are often painless. It has been suggested that routine DEXA testing should be part of the diagnostic approach to Cushing’s syndrome. Chiodini et.al. have reported a 10.8% prevalence of subclinical hypercortisolism in patients with osteoporosis who had no clinically overt hypercortisolism or other secondary causes of osteoporosis. Hypercalciuria has been reported in 40% of patients with Cushing’s syndrome, and is due to increased bone resorption and decreased renal calcium reabsorption. 15% of patients have renal calculi. Aseptic necrosis of the femoral head, and less often the humeral head, may develop - this is actually rare in endogenous Cushing’s syndrome but more common in iatrogenic hypercortisolism.

**Glucose Abnormalities**: Glucose intolerance in 30-60%, and overt diabetes mellitus in 20-50%; acanthosis nigricans (often seen in insulin-resistant states).

**Neuro-Behavioral Abnormalities**:

*Psychological Changes (31-86%)*: Irritability; restlessness; emotional lability; fatigue; lethargy; crying; insomnia; anxiety; depression (which can be severe, even resulting in suicide) (the time course of the depressed mood is characteristically intermittent, rarely lasting more than three days at a time, and Cushing’s patients feel best – not worst – in the morning); sometimes psychosis with delusions, hallucinations and/or paranoia; sometimes euphoria or even overt mania. Rapid eye movement and delta wave sleep patterns are reduced.

*Cognitive Changes*: Decreased ability to concentrate; impaired memory.

**Gonadal Abnormalities**: Hypercortisolism inhibits GnRH pulsatility and gonadotropin secretion. This results in oligomenorrhea or amenorrhea (60%), infertility, decreased libido in men (commonly associated with impotence), and to a lesser extent in women (44%) (a finding of increased libido in women would suggest hyperandrogenism from an adrenal carcinoma), gynecomastia, decreased body hair, and small, soft testes. In addition, cortisol directly inhibits Leydig cell function.

**Thyroid Abnormalities**: Cortisol excess inhibits TRH and TSH secretion, and also inhibits 5’-deiodinase. Central hypothyroidism may persist for 3-6 months after surgical cure.

**Immune/Inflammatory Abnormalities**: tinea versicolor infection on the anterior chest or back (0-30%); lymphocytopenia (lymphocytes are < 25% of total WBC's in 50% of cases; total lymphocytes are below normal in 35% of cases); decreased eosinophils (total eosinophils are < 100/mm³ in most cases; <10/mm³ in 30% of cases); onychomycosis; oral Candidiasis (only when hypercortisolemia is severe); verruca vulgaris (occasionally large and multiple). There is an increased risk of opportunistic and fungal infections *(Pneumocystis*
carinii, Cryptococcus, Candida, Nocardia, Aspergillus, Histoplasmosis, and other organisms). Reactivation of tuberculosis has been reported, and has even been the presenting feature. Glucocorticoids inhibit activation of nuclear factor Kβ, which interferes with the production of a number of cytokines, including interleukin-6, that help mount the response against bacterial infection. There is a suppressed inflammatory and febrile response to bacterial infection. Bowel perforation is more common in patients with extreme hypercortisolism, and may present with surprisingly little tenderness and few signs of peritonitis because of the anti-inflammatory effects of cortisol.

**Coagulopathy:** Patients with Cushing’s syndrome have a thrombophilic state related to hypercoagulability and impaired fibrinolysis. Excess cortisol stimulates synthesis of several clotting factors (factor VIII, factor IX), including synthesis of fibrinogen by hepatic cells and synthesis of von Willebrand factor by endothelial cells. Cortisol also stimulates synthesis of plasminogen activator inhibitor type 1, which is the main inhibitor of the fibrinolytic system. Hypercortisolism is also associated with hyperhomocysteinemia and reduced serum folate concentrations, which may contribute to the prothrombotic state and increased cardiovascular risk of Cushing’s syndrome. The aPTT is often shortened. A statistical increase in plasmin-antiplasmin complex (PAP), tissue-type plasminogen activation: antigen (t-PA:Ag), and α2-antiplasmin activity. Patients with Cushing’s syndrome have a 1.9% to 2.5% risk of unprovoked venous thromboembolic disease (VTE). Postoperative VTE was < 6% in most studies (0-5.6%), but was 20% in one study. VTE was reported as the cause of death in 0-1.9% of Cushing’s syndrome patients, mostly within 3 months of surgery. Levels of factor VII, factor IX, and von Willebrand factor tend to normalize after successful treatment. Thromboprophylaxis (low dose heparin, enoxaparin, fondaparinux) has been recommended for patients with Cushing’s syndrome undergoing petrosal sinus sampling, transsphenoidal surgery, or adrenal surgery (including laparoscopic surgery).

**Ocular Abnormalities:** Increased intraocular pressure; exophthalmos; chemosis; cataracts are a well-recognized side effect of exogenous glucocorticoid therapy but are uncommon in endogenous Cushing’s syndrome except when caused by the diabetes.

**Mineralocorticoid Excess:** Hypertension 74%; edema 39%; hypokalemic alkalosis 17%. Concentric left ventricular remodeling may be seen, and may partly be due to a direct effect of long-term exposure of the myocardium to excess cortisol. Hypokalemic alkalosis is more common in ectopic ACTH (because the extremely high cortisol levels exert significant mineralocorticoid activity) and adrenocortical carcinoma (due to secretion of other steroids, such as deoxycorticosterone, which exert a mineralocorticoid effect). It has been described in only 10% of patient’s with pituitary tumors secreting ACTH.

**Androgen Effects (Mostly Seen in Adrenocortical Carcinoma and Ectopic ACTH Production):** Hirsutism (65%) (vellus hypertrichosis of the face, upper cheeks, forehead, and trunk is the most common presentation; terminal hair growth on the face, trunk and extremities can occur, but is less common); oily skin and acne (45%); thinning of the scalp hair is common; virilization (clitoromegaly, temporal balding) is uncommon except in adrenocortical carcinoma. The features that best discriminate Cushing’s syndrome (though they do not have high sensitivity) are easy bruising (especially spontaneous bruising), facial plethora, proximal
muscle weakness, striae (especially if reddish purple, deep, and > 1 cm wide), unexplained osteoporosis, thin skin in young patients, and weight gain with decreasing growth velocity in children.

Patients with Cushing’s syndrome have a mortality rate that is four times higher than age- and sex-matched controls, mainly due to cardiovascular complications.

Old photographs can be extremely useful in the evaluation of the physical features of a patient suspected of having Cushing’s syndrome.

The presentation of Cushing's syndrome can be different in different age groups. In infants the presentation is usually one of marked obesity with stunting or arrest of linear growth. In children it presents with growth failure and generalized obesity (though the growth rate may be accelerated in virilizing adrenal carcinoma). (Cortisol inhibits growth hormone secretion, possibly by increasing somatostatin secretion - Cushing’s syndrome is highly unlikely in a child who is growing along a centile line.) Androgen excess in children can cause pseudoprecocious puberty in boys. In adolescents it is growth arrest, generalized obesity, and hypogonadism. In the elderly it is unexplained osteopenia and uncontrolled hypertension.

The presentation of Cushing's syndrome may also differ according to the cause of the Cushing's syndrome. The large concentrations of ACTH and cortisol seen in ectopic ACTH production can cause hyperpigmentation (usually not seen in pituitary Cushing's) and mineralocorticoid effects. The rapid onset and progression of ectopic ACTH often make these patients present without the more classic manifestations of Cushing's syndrome. Adrenal adenomas are often purely cortisol-secreting tumors, so the protein-catabolic effects of cortisol (proximal myopathy, poor wound healing, plethora, easy bruising, striae, thin skin, osteopenia) are not cushioned by the anabolic effects of androgens. Adrenal carcinomas tend to produce more androgens, leading to more prominent androgenic effects (acne, hirsutism, temporal balding, clitoromegaly) and less of the protein-catabolic effects.

The presentation of Cushing’s syndrome caused by a pituitary tumor may include compressive symptoms if the tumor is large. These could include hypopituitarism, visual field abnormalities, and even cranial nerve deficits (especially III, but also IV and VI).

Etiology:

Iatrogenic: Cushing's syndrome caused by exposure to exogenous, man-made cortisol-like compounds is the most common cause of Cushing's syndrome. Recent studies have shown that even intra-articular, epidural, inhaled, nasal, ocular, and dermal glucocorticoids can cause features of Cushing’s syndrome in large doses, and can suppress the hypothalamic-pituitary-adrenal axis. There is one report in the literature of Cushing's syndrome due to prolonged therapy with high-dose medroxyprogesterone acetate. There is another report of secondary Cushing’s syndrome and suppression of the adrenal axis persisting for 12 months after a single epidural injection of 60 mg of methylprednisolone acetate.

The rapidity of onset of the symptoms depends on the dose of glucocorticoid used, but they can occur within one month. Some features of Cushing’s syndrome are more
commonly seen with iatrogenic than with endogenous Cushing’s. This would include increased intraocular pressure, cataracts, benign intracranial hypertension, aseptic necrosis of the femoral head, osteoporosis, and pancreatitis. On the other hand, hypertension, hirsutism, and menstrual abnormalities are less common than in endogenous Cushing’s.

**ACTH-Dependent (80-85%):**

**Pituitary Cushing’s ("Cushing’s Disease") (80% of all ACTH-Dependent Cushing’s Syndrome, 90% of all ACTH-Dependent Cushing’s Syndrome in Women):** Usually caused by a pituitary adenoma of monoclonal origin secreting ACTH, though basophil hyperplasia alone has been reported in 9-33% of pathologic series; a 4:1 female: male preponderance has been reported; the age range is usually 25-45; 50% of patients with pituitary Cushing's syndrome will have a normal MRI of the pituitary; in some cases, adenomas may develop in ectopic pituitary tissue that is not in continuity with the intrasellar pituitary tissue – CT of the parasellar region and sphenoid sinus may identify such ectopically-located pituitary adenomas; about 10% of pituitary tumors causing Cushing’s syndrome will be macroadenomas; most pituitary adenomas secreting ACTH are in the periphery of the pituitary, but they are occasionally found deep in the central wedge, and can be missed on imaging or at surgery; symptoms usually begin 2-6 years before the diagnosis is made - in milder cases, it may be 5-10 years; hirsutism is mild, and virilization is rare; DHEA levels are increased, but testosterone is normal or low; patients are frequently moderately hypertensive; ACTH levels are rarely high enough to cause hyperpigmentation. Hypercortisolemia suppresses the normal corticotrophs in the pituitary, causing them to atrophy. The adenomatous cells respond to decreased serum cortisol with increased ACTH production, and to increased serum cortisol with decreased ACTH production, but the set point is higher than normal. Some very well differentiated tumors suppress with low dose dexamethasone just like normal corticotrophs. On the other hand, about 10% of pituitary tumors are resistant to suppression, resembling the ectopic ACTH syndrome.

**Ectopic ACTH (20% of All ACTH-Dependent Cushing’s Syndrome):**
Caused by autonomous production of ACTH by a non-pituitary tumor; male to female ratio 1:1; the age of onset is 37.6 +/- 14.8 years (range 8-80); 6-14% of these tumors will decrease their ACTH secretion in response to suppressive doses of glucocorticoids (most of these patients have pulmonary carcinoids), and 6-9% respond to CRH.

The basal ACTH levels and the degree of hypercortisolism tend to be higher than in pituitary Cushing's, but there is considerable overlap; about 20% of ectopic ACTH cases are due to indolent tumors; the majority of cases of ectopic ACTH production are due to malignancies, with half of them being small cell carcinomas of the lung; 41-60% of ectopic ACTH-secreting tumors are intrathoracic neoplasms (small cell carcinomas of the lung (17.5-50%) or bronchial carcinoids (2-37%)), but other tumors have also been reported to secrete ACTH: thymic carcinoids (8-12%), pancreatic carcinoids and islet cell tumors (4-12%), pheochromocytomas/ neuroblastomas/ gangliomas/ paragangliomas (5-12%), medullary carcinomas of the thyroid (0-5%), and several other miscellaneous tumors. (One intriguing “miscellaneous” cause is “Pulmonary Tumorlets,” which are multiple microscopic nests of neuroendocrine cells in the lungs.) (Leukemic cells in AML have also been reported to secrete ACTH.) Only about 0.5-1.0% of cases of small cell carcinoma of the lung are associated with Cushing’s syndrome.
As many as 26% of patients with ectopic ACTH production will have an abnormal MRI of the pituitary gland; in 12-19% of cases, the tumor making the ACTH cannot be located - most of these bronchial carcinoids, but foregut and appendiceal carcinoid tumors and small cell carcinomas of the lung may also present this way; the majority of patients present with classical signs and symptoms of Cushing’s syndrome; however, ectopic ACTH production can present with rapid onset (symptoms present for 3-6 months prior to diagnosis) of extreme hypercortisolism resulting in a much higher incidence of hypokalemia (60%) than is seen in pituitary Cushing's (10%); the typical Cushingoid habitus may be absent, and hirsutism is unusual; the major manifestations may be those of excess mineralocorticoid effect - hypertension, edema, hypokalemic alkalosis, hypernatremia - due to the extremely high cortisol levels; patients may have muscle wasting and weakness (partly due to hypokalemia). Glucose intolerance may be prominent. In addition, patients may present with manifestations of the underlying malignancy such as anorexia, weight loss, anemia, and focal symptoms of organ involvement; hyperpigmentation (hands, palmar creases, elbows, knees, gums, and oral mucosa) can be seen because ACTH levels are often 5-10 times higher than in pituitary Cushing’s.

In addition to being unresponsive to suppression with high dose dexamethasone, ectopic ACTH-producing tumors are usually unresponsive to stimulation with metyrapone or vasopressin; bronchial or mediastinal carcinoids, however, often have the same suppression by dexamethasone that is seen in pituitary Cushing's (about 1/3 to ½ of them will suppress their ACTH production when exposed to high dose dexamethasone, and there are some well-documented cases in which an ACTH response to metyrapone and/or CRH stimulation has been demonstrated).

Hypercortisolism from ectopic ACTH production suppresses the normal pituitary corticotrophs, causing them to atrophy. The DHEAS and urinary 17-ketosteroids are increased in proportion to the cortisol. The ectopic secretion of other hormones, such as ADH, may complicate the clinical presentation of these tumors.

**Ectopic Corticotropin-Releasing Hormone (CRH) Secretion (<<1%):** A number of cases have been reported in which the tumor (usually a bronchial carcinoid, medullary carcinoma of the thyroid, or small cell carcinoma of the prostate) contained CRH but not ACTH. Ectopic secretion of CRH has been described in many of the same tumors that secrete ACTH (bronchial carcinoid, mediastinal carcinoid, thymic carcinoid, primary hepatic carcinoids, medullary carcinoma of the thyroid, pheochromocytoma, paraganglioma) (other patients with small cell carcinoma of the lung and Ewing’s sarcoma have had suggestive but not definitive evidence of CRH secretion); tumors may co-secrete ACTH and CRH (from two distinct cell populations); many tumors have been found to contain CRH without actually secreting it – thus, the diagnosis of ectopic CRH production requires demonstration of elevated plasma CRH levels; there are two reported cases of CRH-secreting gangliocytomas within the sella turcica that caused both corticotroph hyperplasia and microadenomas; the response to dexamethasone and metyrapone testing in ectopic CRH secretion has sometimes been similar to pituitary Cushing’s and sometimes similar to ectopic ACTH. One author suggests that ectopic CRH secretion should be suspected when the dynamic testing suggests pituitary Cushing’s, but the clinical course is of short duration and plasma ACTH levels are high.

**ACTH-Independent (15-20%):**

*Benign Adrenocortical Adenoma (60% of ACTH-Independent Cushing’s):*
Both adrenal adenomas and carcinomas have a bimodal age distribution - a small peak in the first decade, and a large peak at 39 for carcinoma and 52 for adenoma; women are 4-5 times more likely to have adrenal tumors causing Cushing's syndrome than men. In children over 7 years of age the most common cause of Cushing’s syndrome is Cushing’s disease. However, in children younger than 7, adrenal tumors are more common. Adrenal adenomas cause about 15% of all cases of Cushing’s syndrome in children; patients usually have a long history of gradual onset of manifestations of Cushing's syndrome before the diagnosis is made; adrenal adenomas are often purely cortisol-secreting tumors, so the major clinical manifestations are catabolic (proximal myopathy, plethora, easy bruising, striae, thin skin, poor wound healing, osteopenia) without modulation by the anabolic effects of androgens; a low plasma DHEAS level is suggestive of adrenal adenoma, but plasma DHEAS and urinary excretion of DHEAS and 17-ketosteroids may be normal or proportionately elevated compared to cortisol excretion; urinary 17-ketosteroids are usually < 20 mg/day; typical manifestations of Cushing's syndrome are prominent, while acne and hirsutism are rare; however, an occasional adenoma will produce large amounts of androgen, and may even produce only androgens; occasionally, ectopic adrenal adenomas are found in the scrotum, broad ligament, ovary, perirenal area, liver or pancreas. Hypercortisolism suppresses the normal corticotrophs in the pituitary, causing them to atrophy; similarly, the lack of ACTH causes the normal cortisol-producing cells in the adrenal cortices to atrophy. There is one report in the literature of an adrenocortical tumor that secreted both cortisol and ACTH.

**Adrenocortical Carcinoma (40% of ACTH-Independent Cushing’s):** This is a rare disease with an annual incidence of 0.5-2 cases per million (except in children in southern Brazil, where the incidence is 10 times higher than anywhere else in the world – related to a TP53 tumor suppressor gene mutation); women are affected more often than men (ratio 1.5:1) but the men tend to be older and have larger tumors at diagnosis; the age at presentation is bimodal, most commonly occurring between the fourth and fifth decades of life with a secondary peak in children under 5 years of age; tumor aggressiveness is higher in adults than in children; in adults, about 40% present with a nonsecreting abdominal mass detected incidentally or during evaluation for abdominal or flank pain; of the 60% with a hormone-secreting tumor, 45% have pure Cushing’s syndrome, 25% have a mixture of Cushing’s syndrome and virilization, and 10% have pure virilization; estrogen or mineralocorticoid excess occurs in less than 10% of cases; in children, 90% of adrenocortical carcinomas secrete hormones, with androgen secretion alone seen in 84% and cortisol alone in 6% (adrenocortical carcinoma is responsible for about 50% of all cases of Cushing’s syndrome in children); fever and leukocytosis may occur from tumor necrosis or secretion of chemokines; rapidly progressing Cushing’s syndrome with or without virilization is the most common presentation, and symptoms are usually of shorter duration prior to diagnosis in adrenocortical carcinomas than in adenomas or Cushing's disease (4-6 months).

The median tumor size at presentation in adults is about 10 cm, and 30-40% of patients have clear evidence of metastatic disease at diagnosis; the most common sites of metastasis are liver, lungs, lymph nodes, and bone; imaging of the chest and abdomen should be performed if adrenocortical carcinoma is suspected; PET is more sensitive than but can miss small pulmonary lesions: bone scan or brain MRI should be performed if symptoms of metastases to these locations are present; excess hormone production is due to the large size of the tumor - cortisol production is inefficient per unit weight of tissue, and secretion of cortisol precursors is high; urinary 17-ketosteroids are usually > 20 mg/day, and sometimes extremely high; increased levels of cortisol precursors – 11-deoxycortisol, and pregnenelone – are often
present due to partial deficiencies in steroid synthesizing enzymes; many patients with seemingly hormonally inactive tumors have high serum concentrations of steroid precursors such as androstenedione and 17-hydroxyprogesterone that confirm the adrenal origin of the tumor; high concentrations of DHEAS suggest adrenocortical carcinoma, whereas decreased concentrations suggest a benign adenoma; they may be palpable on abdominal examination, or may make the lower pole of the left kidney palpable; hepatomegaly may be present if there are hepatic metastases; adrenocortical carcinoma may present with abdominal, back, or flank pain, or other tumor-related symptoms.

Adrenal carcinomas have been reported as part of the Li-Fraumeni syndrome – a syndrome of multiple hereditary cancers (soft-tissue sarcomas, brain tumors, leukemia, lymphoma, adrenal cortical carcinomas, and early-onset breast cancers) caused by mutations in the TP53 tumor-suppressor gene. Adrenocortical carcinoma is also a component of the Beckwith-Wiedemann syndrome, which presents with developmental defects such as macroglossia, abdominal wall defects, hemihypertrrophy, and specific malignancies such as adrenocortical carcinoma, Wilms’ tumor, and hepatoblastoma. Beckwith-Wiedemann syndrome is caused by a mutation at the genetic locus 11p15 (IGF-II overexpression).

Nodular Adrenal Disease:

ACTH-Independent Macronodular Adrenal Hyperplasia (AKA AIMAH, Massive Macronodular Hyperplasia, Massive Macronodular Adrenal Disease): Clinical manifestations of this disorder usually do not appear before the fifth or sixth decade of life; there is a male predominance; the symptoms evolve slowly, often taking years to unfold; grossly there are large, bilateral adrenal nodules which secrete cortisol autonomously; the nodules are yellow and the intervening cortex is atrophic; nodules may be up to 5 cm in diameter, but patients may also present with diffusely enlarged adrenal glands without macroscopic nodules – occasionally mimicking a unilateral lesion; most cases appear to be sporadic, but there are now several reports of familial cases with presentations suggesting autosomal dominant transmission; the pathogenesis of this picture is unclear; ACTH levels are suppressed, with failure to respond to CRH and no suppression to high dose dexamethasone (responses similar to those seen in ectopic ACTH production); cortisol levels increase in response to cosyntropin in most cases, but the response to metyrapone is minimal (though a normal response was reported in one patient); this syndrome is rarely familial; no evidence of pituitary tumor is found, and no ACTH receptor-stimulating antibodies have been found; feminization has been reported; treatment is with bilateral adrenalectomy; this condition was once felt to be due to late development of adrenal autonomy after longstanding stimulation by ACTH from pituitary Cushing’s disease, but 3 lines of evidence contradict this hypothesis: (1) the internodular tissue is usually dormant, in contrast to the tissue seen in the adrenals after longstanding Cushing’s disease; (2) the signal intensity of these adrenal nodules on MRI scanning is greater than what is usually seen in the adrenal nodules in longstanding Cushing’s disease, and (3) Nelson’s syndrome does not occur in these patients following bilateral adrenalectomy.

This appears to be a very heterogeneous disorder. The cause is unknown. The current theories focus on the aberrant expression of various receptors on the adrenocortical cell surface membranes: receptors for GIP, TSH, vasopressin, LH/HCG, serotonin, angiotensin II, leptin, estrogen, and interleukin-1 (the TSH-responsive condition was successfully treated with T3.)
Activating mutations in Gs have also been reported as a cause of AIMAH. Such mutations have also been reported in McCune-Albright syndrome in association with adrenal nodules, fibrous dysplasia, cutaneous pigmentation, and hyperfunction of the pituitary, thyroid, gonads, and adrenal glands. The constitutive activation of the stimulatory G protein can mimic the effect of constant ACTH stimulation in the adrenal glands. Suppressed ACTH levels and adrenal adenomas can develop. Although Cushing’s syndrome has been reported in patients with McCune-Albright syndrome, the most common endocrine manifestations are growth hormone excess and precocious puberty.

**Primary Pigmented Nodular Adrenocortical Disease (PPNAD) (AKA Micronodular Adrenal Disease):** a rare, genetically heterogeneous disorder; the adrenal glands are enlarged and contain small (2-4 mm, sometimes larger) pigmented (black or brown) nodules; the internodular adrenal tissue is usually atrophic; the nodules may not be pigmented; CT scanning shows adrenal glands of normal size in half the cases; the presence of multiple small adrenal nodules with intervening atrophic cortex can create a “strong of beads” appearance that is characteristic of PPNAD, especially in the 12- to 18- year old age group; in adults, however, the nodules can be as much as 1-2 cm in size; cases of PPNAD without Cushing’s syndrome have been reported; Cushing’s syndrome always develops before age 30, and presents before age 15 in about half of the cases; cortisol secretion is ACTH independent; patients are resistant to suppression of cortisol with dexamethasone – in fact, a paradoxical increase of cortisol secretion by > 50% in response to dexamethasone (20 μg/kg po q6h for 2 days followed by 80 μg/kg po q6h) is considered one of the major criteria for the Carney complex, and an increase of 100% identifies PPNAD with 100% specificity; most patients don’t show cortisol stimulation in response to ACTH, metyrapone or CRH (occasional responses to ACTH are subnormal, and are probably due to variable daily steroid production or the response of the atrophic adrenal cortical cells); ACTH levels vary from undetectable to modestly elevated – the lack of ACTH suppression seen in some patients may be due to mild or periodic cortisol secretion; hypercortisolism usually progresses slowly and, in some cases, excessive cortisol secretion is episodic – the clinical and laboratory features may be normal during periods of normal cortisol secretion, and the typical growth failure of children with Cushing’s syndrome is not constant.

PPNAD can be sporadic, but 20-50% of the cases of PPNAD are familial, inherited in an autosomal-dominant fashion, and presenting with a bimodal age distribution: a minority presenting in the first 2-3 years, and the majority presenting in adolescence or early adulthood; both familial and sporadic cases of PPNAD have been associated with germline inactivating mutations of the PKRRA1A gene (see below), though somatic mutations have also been reported; PPNAD may occur alone but is associated with the “Carney Complex” in 90% of the cases. The “Carney complex” is an inherited (autosomal dominant with almost 100% penetrance but variable expression) tendency to develop mesenchymal tumors (myxomas of the heart, skin, bone, and breast), pigmented skin lesions (pigmented lentigines of the face, neck and trunk, ephelides (freckles), café-au-lait spots, depigmented lesions, and blue and other nevi), functioning endocrine tumors (testicular tumors, adrenal adenomas, thyroid adenoma - which may be hyperfunctioning - or carcinoma, growth hormone and prolactin-secreting pituitary adenomas, and ovarian cysts), peripheral nerve tumors (schwannomas), mammary fibroadenomas, and rare bone tumors. Thyroid nodules are palpable in 5% of patients with the complex, but ultrasound abnormalities are present in 75%. PPNAD is the most frequent endocrine manifestation of the complex. It has been reported that only 20-45% of patient's with the Carney complex have
Cushing's syndrome, but this percentage is much higher (maybe even 100%) when biochemical screening and autopsy studies are taken into account. More than 80% of patients with bilateral micronodular dysplasia have the Carney complex. The adrenal CT scan may be unremarkable or may demonstrate nodularity (however, nodules are also frequently present in other primary forms of Cushing’s syndrome and in normal elderly persons); hypercortisolism develops slowly over several years and the clinical manifestations may be subtle; immunoglobulins that bind to and stimulate the ACTH receptor (similar to Graves' disease) have been reported in a few patients, but this potential explanation of the syndrome would not account for the fact that the internodular tissue is atrophic. Unlike patients with sporadic cardiac myxomas, intracardiac myxomas in the Carney complex occur in young persons of both sexes, are often bilateral and/or multicentric, and often recur (many times at sites other than that of the initial resection). Lentigines are present at birth and intensify during childhood, but may disappear during adulthood, and can vary greatly from person to person.

About 40% of the kindreds with the Carney complex have mutations in the PRKAR1A gene, which resides on chromosome 17. This is a classic tumor suppressor gene that encodes the type 1α regulatory subunit of Protein Kinase A. When this subunit is bound to Protein Kinase A, it inactivates it. Binding of cAMP to the regulatory subunit releases the Protein Kinase A. Thus, PRKAR1A mutations produce a truncated protein that is inactive, thus leading to increased intracellular PKA signaling and consequent endocrine hyperactivity or tumor formation. It is still unclear exactly how haploinsufficiency of PRKAR1A causes the Carney complex. Mutations in at least one other gene may also be responsible, and the disorder is probably genetically heterogeneous. The diagnosis of the syndrome is based on criteria proposed by Stratakis et.al. in 2001. Genetic testing might be of great help in the diagnosis of this disease. Recurrent screening for cardiac myxomas should be considered in patients who present with isolated PPNAD (see below).

Patients with PPNAD should be followed long-term (decades) with periodic screening for manifestations of the Carney complex, and in particular should have annual screening for potentially lethal cardiac myxomas with echocardiography. A physical examination of the thyroid gland, breast, and testes would also be prudent. Thyroid and testicular ultrasounds should be performed at diagnosis and should be repeated only when necessary. First-degree relatives should also be evaluated with clinical, laboratory, and imaging tests, if necessary), but the highly variable pattern of expression can make it difficult to rule out the Carney complex in a person at risk. Sporadic cases have been found in patients whose parents were not affected. Screening for PRKAR1A mutations in those affected and their families is not recommended at this time, since such mutations are present in only about 40% of families with the Carney complex. The treatment of choice for PPNAD is bilateral adrenalectomy.

*Nodular Hyperplasia Due To Abnormal Steroidogenesis:* A form of adrenal hyperplasia has been described in which abnormally large amounts of 21-deoxycortisol are secreted. This 21-deoxycortisol blocks the cortisol receptors on the pituitary corticotrophs, which causes excessive ACTH secretion. The high 21-deoxycortisol levels result from an acquired aberrancy in which 17-hydroxyprogesterone undergoes 11-hydroxylation but not 21-hydroxylation. The high ACTH causes increased adrenal cortisol secretion and Cushing's
syndrome. ACTH secretion increases in response to CRH. The ACTH levels actually decrease during metyrapone treatment, because metyrapone inhibits the abnormal 21-deoxycortisol synthesis. ACTH levels also decrease after subtotal adrenalectomy, presumably because this removes the source of 21-deoxycortisol.

**Ectopic Cortisol Production:** Has been reported in one case of ovarian carcinoma.

**Factitious Cushing's Syndrome:** This is a rare psychiatric disorder in which glucocorticoid is ingested surreptitiously. Since hydrocortisone and prednisone are both detected by the cortisol assay, it may be difficult to distinguish this syndrome from ACTH-independent Cushing's syndrome. It usually presents with few or no mineralocorticoid and androgen manifestations.

**Cortisol Hyperreactive Syndrome:** There is one case report of a 54-year-old man who developed central obesity, moon facies, and diabetes mellitus. The blood pressure was normal and there were no striae. Cortisol production was low, and ACTH was undetectable. There was a markedly decreased response to cosyntropin, insulin-induced hypoglycemia, and CRH/lysine vasopressin. There was no response to metyrapone. After two days of IV cosyntropin the plasma cortisol and urinary free cortisol rose appropriately. The syndrome was felt to be due to hyperresponsiveness to normal circulating levels of cortisol, though the authors never explained why the Cushing's syndrome didn't develop until the patient was in his fifties.

**Considerations In Children:** Pituitary disease causes only 35-50% of the Cushing's syndrome in children, usually in those older than 8-10 years of age. In childhood the incidence of pituitary tumors causing Cushing’s syndrome is the same in girls and boys. Most children with pituitary Cushing’s have pituitary tumors, but a few cases of corticotroph hyperplasia have been reported. The ectopic ACTH syndrome is very rare in children. Adrenal adenomas cause one-sixth of childhood Cushing's, and are seen more frequently in girls than in boys. 80% of childhood adrenocortical tumors occur before age 5, with the peak at ages 0-2. Adrenal cancers cause half of all cases of childhood Cushing's syndrome, in girls slightly more frequently than in boys. Cushing’s syndrome in infants is exceedingly rare (less than 100 cases have been described). Almost all of the cases of ACTH-independent Cushing’s syndrome that have been reported in infants have been due to bilateral macronodular adrenocortical disease, and have been early presentations of the McCune-Albright syndrome. Most patients with Primary Pigmented Nodular Adrenal Disease (PPNAD) are children or young adults. A minority of patients with PPNAD present in the first 2-3 years.

**Considerations in Pregnancy:** Pregnancy is rare in patients with Cushing’s syndrome due to the associated amenorrhea. When pregnancy does occur in Cushing’s syndrome, adrenal adenomas are the cause in 40-50% (the figure is 15% in nonpregnant women). On the other hand, pituitary Cushing’s is the cause of Cushing’s syndrome in only 33% of pregnant women, compared with 58-70% of nonpregnant women. Ectopic ACTH production is a rare cause of Cushing’s syndrome in pregnant women, perhaps because it usually results in cortisol levels so high that they commonly cause anovulation.
Diagnosis:

Prior to testing, it is very important to take a thorough drug history, including current or past use of oral, rectal, inhaled, topical, or injected medications that may contain glucocorticoids. Don’t forget skin creams (including bleaching agents), herbal medications, tonics, and joint or nerve injections. Megestrol acetate in high doses may cause Cushing’s syndrome. In 2009, Hosein and Brown (Am J Med 2009; 122(3):236-238) reported iatrogenic Cushing’s syndrome in a woman who had been taking a Chinese Allergy Fighter that contained betamethasone.

Establishing the Diagnosis: The screening tests available are the 24 hour urinary free cortisol, the 1 mg overnight dexamethasone suppression test, the midnight salivary cortisol, and the 2-day, low dose dexamethasone suppression test. In the May, 2008 issue of the Journal of Clinical Endocrinology and Metabolism, The Endocrine Society published an extremely helpful set of guidelines for the diagnosis of Cushing’s syndrome (see below).

24 Hour Urinary Free Cortisol: A high urinary free cortisol has a reported sensitivity for Cushing’s syndrome of 85-92%. However, at a specificity of 100%, the sensitivity may be only 45-71%. False negatives can be seen in patients with periodic hormonogenesis (intermittent hormone secretion) and patients with "warm nodules" of the adrenal (secreting cortisol autonomously, but with urinary free cortisols still within normal limits). In obesity, the urinary free cortisol is increased in proportion to the waist-to-hip ratio, and an 18.5% false positive rate has been reported in patients with a BMI over 30. This is believed to be the result of increased cortisol production particularly in the liver and adipose tissue. In hyperthyroidism and pregnancy there is both increased production and increased excretion of cortisol. The urinary free cortisol is still usually normal in hyperthyroidism, but may be mildly elevated in pregnancy (and may overlap the values seen in Cushing’s syndrome). The urinary free cortisol is not affected by most drugs or by changes in cortisol binding globulin (CBG) levels when measured by RIA, but can be influenced by various cortisol metabolites and some synthetic glucocorticoids. High Pressure Liquid Chromatography (HPLC) can separate various urinary glucocorticoids and metabolites, but interfering substances such as carbamazepine, digoxin, and fenofibrate can coelute with cortisol and falsely elevate the urinary free cortisol. The combination of mass spectrometry with gas chromatography or HPLC may overcome these problems. Urinary cortisol excretion is decreased when the GFR is < 60 ml/min, and may be normal despite increased cortisol production. In children, the urinary free cortisol should be expressed per 1.72 m² to correct for body surface area. However, adult values may be used on children who weigh > 45 kg. The urinary free cortisol may be elevated in patients under emotional or physical stress, or in those with acute illness (ICU patients may have urinary free cortisol levels of 400-600 mcg/day), affective disorders, alcoholism, alcohol or narcotic withdrawal, strenuous exercise, malnutrition, surgery, polycystic ovary syndrome, sleep apnea, hyperthyroidism, familial glucocorticoid resistance, and anorexia bulimia and nervosa.

Increased urine volume (≥ 5 liters/24 hours) of any etiology (including patients who are simply pushing fluids as part of a weight loss program) can result in an increased urinary free cortisol. This is because increased urine volume decreases the fraction of the filtered cortisol that is metabolized or reabsorbed.

A recent study by Lin et al. evaluated patients with both a high
performance liquid chromatography assay and a competitive protein binding assay. They reported that 7 of 29 patients with Cushing’s syndrome had a normal urinary free cortisol with either method. Niemann and Cutler have reported that 10-15% of patients with Cushing’s syndrome will have at least one out of four urinary free cortisol measurements come back within normal limits. For these reasons the Endocrine Society guidelines recommend that you measure the urinary free cortisol in at least two different 24-hour urine collections. If the total creatinine in the two specimens differs by > 10%, you should obtain at least two more. The conventional wisdom is that the urinary free cortisol is not absolutely diagnostic of Cushing’s syndrome unless it is more than 3 (some say 4) times greater than the upper limit of normal for the assay.

**1 mg Overnight Dexamethasone Suppression Test:** In the 1 mg overnight dexamethasone suppression test (DST), 1 mg of dexamethasone is administered orally at 11 PM-to-midnight and a serum cortisol is drawn at 8-9 AM the next morning. Classically, it has been taught that a level < 5 mcg/dL rules out Cushing’s syndrome, a level > 10 mcg/dL is highly suggestive of Cushing's syndrome, and levels between 5-10 are equivocal. (The ACTH-IRMA, if measured along with the cortisol, should be <9 pg/mL.) However, we now know that very well-differentiated pituitary tumors may suppress to < 5 mcg/dL on low dose dexamethasone, and the use of the 5 mcg/dL cutoff has been reported to result in up to a 15% false negative rate. In 1997, Wood et.al. published a consensus opinion from pathologists in the United Kingdom which recommended that a cutoff of <1.8 μg/dL be used, since they felt that this effectively excludes Cushing’s syndrome. This results in a sensitivity of >95% with a specificity of 80%. They noted that such a low cutoff will increase the false positive rate, so an abnormal test will require further evaluation with other types of testing. On the other hand, Findling et.al. have reported suppression of the serum cortisol to < 2 μg/dL in 6 of 103 patients with Cushing’s syndrome, and have estimated that the test has a 93-96% sensitivity when a cutoff of < 2μg/dL is used. In studies with a low prevalence of Cushing’s syndrome, this test has similar performance characteristics to those of the other tests recommended for initial testing.

It has been reported that 8% of all cases of Cushing’s syndrome can show suppression of the serum cortisol to less than 2 mcg/dL in this test. False negative tests can be due to intermittent hormone secretion, slow metabolism of dexamethasone (liver and/or renal failure), and pituitary Cushing’s in which the set point is just barely above the normal range. Low cortisol binding globulin levels, e.g. from critical illness or nephrosis, may result in a false negative test. It has been suggested that simultaneous measurement of serum dexamethasone levels may help reduce the false negative rate.

The major problem with this test is the false positive rate (10-15%, and up to 30% in hospitalized patients). Some causes of a false positive result include failure to take the dexamethasone, taking it at the wrong time, reduced dexamethasone absorption (which can be seen in alcoholics), episodic ACTH secretion, rapid dexamethasone metabolism (including the use of drugs such a phenytoin, phenobarbital, meprobamate, methaqualone, glutethimide, rifampin, carbamazepine and primidone), depression, other affective disorders (mania, schizophrenia, obsessive-compulsive disorder, dementia), Alzheimer’s disease, alcoholism (the test must be performed after at least three weeks of abstinence in alcohol abusers), alcohol withdrawal, mild-to-moderate exercise, increased CBG levels (hyperthyroidism, pregnancy, estrogens), increased dexamethasone clearance, and obesity. In obesity, it has been reported that a 2 mg overnight dexamethasone suppression test is more specific than the 1 mg test. Normal suppression would not be expected to occur in a patient who was acutely ill, and the test should
not even be attempted under such circumstances. In pregnancy, baseline serum cortisol levels can be 40-60 mcg/dL. Patients with chronic renal failure may have incomplete cortisol suppression due to delayed cortisol metabolism and poor dexamethasone absorption. In chronic renal failure, false positive tests can be avoided by the use of intravenous dexamethasone, measurement of plasma dexamethasone levels, and the use of the two-day suppression test. There is a 50% false positive rate in women taking oral contraceptive pills (due to the increase in CBG levels) so estrogen-containing drugs should be withdrawn for 6 weeks prior to using this test. There are no specific data regarding the interpretation or performance of this test in children.

As mentioned above, measurement of serum dexamethasone levels routinely during dexamethasone suppression tests may be useful to insure the adequacy of the plasma dexamethasone concentrations (which should be over 5.6 nmol/liter or 0.22 mcg/dl).

**Diurnal Variation Measurements:** Measurement of diurnal variation can be an excellent way of distinguishing Cushing's syndrome from other states of hypercortisolism, but it is clear that simply measuring morning and late afternoon cortisol values is not useful. Morning plasma cortisol levels vary significantly, yielding a false positive rate of 9% and a false negative rate of 60%. A diurnal variation in cortisol levels is seen in 30% of patients with Cushing’s syndrome, and a lack of diurnal variation is seen in 18% of patients without Cushing’s syndrome. However, a midnight plasma cortisol level > 1.8 μg/dL (measured while the patient is asleep) has been reported to have a 100% sensitivity for Cushing’s syndrome. The specificity for this cutoff is poor (20.2%) and a cutoff of > 7.5 mcg/dL has a higher specificity (87%). In patients who are awake when the test is drawn, a cutoff of >7.5 mcg/dl has a specificity of 83%. In patients with a low clinical index of suspicion but lack of suppression on dexamethasone testing and a mildly elevated urinary free cortisol, a sleeping midnight cortisol < 1.8 μg/dl effectively excludes the diagnosis of Cushing’s syndrome. Raising the cutoff provides greater specificity at the expense of sensitivity. Values of serum midnight cortisol > 8.3-12 μg/dl have a reported sensitivity of 90-92% and a specificity of 96%. The problem is that these results have been verified only in patients who are hospitalized for the test. Data on outpatient midnight plasma cortisol levels do not exist. Therefore, in order to perform the test properly, overnight hospitalization is required. One author even suggests that the patient be hospitalized for 3 nights: one to get over the stress, and 2 to give duplicate p.m. cortisol samples. This restriction makes the test impractical in today’s health care environment in the US.

**Midnight Salivary Cortisol:** This test is performed by measuring the level of cortisol in a sample of saliva collected between 11 PM and midnight. In one method, a cotton tube is chewed for 2-3 minutes, then frozen or transferred to a laboratory. In another, saliva is allowed to flow freely for 5-10 minutes into a 10 mL tube. The normal reference ranges are assay-dependent. An increase in blood cortisol levels is reflected by an increase in salivary cortisol levels within a few minutes. The best-validated assays are an ELISA and an assay performed by liquid chromatography and mass spectrometry (LC-MS/MS). With these assays the midnight salivary cortisol is normally under 145 ng/dL, though it is best if each local assay is validated independently. It should be kept in mind that the circadian rhythm is abnormal in many patients with depression, critical illness, and in shift workers. Stress, obesity, and poorly-controlled diabetes mellitus can cause false positives.

Studies of the late-night salivary cortisol measurement in the diagnosis of
Cushing’s syndrome have reported a sensitivity of 88-100% and a specificity of 82-100%. If two late-night salivary cortisols are normal, Cushing’s syndrome is excluded with 90-95% certainty. If they are both above reference range, Cushing’s syndrome is proven with about 90-95% certainty. Waiting 1-2 months and then repeating the salivary cortisol measurement often resolves discordant results.

Because the salivary glands contain 11β-hydroxysteroid dehydrogenase (the enzyme that converts cortisol to cortisone in renal tubular cells), it is theoretically possible that patients using chewing tobacco or ingesting large amounts of licorice might have falsely elevated midnight salivary cortisol levels. Cigarette smoking increases midnight salivary cortisol levels, and it may be prudent for patients to avoid smoking on the day of the test. Direct contamination of the cotton tube with steroid-containing lotions or oral gels may cause a false positive. The timing of the test should be adjusted to the time of sleeping for patients with bedtimes consistently long after midnight. Patients with extremely variable bedtimes may benefit from using other screening tests. Nocturnal salivary cortisols may be transiently abnormal in patients who have recently crossed widely different time zones. Theoretically, contamination with blood (gingivitis, oral ulcers) might increase salivary cortisol levels. Stress immediately before collection can result in a false positive, and ideally the sample should be collected on a quiet night at home.

The Endocrine Society guidelines recommend that the test be done on two different occasions. If the samples are discordant then either a few more midnight salivary cortisols may be measured or another screening test may be used. It has been suggested that cyclic Cushing’s could be detected by measuring the midnight salivary cortisol every night for a month, though at over $300 a test the cost of this strategy might be viewed as excessive.

In 2005, Viardot et.al. reported that in late pregnancy the preserved diurnal variation at a higher level of salivary cortisol reduced the specificity of the nighttime salivary cortisol from 100% to 75%.

2-Day Low Dose Dexamethasone Suppression Test: In this test dexamethasone 0.5 mg is given q6h for 48 hours beginning at 9 AM. Serum cortisols are obtained at 9 AM at 24 and 48 hours after beginning the test (6 hours after the most recent dose of dexamethasone). A serum cortisol < 1.82 mcg/dL at 48 hours makes it 94% certain that a patient does not have Cushing’s syndrome, and a serum cortisol < 1.82 mcg/dL at both 24 and 48 hours made it 98% certain that a patient does not have Cushing’s syndrome. (The initial test described by Liddle et. al. used urinary hydroxycorticosteroids, and had a sensitivity and specificity of only 70-80%; the results are the same when urinary free cortisol levels are used.) A sensitivity of 94% has been reported in children. For children > 40 kg the adult doses and cutoffs are used. For patients weighing less than 40 kg, the dose is 30 μg/kg•day in divided doses. As already described, certain psychiatric disorders, morbid obesity, alcoholism, and uncontrolled diabetes mellitus can cause decreased suppressability of cortisol without true Cushing’s syndrome. In these conditions, the 2-day low dose dexamethasone suppression test is superior to the 24 hour urinary free cortisol. Overall, the test has similar or slightly less diagnostic accuracy than the other tests recommended for initial testing.

Summary - Screening For Cushing’s Syndrome: The Endocrine Society guidelines recommend one of the following tests for initial screening for Cushing’s syndrome, based on the suitability for a given patient:
- 24 hour Urinary Free Cortisol (at least 2 measurements)
- Late-night salivary cortisol (2 measurements)
- 1 mg overnight dexamethasone suppression test
- 2 mg/day 48 hour dexamethasone suppression test

Further suggestions:
- In patients who do not have a particularly high pretest probability of disease and whose initial test results are normal, reevaluation in 6 months is suggested if signs or symptoms progress.
- If an initial test is abnormal, performance of another recommended test is suggested.
- They recommend against further testing for Cushing’s syndrome if there are concordantly negative test results on two occasions, unless patients are suspected of having the very rare condition of cyclical Cushing’s.
- They suggest further evaluation and follow up for the few patients with concordantly negative results who are suspected of having cyclical disease, and also for patients with discordant results – especially if the pretest probability of disease is high.
- They recommend using the urinary free cortisol rather than dexamethasone testing in pregnancy. However, cortisol excretion increases up to 3-fold in the second and third trimesters. Therefore, in the second and third trimesters, only urinary free cortisol values > 3 times the upper limit of normal can be taken to indicate Cushing’s syndrome.
- They also recommend measuring nonsuppressed cortisol in saliva or urine and against dexamethasone testing in patients using antiepileptic drugs known to enhance dexamethasone clearance. There are no data to guide the length of time needed after withdrawal of such medications to allow dexamethasone metabolism to return to normal.
- They suggest using the 1 mg overnight dexamethasone suppression test rather than the urinary free cortisol for initial testing in patients with severe renal failure. The absorption and metabolism of dexamethasone, as well as the cortisol response, have been reported to be both normal and abnormal. Therefore, an abnormal response cannot be considered to be diagnostic in this setting.
- In cases suspected of having cyclic Cushing’s they recommend using the urinary free cortisol or midnight salivary cortisol rather than dexamethasone suppression testing. The peak cortisol production can occur at intervals of several days to several months. If clinical suspicion is high but initial tests are normal, repeat testing is
recommended, if possible to coincide with clinical symptoms.

- In adrenal incidentalomas they recommend using the 1 mg overnight dexamethasone suppression test or late-night cortisol test rather than the urinary free cortisol.

**Workup When Results Are Equivocal, And In "Pseudo-Cushing's:"

The term "Pseudo-Cushing's" refers to the fact that certain individuals have increased cortisol production rates and decreased cortisol suppressability that may be difficult to distinguish from true Cushing's syndrome. Of the conditions associated with hypercortisolism in the absence of Cushing’s syndrome, some may present with some clinical features suggestive of Cushing’s syndrome (pregnancy, depression, anxiety disorder, obsessive-compulsive disorder, alcoholism, glucocorticoid resistance, morbid obesity, poorly controlled diabetes mellitus) while others are unlikely to have any clinical features suggestive of Cushing’s syndrome (physical illness/hospitalization, surgery, pain, malnutrition, anorexia nervosa, intense chronic exercise, hypothalamic amenorrhea, renal failure, and cortisol binding globulin excess). Patients with alcoholic pseudo-Cushing's may present with a round, plethoric face, central obesity, thin extremities, and other clinical features of Cushing's syndrome.

The pathogenesis of Pseudo-Cushing’s is unclear, but may involve increased activity of the CRH neurons, with hypertrophic adrenals eventually producing excessive glucocorticoid in response to normal ACTH levels. Cortisol dynamics normalize quickly with abstinence from drinking (urinary free cortisol normalize within a few days, and dexamethasone suppressability returns within three weeks) or successful treatment of the depression (for this reason anti-depressants need not be stopped – indeed, should be encouraged - during the workup for Cushing’s syndrome). In patients not acutely ill, a urinary free cortisol > 4 times the upper limit of normal is considered the most reliable biochemical marker for Cushing's syndrome. Intermediate levels deserve further evaluation. (Either perform additional tests or repeat testing in several weeks, depending on the level of clinical suspicion.)

Several tests are available for use in equivocal cases, but none is ideal. The test that has emerged as the test of choice in this situation is the 2-day low dose dexamethasone/CRH stimulation test. It is the test recommended in the Endocrine Society guidelines for patients with equivocal results from other testing. They recommend measuring dexamethasone levels to exclude false positive results. The cortisol assay used must be accurate at these low levels of detection.

The injection of corticotropin releasing hormone (CRH) by itself has been of limited use in distinguishing patients with Cushing's syndrome from those without (100% specificity, 64% sensitivity, and 76% diagnostic accuracy). However, it has been reported that the combination of the 2-day low dose dexamethasone suppression test with injection of oCRH can distinguish Cushing’s from pseudo-Cushing’s with a high level of diagnostic accuracy. Pituitary tumors secreting ACTH are exposed to very little endogenous CRH, because CRH is suppressed by cortisol. The response to exogenous CRH is therefore brisk. In pseudo-Cushing's, however, the corticotrophs are exposed to a large amount of endogenous CRH, and the response to exogenous CRH is blunted. In this test, dexamethasone 0.5 mg is given po every 6 hours for 2 days (6 AM, noon, 6 PM, and midnight). Ovine (= sheep) CRH is injected 2 hours after the last dose of dexamethasone, at a dose of 1 mcg/kg IV over 1 minute. Facial flushing, a sense of warmth, transient chest tightness, tachycardia or a mild decrease in blood pressure is
observed in about 10% of patients. A plasma cortisol is measured 15 minutes after the injection. A cortisol level >1.4 mcg/dL predicted Cushing’s syndrome with 100% specificity, 90% sensitivity, and 91% diagnostic accuracy in the original study.

As is so often the case, subsequent testing has not confirmed these impressive numbers. In 2006, Martin et.al. reported that 5 out of 24 patients with suspected Cushing’s syndrome were misdiagnosed with this test. Also in 2006, Gatta et.al. reported 100% sensitivity but only 76% specificity with the Dex-CRH test. In 2007, Pecori Giraldi et.al. reported a specificity of only 62% using a cortisol cutoff of 1.4 μg/dl, and 80% with a cutoff of 4 μg/dl. Sensitivity fell to 94% with the higher cutoffs. In 2007, Erickson et.al. from the Mayo Clinic reported a maximal sensitivity and specificity of 90% with this test using a 15-minute cortisol threshold of 2.5 μg/dl. Erickson et.al. have reported that a 15-minute plasma ACTH > 27 pg/mL detected Cushing’s syndrome with a sensitivity and specificity of 97%, but this was not statistically significantly different from the result of cortisol testing (JCEM 2007; 92:2972-2976). Taking all of these reports together, in 92 patients without Cushing’s syndrome, the specificity of the low dose dexamethasone suppression test by itself was 79%, and the specificity of the dex-CRH test was 70%. In patients with Cushing’s syndrome, the sensitivity of the low dose dexamethasone suppression test alone was 96% and the specificity of the dex-CRH test was 98%. Also in 2007 Gatta et.al. reported a sensitivity of 100%, specificity 50%, diagnostic accuracy 77%. When they changed the cutoff to 2 mcg/dL the sensitivity was 94%, specificity 86%, and diagnostic accuracy 90%. (An excellent summary of these studies can be found in Nieman L, JCEM 2007; 92(8):2876-2878. I am particularly grateful to Dr. Rundsarah Tahboub for having pointed this article out to me.) Interestingly, in 2009 Valassi et.al. reported that the sensitivity and specificity of the test was 93.1% and 92.3% in patients off all medications, and dropped to 88.2% and 75% in patients taking one or more of a variety of medicines that were felt to potentially affect dexamethasone metabolism (including antidepressants, statins, CCB’s, ARB’s, atypical antipsychotics, PPI’s, TZD’s, quinidine, propranolol, clonazepam, and anticonvulsants). It should also be kept in mind that the accuracy of this test is not known in patients with severe depression, cortisol resistance syndrome, or recent surgical stress. In 1999, Duclos et. al. reported that an abnormal oCRH/dexamethasone suppression test can be found in patients with anorexia nervosa. The test is not valid if the patient is taking estrogens (estrogens should be stopped for 8 weeks prior to the test). Its use with human-sequence CRH remains to be validated.

Despite all of its failings, when the experts today talk about how to distinguish Cushing’s syndrome from Pseudo-Cushing’s, this is the test that they reference.

**Approach To Workup For Equivocal Results and "Pseudo-Cushing's Syndrome:"

In cases where the urinary free cortisol, midnight salivary cortisol, and 1 mg overnight dexamethasone suppression test have not resulted in a firm diagnosis of Cushing’s syndrome, it seems reasonable to proceed with the combination 2 day dexamethasone suppression/oCRH stimulation test. If periodic hormonogenesis is suspected, it can be detected by measuring several weekly 24-hour urinary free cortisols or midnight salivary cortisols. If after all these tests the diagnosis is still in doubt, it is reasonable to simply monitor the patient's course for several months. True Cushing's syndrome will persist and progress. Pseudo-Cushing's will frequently correct spontaneously or resolve with treatment of depression or alcoholism. In one study, all four alcoholics studied had a normal 1 mg overnight DST within 18 days of abstinence, and the urinary free cortisol was normal in all by day 4. In another, it was
reported that hypercortisolism subsides after 7-10 days of abstinence.

**Differential Diagnosis:** Once the diagnosis of Cushing's syndrome is made, it will be necessary to determine whether the source is a pituitary tumor, ectopic ACTH production or adrenal disease.

**ACTH-Dependent vs. ACTH-Independent Cushing's:** The first step in the workup of confirmed Cushing’s syndrome is to determine whether the disease is ACTH-dependent or ACTH-independent. This can be accomplished by measuring the plasma ACTH by an immunoradiometric assay (a "sandwich" assay requiring recognition of the molecule at two different sites) (many experts recommend repeating the test twice). ACTH is broken down by proteases in the plasma, and so the blood should be collected in a pre-chilled EDTA tube placed in an ice-water bath, and delivered quickly to the laboratory for refrigerated centrifugation. ACTH levels are consistently low (< 5 pg/mL – some say < 10 pg/mL) in ACTH-independent Cushing's. Levels > 15 pg/mL indicate active, ACTH-dependent cortisol secretion. Intermediate levels (5-20 pg/mL – some say 5-15 pg/mL) require further workup. They could indicate adrenal Cushing’s in which the ACTH is not yet fully suppressed, either due to intermittent cortisol secretion or very modest cortisol hypersecretion. Some patients with pituitary tumors secreting ACTH can have ACTH levels < 10 pg/mL.

A CRH stimulation test can help distinguish pituitary tumors secreting ACTH from ACTH-independent Cushing’s syndrome (which would be the most likely differential diagnostic dilemma in patients with ACTH levels of 5 or 10-20 pg/mL). Two pre-injection cortisol levels are drawn, and cortisols are drawn 15 and 30 minutes after injection. The mean cortisol should increase > 50% in pituitary Cushing’s. Patients with ACTH-independent Cushing’s syndrome usually have blunted ACTH response to CRH injection (usually a peak ACTH of < 30 pg/mL, often < 10 pg/mL). The sensitivity and specificity of the CRH test in this context (using the ACTH level as the test result) are only about 90%.

Plasma ACTH levels are unchanged in chronic renal failure. The best time to draw the plasma ACTH is in the late afternoon. It should be noted that ectopic tumors secreting ACTH have been reported which make an abnormal ACTH molecule that shows up as a fairly low (but not undetectable) ACTH level on testing by standard radioimmunoassays. This abnormal ACTH molecule is detectable by the immunoradiometric assay. On the other hand, it has also been reported that ectopic tumors can make an ACTH molecule that the immunoradiometric assay fails to detect.

Falsely low ACTH levels have also been reported. It has been said that patients with random ACTH levels < 10 pg/mL, or even undetectable levels, may still have ACTH-dependent Cushing's syndrome. In one study, 12 of 219 patients with pituitary Cushing's had ACTH levels less than 10 pg/mL. If the ACTH is low while other factors suggest pituitary disease, it seems reasonable to proceed with a CRH test.

ACTH levels may not be suppressed in adrenal causes of Cushing’s syndrome in pregnancy (perhaps because of continued stimulation of the maternal pituitary by placental CRH). The 8 mg overnight dexamethasone suppression test remains useful (see below).

Once the diagnosis of ACTH-independent Cushing's is confirmed, a CT scan of the adrenals should be very helpful in identifying the cause (MRI does not appear to be much more sensitive than CT, but on T2-weighted images, adrenal adenomas remain of low intensity whereas adrenal carcinomas become bright). Most of the time this will show a unilateral adrenal
tumor. If the cause of Cushing’s syndrome is a unilateral adrenal tumor, then the contralateral adrenal gland should be atrophic (unless the diagnosis is made very early). Adrenal adenomas causing Cushing’s syndrome tend to be homogeneous and 3-6 cm in diameter. Larger tumors may be carcinomas. On ultrasound malignant lesions are heterogeneous with focal or scattered echopenic or echogenic zones. Measurement of the DHEAS level can help distinguish between the two. DHEAS is usually suppressed in patients with adrenal adenomas causing Cushing’s syndrome, and elevated in patients with adrenocortical carcinomas causing Cushing’s syndrome.

If the adrenals are "normal" on CT scanning, then either primary pigmented nodular adrenocortical disease or factitious Cushing's is present. Young age, familial Cushing's, Carney complex, and irregularity of the adrenals favor the former. If necessary, an iodocholesterol scan could be done to distinguish hyperplasia (bilateral tracer uptake) from factitious Cushing's (little uptake in either gland). Also, patients with adrenocortical carcinomas will fail to take up radiotracer on both sides. If the CT scan reveals bilateral adrenal enlargement, the patient has one of the ACTH-independent macronodular hyperplasias. In the rare ACTH-independent form, repeated ACTH levels will consistently be suppressed, there will be no response to oCRH and no response to high dose dexamethasone. In the ACTH-dependent form, some ACTH levels may be detectable, virtually all will respond to oCRH, and 50% will suppress on high dose dexamethasone. Lacroix et. al. have published a protocol for evaluating patients with bilateral macronodular hyperplasia (or unilateral adrenal tumor) for the presence of abnormal or ectopic receptors (e.g. for GIP or catecholamines).

Workup For ACTH-Dependent Cushing's: If the Cushing's syndrome is determined to be ACTH-dependent, then the next step is to determine whether it is pituitary Cushing's (=Cushing's disease) or ectopic ACTH production. Given the sex ratio, ACTH-dependent Cushing's in a man should suggest ectopic ACTH. Basal ACTH levels and the degree of hypercortisolism tend to be higher in ectopic ACTH (ACTH levels > 200 pg/ml are particularly suspicious for ectopic ACTH), but there is considerable overlap. The incidence of hypokalemia is 60% in ectopic ACTH and 10% in Cushing's disease.

High Dose Dexamethasone Suppression Test: The traditional test used to distinguish between pituitary Cushing's and ectopic ACTH is the high dose dexamethasone suppression test. Two baseline 24-hour urines are obtained, and then dexamethasone is given at a dose of 2 mg po q6h for 2 days. Urinary free cortisol and 17-hydroxycorticosteroids that suppress to < 50% of baseline suggest pituitary Cushing's, since pituitary adenomas usually retain some degree of suppressability in the face of large amounts of glucocorticoid. However, about 6-14% of patients with ectopic ACTH production, mostly from bronchial carcinoids, will also suppress. In addition, some patients with pituitary Cushing's disease fail to suppress - especially those with severe hypercortisolism (plasma cortisol > 90 mcg/dL, urinary free cortisol > 3000 mcg/day). Patients with Cushing's disease who have a very high basal steroid production may require 16, 32 or 64 mg of dexamethasone a day to suppress. Any patient who otherwise appears to have Cushing's disease but doesn't suppress on 8 mg/day of dexamethasone can be tried on the higher doses. One problem is that patients with Cushing's disease may only suppress to 70-80% of the basal levels. Most of the reported >12% false positives in the literature have adhered to the 50% suppression criterion. It has been suggested in the literature that the test should be interpreted as showing lack of suppression only if the
second 24 hour urinary free cortisol remains >90% of baseline, or if the second 24 hour urinary 17-hydroxysteroid excretion remains > 64% of baseline (=86% accuracy). If the cutoff is set at 80%, the specificity of the test is above 80%. As with the low dose dexamethasone suppression test, chronic renal failure may cause false positives. The rare patient with Cushing's disease with entirely autonomous ACTH secretion has a large, locally invasive low-grade corticotroph adenocarcinoma.

In pregnancy, the high dose dexamethasone suppression test cannot distinguish Cushing’s Disease from the ectopic ACTH syndrome very well, but it works well in distinguishing adrenal forms of Cushing’s syndrome from Cushing’s Disease. Given the lack of reliability of plasma ACTH levels in making this distinction, as well as the increased prevalence of adrenal disorders in pregnancy, the high dose dexamethasone suppression test seems to be useful in this setting. The workup in pregnancy should include ultrasound of the adrenals, plasma ACTH, and the high dose dexamethasone suppression test. Patients with borderline or low plasma ACTH levels, or those without suppression on the high dose dexamethasone suppression test, are likely to have an adrenal etiology. Ultrasound can identify about 73% of adrenal causes of Cushing’s syndrome, but MRI may be needed in the event of a negative ultrasound. Gadolinium should not be given to pregnant women until more is known about its effect in pregnancy. MRI is contraindicated in the first trimester because its potential teratogenic effects are unknown. However, it is considered safe after 32 weeks. In the middle trimester, its risk-to-benefit ratio must be weighed against the fact that up to 10% of healthy individuals have a pituitary incidentaloma up to 6 mm in size. Lesions larger than 6 mm may warrant surgery, but smaller lesions require further testing. CRH is recommended in pregnancy only when absolutely clinically indicated. Animal studies have shown no teratogenic or adverse behavioral effects. The CRH test has not been systematically studied in pregnancy, but it has been reported to have successfully distinguished Cushing’s Disease from the ectopic ACTH syndrome in a limited number of pregnant women, and its use is advocated when adrenal disease is unlikely after initial testing.

Plasma dexamethasone levels (which are commercially available) should be 8-20 ng/mL six hours after the last dose of dexamethasone (mean = 13.2 ng/mL). Most experts do not routinely send dexamethasone levels, but may save a tube of blood for this purpose in case the question arises.

The sensitivity of this test is about 60-80% and the specificity about 88% when 17-hydroxycorticosteroids are used. Curiously, use of the urinary free cortisol instead of 17-hydroxycorticosteroids has been reported to decrease the sensitivity. It has been suggested that the specificity of the test can be increased to 94-100% and the sensitivity may still remain a respectable 72-83% if the urinary free cortisol is required to suppress to <90% of baseline, or 17-hydroxycorticosteroids to <64% of baseline. An ectopic ACTH tumor and several patients with nodular adrenal hyperplasia or adrenal adenomas have already been reported who suppressed to lower than these new levels.

A simpler test, the 8 mg overnight dexamethasone suppression test, has been shown to have a similar diagnostic accuracy. An AM plasma cortisol is measured. That night, 8 mg of dexamethasone is given po (alternatively, it can be given IV to patients unable to take oral
medication). The next morning, a second plasma cortisol level is obtained. Pituitary Cushing’s is suspected if the repeat plasma cortisol suppresses to < 50% of the baseline plasma cortisol. (It has been reported that suppression to < 50% of baseline yields a sensitivity of 88% and a specificity of 57%. Suppression to < 68% yields a sensitivity of 71% and a specificity of 100%.) Plasma dexamethasone levels should be higher than the 8-20 ng/mL seen in the two-day high dose dexamethasone suppression test. A comparison of the two-day and overnight tests yielded sensitivities of 71% and 65% respectively, with specificities of 100%.

The high-dose dexamethasone suppression test has been criticized for yielding a diagnostic sensitivity, specificity, and accuracy of only 80% when the pre-test probability of pituitary Cushing’s is at least 90%. Aron, Raff, and Findling have reported that the results of high-dose dexamethasone suppression testing in patients with the ectopic ACTH syndrome are similar to those in patients with pituitary Cushing’s. Raff and Findling, in their review in the *Annals of Internal Medicine*, conclude that “…this diagnostic approach can no longer be recommended.”

The CRH stimulation test has also been used to distinguish pituitary Cushing’s from ectopic ACTH production. Patients with Cushing’s disease will respond to CRH with an increase in ACTH and cortisol secretion, whereas patients with the ectopic ACTH syndrome will not. ACTH and cortisol levels are measured at -5, -1, 15, 30, and 45 minutes after slow IV infusion of 1 μg/kg or 100 μg of synthetic ovine or human CRH at 8-9 AM. When ovine CRH is used, a cortisol rise > 20% has been reported to predict Cushing’s disease with a sensitivity of 93% at a specificity of 100%. An ACTH rise > 50% was reported to predict Cushing’s disease with a sensitivity of 91% at a specificity of 88%. When human CRH is used, it has been reported that a rise in the serum cortisol of > 14% predicts Cushing’s disease with a sensitivity of 85% at a specificity of 100%. A rise of > 105% in plasma ACTH predicts Cushing’s disease with a sensitivity of 70% at a specificity of 100%. The utility of this test is diminished by the fact that recommendations vary a great deal in the type of CRH to be used (ovine vs. human), the parameters to be used (ACTH increase of >35-105%; cortisol increase of >14-20%), and the time points for evaluation (ACTH 15-30 minutes; cortisol 15-45 minutes). Most patients with ectopic ACTH-producing tumors do not increase their ACTH production in response to CRH, but ectopic tumors that express CRH receptors have been found. Both false positives and false negatives have been reported. It has been reported that 8-9% of patients with ectopic ACTH production will respond to CRH.

10 μg of IV AVP (desmopressin) will increase ACTH in 80-90% of patients with Cushing’s disease, but only rarely in normals or patients with pseudo-Cushing’s. Cortisol levels are drawn 10, 20, and 30 minutes after the injection. However, 20-50% of patients with ectopic ACTH-secreting tumors will also respond to desmopressin. It has been reported that the combination of oCRH and AVP discriminates Cushing’s disease from ectopic ACTH better than either test alone, but this has been disputed. Raff and Findling in their review article in the *Annals of Internal Medicine*, conclude that “…neither test provides adequate information to justify its use in the differential diagnosis of ACTH-dependent Cushing’s syndrome.” The Desmopressin Stimulation Test has also been used in the initial workup for Cushing’s syndrome. The Endocrine Society guidelines reference a sensitivity for Cushing’s disease of 82-87%, but
only 63-75% when other patients with Cushing’s syndrome are included. They quote a specificity of 85-91% and conclude that “until additional data validate the utility of the test in a larger population of patients with all causes of Cushing’s syndrome, it seems prudent to restrict this test to research studies.”

**Approach To Distinguishing Pituitary Cushing’s From Ectopic ACTH Production:** It is easy for the endocrinologist to become frustrated when trying to decide the best algorithm for distinguishing pituitary Cushing’s syndrome from the ectopic ACTH syndrome. Authorities differ dramatically in their recommendations. Some recommend starting with the high dose dexamethasone suppression test or a combination of this test plus the CRH test (the combination has been reported to have excellent specificity (98%), but a sensitivity for Cushing’s disease of only 79%; 18-65% of patients with Cushing’s disease will have either a non-suppressible 8 mg overnight dexamethasone suppression test or lack of stimulation with a CRH stimulation test). Some authors recommend skipping non-invasive testing entirely and going straight to Bilateral Inferior Petrosal Sinus Sampling in every case!

One approach is to start with both the high dose dexamethasone and CRH tests, using the criteria for 100% specificity. If the test results are both consistent with pituitary Cushing’s and a pituitary tumor > 6 mm in size is found, proceed with trans-sphenoidal surgery. Use bilateral inferior petrosal sinus sampling if the MRI shows no tumor, or if it shows a small pituitary abnormality. On the other hand, if the test results are both consistent with ectopic ACTH secretion, proceed to localization procedures. If the results are discordant, proceed with inferior petrosal sinus sampling. In a group of 23 patients with known Cushing’s disease reported by Wiggam et. al., the high dose dexamethasone suppression test and oCRH test were concordant and correct in 35%, discordant in 43%, and discordant and wrong in 22%. Inferior petrosal sinus sampling yielded a true positive result in 82%. Although it makes sense to use petrosal sinus sampling in those with inconclusive responses to dynamic testing, the diagnostic accuracy of petrosal sinus sampling in this subgroup of patients is not well studied, and a sensitivity of only 76% with a diagnostic accuracy of 81% have been reported.

**Pituitary Imaging:** If biochemical testing suggests pituitary Cushing's, an MRI of the pituitary should be ordered. MRI with gadolinium enhancement will detect about 40-52% of pituitary tumors secreting ACTH. Most pituitary adenomas secreting ACTH that are < 1 cm in size have a hypo-intense signal that fails to enhance with gadolinium. If no adenoma is detected, proceed to bilateral inferior petrosal sinus sampling. If an adenoma > 6 mm in size is detected, then it is probably reasonable to proceed with trans-sphenoidal surgery. However, as many as 15% of patients with ectopic ACTH production are reported to have abnormal results on MRI of the pituitary (recall that autopsy studies reveal a 10-15% incidence of unexpected pituitary tumors in the general population, though the majority of these are < 5 mm in size). In light of the fact that 10% of patients with ectopic ACTH production will suppress on high dose dexamethasone, some experts prefer to proceed with bilateral inferior petrosal sinus sampling regardless of the MRI result (particularly if suppression and stimulation tests are equivocal).

**Bilateral Inferior Petrosal Sinus Sampling (BIPSS):** Bilateral inferior petrosal sinus sampling must be performed by an experienced invasive radiologist. Two
catheters are inserted, one into each inferior petrosal sinus (blood drains from the pituitary through the cavernous sinuses into the inferior petrosal sinuses). IV oCRH is injected slowly, 1 μg/kg, and blood is obtained simultaneously from both inferior petrosal sinuses and a peripheral vein at 0, 2, 5 and 10 minutes after the oCRH injection. An inferior petrosal sinus-to-peripheral ACTH ratio >2 before CRH or >3 after CRH confirms the presence of Cushing's disease (sensitivity 94-98%, specificity 94%, diagnostic accuracy > 95% when a ratio of >2.0 is used; sensitivity 97%, specificity 100%, diagnostic accuracy reportedly 100% when a ratio of >3.0 is used).

The reported ~10% false negative rate may result from technical factors, anomalous venous drainage, or periodic hormonogenesis. Technical factors include improper catheter placement, atrophic petrosal sinuses, a corticotroph adenoma not responsive to CRH, and errors in processing the ACTH sample. It has been suggested that a midnight salivary cortisol be done the night before the test to ensure that the tumor is active at the time of testing.

The ratio is <1.8 in ectopic ACTH production. It has been suggested that the false negative rate can be decreased by using the petrosal sinus-to-periphery ratio of prolactin to confirm successful catheterization of the inferior petrosal sinus. Swearingen et al. from the Massachusetts General Hospital have reported a sensitivity (for correct diagnosis of pituitary tumors) of 90% after CRH stimulation, with a specificity of only 67%, a positive predictive value of 99%, but a negative predictive value of only 20%. They recommend consideration of surgical referral for all patients with unsuccessful inferior petrosal sinus catheterizations after negative body imaging if other endocrine evaluation is consistent with a pituitary source, and also for patients with negative inferior petrosal sinus sampling in whom no ectopic source is found, especially when the pituitary MRI is positive or suggestive, or if there is a robust increase in peripheral ACTH levels after CRH administration. They also recommend that patients being managed as having a presumed ectopic source on the basis of negative inferior petrosal sinus sampling, in whom no ectopic source has yet been found, be periodically reimaged with pituitary MRI to monitor for an undetected pituitary adenoma, and consideration should be given to pituitary exploration.

It has been suggested that IPSS may be done in pregnant women only after the completion of a noninvasive assessment, and only in experienced centers. Certain precautions are necessary, including use of a direct jugular approach and use of an additional lead barrier for protection. Patients with a definite pituitary tumor on imaging and CRH results (+/- high dose dexamethasone results) consistent with Cushing’s Disease have a near 100% probability of having Cushing’s Disease and do not need IPSS.

The use of bilateral inferior petrosal sinus sampling to localize the tumor to the right or left side is controversial, and its diagnostic accuracy for this purpose is disputed. Adverse reactions have been rare, but brain stem infarction, subarachnoid hemorrhage with hydrocephalus, and cases of transient neurologic symptoms prompting immediate discontinuation of the test have been reported out of several hundred patients studied. The rate of serious neurologic complications has been very low in experienced hands - at the NIH it has been 0.001% (1 in 1200 cases). Other complications have also been reported, including pulmonary emboli, uncomplicated deep venous thromboses, an internal jugular venous thrombosis, severe vasovagal reactions, atrial perforation, femoral AV fistula, and transient dysrhythmias. The use of intravenous heparin during the procedure has been advocated to help prevent thrombosis. The NIH practice at this time is to forego petrosal sinus sampling if an obvious tumor is present by pituitary MRI, unless the biochemical tests are inconsistent, or indicative of ectopic ACTH production. Ectopic CRH production can result in a false positive
petrosal sinus sampling study, and it has been recommended that all patients undergoing this test have peripheral CRH levels measured first.

Tsagarakis et. al. (JCEM 2007) reported a sensitivity of 97.9% and a specificity of 100% when both CRH and desmopressin were used to stimulate ACTH secretion.

Workup For Occult Ectopic ACTH Tumors: Up to 50% of tumors that secrete ACTH ectopically cannot be localized. In up to 30% of cases the tumor remains occult for a long time after diagnosis. The most common location for these tumors is intrathoracic (83%) - usually bronchial carcinoids and occasionally thymic carcinoids. Zemskova et.al. (JCEM 2010 – Lynette Nieman was the senior author) recommended initial imaging with thoracic CT and MRI followed by octreotide scanning. High definition multi-slice CT scanning is required. The octreotide scan only detected lesions seen by CT/MRI, but lesion confirmation by two modalities increased the positive predictive value of testing to 93% (CT) and 100% (MRI). It was recommended that further scanning be done if the initial scanning was negative. This included CT/MRI of the neck, abdomen, and pelvis (one might reasonably ask if it wouldn’t be simpler – but more costly? - just to scan these areas at the same time as the thorax). Note that both CT and MRI are useful (at least in the chest) because some bronchial carcinoids have a central location and may be mistaken for blood vessels on CT scanning. The neck is included to look for medullary carcinomas of the thyroid, and the abdomen is included to look for pancreatic islet cell tumors and pheochromocytomas. Octreotide scanning is helpful because some bronchial carcinoids have somatostatin receptors and will be visible on these scans. In one study, octreotide scanning detected 86% of 451 carcinoids. However, the test is not very specific. In a study reported by Torpy et. al., breast cancer, brain tumors, lymphomas, and almost all sites of active autoimmune inflammatory or granulomatous disease took up octreotide. Uptake in chronic granulomatous disease appears to be uncommon. In the Zemskova study, PET scanning detected only lesions seen by CT/MRI. [18F]-DOPA-PET (6-fluor-[18F]L-dihydroxyphenylalanine) positivity improved the positive predictive value, but is not commercially available at this time. Venous sampling for ACTH gradients throughout the body has not been helpful in localizing these neoplasms. Occasionally measurement of serum calcitonin or urinary 5-HIAA may help direct the search. Re-imaging should be done every 6-12 months.

Treatment:

Cushing's Disease (Pituitary Cushing's): The treatment of choice for pituitary Cushing's is trans-sphenoidal resection of the pituitary tumor. The cure rate is 80-90% for microadenomas and 50-80% for macroadenomas (0% in less experienced hands). Hypopituitarism is rare, but the prolonged hypercortisolism causes a secondary adrenal insufficiency that may last 6-24 months after surgery. In these cases glucocorticoid replacement therapy (e.g. hydrocortisone 12-15 mg/m^2) is required until the axis recovers. Basal and ACTH-stimulated cortisol values determine whether glucocorticoid replacement can be discontinued. The suppression appears to be at the level of the hypothalamus or higher, rather than in the pituitary itself. Many, but not all, authorities recommend intraoperative and postoperative steroid coverage (200, 100, 75 and 50 mg/day respectively on the day of the operation and the first, second, and third postoperative days, then 10-25 mg qAM for maintenance). However, Rollin et.al. have shown that it is safe to withhold glucocorticoid therapy until there is clinical or
laboratory evidence of adrenal insufficiency.

The mortality rate for trans-sphenoidal surgery is < 1%. Transient diabetes insipidus is common, but becomes permanent in only a small percentage of cases. Perioperative morbidity, transient diabetes insipidus, cerebrospinal fluid leak and meningitis occur in less than 10% of cases. Permanent complications include anterior pituitary insufficiency and permanent diabetes insipidus. Cerebrospinal fluid fistulas occur in 4%. Other complications including meningitis, injury to the carotid arteries, nose, optic nerves, or nerves of the cavernous sinus (causing ptosis or diplopia), and hypothalamic injury occur in 1-2% of initial resections of microadenomas. Long-term relapse rates of 3-46% have been reported.

There have been several different recommendations for defining remission. Remission has been defined as resolution of clinical stigmata plus a series of normal postoperative cortisol levels, obtained throughout the day, of 5.4-10.8 μg/dL, or a normal urinary free cortisol. However, a recurrence rate of ~25% at 10 years has been reported using these criteria. Alternatively, it has been suggested that an AM ACTH and cortisol level should be obtained 24 hours after the patient has been tapered down to a maintenance dose of hydrocortisone (20 mg po qAM), 5-14 days after surgery. A cortisol level < 2 mcg/dL is a strong predictor of remission, but some patients who are in remission do not drop their cortisol levels immediately. In addition, occasional late relapses have been reported even using this criterion, and it’s use decreases the surgical remission rate to 40-65%. A urinary free cortisol of less than 20 mcg/day suggests cure.

(a) Simmons et. al. have reported that postoperative cortisol values lower than the preoperative midnight level and less than 10 mcg/dL indicate surgical remission. Cortisol levels were measured at midnight on the night before surgery, and every six hours postoperatively until a diagnosis of remission was made. Exogenous steroids were withheld until after a diagnosis of remission had been made. Delayed remission occurred in a small number of patients. Those patients who had cortisol levels consistently > 20 mcg/dL during the first postoperative day often turned out to be surgical failures. The presence of measurable cortisol levels during the postoperative period did not necessarily indicate failure.

(b) Rollin et.al. reported that a cortisol nadir < 7.5 μg/dL during the first 10-12 days after surgery separated the patients in remission from treatment failures with 100% sensitivity and specificity.

(c) Pereira et.al. discharged their patients on hydrocortisone 10 mg bid until two weeks after surgery. At that time, they found that an 0900 serum cortisol < 5 mcg/dL (24 hours after the last hydrocortisone dose) correctly predicted cure in all of 50 patients. In addition, 8 of 30 patients (27%) with values > 5 ultimately turned out to have been cured as well. (6 of those 8 had cortisol levels < 1.8 mcg/dL 3 months after surgery).

(d) Findling and Raff (2006) suggested that patients whose cortisol levels decrease to < 2-3 mcg/dL (preferably undetectable) within 24-72 hours after surgery usually are in remission.

(e) In 2008, Patil, Prevedello, Lad, Vance, Thorner, Katsnelson, and Laws defined remission by withholding preoperative and intraoperative glucocorticoids and then measuring serum cortisol levels every 6 hours postoperatively until the serum cortisol was less than 2 μg/dl or until 72 hours after surgery. Adrenal insufficiency was defined as a serum cortisol of less than 5 μg/dl and/or onset of Addisonian symptoms. The first postoperative evaluation was performed 6-8 weeks after surgery. Patient’s were told to stop hydrocortisone 2 days before the visit. If the serum cortisol was less than 5 μg/dL, hydrocortisone replacement
was resumed. If the serum cortisol was $\geq 5 \mu g/dL$, a 24-hour urinary free cortisol was performed. Remission was defined as a normal postoperative 24-hour urinary free cortisol or continued need for corticosteroid replacement. Recurrence was defined as an elevated 24-hour urinary free cortisol with clinical symptoms consistent with Cushing’s disease. Of the patients who achieved remission, 17.4% ultimately had a recurrence. The median time to recurrence was 39 months. Patients with a postoperative serum cortisol $> 2 \mu g/dL$ were 2.5 times more likely to have a recurrence than patients who had a serum cortisol $\leq 2 \mu g/dL$.

If a tumor cannot be found, then a hemihypophysectomy on the side identified by bilateral inferior petrosal sinus sampling can be performed. If bilateral inferior petrosal sinus sampling wasn't performed preoperatively and fertility is not an issue, an 80-90% hypophysectomy can be done.

If the patient has not been cured by the surgery, the options (which are also the options for late recurrences of Cushing’s disease) are repeat trans-sphenoidal surgery, radiation therapy, and medical or surgical adrenalectomy. Each of these is discussed further below. Repeat surgery for persistent or recurrent disease has been reported to have a success rate of 71% (see below). One approach to persistent Cushing’s disease that has been suggested, and seems attractive, is repeat trans-sphenoidal surgery (if deemed appropriate by the surgeon) or gamma knife therapy (in appropriately selected patients) plus ketoconazole therapy until remission occurs. In this scenario, bilateral adrenalectomy is offered to patients who cannot tolerate ketoconazole, develop hepatic toxicity on ketoconazole, or are extremely sick from their Cushing’s syndrome.

In children, successful treatment results in catch-up growth or resumption of the growth rate. Hypogonadism gives way to pubertal maturation. Growth may be permanently stunted if effective treatment is not begun in time to prevent premature fusion of the epiphyses.

In 2007 Pouratian et.al. reported on 111 cases of suspected Cushing’s disease in which no tumor was found at surgery. “Adenomectomy” was the procedure in 34, hemihypophysectomy in 15, subtotal hypophysectomy in 34, and total hypophysectomy in 28. Surgical failures were defined as patients whose plasma cortisol levels did not fall to 2 $\mu g/dL$ or lower within 72 hours after surgery. 50% of the patients achieved remission (compared to 88% in patients with histological confirmation of an ACTH-staining tumor. Of the 33 patients evaluated for recurrence, 7 were found to have recurred – 3 of them within 4 months after remission. Recurrences were treated with repeat transsphenoidal surgery, gamma knife radiosurgery, or bilateral adrenalectomy.

**Repeat Trans-Sphenoidal Surgery:** In 1994, Ram et.al. from the NIH reported using early repeat trans-sphenoidal surgery in 17 of 29 patients who were not cured by their initial surgery. 12 (71%) had resolution of hypercortisolism, but 3 of them recurred within the next 24 months. 7 of the 17 who underwent early repeat surgery (41%) developed hypopituitarism requiring pituitary hormone replacement. In 2005 Locatelli et.al. from the University of Virginia reported that 8 of 12 patients with a postoperative plasma cortisol level of $> 2$ mcg/dL achieved remission after prompt (within 15 days) reoperation. All patients in remission developed postoperative hypopituitarism.

**Surgical Adrenalectomy:** Some consider this the preferred treatment for patients with advanced Cushing’s syndrome who have failed trans-sphenoidal surgery. However, the morbidity of surgery in patients with severe Cushing’s syndrome is not negligible.
In untreated Cushing's syndrome, bilateral adrenalectomy has been associated with a 5-10% mortality rate and a high incidence of postoperative complications (poor wound healing, infection, pancreatic injury, and thromboembolism). (These statistics, however, come from the days prior to laparoscopic surgery.) Surgical morbidity may be decreased in patients with severe Cushing’s syndrome by treating the patient with medical therapy for a period of time prior to surgery. Surgical adrenalectomy has a reported recurrence rate of 10%. An unusual cause of failure is the existence of ectopic adrenal tissue in the liver, adrenal beds, or gonads. This tissue may be located by iodocholesterol scanning. Permanent glucocorticoid and mineralocorticoid deficiency and the risk of Nelson's syndrome are the major drawbacks to surgical adrenalectomy.

Corticotroph tumor progression after adrenalectomy (= “Nelson’s syndrome”) has been reported in about 47% of patients after 7 years. It has been suggested that Nelson’s syndrome may be prevented by radiation therapy. However, Assiè et. al. (2007), after reporting a series of patients with corticotroph tumor progression after adrenalectomy, recommended close follow up without radiation therapy. They noted that patients with recent onset of Cushing’s disease, a visible adenoma on MRI, and probably those with exaggerated ACTH increases on Mitotane were at a higher risk of developing corticotroph tumor progression. At the annual meeting of the Endocrine Society in 2007, one of the authors (Dr. Xavier Bartagna of Cochin Hospital in Paris) recommended MRI before and 6 months after adrenalectomy, and then every year for at least 5-6 years. Repeated determinations of plasma ACTH can also add valuable information, though there is no generally accepted threshold ACTH level that predicts Nelson’s syndrome.

Radiation Therapy: Pituitary radiation is an option when surgery has failed or alternative forms of therapy are desired. Radiation therapy can be delivered in two ways: stereotactic radiosurgery (by gamma knife, linear accelerator, CyberKnife, or proton radiation) and fractionated radiation therapy. Stereotactic radiosurgery (SRS) is preferred because it is more convenient (typically a single treatment visit) and results in a faster biochemical response to treatment. However, the tumor target should be at least 3-5 mm removed from the chiasm and less than 3 cm in diameter in order to use this modality. Fractionated radiation therapy carries a lower risk of injury to normal tissues, and is preferred when the tumor target is less than 5 mm from the chiasm and larger than 3 cm in diameter. SRS achieves normalization of ACTH levels in a median time of approximately 7.5 – 33 months, and remission rates of 35 to 80% have been reported. Fractionated radiotherapy has a median time to remission of 18 to 42 months and remission rates using modern techniques are likely 50-80%. Control of tumor growth is achieved in 80-100% of patients by either technique.

The major adverse reaction is hypopituitarism, which occurs in virtually all patients if they are followed for a long enough time (most published reports average less than 10 years of follow up). The 5-year incidence of radiation-associated abnormalities in at least one pituitary hormone is about 20% with either SRS or fractionated radiation therapy, and the incidence of panhypopituitarism is approximately 5-10% at 5 years from treatment.

Other possible adverse effects of pituitary radiation include damage to vision, damage to ocular motor function, temporal lobe epilepsy (uncommon), stroke, and second tumor formation (astrocytoma). The largest series’ include data spanning treatment over several decades and include antiquated treatment methods. The true incidence of these complications is likely less than 1%. The risks increase slowly with each decade of treatment and generally do not arise within the first 5 years.
Medical therapy to reduce cortisol production should be given while awaiting the full effect of radiation therapy. Ketoconazole has emerged as the drug of choice for this purpose.

**Adrenal Enzyme Inhibitors:** Therapy with adrenal enzyme inhibitors may be useful in patients who are waiting for radiation therapy to have its full effect, in patients with ectopic ACTH production of unknown source, or in preparation for surgery in patients severely ill from Cushing's syndrome. Combinations of these drugs may have additive or synergistic effects, allowing smaller doses with fewer side effects to be used. Ketoconazole has emerged as the agent of choice.

**Ketoconazole:** Ketoconazole inhibits mainly the first step in cholesterol synthesis (by blocking demethylation of lanosterol), but it also inhibits mitochondrial cytochrome P450-dependent enzymes, such as 11-hydroxylase and the enzymes needed for cholesterol side chain cleavage. In addition, it inhibits ACTH secretion by impairing the activation of adenyl cyclase in the pituitary corticotrophs. It appears to be the drug of choice because it is effective in most patients and is comparatively well tolerated. The usual dose is 200-400 mg bid-tid, and the dose must be titrated to avoid adrenal insufficiency. The initial dose may be increased every 2-3 weeks. Clinical and metabolic manifestations of Cushing’s syndrome disappear within 4-6 weeks. Nausea, vomiting, abdominal pain, and pruritis occur in about 1-3%, and headache, sedation, gynecomastia, decreased libido and impotence (due to interference with testosterone synthesis) have been reported. The most feared adverse reaction is a reversible hepatotoxicity, and liver function tests should be monitored. Serum hepatic aminotransferase levels increase in 5-10% of patients, and serious hepatic impairment occurs in 1 in 15,000.

**Metyrapone:** Metyrapone is now only available on a compassionate need basis. It mainly inhibits the conversion of 11-deoxycortisol to cortisol, and at high doses may inhibit ACTH secretion directly. At a dose of 4 grams per day it can significantly decrease cortisol levels, but it usually doesn't normalize them. The dose is 500-1000 mg tid-qid and can be increased every 72 hours. In Cushing's disease, inhibition of cortisol synthesis generally results in increased ACTH secretion, which can be enough to overcome the partial block in hormone synthesis. Increased deoxycorticosterone synthesis can lead to hypertension and hypokalemic alkalosis. Hirsutism or acne may be worsened by increased synthesis of adrenal androgens. Nausea, vomiting, dizziness, headache, sedation and rash can occur. This drug is useful mainly in patients with mild disease and after radiation therapy (when doses of 500-750 mg tid-qid are usually adequate.) Metyrapone is not teratogenic and has been used successfully to treat hypercortisolism during pregnancy.

**Aminoglutethimide:** Aminoglutethimide blocks cholesterol side chain cleavage and the conversion of cholesterol to pregnenelone. Synthesis of cortisol, aldosterone and adrenal androgens is inhibited. The dose is 250 mg bid or tid. Cortisol levels fall slowly, and eventually glucocorticoid replacement therapy is needed. In patients with cortisol-secreting adrenal carcinomas, the beneficial effect of aminoglutethimide can be maintained for many months. However, in untreated Cushing's disease, increased ACTH secretion results when cortisol production is diminished. This frequently overcomes the
biosynthetic inhibition, and cortisol levels return to pre-treatment values within days. Metyrapone and aminoglutethimide, which inhibit different enzymes of cortisol synthesis, have been used effectively together. Aminoglutethimide can cause anorexia, nausea, vomiting, somnolence, headache, dizziness, depression, and blurred vision. It can block thyroid hormone synthesis, resulting in goiter and hypothyroidism in about 5% of patients. Cholestasis and bone marrow suppression are rare. A skin rash and fever are seen in about 1/5 of patients within the first two weeks of therapy, but usually subside if therapy is continued, and may be treated with antihistamines. Headache has been observed with larger doses. This drug increases the metabolism of dexamethasone, but not hydrocortisone. Thus, hydrocortisone or cortisone acetate would be the replacement therapy of choice. Florinef may occasionally be necessary as well.

**Etomidate:** This is an anesthetic agent that can inhibit cholesterol side chain cleavage and 11β-hydroxylase. It represents a potentially life-saving therapy in patients who cannot take medications orally. Krakoff et al. have reported using the propylene glycol-containing etomidate formulation that is available in the US to treat a patient intravenously for 5.5 months until he could take oral medications. At the annual meeting of The Endocrine Society in 2007, Xavier Bertagna of Cochin Hospital in Paris reported successfully using etomidate for two weeks prior to bilateral adrenalectomy in a patient with severe Cushing’s syndrome.

**Medical Adrenalectomy-Mitotane:** Mitotane (o,p'-DDD) is an adrenocorticolytic drug that also inhibits the 11-hydroxylase and cholesterol side-chain cleavage enzymes. This inhibits synthesis of cortisol, aldosterone, and androgens. However, Mitotane has more effect on the zona fasciculata and zona reticularis, and aldosterone secretion is usually spared. It appears to have some suppressive effect on ACTH secretion as well, since its suppression of cortisol secretion results in a minimal feedback increase in ACTH secretion. (The reported incidence of Nelson's syndrome is 0-12.5%.) When used in doses sufficient to ablate, rather than attenuate, cortisol secretion, Control over cortisol secretion with Mitotane is more difficult in patients who have not been radiated. 80% of patients treated with Mitotane plus pituitary irradiation have been reported to undergo clinical and biochemical remission. Half of those patients showed suppression of their elevated cortisol levels within four months of starting therapy. As the effect of the radiation becomes apparent with suppression of ACTH secretion, the dose of the drug can be tapered.

It is started at a dose of 0.5 grams po qHS, and then 0.5-gram increments can be added every few days at mealtimes up to a dose of 4 grams per day, with half of the dose given at HS to decrease nausea. The drug is given with fat-containing food, because its absorption appears to be coupled to lipoproteins. It should not be given during pregnancy. Several reports have established the importance of monitoring blood levels of this drug to insure maximum efficacy with minimum toxicity. One cannot predict when the patient will become hypocortisolemic, so replacement therapy is begun with the Mitotane or when the dose reaches 2 grams per day. Mitotane increases CBG levels and cortisol metabolism, so patients eventually require a 2- to 3-fold increase in hydrocortisone dose. Mitotane also increases the metabolism of dexamethasone and fludrocortisone, so the replacement doses of these drugs may need to be increased 3-7 fold. The dose may be adjusted with reference to serum dexamethasone levels or by amelioration of symptoms of hypercortisolism. The zona glomerulosa is more resistant than
the zona fasciculata, and aldosterone deficiency may not occur for several months. Mitotane is taken up by fat and persists in plasma for long periods after the drug is discontinued, so replacement therapy should be tapered down to normal maintenance doses over several weeks to months after Mitotane is discontinued. It should not be used in women desiring fertility within 2-5 years.

Mitotane can be difficult to tolerate, especially when serum levels are above 20 μg/mL. Most patients will accept a dose of 4 grams per day. It causes anorexia, nausea, vomiting, diarrhea, rash, pruritis, ataxia, gait disturbance, dizziness or vertigo, sedation, confusion, problems with language expression (including anomia), fatigue, gynecomastia, arthralgias, hypercholesterolemia, hypouricemia, hepatotoxicity, leucopenia, and reversible growth arrest in children. Mitotane can increase TBG and SHBG concentrations.

*Mifepristone (RU-486):* This is an anti-progestational agent that at higher doses also competes with glucocorticoid for its receptor. It has been used acutely in the management of Cushing's disease. Cortisol levels rise two-fold. In patients with pituitary Cushing’s, the blocking effect of the compound can increase ACTH secretion enough to overcome the anti-glucocorticoid effect. The fact that this drug also blocks the effects of exogenous glucocorticoids renders treatment of the resultant glucocorticoid deficiency difficult. Its use in this disease is still investigational.

**Central Treatments For Cushing's Disease:** Bromocriptine, cabergoline, cyproheptadine and valproate are centrally acting drugs that have been reported to lower ACTH levels in Cushing's disease. Occasional successes have been reported, but the results have generally been disappointing. In 2009, Pivonello et.al. (JCEM 94:223-230) reported that that 15 of 20 patients with Cushing’s disease unsuccessfully treated with surgery responded to cabergoline (1-7 mg/week, median 3.5) with normalization of the urinary free cortisol maintained in 10. Two of those ten withdrew within 12-18 months for cabergoline intolerance. Lila et.al. (Endo Pract 2010; 16:968) reported that 17% of 18 patients responded with normalization of either the low dose DST or the midnight plasma cortisol on cabergoline at a mean dose of 3.6 mg/week. The response shouldn’t come as a complete surprise, since de Bruin et.al. in 2009 (J Clin Endo Metab 2009; 94(4):1118-1124) reported that more than 80% of corticotroph adenomas from two university centers expressed dopamine receptors. A newer multi-ligand somatostatin analog, pasireotide, normalizes the urinary free cortisol in 15% of patient’s with pituitary tumors secreting ACTH.

*Quality of Life* has been reported to be decreased in patients with cured Cushing’s disease. Van Aken et.al. have reported reduced general perceived well-being, fatigue, anxiety, and depression. Despite conventional hormone replacement therapy, hypopituitarism was an independent risk factor for reduced quality of life. Hypercortisolism has been reported to cause long-lasting and possibly irreversible changes in cognitive function (memory and executive function).

*Prognosis:* Hypertension, diabetes, hypercoagulability, endothelial dysfunction, and ventricular morphologic and functional abnormalities persist for up to 10 years after resolution of hypercortisolism. Despite long-term cure, patients with a history of Cushing’s syndrome exhibit persistent accumulation of central fat with a consequent unfavorable adipokine
profile and a state of low-grade inflammation. The standardized mortality ratio of Cushing’s
disease and adrenal adenoma ranges from 0.98 to 3.80. Cardiovascular disease is responsible for
most of the increased mortality (standardized mortality ratio 3.95-5.00). Restoration of
eucortisolism is associated with a standardized mortality ratio that is no longer different from
that expected in the general population over a 10-20 year period (JCEM 2011; 96:632-642).

**Ectopic ACTH:** The best treatment for this syndrome is treatment of the
underlying tumor. Cure is typically achieved only in tumors that are usually benign, such as
carcinoids and pheochromocytomas. If the tumor cannot be adequately treated, or if the source
of the ACTH secretion cannot be found, adrenal enzyme inhibitors (ketoconazole, metyrapone,
aminogluthethimide) are the treatment of choice. Ectopic ACTH tumors usually don't increase
ACTH secretion when cortisol levels drop. On the other hand, ACTH levels may already be so
high that they overcome the suppressive effect of the drugs. Replacement therapy should be
started at the same time as the adrenal enzyme inhibitors. Aminogluthethimide, ketoconazole, and
metyrapone may be used alone or in combination. Patients can escape suddenly from enzymatic
blockade, even when peripheral ACTH levels remain constant. Metastases to the adrenal glands
are common, especially from small cell carcinomas of the lung, and can expose the adrenal gland
to very high concentrations of ACTH. The treatment is to increase the dose of the adrenal
enzyme inhibitor(s). If hypercortisolism cannot be controlled with adrenal enzyme inhibitors,
addition of small doses of Mitotane (1-3 grams/day) will usually induce adrenal insufficiency
within a few days. Medical or surgical adrenalectomy may be warranted if eucortisolism cannot
be attained with maximal medical therapy, or if side effects force discontinuation of adrenal
enzyme inhibitors. Medical or surgical adrenalectomy might reasonably be attempted if the
tumor is indolent enough to warrant this approach. Surgical adrenalectomy is required in 28%
before tumor localization (because steroidogenesis inhibitors were ineffective, poorly tolerated,
or rejected by patients) and 9% after localization (because of residual tumor). Treatment with
somatostatin analogs can be effective even when the somatostatin receptor scan is negative, but
the beneficial effect can be temporary. Opportunistic infections and pulmonary emboli can be
the cause of death in these patients, and prophylaxis for opportunistic infections and venous
thrombosis should be considered.

Potassium and/or spironolactone may be needed initially to control hypokalemia. When
the source of the ACTH cannot be found, enzyme inhibitors can be administered and
periodic investigation (e.g. every 6-12 months) undertaken until the tumor can be found and
treated. Chest and abdominal CT, chest MRI, pituitary MRI (to exclude misdiagnosis) and
clectrotide scanning have been proposed. Patients whose hypercortisolism is controlled by any
means may occasionally develop rebound thymic hyperplasia, which can be confused with tumor
recurrence or metastatic disease in the anterior mediastinum. Extrathoracic neuroendocrine
tumors, thymic carcinoids, small cell lung cancers, medullary carcinomas of the thyroid, and
gastrinomas usually present as overt tumors with metastases, and death occurs at an average of
24.2 months. On the other hand, pulmonary, appendiceal, and pancreatic carcinoids and
pulmonary or mediastinal neuroendocrine tumors tend to be initially occult and are less likely to
metastasize. Patients with occult tumors tend to do well, with a mortality of 18% over a median
of 26 months.

**Primary Adrenal Causes of Cushing's Syndrome:** When possible, adrenal tumors
should be surgically removed. This will cure adrenal adenomas and a minority of adrenal carcinomas. Laparoscopic adrenalectomy is the treatment of choice for benign adrenal tumors. Cushing’s syndrome from an adrenal adenoma located in ectopic adrenal tissue in the pararenal region has been reported. Because they suppress the hypothalamic-pituitary-adrenal axis, removal of cortisol-secreting adrenal adenomas can result in postoperative adrenal insufficiency that can take 6-24 months to resolve, or even longer. Patients should be treated with glucocorticoids perioperatively and recovery of endogenous cortisol secretion should be evaluated every 6-8 weeks, typically by measuring an AM cortisol prior to the first morning dose of glucocorticoid.

Surgery is the treatment of choice in adrenocortical carcinoma. Complete resection is possible in patients with stage I-III disease, but recurrence is high (within 2 years the recurrence rate is 27% for stage I, 46% for stage II, and 63% for stage III). If the entire tumor cannot be removed, debulking may improve survival and help to control hormone hypersecretion. Untreated patients with unresectable disease survive only 3-9 months. In 2007 Terzolo et.al. reported that adjuvant therapy with Mitotane postoperatively led to longer recurrence-free survival (median 42 vs 10 and 25 months), fewer deaths (25% vs 55 and 41%), and longer overall survival (110 vs 52 and 67 months) than in Italian and German control groups. The efficacy of adjuvant radiotherapy after surgery is controversial. There are no randomized trials, and data from retrospective series’ are conflicting.

Mitotane is used to treat patients with adrenal carcinoma who are known to have residual or recurrent disease. A decrease in hormone secretion occurs in up to 75% and tumor regression in up to 1/3 of cases. Treatment benefits are generally short-lived and survival is not consistently prolonged. Rare long-term survivors have been reported. Resection of local recurrences is indicated if surgery will remove a majority of the tumor or decrease severe hypercortisolism.

A 53.5% response rate has been reported with the “Italian protocol” (etoposide, doxorubicin, cisplatin, and Mitotane) but 13 of the 15 responses were only partial. Mitotane blood levels were monitored closely in this protocol. The combination of streptozotocin and Mitotane has been reported to achieve a complete or partial response in 36.4% of 22 patients. In 2003, an International Consensus Conference on Adrenal Cancer held at Ann Arbor, Michigan recommended the combination of Mitotane either with etoposide, doxorubicine, and cisplatin or with streptozotocin as the two best choices of treatment for advanced adrenocortical carcinoma (see Allolio and Fassnacht, JCEM 2006). These two treatment options are now being compared in the FIRM ACT trial (www.firm-act.org), but the failure of many patients to respond to both protocols has led to an urgent demand for salvage therapy (see www.nebennierenkarzinom.de if you can read German). A 2-year remission has been reported in a patient who failed treatment with standard chemotherapy and was treated with mebndazole.

Children may have less aggressive tumors, and patients younger than age 4 survive longer than older patients. Adrenocortical carcinoma has been regarded as resistant the radiation therapy, but several reports have described response rates of up to 42%, and radiation may be useful to control localized disease not amenable to surgery. Radiation is the treatment of choice for most bone and brain metastases.

ACTH-independent bilateral macronodular disease and bilateral nodular dysplasia are treated with bilateral adrenalectomy.
In pregnancy, there are several case reports of live births after conservative management during the last trimester. However, untreated Cushing’s syndrome in pregnancy is associated with significant maternal morbidity including diabetes hypertension, heart failure, and preeclampsia. A trend toward an increased number of live births in treated patients has been reported, but it did not reach statistical significance. Treatment did not prevent premature births, but only one stillbirth and one intrauterine death have been reported in treated pregnancies. Rates of intrauterine growth retardation are similar in treated and untreated pregnancies, but the number of treated cases is very small. Medical therapy for Cushing’s syndrome has been reported in 20 women. The largest experience is with metyrapone, which seems to be tolerated well. However, hypertension and progression to preeclampsia have been reported with metyrapone, and it may best serve as an interim treatment pending definitive therapy. Ketoconazole has been used successfully in 3 pregnancies, without adverse effect. Ketoconazole is category C in pregnancy, because in the rat it is known to be teratogenic and abortifacient. Ketoconazole should probably be reserved for patients who need emergent therapy and cannot tolerate metyrapone. Aminoglutethimide causes fetal masculinization. Mitotane is contraindicated in pregnancy because it crosses the placenta and is teratogenic. Surgical treatment is recommended as the primary therapy for Cushing’s syndrome in pregnancy, except perhaps late in the third trimester. Medical therapy is the secondary choice. There doesn’t appear to be a rationale for supportive therapy alone. The prognosis for the fetus is guarded when hypercortisolism persists. See the reference by Lindsay et. al. for an excellent review of this topic.

INCIDENTALOMAS

Unexpected adrenal masses are found in 4.4% of abdominal CT scans. Autopsy studies report an average incidence of adrenal adenomas of 5.9% (range 1.1-32.0%). The autopsy studies show that the prevalence increases with age, so that the probability of finding an incidentalomas in a patient age 20-29 would be about 0.2% compared with about 7% in a patient over 70. Cancer has been found in 0-7% of incidentalomas. In one study, 42% of incidentalomas were non-functioning, 15% were cortisol-secreting, 10% were metastases from cancers elsewhere in the body, 8% were pheochromocytomas, 6% were myelolipomas, 6% were cysts, 4% were carcinomas, 4% were lymphomas, 4% were due to tuberculosis, and 2% were aldosteronomas. Thus, 25% of the masses were functioning. With the exception of one pheochromocytoma, one cyst, and one myelolipoma, all incidentalomas larger than 6 cm were carcinomas. In one patient the mass grew over 12 months from 3.2 to 4.4 cm, but it proved to be a benign adenoma. Evidence of cortisol hypersecretion developed after 24 months in one patient. Other possible causes of adrenal incidentaloma include hematomas, adrenolipomas, neurofibromas, ganglioneuromas, hamartomas, teratomas, macronodular adrenal hyperplasia, congenital adrenal hyperplasia, and masses that are not really adrenal in origin (renal, pancreatic, gastric, mistaken vasculature, retroperitoneal bronchogenic cyst, retroperitoneal schwannoma, and technical artifacts). (see Young: NEJM 2007; 356:51-60.)

Adrenocortical carcinoma is rare in masses < 5 cm in diameter. The prevalence of adrenal carcinoma is 2% in masses < 4 cm, 6% in masses that are 4.1 - 6 cm in diameter, and 25% in masses > 6 cm in size. This gives rise to the recommendation that all solid masses > 6 cm in diameter should be surgically removed, and surgery should be considered in masses 4-6
cm in size (see below).

Everyone agrees that the workup of an adrenal incidentalomas should begin with a
history and physical examination, looking particularly for symptoms and signs of adrenal
hyperfunction (Cushing’s syndrome, pheochromocytoma, aldosteronism, masculinizing and
feminizing tumors) and malignancy.

In 2002 an NIH State-of-the-Science conference published recommendations for the
appropriate workup for adrenal incidentalomas (see references). In 2008 the American
Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons
issued new guidelines for the management of adrenal incidentalomas. These were published in
the July/August, 2008 issue of Endocrine Practice. They recommend that every patient with an
adrenal incidentaloma be screened for abnormal production of aldosterone (if hypertensive),
catecholamines, and cortisol. They also recommend that any adrenal mass with concerning
radiographic characteristics and most lesions ≥ 4 cm in size should be resected because of an
increased risk of adrenal cancer. (Radiographic characteristics generally considered to be
concerning would include high unenhanced CT attenuation values (> 10 HU, and especially >20
HU), marked enhancement with IV contrast on CT, high-to-intermediate signal intensity on MRI
T-2 weighted images, irregular shape, inhomogeneity, and delayed contrast washout (see
below)). Hamrahian et.al. have reported that an attenuation value of < 10 HU differentiates
adenoma/hyperplasia from nonadenoma with a sensitivity of 40.5%. Other studies not limited to
surgical data have reported 68-83% sensitivity. The AACE/AAES guidelines recommend open
adrenalectomy if adrenocortical carcinoma is suspected. The previous NIH guidelines
recommended surgical excision of any lesion that grows by >1 cm during follow up. It has been
reported that 5-25% of all adrenal masses will increase in size by at least 1 cm over time.

The AACE/AAES guidelines state that an adenoma can be also be identified by
measuring contrast-washout kinetics on CT scans. In this procedure, a CT scan is done
immediately after intravenous administration of a contrast agent and then again after a 10- to 15-
minute delay. Benign adrenal lesions will commonly enhance up to 80 to 90 HU and wash out
more than 50% on the delayed scan, whereas lesions such as metastatic tumors, carcinomas, or
pheochromocytomas will not. Pheochromocytomas usually show enhancement to more than 100
HU, which distinguishes them from adenomas.

The guidelines go on to note that on noncontrast CT scans, some benign adrenal lesions
do not have attenuation values of less than 10 HU and may have values of 20 to 40 HU. This
result is found in lipid poor adenomas. “In these cases, a washout of >50% will often allow the
diagnosis of an adenoma to be made. This observation, however, needs to be confirmed with
larger studies.”

The AACE/AAES guidelines do not specify how to screen for Cushing’s syndrome.
They note that the simplest screening test is a 1 mg overnight dexamethasone suppression test
(using a cutoff of > 5 mcg/dL), but if clinical suspicion is high (such as in patients with
hypertension, obesity, diabetes mellitus, or osteoporosis) “…3 tests (salivary cortisol,
dexamethasone suppression, and urine free cortisol [UFC]) can be used.” Screening for
pheochromocytoma can be done with plasma fractionated metanephrines and normetanephrines,
or a 24-hour urine for total metanephrines and fractionated catecholamines. In some cases both
plasma and urine studies may be warranted. (Plasma free metanephrines have a sensitivity of
96-100% but a specificity of only 85-89%, and only 77% in patients over age 60.) Screening for
hyperaldosteronism is done with an aldosterone-to-renin ratio. If the ratio is > 20 then the
diagnosis should be confirmed by demonstrating lack of aldosterone suppression with a 24-hour urinary aldosterone level collected under conditions of salt loading.

The AACE/AAES guidelines define subclinical Cushing’s syndrome (SCS) as a positive (> 5 mcg/dL) 1 mg dexamethasone suppression test in a patient with an adrenal adenoma and absence of typical physical stigmata of Cushing’s syndrome. In such patients, until further evidence is available regarding the long-term benefits of adrenalectomy, surgical resection should be reserved for those with worsening of hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis. Some would also add that younger patients (e.g. less than 40 years old) with subclinical Cushing’s syndrome may benefit from surgery. Dexamethasone suppression testing suggests that 2-12% of adrenal incidentalomas hypersecrete cortisol. In one study, 24% of patients with incidentally discovered adenomas had abnormal dexamethasone suppression tests despite having normal 24-hour urinary free cortisols. There was an increased incidence of obesity, hypertension, diabetes mellitus, impaired glucose tolerance, and abnormal serum lipid levels which improved with adrenalectomy. A low serum DHEAS can provide additional confirmation of ACTH-independent cortisol secretion. It has been reported that high dose dexamethasone can trigger a pheochromocytoma crisis, so such testing should be deferred until pheochromocytoma is ruled out.

According to the AACE/AAES guidelines, if the patient does not meet criteria for surgical removal of the tumor, radiographic reevaluation should be performed at 3-6 months and then annually for 1-2 years. Hormonal reevaluation should be performed annually for 5 years.

The 2002 NIH guidelines recommended that fine needle aspiration biopsy should be done in those patients who have factors in their presentation that suggest the possibility of an extra-adrenal malignancy or an infectious etiology. In patients known to have cancer, up to 75% of adrenal incidentalomas are metastases. The most common malignancies metastatic to the adrenals include lung, breast, melanoma, stomach, kidney, pancreas and colon. (However, in patients with known malignancies, half of all incidentalomas are still benign adenomas.) They also recommended that patients younger than age 21 undergo ACTH stimulation testing for 17-hydroxyprogesterone responsiveness because there is an increased incidence of adrenal nodules in heterozygotes for 21-hydroxylase deficiency.

Bilateral adrenal masses are present in up to 15% of patients with adrenal incidentalomas. The most common causes are myelolipomas, hemorrhage, metastatic disease, bilateral pheochromocytomas, Cushing’s syndrome (ACTH-independent macronodular adrenal hyperplasia), lymphoma, infection, congenital adrenal hyperplasia, bilateral cortical adenomas, and infiltrative diseases of the adrenal glands. Screening for adrenal insufficiency may be prudent in such patients. In 2008, Young et. al. published recommendations for the management of subclinical Cushing’s syndrome in patients with bilateral masses. Bilateral adrenal vein sampling is recommended.

**GLUCOCORTICOID RESISTANCE**

In this disorder, target organ resistance to cortisol due to an abnormal number or quality of cortisol receptors is seen. (There is one report in the literature of five patients with glucocorticoid resistance but no alteration in the glucocorticoid receptor. A problem at the transcriptional level seems likely.) This disorder presents as hypercortisolism without Cushing’s syndrome. Pituitary resistance to cortisol results in ACTH hypersecretion, which stimulates
hypersecretion of cortisol, androgens (such as androstenedione, DHEA, and DHEAS), and mineralocorticoids (such as DOC and corticosterone). In addition, the increased cortisol can overwhelm the renal 11-beta hydroxysteroid dehydrogenase, resulting in excess delivery of cortisol to the mineralocorticoid receptor. The result of the increased cortisol, androgen, and mineralocorticoid secretion is hypertension with or without hypokalemic alkalosis, acne, hirsutism, virilization, oligo-amenorrhea, and oligo-anovulation. In men, oligospermia and infertility have been reported, perhaps due to suppression of FSH by androgens or growth of intratesticular adrenal rests. Children may present with ambiguous genitalia (in genetic females) and pseudo-precocious puberty. Generally, clinical manifestation of glucocorticoid deficiency have not been reported in these patients, except for chronic fatigue. This fatigue may be due to inadequate compensation by the increased cortisol levels for glucocorticoid resistance in certain tissues such as the CNS and muscle. The clinical spectrum of the disease is wide, ranging from completely asymptomatic through mild to severe symptoms. The diagnosis is suggested by increased serum and urine cortisol levels without stigmata of Cushing’s syndrome. The plasma ACTH may be normal or high. Normal diurnal variation and response to insulin-induced hypoglycemia are seen. Inheritance is usually autosomal dominant. Patients are resistant to dexamethasone. Confirmation of the diagnosis requires sequencing of the glucocorticoid receptor gene in association with thymidine incorporation and dexamethasone-binding assays on peripheral blood mononuclear cells. Once a structural defect has been determined, its adverse effect on receptor function should be confirmed using in vitro mutagenesis and standardized assays that examine the ability of the mutant receptor to activate gene expression. Asymptomatic patients may not require treatment. Symptomatic patients are treated with individualized doses of dexamethasone to normalize the hormonal abnormalities and control the clinical manifestations.

ADRENAL INSUFFICIENCY

Clinical Manifestations:

Chronic Primary Adrenal Insufficiency: Symptoms of chronic primary adrenal insufficiency include nonspecific symptoms (there is a 94.8-100% frequency of chronic malaise, lassitude, weakness and fatigue - worse with exertion, better with rest), gastrointestinal symptoms (56-92%: anorexia 84.1-100%, nausea 84.3-86%, vomiting 74.5-86%, vague abdominal discomfort 31-63.8%, constipation usually alternating with diarrhea 33%, diarrhea alone 16%), salt craving – (including eating salt by the spoonful) – 16-80.3%, and arthralgias/myalgias 6-68.6%. Vomiting and abdominal pain often signal an impending adrenal crisis. Increased thirst for iced liquids is common. Postural dizziness is reported in 12-84.3%, occasionally with syncope. Amenorrhea is reported in about 25%, probably due to weight loss, chronic illness, or, in autoimmune adrenal insufficiency, primary ovarian failure. Loss of axillary and pubic hair and libido are common in women, due to loss of adrenal androgens. Headache is reported in 55.2%. Psychiatric symptoms are reported in most patients, including mild-to-moderate organic brain syndrome with difficulty concentrating in 75.4%, impaired memory (which can progress to confusion, delirium and stupor) in 5-20%, depression in 20-40%, and psychosis in 20-40% (social withdrawal, irritability, negativism, poor judgment, agitation, hallucinations, paranoid delusions and catatonic posturing). There may be unusual sensitivity to drugs such as narcotics and anesthetics. Pseudotumor cerebri with headache, papilledema, and
high CSF pressure has been associated with adrenocortical insufficiency, glucocorticoid withdrawal, and within 2-4 weeks after treatment of hypercortisolism or cessation of hydrocortisone replacement.

Signs of chronic primary adrenal insufficiency include a 91.4-100% frequency of weight loss (2 to 15 kg) - primarily due to anorexia but also dehydration, and an 89.2-94% frequency of hyperpigmentation. The hyperpigmentation may precede other manifestations. It is a generalized hyperpigmentation due to stimulation of melanocytes by ACTH, beta-LPH, or both. It is more prominent in sun-exposed areas and areas of pressure or friction such as elbows, spine, knees, knuckles, toes, waist (belt), midriff (girdle), and shoulders (bra straps).

Hyperpigmentation may also been seen in the palmar creases, nail beds (including longitudinal bands of hyperpigmentation), buccal mucosa, gingival border, hard palate, tongue, nipples, areolae, axillae, perineum, vaginal and anal mucus membranes, and the navel. Scars acquired after development of Addison's disease may be hyperpigmented, but not those acquired before the Addison's or after initiation of effective treatment. Hair may be darker, and numerous black or brown freckles may develop on the skin. Pre-existing freckles darken. Hypotension, especially orthostatic hypotension (systolic BP < 110 mm Hg), is seen in 88-94%. In many patients, this hypotension is not profound enough to suggest the diagnosis by itself, and initially the hypotension may only be postural. Blood pressure control improves in patients with pre-existing hypertension. The presence of systolic hypertension is strong evidence against the diagnosis. Vitiligo, an autoimmune destruction of the melanocytes, may be seen in 4-20% of patients with autoimmune primary adrenal insufficiency, but not with other causes. The incidence of dental caries may be high. Auricular calcification is noted in 5%. Splenomegaly and lymphoid tissue hyperplasia, especially in the tonsils, may occur.

Laboratory abnormalities include a normochromic, normocytic anemia (40%) (due to cortisol and androgen deficiency), with relative lymphocytosis, neutropenia, and eosinophilia (17%). (The percentage of eosinophils in the differential is rarely > 10%). Hyponatremia is seen in 88%. This is due to aldosterone deficiency, decreased free water clearance, and the fact that cortisol normally exerts a tonic inhibitory influence on vasopressin secretion. Hyperkalemia due to mineralocorticoid deficiency is seen in 64%, and there may be a mild non-anion gap acidosis. Pre-renal azotemia is present in 55%. Mild-to-moderate hypercalcemia is seen in 6%. The cause is not known, but it doesn't seem to be simply a hemoconcentration phenomenon. Spontaneous fasting and/or postprandial hypoglycemia were described frequently in older series' but are not as commonly described in more recent reports. Hypoglycemia can be provoked by fasting, infection, fever, and vomiting. Reactive hypoglycemia has rarely been reported. The serum glucose is usually in the low normal range. Hypoglycemia is more common in infants and children, and in adults with secondary adrenal insufficiency due to an isolated ACTH deficiency. Diabetics who develop adrenal insufficiency may notice a significant decrease in their insulin requirement. A reversible increase in serum TSH and prolactin has also been reported in adrenal insufficiency. The chest x-ray may show a small vertical heart. The EKG may show low voltage, a vertical QRS axis, and a prolonged QT or flattened or inverted T waves. The head CT in untreated chronic primary adrenal insufficiency may reveal pituitary enlargement that reverses with replacement therapy. This usually represents corticotroph hyperplasia, but in rare cases an ACTH-secreting adenoma has developed.
Secondary and Tertiary Adrenal Insufficiency: The clinical manifestations of chronic secondary (=pituitary) and tertiary (=hypothalamic) adrenal insufficiency are generally similar to those of primary adrenal insufficiency. There are, however, several distinct differences. Hyperpigmentation is not seen, and patients often present with pallor. Adrenal crisis with shock is less common because aldosterone secretion is intact. Shock may still occur, however, because cortisol deficiency decreases the expression of vascular catecholamine receptors. The presence of normal aldosterone secretion also means that volume depletion and dehydration are not seen (except when there is severe vomiting). Hypotension is generally less severe, except in acute adrenal insufficiency. Gastrointestinal symptoms are less common. Weakness, easy fatigability, myalgias, arthralgias, and psychiatric symptoms are as common in secondary as in primary adrenal insufficiency. Hyponatremia can occur even in the presence of aldosterone, because cortisol deficiency leads to increased vasopressin secretion and decreased free water clearance. Salt craving is not seen. The potassium, BUN, creatinine, and bicarbonate levels are usually normal, and hypercalcemia is less common. Hypoglycemia is more common than in primary adrenal insufficiency, and is occasionally the presenting feature. This appears not to be simply due to absence of other pituitary hormones, since it is described in isolated ACTH deficiency as well. It may be due to the fact that patients without mineralocorticoid deficiency become less seriously ill, allowing features of glucocorticoid deficiency to become more prominent. The EKG and chest x-ray are generally normal. Other features of pituitary disease may be present, including hypogonadism, hypothyroidism, acromegaly, manifestations of hyperprolactinemia, visual field deficits, headache, and an enlarged sella turcica.

Acute-Onset Adrenal Insufficiency Due To Sudden, Bilateral Adrenal Infarction: Acute adrenal insufficiency can develop when there is bilateral infarction of the adrenal glands associated with hemorrhage, embolus, sepsis, or (very rarely) adrenal vein thrombosis following back injury. Adrenal hemorrhage presents as a deteriorating course in an already complicated hospitalized patient with major illness. Patients at greatest risk include those with thromboembolic disease, spontaneous or iatrogenic coagulopathy, and those in the postoperative state. Anticoagulated patients need not be outside the target coagulation parameters to develop this problem. The patients do not exhibit hyperpigmentation. They usually present with hypotension (46-90%) that can progress to shock and vascular collapse, abdominal, flank, or back pain (77-86%), lower chest pain (13%), abdominal or flank tenderness (38%), abdominal distension (28%), rigidity (28%), and even rebound tenderness (5%). Fever is present in 59-66%. Nausea and vomiting are seen in 47%, confusion and disorientation in 42%, tachycardia in 28%, and cyanosis and lividity in 28%. A sudden drop in the hematocrit may point toward recent hemorrhage. The typical laboratory manifestations are often absent, with hyponatremia and hyperkalemia in a minority, and hypoglycemia seen infrequently. However, azotemia is common and eosinophilia may be present. As the disorder progresses, severe hypotension, volume depletion, dehydration, hyperpyrexia, cyanosis, coma, and death ensue.

Adrenal Crisis: Adrenal crisis is an acute worsening of the problems associated with chronic adrenal insufficiency. It usually presents in one of four ways: (1) Adrenal crisis may present as shock in an asymptomatic patient with undiagnosed chronic adrenal insufficiency when the patient suffers a superimposed physical stress such as surgery, trauma, infection, or dehydration due to salt deprivation, vomiting or diarrhea. How can adrenal crisis develop in a previously asymptomatic patient? If the adrenal destruction occurs gradually, the patient may
pass through a period in which there are no symptoms but the adrenal glands do not have enough reserve to mount a response to a superimposed stress. (2) Adrenal crisis may develop when a physical stress occurs in a patient with symptomatic, but as-yet undiagnosed, adrenal insufficiency. The symptoms of chronic adrenal insufficiency can be very vague and nonspecific, and the cause of the symptoms may not become obvious until adrenal crisis develops. (3) Adrenal crisis may also develop in patients with treated chronic adrenal insufficiency who do not increase their replacement therapy during a physical stress. (4) Finally, adrenal crisis may be precipitated when a cortisol-secreting adrenal tumor or an ACTH-secreting pituitary tumor is removed without provision of replacement glucocorticoid. (In the case of the ACTH-secreting pituitary tumor, glucocorticoid replacement may be withheld intentionally until remission from hypercortisolism is documented – see above.)

When adrenal crisis develops, the blood pressure falls even farther than in symptomatic chronic adrenal insufficiency until the patient is in shock. Mineralocorticoid deficiency is an important factor contributing to the pathophysiology of adrenal crisis, which is less common in secondary and tertiary adrenal insufficiency. Adrenal crisis can occur in patients with primary adrenal insufficiency despite physiologic or even pharmacologic doses of glucocorticoid if the mineralocorticoid deficiency is not replaced. However, the hypotension of adrenal crisis is not due solely to mineralocorticoid deficiency. Glucocorticoid deficiency also contributes to hypotension by decreasing vascular sensitivity to angiotensin II and norepinephrine, and by decreasing the synthesis of renin substrate. Shock may respond poorly to vasopressors in the absence of cortisol. The systemic vascular resistance falls and cardiac output rises, mimicking septic shock. The patient develops extreme weakness to the point of prostration. Lethargy, fatigue, apathy and confusion are seen. Fever is common, whether due to a precipitating infection or to the adrenal insufficiency itself. Muscle and joint pains are present. There is profound anorexia with increased nausea and vomiting resulting in volume depletion and dehydration. Abdominal pain is frequent, and may mimic an acute surgical abdomen. Localizing signs are absent, but there may be tenderness and pain on deep palpation. Hypoglycemia may rarely be the presenting manifestation. If untreated, coma and death result.

“Steroid Withdrawal Syndrome:” A “steroid withdrawal syndrome” has been reported in which patients whose glucocorticoid dose has been reduced develop nonspecific symptoms such as weakness, nausea, and arthralgias. This occurs even when testing of the HPA axis is normal. This syndrome does not predispose to adrenal crisis, and it can develop even when the reduced dose is still supraphysiologic. Patients with this syndrome require slower, smaller dosage reductions in order to tolerate glucocorticoid withdrawal.

Etiology:

Iatrogenic Adrenal Insufficiency: Patients who have been taking exogenous glucocorticoids can suppress ACTH production, with atrophy of the normal corticotroph cells and the adrenocortical cells in the zona fasciculata (where cortisol is synthesized). If these glucocorticoids are then withdrawn too quickly, symptomatic adrenal insufficiency can be the result. Suppression of the hypothalamic-pituitary-adrenal axis has been documented when 25 mg of prednisone is taken bid for as little as five days. However, this suppression is very temporary, lasting only about another five days. Patients who take < 5 mg of prednisone per day have been
reported to have normal cosyntropin stimulation tests. However, when the dose reaches 5 mg of prednisone per day or more, abnormal cosyntropin tests begin to be seen. Virtually everyone chronically taking the equivalent of 15 mg or more of prednisolone per day develops adrenal suppression. Patients taking prednisone or dexamethasone as a single bedtime dose, even at physiologic doses, are more likely to be suppressed, since this interferes with the normal early morning surge of ACTH and cortisol. Patients taking glucocorticoids every other day rather than every day generally do not develop suppression of the hypothalamic-pituitary-adrenal axis. Patients who have been on any glucocorticoid dose for less than 3 weeks rarely have clinically significant adrenal suppression, and can safely discontinue their therapy without tapering. Patients who receive frequent short courses of glucocorticoids may be an exception to this general rule. Recovery from suppression may take 6-9 months or even longer. Patients who no longer need chronic glucocorticoid therapy can be tapered over a few weeks to 20 mg of hydrocortisone once a day, then decreased by 2.5 mg/day once a week to 10 mg once daily. Stress doses should still be used when the patient is physically stressed. Once the cosyntropin stimulation test or insulin tolerance test becomes normal the corticosteroid therapy can be safely withdrawn.

Adrenal insufficiency due to withdrawal of inhaled corticosteroids is a rare occurrence, but has been reported a number of times in the literature. Most of these reports are in children, the majority involved fluticasone, and most (though not all) involved the use of unusually high doses of the medication. Data are scarce regarding the risk of adrenal insufficiency in patients exposed to glucocorticoids in other forms. Adrenal insufficiency has been reported in a patient who used topical betamethasone over 80% of his body for 30 years. There has been one suggested fatality from topical corticosteroid-induced adrenal insufficiency, and several cases have been reported in which enough steroid was absorbed to cause clinical Cushing’s syndrome. Adrenal suppression has been reported with repeated intra-articular injections and with a single intra-articular injection of 100 mg of methylprednisolone. Decreased cortisol levels have been reported for 1-7 days after injection of intra-articular steroids, and in one study a decrease for up to 4 weeks was reported. Adrenal suppression for 7-21 days has been reported after a single epidural injection of 15 mg of dexamethasone acetate.

Primary Adrenal Insufficiency: Adrenal Destruction

Autoimmune Adrenal Insufficiency: Autoimmune destruction of the adrenal glands accounts for over 90% of all cases of primary adrenal insufficiency in North America and European countries. About 90% of the adrenal cortices must be destroyed before clinical adrenal insufficiency develops. Evidence for both humoral and cell-mediated autoimmunity has been found, including lymphocytic infiltration of the adrenal glands and antibodies that can block the stimulating effect of ACTH. Anti-adrenal antibodies (adrenal cortex autoantibodies measured by immunofluorescence and steroid 21-hydroxylase autoantibodies detected by immunoprecipitation assay) are found in more than 90% of patients at the clinical onset of autoimmune adrenal insufficiency. Antibody titers decrease after the onset of overt disease, and sometimes disappear completely. The presence of anti-adrenal antibodies seems to precede the development of overt adrenal insufficiency by several years. (Coco et.al. reported that the cumulative risk of developing overt adrenal insufficiency in patients with positive anti-adrenal antibodies was 48.5%. It is common to find antibodies against other endocrine glands as well. Anti-microsomal antibodies are present in 50-60%, and half of these
patients have overt hypothyroidism. Anti-parietal cell antibodies are present in 30%, anti-intrinsic factor antibodies in 9%, anti-ovarian antibodies in 22%, anti-testicular antibodies in 5%, anti-parathyroid antibodies in 26% and anti-islet cell antibodies in 8%. About 50% of patients have one or more other endocrine disorders.

In 40% of cases, autoimmune adrenal insufficiency is an isolated phenomenon. In 60% it is a part of one of the two Polyglandular Autoimmune (PGA) Syndromes (also known as Autoimmune Polyglandular Syndromes - APS, or Polyglandular Autoimmune Diseases). 70% of these patients are women. Isolated autoimmune adrenal insufficiency has a 71% male predominance in the first two decades. The incidence is equal in men and women in the third decade, and 81% of the patients older than thirty are women.

Type 1 APS is also known as the Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) syndrome. It can be sporadic, but is usually inherited as an autosomal recessive disorder that usually presents in childhood or adolescence – many patients display all of the three main components before the age of 20 years. However, there are reports of cases with a later start and/or unusual presentations. Most patients already have 3-7 different manifestations early in the course of the disease, but other components may appear throughout life. The three most prominent manifestations are adrenal insufficiency, hypoparathyroidism, and mucocutaneous Candidiasis (at least two of these must be present to make the diagnosis). This is a rare disorder. In Finland (where the largest number of reports have originated) the incidence is 1 in 25,000, with a male-to-female ratio variably reported as 0.8-1.5, and as high as 2.4. The incidence of this disorder is also increased among inhabitants of Sardinia, and among Iranian Jews. The disorder is caused by mutations in a single gene, termed the “autoimmune regulator” (AIRE), which maps to chromosome 21q22.3. This gene encodes a transcription factor. Study of mice in whom the AIRE gene has been knocked out has led to the hypothesis that one function of this gene may be to enhance the expression of “peripheral” antigens in the thymus, thereby promoting tolerance.

Candidiasis is seen in 73-100% of patients who inherit this syndrome, and it is the presenting feature in 93%, usually developing before the age of 5. It may be chronic or recurrent, and is relatively resistant to conventional therapy. It almost always involves the mouth, but may just involve the nail beds. It may also involve the skin, vagina and esophagus. The propensity toward Candida infections is explained by a selective T cell deficiency. It can be widespread, but in the majority of cases >5% of the skin area was involved. It develops in adulthood in about 10%. The mean age of onset is 12 years, and the range is 1-37 years of age.

Hypoparathyroidism usually develops before the age of ten (mean 7.5 years, range 3 months to 44 years), and adrenal insufficiency usually develops before the age of fifteen (mean age 12-13 years, range 6 months to 44 years). The complete evolution of the three main diseases in this syndrome usually is completed within the first 20 years of life. Other diseases continue to appear until at least the fifth decade. The mucocutaneous Candidiasis is seen slightly more often in women than in men. 60-100% of individuals who inherit this disorder eventually develop adrenal insufficiency, and 73-93% develop hypoparathyroidism. About 1/3 to 1/2 of affected individuals eventually develop all three features, whereas 49% of affected individuals develop 2 diseases. An association has been reported with HLA A28, DR3, and DR5. Ovarian failure has been associated with HLA A3. Gonadal failure is seen in 17-50%, with ovarian failure being more common than testicular failure. Autoimmune thyroid disease is seen in 2-13%. Atrophic
thyroiditis and Hashimoto's thyroiditis occur with equal frequency, but Graves' disease is not seen. Type 1 diabetes mellitus is seen in 1.2-18%. Hypopituitarism and diabetes insipidus (both due to hypophysitis) are rare. There is a 4-25% incidence of non-endocrine autoimmune disorders such as malabsorption of various causes (15-22%), alopecia (29-37%), autoimmune gastritis with pernicious anemia (11-15%), chronic active hepatitis (8-26%), and vitiligo (8-15%). The disorder is often associated with various forms of ectodermal dystrophy, including dental enamel hypoplasia, pitted dystrophy of the nails, keratoconjunctivitis, and calcified plaques on the tympanic membranes (33%). Unexplained hyposplenia/asplenia and cholelithiasis are also increased, as are immunologic defects (both cellular and humoral). Sjögren’s syndrome is seen in 12%, and calcifications of the basal ganglia are seen in 12-30%. An association with cutaneous vasculitis with traces of cryoglobulinemia, hemolytic anemia, carcinoma of the oral mucosae (which develops if oral Candidiasis isn’t treated aggressively), and adenocarcinoma of the gastric antrum has also been reported. Diarrhea or obstipation may result from autoimmune destruction of gastrointestinal enterochromaffin and enterochromaffin-like cells.

Type 2 APS is more common and develops at a later age than type 1 APS. Adrenal insufficiency is the principle manifestation, occurring in 100% of the cases. The mean age of onset is in the mid-20's. The age of onset can be anywhere from childhood to late adulthood, with most cases occurring between ages 20 and 40. The ratio of women to men is about 1.8:1. About half of the cases are familial, and susceptibility to the disorder appears to be inherited as an autosomal dominant trait. Adrenal insufficiency is the presenting manifestation of the syndrome in about 50% of the patients, with adrenal insufficiency and thyroiditis developing simultaneously in 20%, and adrenal insufficiency following thyroiditis in 30%. The syndrome is associated with HLA B8, DR3 and DR4 antigens. The other two major manifestations of Type 2 APS are autoimmune thyroid disease, seen in 70% (usually atrophic thyroiditis or Hashimoto's thyroiditis, but occasionally Graves' Disease), and type 1 diabetes mellitus, seen in 50%. Hypogonadism has been described in anywhere from 5-50% of these patients, with ovarian failure being more common than testicular failure. Hypoparathyroidism and mucocutaneous Candidiasis are not seen, and diabetes insipidus is rare. Vitiligo has been described in 4%, but other non-endocrine autoimmune disorders (alopecia, pernicious anemia, myasthenia gravis, ITP, Sjögren's Syndrome, rheumatoid arthritis, and primary antiphospholipid syndrome) are rare. Serositis with pericardial or pleural involvement, or both, has been reported.

**Infectious Diseases:**

**Tuberculosis:** This was once the cause of the majority of cases of primary adrenal insufficiency in the United States. It currently accounts for about 7-20% of cases. About 10% of all primary adrenal insufficiency is due to causes other than autoimmune disease and tuberculosis. Worldwide, tuberculosis is the most common cause of primary adrenal insufficiency. Primary adrenal insufficiency from tuberculosis is virtually always accompanied by evidence of tuberculosis in other organs, especially the lungs and kidneys. In a review of 13,492 autopsies and 270 adrenalectomy specimens in Hong Kong, Lam et.al. reported finding adrenal involvement in 6% of patients with pulmonary tuberculosis. In ¼ of those patients, the adrenal gland was the only organ involved by active tuberculosis. Of 53 patients with adrenal involvement, only 7 exhibited signs and symptoms of adrenal insufficiency. Bilateral enlargement of the adrenal glands was common, but FNA was not helpful in establishing the
diagnosis.

Tuberculous adrenalitis develops due to hematogenous spread from a focus elsewhere in the body - usually the lungs, GI tract or kidneys. Clinical tuberculosis is usually evident in these patients, but may be clinically latent. Destruction of the adrenal glands is a gradual process, and the medulla is more often affected than the cortex. Initially the glands are enlarged, but after about 2 years they become normal or small in size. Calcifications develop in about 50%. Thus, the absence of large, calcified glands does not rule out TB. The adrenal insufficiency is sometimes reversible if the disease is treated early. It should be kept in mind that rifampin accelerates cortisol metabolism and may increase replacement needs.

**Fungal Infections:** All commonly occurring disseminated fungal infections except Candida have been reported to cause adrenal insufficiency. Addison’s disease has been reported with histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, cryptococcosis, blastomycosis, pneumocystis, candidiasis, and infections with Bipolaris species. Of these infections, histoplasmosis (7-12%) and paracoccidioidomycosis (9-14%) have had the greatest tendency to spread to the adrenal glands. Latency periods of several years from primary infection to adrenal insufficiency have been reported. In the United States, disseminated Histoplasmosis is the most common cause. More than 1/3 of patients who die of disseminated Histoplasmosis have adrenal involvement. Histoplasmosis is endemic in the Piedmont plateau of the Middle Atlantic States and in the Ohio and Tennessee Valley regions of the Mississippi watershed. In South America, Paracoccidioidomycosis (=South American Blastomycosis) is one of the most common causes of adrenal insufficiency. The adrenal glands are large with peripheral enhancement, central hypodensity, contour preservation, and calcifications during healing (by way of comparison, the contour is usually distorted by metastases and the glands are usually atrophic in autoimmune adrenalitis). The adrenal insufficiency is sometimes reversible with treatment, but it should be kept in mind that ketoconazole inhibits cortisol synthesis and may precipitate adrenal crisis in a patient with marginal adrenal reserve. Reversible adrenal insufficiency has been reported with the use of itraconazole at 600 mg/day. Also, combinations of itraconazole and inhaled glucocorticoids can suppress the adrenal axis.

**Syphilis:** Syphilis is a rare cause of adrenal insufficiency. The adrenal glands are sclerotic with gumma formation. Spirochetes are detectable in the infected glands.

**African Trypanosomiasis:** African trypanosomiasis can result in adrenal insufficiency that is NOT related to its treatment with Suramin, a drug that is known to impair adrenal function in high doses.

**Acquired Immunodeficiency Syndrome:** The HIV virus can infect the adrenal glands, but it is not known if this leads to clinical adrenal insufficiency. Primary adrenal insufficiency in AIDS is usually due to infection with an opportunistic organism - especially cytomegalovirus and M. tuberculosis. Mycobacterium Avium Complex, Pneumocystis, Toxoplasmosis, Cryptococcosis, Kaposi's sarcoma and lymphoma can also involve the adrenal glands in AIDS. Pathologic abnormalities of the adrenal glands at autopsy are common in AIDS, being described in 50-78%. However, overt adrenal insufficiency occurs
in only a 5-8% of patients. An abnormal cortisol response to ACTH has been described in 8-40% of patients with AIDS. Many patients with AIDS have suboptimal increases in their aldosterone secretory reserve and decreased DHEA secretion. However, these subclinical decreases in adrenocortical function are also seen in seriously ill non-HIV patients, and may simply be evidence of a shift from mineralocorticoid and androgen production to glucocorticoid production as an adaptation to chronic illness. Some AIDS patients have symptoms of adrenal insufficiency but high serum cortisol levels. There is some evidence that they may have peripheral resistance to glucocorticoid action due to a decreased affinity of the type II glucocorticoid receptors. The mechanism is unknown. The response to Cortrosyn is usually normal but the response to CRH is blunted. They may present with intense cutaneous hyperpigmentation, but this is not due to high levels of ACTH. In fact, ACTH levels are normal or only slightly elevated. Rather, it is due to increased interferon-α which is increased in AIDS patients with peripheral glucocorticoid resistance and may stimulate melanocortin I receptor expression and melanin synthesis. When hyponatremia is seen it is usually secondary to SIADH. Hyperkalemia can develop in patients taking trimethoprim, which inhibits renal tubular potassium secretion.

**Bilateral Adrenal Hemorrhage/Infarction:** Acute bilateral adrenal hemorrhage is becoming a commonly recognized cause of adrenal insufficiency in this country. The diagnosis is usually made when a critically ill patient is found to have bilateral enlargement of the adrenal glands (which can be massive) on abdominal CT or MRI. Cortisol secretion is then tested, and found to be deficient. Clinical manifestations have been discussed above, but generally consist of fever, relative hypotension, a drop in hematocrit, vague abdominal or flank pain, and sometimes electrolyte abnormalities. Critically ill patients are susceptible to hemorrhage (particularly when anticoagulated or when coagulopathy is present) because there is only one vein draining the glands, while the arterial supply is very rich and is further increased by ACTH stimulation. The adrenal veins may have an eccentric muscular arrangement making them particularly susceptible to formation of platelet thrombi when stasis or turbulence supervenes. In the appropriate clinical setting the result is adrenal vein thrombosis and adrenal hemorrhage. The primary antiphospholipid syndrome is being increasingly recognized as a contributing factor to this entity, and patients with bilateral adrenal hemorrhage or unexplained enlargement should be screened for this problem.

Bilateral adrenal hemorrhage can also occur with sepsis. In children the most common causes are meningococcemia and Pseudomonas septicemia. The Waterhouse-Friderichsen Syndrome is a syndrome that is generally associated with fulminant meningococcemia. It is characterized by petechial rash, coagulopathy, cardiovascular collapse, and bilateral adrenal hemorrhage. Adrenal hemorrhage is due to septic emboli and/or disseminated intravascular coagulation. Other organisms may occasionally be associated with this syndrome, including Streptococcus pneumoniae, beta-hemolytic Streptococcus, Neisseria gonorrhoeae, E. coli, Staphylococcus aureus, and H influenzae.

Bilateral adrenal hemorrhage can also be caused by other life threatening disorders including trauma, severe cardiovascular diseases, CHF, pulmonary emboli, acute renal failure, local infection, leukemia, lymphoma, malignancy, pregnancy, the neonatal period, and severe burns. It is most common in the postoperative setting, and in patients over the age of 50. Cortisol secretion occasionally returns to normal in patients who survive. Long-term mineralocorticoid replacement is usually not necessary. Bilateral infarction of the adrenal glands can also be seen in embolic disease and arteritis.
**Adrenoleukodystrophy:** This is an inherited disorder in which abnormal fatty acid metabolism (defective beta-oxidation in the peroxisomes) leads to accumulation of Very Long Chain Fatty Acids (VLCFA) as cholesterol esters and gangliosides in brain, spinal cord, peripheral nerves, adrenal cortex, testes and liver. The disease is apparently caused by an abnormal peroxisomal transporter protein that prevents the appropriate metabolism of the VLCFA's. Accumulation of the resulting products alters the adrenal cell membrane and interferes with ACTH receptor function. Perry et. al. reported that this disease caused 3.9% of all childhood adrenal insufficiency in their series. The disorder is inherited as an X-linked recessive, so most affected individuals are male. Penetrance is incomplete. DNA probes can be used for genetic and diagnostic purposes, including family screening and prenatal diagnosis. The gene is now known, and it codes for a peroxisomal integral membrane protein. However, mutational analysis of the ALD gene is not routinely indicated because the biochemical finding of elevated VLCFA is accurate in 99.9% of affected males. On the other hand, 15% of obligate female carriers will have normal VLCFA levels and will require mutational analysis for accurate determination of carrier status. The adrenal insufficiency usually develops prior to neurologic symptoms, so any young man with idiopathic primary adrenal insufficiency should be screened for this disorder. Two clinical phenotypes, called "cerebral adrenoleukodystrophy" and "adrenomyeloneuropathy" have been described within the same kindreds. Both adrenoleukodystrophy and adrenomyeloneuropathy have in common an abnormal gene (ALDP) mapped to Xq28.

"Cerebral adrenoleukodystrophy" is the classic form, which occurs in about 60% of affected individuals. It presents in childhood before age 21. The X-linked form of the disease affects principally males, but with modified expression in some females. The neurologic manifestations include cognitive dysfunction, behavioral problems, emotional lability, and visual and gait disturbances. This may progress to dementia, blindness, quadriplegia, and eventual vegetative state after apparent normal development. About 30% of these patients develop adrenal insufficiency 2-3 years before the neurologic symptoms.

A milder and more slowly progressive phenotypic variant is called "adrenomyeloneuropathy." This has its age of onset in adolescence and young adulthood, usually in the second through fourth decades. About 90% of these patients develop adrenal insufficiency prior to the onset of neurological symptoms. The neurologic manifestations are due to spinal cord and peripheral nerve demyelination, and develop over years. The initial manifestations are weakness, spasticity and polyneuropathy. This may progress to loss of ambulation, cognitive dysfunction, urinary retention, and impotence. 20-60% develop a hypergonadotrophic hypogonadism. Occasional patients develop adrenal insufficiency without neurologic manifestations.

The diagnosis can be confirmed by demonstrating abnormal accumulation of saturated VLCFA (especially C26:0) in plasma, cultured skin fibroblasts and erythrocytes. MRI of the brain shows demyelination in the periventricular parieto-occipital region, optic radiation and corpus callosum. Treatment with dietary monounsaturated fatty acids (especially C18:1 and/or C22:1) and dietary fat restriction may prevent or delay the neurologic manifestations but cannot reverse them. There are no data on the effect of diet therapy on adrenal function.

**Zellweger Syndrome:** This is one of several peroxisomal disorders caused by mutations in proteins that are necessary for peroxisomal biogenesis and proliferation (the so-
called PEX proteins). Patients present with glucocorticoid and mineralocorticoid deficiencies, global developmental delay, hypotonia, dysmorphic facial features, neurosensory deafness, and optic atrophy. Mutational analysis of the PEX proteins is currently not routinely performed or available.

**Wolman Disease:** Another rare genetic cause of adrenal failure, this is a lethal autosomal recessive storage disease caused by a deficiency of lysosomal acid lipase. The clinical presentation is one of failure to thrive with vomiting, diarrhea, steatorrhea, hepatosplenomegaly, hepatic fibrosis, esophageal varices, intestinal malabsorption, abdominal protuberance, pulmonary hypertension, poor weight gain, nutritional failure, and finally death in infancy. The diagnosis should be considered in any neonate with bilateral adrenal calcifications, especially if there is a family history of consanguinity or early neonatal deaths. It should also be considered if bilateral adrenal calcification is noted on prenatal ultrasound. The diagnosis is made by demonstrating a deficiency of lysosomal acid lipase peripheral blood leukocytes or cultured fibroblasts. Cells from a person with Wolman disease will have less than 10 percent the usual amount of lysosomal acid lipase. A prenatal diagnosis can be made by measuring acid esterase activity in cultured embryonic cells. Encouraging progress has been made in treating this disorder by transferring the gene for lysosomal acid lipase into affected fibroblasts, with phenotypic correction of the lipid storage and of the growth arrest. It is not yet clear whether patients surviving past the first few months will require glucocorticoid and/or mineralocorticoid replacement. A milder form of the disease is called “Cholesterol Ester Storage Disease.”

**Adrenal Metastases/infiltrative Diseases:** Metastases to the adrenal glands are common, probably because of the rich sinusoidal blood supply of the adrenals. Autopsy studies reveal adrenal metastases in 40-60% of patients with disseminated lung and breast cancer, 30% of melanomas, and 14-20% of stomach and colon cancers. Renal neoplasms also metastasize to the adrenals. Hodgkin’s disease and non-Hodgkin’s lymphoma sometimes present primarily as adrenal insufficiency with bilateral adrenal enlargement, but rarely cause clinical adrenal insufficiency. This may be because symptoms due to adrenal insufficiency are attributed to the neoplasm, or it may be because it takes so much adrenal destruction (>90%) to cause clinical adrenal insufficiency. 20% of patients with metastases to the adrenal glands have an abnormal cosyntropin stimulation test, but overt, clinically significant adrenal insufficiency is uncommon. When adrenal insufficiency does occur in association with malignancy, it is usually from an infiltrative malignancy such as lymphoma or leukemia.

Amyloidosis, sarcoidosis and hemochromatosis are other infiltrative diseases that have rarely been associated with adrenal insufficiency.

A non-Langerhans form of histiocytosis called Erdheim-Chester Disease has been reported to cause adrenal insufficiency due to infiltration of the adrenal glands with histiocytes. It presents with bone pain, exophthalmos, xanthelasma, interstitial lung disease, retroperitoneal “fibrosis” with perirenal and/or ureteral obstruction, renal failure, CNS and cardiovascular involvement, and diabetes insipidus.
Primary Adrenal Insufficiency: Adrenal Dysgenesis or Hypoplasia

SF-1 Deficiency: Steroidogenic Factor-1 (SF-1) is a receptor located in the nucleus that is a product of the fushi tarazu factor-1 gene (the FTZF1 gene). It influences gene transcription at multiple levels and at different stages of development, and is necessary for proper development of the adrenal cortex, gonads, and ventro-medial nucleus of the hypothalamus. SF-1 response elements are found in the promoters of the genes for the α-subunits of the pituitary glycoprotein hormones, Müllerian inhibiting substance, and the promoter of the DAX-1 gene (see below). It also regulates expression of the genes for several steroidogenic enzymes. Men with mutations in the FTZ1-F1 gene present with adrenal insufficiency, normal Müllerian structures (fallopian tubes, uterus, and proximal vagina), no androgen response to HCG stimulation, and gonads made up of poorly-differentiated tubules and connective tissue streaks. Women present only with adrenal insufficiency. Recently, heterozygous missense mutations in SF-1 have been reported that cause disordered impaired fetal and postnatal testicular function but leave adrenal steroid biosynthesis intact.

Congenital Adrenal Hypoplasia (AKA Adrenal Hypoplasia Congenita): This is a rare familial disorder that presents as glucocorticoid and mineralocorticoid deficiency shortly after birth. The adult adrenal cortex does not develop normally. Levels of adrenal androgens are low. Four forms have been described: (1) a sporadic form with pituitary hypoplasia, (2) an autosomal recessive form with a distinct miniature adult adrenal morphology, (3) an X-linked cytomegalic form with hypogonadotrophic hypogonadism (due to mutations in a gene called DAX-1 (dosage-sensitive sex reversal-adrenal hypoplasia gene 1) (also known as NROB1), which is part of a regulatory cascade required for normal gonadal, adrenal, and hypothalamic development), and (4) an X-linked form with glycerol kinase deficiency, psychomotor retardation, muscular dystrophy, testicular abnormalities (anorchia or cryptorchidism), short stature, osteoporosis, and a characteristic facies with hypertelorism, alternating strabismus, and drooping mouth. This last form is due to variable deletions in a gene sequence that includes ornithine transcarbamylase, Duchenne muscular dystrophy, glycerol kinase, and DAX-1/NROB1.

Familial Glucocorticoid Deficiency (FGD) (AKA Hereditary Unresponsiveness to ACTH, AKA Isolated Glucocorticoid Deficiency): This is a rare autosomal recessive disorder in which secretion of cortisol and androgen is deficient and unresponsive to ACTH stimulation. Mutations in the adrenal receptor for ACTH are found in about 25% of FGD kindreds (FGD type 1). The majority of these mutations lead to defective transport of the receptor to the cell surface. The disorder usually presents in the first year of life, though it can present in infancy or later childhood. The presenting features are hyperpigmentation, muscle weakness, hypoglycemia, and seizures. Patients in whom no mutation in the ACTH receptor gene has been found are labeled FGD type 2. Some patients with FGD type 2 have been found to have a mutation in the gene for a small single transmembrane domain protein known as melanocortin 2 receptor accessory protein, which contributes in part to promoting the expression of the receptor at the cell’s surface. This abnormality accounts for another 15-20% of cases of FGD, so about half of all cases are caused by problems in other genes not yet identified. Absence of normal feedback inhibition results in ACTH levels over 1000 pg/mL.
Mineralocorticoid secretion is normal or only partially deficient, and patients with this disorder respond to postural stimuli and volume depletion. Indeed, the preservation of the renin-angiotensin-aldosterone system in a patient who otherwise appears to have primary adrenal insufficiency distinguishes this disorder from other causes of adrenal failure. Affected individuals who are not treated are likely to succumb to hypoglycemia or overwhelming infection in infancy or childhood. The disorder may be associated with autonomic and motor neuropathies. A syndrome of familial unresponsiveness to ACTH associated with achalasia and alacrima has also been reported - the so-called “Triple-A” Syndrome or Allgrove’s Syndrome.

Other Rare Causes of Adrenal Hypoplasia include IMAGe Syndrome (intrauterine growth retardation, metaphysical dysplasia, adrenal hypoplasia, and genital anomalies), Smith-Lemli-Opitz Syndrome (microcephaly, micrognathia, syndactyly, sexual ambiguity, and kidney and heart malformations – diagnosed by measuring cholesterol and its metabolites – 7 and 8 dehydrocholesterol), and Antley-Bixler Syndrome.

Primary Adrenal Insufficiency: Impaired Steroidogenesis

Congenital Adrenal Hyperplasia: This is a group of disorders characterized by deficiencies of various steroidogenic enzymes. The most common form, the 21-hydroxylase deficiency, causes ambiguous genitalia in females, who are usually diagnosed at birth. Males often go undiagnosed until they present with salt-wasting crisis 2-3 weeks after birth. A deficiency of 3β-hydroxysteroid dehydrogenase can also present with neonatal adrenal insufficiency, and males have ambiguous genitalia or are phenotypically female. It has been reported that most infants with CAH are born at 36 weeks or more, with a median age of 40 weeks – consistent with the concept that deficient cortisol production by the fetal adrenal may delay the onset of labor.

Lipoid Congenital Adrenal Hyperplasia (Previously Known As 20,22-Desmolase Deficiency): Patients with Lipoid Congenital Adrenal Hyperplasia were previously thought to have a 20,22-desmolase deficiency (20,22-desmolase is the old name for the enzyme that converts cholesterol to pregnenelone; the new name is P₄₅₀ₙₑc). It is now known that these patients do not have mutations in the gene that synthesizes P₄₅₀ₙₑc (which is known as the CYP11A1 gene), but instead to have mutations in the gene that encodes a mitochondrial steroidogenic acute regulatory protein (StAR). This enzyme facilitates the transport of cholesterol into mitochondria, thus providing the substrate for steroid hormone biosynthesis. It is especially important in adrenocortical and gonadal cells. It has been hypothesized that a deficiency of this enzyme leads to lipid deposition in steroidogenic cells that gradually destroys their function. This is a rare autosomal recessive disorder characterized by a greatly diminished or absent ability to synthesize all adrenal and gonadal steroids. The disease is called “lipoid” congenital adrenal hyperplasia because it is characterized by lipid droplet accumulation in the cytoplasm of the adrenocortical cells as well as deficient steroid hormone production. Most patients have enlarged adrenal glands, but a small number have normal-sized adrenals. Affected infants present during the first weeks of life with failure to thrive, shock, hyponatremia, hyperkalemia, hypoglycemia, hyperpigmentation, and high ACTH and renin levels coupled with low cortisol and aldosterone levels. Some patients do not present until later in infancy. All patients have a female phenotype regardless of genetic sex (the fetal testis is affected early in
gestation due to stimulation with HCG, and the fetal zone of the adrenal gland responsible for
DHEA secretion is similarly affected). Affected females undergo a normal puberty but have
progressive hypergonadotropic hypogonadism (the fetal and childhood ovary does not build up
lipid deposits until after puberty when LH and FSH stimulate steroidogenesis). Hormonal
replacement therapy permits long-term survival, but one study has reported pre-malignant
changes in the excised testes of a 1-year old, suggesting that early gonadectomy might be
beneficial to prevent testicular tumors. StAR mutations have been described most frequently in
the Japanese, Koreans, eastern Saudi Arabians, Swiss, and Palestinians. Recently 3 children
from 2 families have been reported who had a mild form of lipoid CAH. They initially presented
at age 2-4 and the 46, XY individuals had normal male genitalia. These patients had
homozygous StAR mutations that retained 20% of wild-type activity. The disorder is being
called “nonclassic lipoid CAH.” One case of late-onset nonclassical lipoid CAH has been
described with normal-sized adrenal glands.

Thus, STAR mutations seem to present with a spectrum of phenotypes,
from classical Lipoid Congenital Adrenal Hyperplasia through adrenal dysfunction presenting as
if it were Familial Glucocorticoid Deficiency (with or without disordered sex development –
hypospadias, cryptorchidism) and can even result in a phenotype so mild that it remains
unrecognized.

Once the true pathogenesis of this disorder was delineated, it was then
suggested that we might never find a mutation in the CYP11A1 gene in a live born human
because the P_{450}sc enzyme is necessary for synthesis of progesterone by placental
syncytiotrophoblast cells. (Progesterone, of course, is essential for maintenance of a pregnancy.)
However, there have now been reports of 9 cases of deficiency of cytochrome P_{450}sc in live born
children, giving evidence that in some cases the in vivo enzyme level is sufficient to sustain
pregnancy. The disorder can present with adrenal insufficiency at any time from infancy to early
childhood. ACTH and renin levels are high, and genetic males present with female external
genitalia. None of the 9 patients have been reported to have adrenal hyperplasia. There are also
3 reports of a nonclassical presentation with hypospadias, cryptorchidism, and adrenal failure
due to mutations in P_{450}sc resulting in a partial defect in enzymatic activity.

**Secondary (Pituitary) and Tertiary (Hypothalamic) Adrenal Insufficiency:** The
most common cause of adrenal insufficiency is secondary adrenal insufficiency due to iatrogenic
suppression of ACTH secretion from exogenous glucocorticoids. Treatment of ACTH-dependent
Cushing’s syndrome or unilateral cortisol-secreting adrenal tumor can also result in secondary
adrenal insufficiency due to suppression of the hypothalamus and pituitary by the previous
endogenous cortisol hypersecretion. Allan et.al. have reported a case of postoperative adrenal
insufficiency following removal of an adrenal adenoma that was thought to be secreting only
aldosterone. The adenoma had atypical features for an aldosteronoma by MRI scanning: bright
areas of high signal intensity on T2-weighted images and failure of the intensity to fade in the
“out of phase” images.

Any lesion of the hypothalamus or pituitary can result in adrenal insufficiency.
When pituitary or hypothalamic tumors cause hypopituitarism, adrenal insufficiency virtually
always is accompanied by deficiencies of other pituitary hormones. Growth hormone and
gonadotropin secretion are usually the first to be impaired, followed by TSH and finally ACTH.
Pituitary dysfunction occurs in up to 30% of patients with trauma to the brain and may not
appear until months or years after the incident.
Pituitary infections, which are rare, are most commonly due to bacteria. Fungi are much less frequent. Pituitary fungal infections may occur from hematogenous spread, extension from adjacent anatomical sites, or iatrogenic inoculation (e.g. with Aspergillus of Candida species during transsphenoidal adenoma resection). Fungal pituitary infections are often indistinguishable from bacterial infections and tumors. The diagnosis is often made unexpectedly at surgery or at autopsy. Certain MRI findings are thought to be specific for pituitary infection. Infection is favored over tumor when peripheral enhancement, hypointensity, or calcifications are seen on T2-weighted images.

There are genetic disorders that can affect ACTH secretion, including mutations in the gene encoding the pituitary transcription factor paired-like homeobox 1 (PROP1). In this disorder there is progressive deterioration of anterior pituitary function which necessitates replacement therapy at a mean of 18 years of age. Secondary adrenal insufficiency has also been noted in up to 60% of patients with the Prader-Willi syndrome.

**Isolated ACTH Deficiency**: This is a rare pituitary deficiency of ACTH secretion unaccompanied by deficiency of secretion of any other pituitary hormones. It is usually an acquired disorder with a mean age of onset of 50 (range 24-79). Men comprised 54% of cases in one series. The disorder may have many causes, but it is felt that an autoimmune process causes most cases. In many instances it appears to be a sequel to lymphocytic hypophysitis, which is an autoimmune attack on the pituitary gland usually seen in the peripartum period. Lymphocytic hypophysitis presents as a pituitary mass mimicking a neoplasm. It is rarely seen as part of the Autoimmune Polyglandular Syndrome. Anterior pituitary function may completely recover, or the patient may be left with an isolated ACTH deficiency. It is not known if the isolated ACTH deficiency seen in men is also autoimmune.

Other possible etiologies of isolated ACTH deficiency include congenital defects, birth trauma, and partial pituitary infarction associated with pregnancy.

A reversible increase in TSH, prolactin and LH secretion and a decrease in growth hormone secretion have been described in isolated ACTH deficiency. These abnormalities normalize with glucocorticoid treatment. A reversible decrease in plasma renin activity and aldosterone secretion has also been described in patients with isolated ACTH deficiency. These patients may have hypotension and hyponatremia, but hyperkalemia is rare. Isolated CRH deficiency has also been described, and it is felt that testing with CRH may be discriminate between the two. A “Triple H Syndrome” has been described in two patients, in which isolated ACTH deficiency was accompanied by impairment of anterograde memory and alopecia areata.

**C RITICAL ILLNESS**: There are no studies that would allow us to say with certainty what a “normal” adrenal response to critical illness should be. Cortisol levels may be high in critically ill patients, but what is “high enough?” Patients who are critically ill may have adrenal insufficiency from pre-existing disease of the hypothalamic-pituitary-adrenal axis, head injury, CNS depressants, pituitary infarction, the anesthetic “etomidate,” ketoconazole, adrenal hemorrhage, and previous use of exogenous glucocorticoids, medroxyprogesterone, or megestrol acetate.

There is evidence in the literature that some critically ill patients may develop a transient, relative adrenal insufficiency as a part of their illness. This is now being referred to as
“critical illness-related corticosteroid insufficiency.” In patients with sepsis, it has been suggested that this relative adrenal insufficiency is due at least in part to inhibition of adrenal cortisol synthesis by inflammatory cytokines. One might be able to diagnose such a state with a cosyntropin stimulation test. You might think that the adrenal glands would already be working maximally in a critically ill patient and wouldn’t ordinarily respond to an injection of even more ACTH. However, this doesn’t seem to be the case. Widmer et.al. have shown that under stressful conditions the ability of the adrenal glands to secrete cortisol in response to acute ACTH stimulation is actually upgraded. Arafah et.al. have reported similar findings. The limiting factor that determines the amount of cortisol secreted during severe stress seems to be pituitary ACTH secretion, not the biosynthetic potential of the adrenal glands. If the adrenal glands are not able to secrete more cortisol in response to an acute IV injection of ACTH, this may indicate that their activity is being inhibited by external influences – such as inflammatory cytokines.

On the other hand, it has also been suggested that inflammatory cytokines in septic patients may cause relative adrenal insufficiency by inducing a state of tissue resistance to circulating cortisol. Such a state would have to be diagnosed clinically, since measurements of circulating cortisol or the cortisol response to ACTH stimulation wouldn’t necessarily reflect the unresponsiveness of the tissues. To complete the picture, it is certainly possible that inflammatory cytokines could cause a transient, relative adrenal insufficiency by decreasing pituitary ACTH secretion.

Studies in the 1990’s suggested that critically ill patients with a poor response to corticotropin were more likely to die, and that the pressor response to norepinephrine is improved with hydrocortisone. These studies led to further investigation of the role of hydrocortisone in critical illness. Encouraging results in small trials led to a larger trial by Annane et.al. in 2002. This study reported that hydrocortisone (plus fludrocortisone) therapy in patients with a poor response to IV ACTH allowed discontinuation of pressors within 28 days in 57% of treated patients vs. 40% in the placebo group. Mortality was 53% in treated patients and 63% in the placebo group. As a result of these studies (primarily the Annane study), guidelines began to recommend the widespread use of hydrocortisone in patients with septic shock. However, problems with the Annane study (the finding of an unexpectedly large number of corticotropin non-responders, the higher mortality rate in corticotropin responders, questions about the need for the fludrocortisone used in the study, and the use of etomidate in 24% of the study patients) prompted the initiation of the CORTICUS study. This study, published in 2008, reported that shock was reversed more rapidly in patients receiving hydrocortisone, but there was no difference in the rate of death at 28 days between those who did and did not receive hydrocortisone. The presence or absence of a response to corticotropin did not affect the outcome. Of some concern was the fact that there was an increased incidence of superinfection in the corticosteroid-treated patients (odds ratio 1.37). The incidence of hyperglycemia and hypernatremia was also increased in the corticosteroid group. This study has been criticized for being underpowered to detect a clinically important treatment effect, for the continued inclusion of patients who had received etomidate, and for selection bias.

In 2008, recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill patients were published by the American College of Critical Care Medicine. Their recommendations were:

- At this time, adrenal insufficiency in critical illness is best diagnosed by a delta cortisol (after 250 μg cosyntropin) of < 9 μg/dL, or a random total cortisol of < 10 μg/dL.
• The ACTH stimulation test should not be used to identify those patients with septic shock or ARDS who should receive glucocorticoid. The task force refers to six randomized, placebo-controlled studies of hydrocortisone treatment in septic shock and recent randomized controlled trials in patients with early ARDS, and concludes that “In those patients (severe sepsis, septic shock, and ARDS) most likely to benefit from treatment with moderate-dose glucocorticoids, it is not clear that treatment should be based on the results of adrenal function testing...in patients with septic shock and early ARDS, the decision to treat with moderate-dose corticosteroids should be based on clinical criteria and not on the results of adrenal function testing.”

• Hydrocortisone should be considered in the management strategy of patients with septic shock, particularly those patients who have responded poorly to fluid resuscitation and vasopressor agents. IV hydrocortisone should be given in a dose of 200 mg/day in four divided doses or as a bolus of 100 mg followed by a continuous infusion at 10 mg/hr (240 mg/day). Significantly more rapid resolution of shock has been demonstrated when hydrocortisone is given, though the effect on mortality seems less clear.

• The optimal duration of glucocorticoid treatment in patients with septic shock and early ARDS is unclear. However, based on published studies and pathophysiological data, patients with septic shock should be treated for ≥7 days before tapering, assuming there is no recurrence of signs of sepsis or shock.

Note that a continuous infusion of 200 mg/day of hydrocortisone yields serum cortisol levels of around 70-100 mcg/dL.

If it seems unreasonable to treat every septic shock patient with hydrocortisone, you might follow the advice of Marik and Zaloga from their study published in Critical Care Medicine in 2003. They took 59 patients with septic shock and performed cosyntropin testing on all of them. Then they put all of them on hydrocortisone 100 mg q8h for 24 hours. “Responders” were patients who were able to stop pressors within 24 hours of starting hydrocortisone. They found that the one test that best differentiated responders from non-responders was a baseline serum cortisol less than 23.7 mcg/dL. They recommended that a diagnosis of adrenal insufficiency should be made in a highly stressed patient when a random serum cortisol was less than 25 mcg/dL. Also, in 2008, Raff et.al. demonstrated that an ACTH-stimulated salivary cortisol measurement could help avoid the unnecessary use of glucocorticoid therapy in hospitalized patients (Endocrine 2008).

DRUGS: Drugs such as phenytoin, barbiturates, and rifampicin can provoke adrenal insufficiency in patients with limited pituitary or adrenal reserve, and in those with adrenal insufficiency receiving replacement glucocorticoids. These drugs accelerate the metabolism of cortisol and most synthetic steroids by inducing hepatic mixed function oxidases. Megestrel acetate has an affinity for the glucocorticoid receptor and can cause suppression of the hypothalamic-pituitary-adrenal axis. Antifungal therapies (e.g. ketoconazole and, in high doses, itraconazole and fluconazole) interfere with glucocorticoid synthesis and predispose patients to adrenal insufficiency during states of increased glucocorticoid requirement. Etomidate, a commonly used potent hypnotic agent that is used prior to intubation, can also lower cortisol levels. Some novel tyrosine kinase-targeting drugs (e.g. sunitinib) have been shown to cause adrenal dysfunction and hemorrhage in animals.
Diagnosis:

*Random Serum Cortisol:* Random cortisol levels are of little help in the diagnosis since they are commonly within “normal limits” in patients with adrenal insufficiency. The one instance in which a random cortisol level may be helpful is in a critically ill, stressed individual. A random cortisol level >25 mcg/dL makes adrenal insufficiency highly unlikely. A cortisol level less than 25 mcg/dL in a critically ill patient raises the question of an inappropriate adrenal response to stress, but there are reports in the literature of critically ill patients with cortisol levels lower than this who were not felt to have adrenal insufficiency. Schein et.al. found cortisol levels as low as 15.6 mcg/dL in patients with septic shock and no evidence of adrenal insufficiency (though 94% of their patients with septic shock did have cortisol levels > 19.9 mcg/dL). Devin et.al. have stated that cortisol levels < 15 mcg/dL should be considered suggestive of adrenal insufficiency. One problem with cortisol levels in critically ill patients, as mentioned above, is that they often have low levels of circulating plasma proteins. Cortisol is 90-97% protein bound in plasma. Most of this is bound to CBG (cortisol binding globulin), and the rest is bound to albumin. Serum free cortisol levels are available commercially, and the normal response to cosyntropin has been determined. However, the level of free serum cortisol that rules out adrenal insufficiency in a critically ill person has not been determined, and the levels often take several days to come back.

If it is only primary adrenal insufficiency that is suspected (e.g. in patients with unexplained hyperkalemia), a diagnosis can be made by sending a simultaneous serum cortisol and plasma ACTH. In primary adrenal insufficiency the ACTH is invariably > 100 pg/mL even when the cortisol is within “normal limits.” A normal plasma ACTH rules out primary adrenal insufficiency but not, of course, secondary or tertiary adrenal insufficiency. Renin will be high and aldosterone will be low in primary adrenal insufficiency.

Decaux et.al. have suggested that the plasma bicarbonate may help distinguish secondary adrenal insufficiency from SIADH in hyponatremic patients. They reported a plasma bicarbonate lower than 22 nmol/liter in 9 of 13 patients who were hyponatremic due to ACTH deficiency, and in none of 30 patients with hyponatremia due to SIADH that was not related to adrenal function.

Characteristically serum DHEAS levels will be low in adrenal insufficiency, but this only has diagnostic value in patients younger than 40 years of age, due to the age-associated decline in adrenal DHEAS secretion.

*Rapid ACTH (Cosyntropin) Stimulation Test:* The test most often used to make a diagnosis of adrenal insufficiency is the cosyntropin stimulation test. Cosyntropin is synthetic ACTH (actually the first 24 amino acids of the 39 amino acid molecule). IV injection of one vial (250 µg) leads to enormous levels of ACTH in the blood (on the order of 10,000 pg/mL) and serves as a maximal stimulus to the adrenal glands. Ideally the test is performed before 10 am. Though other criteria have been used in the past, current thinking is that a 30 or 60 minute cortisol of > 18-20 mcg/dL is normal (both cutoffs have been suggested in the literature; use of the higher cutoff may be preferable, since this minimizes false negatives.) The increment is no longer considered important (except possibly in critical illness – see the discussion above). Caution should be used in interpreting the test in patients who might have high cortisol binding globulin (CBG) levels, (e.g. pregnant women), or in patients who might have low CBG levels
A subnormal response establishes a diagnosis of adrenal insufficiency, and correlates well with the results of metyrapone and insulin tolerance testing. A normal test rules out primary adrenal insufficiency, but not partial secondary or tertiary adrenal insufficiency. This is because it is possible for a diseased pituitary to secrete enough ACTH to maintain its trophic effect on the adrenal glands without being able to mount an adequate response to stress. Dorin et al. have reported that, at a specificity of 95%, the rapid ACTH test has a sensitivity of 97% for primary adrenal insufficiency and 57% for secondary adrenal insufficiency. Thus, if secondary or tertiary adrenal insufficiency is suspected, a normal cosyntropin stimulation test should be followed by a metyrapone test or an insulin tolerance test. I have one reference saying that the high dose test is considered a reliable indicator of hypothalamic-pituitary-adrenal axis function within 12 days after pituitary surgery. Another reference says that the diagnostic value of the cosyntropin test is only compromised within the first 4 weeks after a pituitary insult.

In 1991, Dickstein et al. reported that the cosyntropin stimulation test was significantly more sensitive when only 1 μg of cosyntropin was used. Since then, many – but not all – studies have suggested that the 1 μg test is superior. Tordjman et al. (Jcem 1995) reported a striking difference in 10 patients with documented central adrenal insufficiency. All 10 had correctly abnormal 1 μg tests, but only 1 of the 10 patients had a correctly abnormal 250 μg test.

However, not all of the studies have reported such a large difference between the two tests. Abdu et al. (Jcem 1999) studied 64 patients with pituitary disease and found that 2 of the 64 patients (3%) had a falsely normal 250 μg test (using the insulin tolerance test as the gold standard). None of the 64 patients had a falsely normal 1 μg test. There were 7 false positive tests using the 1 μg dose. Mayenknecht et al. (Jcem 1998) found no significant difference in sensitivity between the two tests in 44 patients with pituitary dysfunction. Weintrob et al. (Jcem 1998) found no significant difference in sensitivity between the low and high dose tests in 30 children with idiopathic multiple pituitary hormone deficiencies (MPHD). Rasmuson et al. (Clin Endo (Oxf) 1996) found that the correlation coefficient between the 1 μg test and the insulin tolerance test was 0.93. The correlation coefficient between the 250 μg test and the insulin tolerance test was significantly lower, but was still 0.89. Dorin et al. (Ann Int Med 2003) published a meta-analysis in which area under the curve methods were used to compare receiver operating characteristic curves generated from sensitivity and specificity data for the 1 μg and 250 μg tests. At a specificity of 95% the sensitivity of the 250 μg test for secondary adrenal insufficiency was 57% and the sensitivity of the 1 μg test was 61%. The area under the curve did not differ significantly between the two tests. Suliman et al. (Clin Endo (Oxf) 2002) compared the standard dose and low dose test in 51 patients who were being evaluated for possible secondary adrenal insufficiency. At a cortisol cutoff of 18.1 μg/dL the standard test had a sensitivity of 67% and a specificity of 100%. The 1-μg test had a sensitivity of 73% and a specificity of 81%. They concluded that the specificity of the standard-dose ACTH test was higher than the specificity of the low-dose ACTH test at any given level of sensitivity. Nasrallah and Arafah (Jcem 2003) reported normal 1 μg tests in 10 of 31 patients with adrenal insufficiency diagnosed by the insulin tolerance test. On the other hand, Magnotti and Shimshi (Endocr Prac 2008) reviewed the literature and concluded that, in nonstressed patients with possible secondary adrenal insufficiency, the low dose test with a cutoff of 18-20 mcg/dL has the greatest sensitivity. Kaslauskaitė et al. performed a metaanalysis in 2008 using receiver operator curves, which showed that the area under the curve for the low dose test was significantly better than for the standard test. The AUC was 0.92 for the low dose test vs 0.79 for the standard test. In paired data the AUC was 0.94 for the low dose test and 0.85 for the standard test. In the
unadjusted analysis the low dose and standard tests performed similarly, but when the analysis was adjusted for study size and the type of cortisol assay, the superiority of the low dose test became more dramatic.

In 2010 Fleseriu et.al. reported a retrospective study of 26 patients who were suspected of pituitary dysfunction and had undergone both high and low dose testing. 23 patients had a normal high dose test and an abnormal low dose test. Hydrocortisone therapy was either stopped or not started in all of these patients. After follow up of 19 to 24 months, no episodes of adrenal insufficiency were reported. Failure of the low dose test did not correlate with the presence of symptoms of adrenal insufficiency, the presence or size of a pituitary tumor, or history of pituitary surgery. The authors concluded that the low dose test can be misleading and should not be used in isolation to determine the need for long-term glucocorticoid therapy.

Thus the 1 μg test seems to be more sensitive for the diagnosis of central adrenal insufficiency than the standard 250 μg test, but its superiority is still a matter of controversy and it is not clear that the difference between the two tests is very large. There doesn’t seem to be any benefit to the low dose test in diagnosing primary adrenal insufficiency.

Cosyntropin usually comes in 250 mcg vials. The 1 mcg dose can be prepared by removing 1 cc of normal saline from a 250 ml bag, injecting it into the 250 mcg vial of cosyntropin, and injecting the resulting mixture back into the 250 ml bag.

It has recently been demonstrated that measuring salivary cortisol can be useful during a low dose cosyntropin test in patients with secondary adrenal insufficiency and in hyperestrogenemic women (Marcus-Perlman et.al., Clin Endo (Oxf) 2006). A low dose IM cosyntropin test with salivary cortisol assessment has also been proposed by Contreras et.al. (Clin Endo (Oxf) 2004).

**Insulin Tolerance Test:** This is the gold standard for diagnosing adrenal insufficiency, though occasional false negatives have been reported. After an overnight fast, 0.15 units/kg of regular insulin are injected IV and glucose and cortisol levels are measured at 0, 15, 30, 45, 60, 75, and 90 minutes. Glucose levels must drop to < 40 mg/dL for the test to be valid. A normal response is a peak serum cortisol > 18-20 mcg/dL (both cutoffs have been suggested in the literature. Again, use of the higher cutoff may be preferable because it minimizes false negatives.) The test is contraindicated in the elderly, those with acute illness, and those with a history of coronary artery disease, cerebrovascular disease, or seizures. Concomitant measurement of ACTH levels increases the sensitivity of the test.

**CRH Test:** This test is less well studied than the metyrapone and insulin tolerance tests, but has the advantage of being able to distinguish secondary from tertiary adrenal insufficiency. Ovine or human CRH is given at a dose of either 1 mcg/kg or 100 mcg IV. ACTH and cortisol levels are measured every 15 minutes for 2 hours. ACTH levels usually peak at 15-30 minutes, and cortisol levels at 30-45 minutes. The test has not been well-standardized and stimulated ACTH and cortisol levels vary substantially from person to person. Schmidt et.al. studied the use of human CRH to detect adrenal insufficiency, and concluded that the test could not be recommended because of a sensitivity of only 76% at a specificity of 96%.

**Distinguishing Primary From Secondary/Tertiary Adrenal Insufficiency:** If the cosyntropin or Insulin Tolerance Test is abnormal, a plasma ACTH level should be sent. In order for the test to be accurate, the specimen must be handled properly. ACTH adheres to glass,
is unstable in plasma, and deteriorates at room temperature. The specimen should be collected in EDTA or heparin, in a plastic or siliconized tube, centrifuged in the cold within one hour, and frozen until the test is performed. Patients with untreated primary adrenal insufficiency will have ACTH levels >200 pg/mL, usually 400-2000 pg/mL. In secondary or tertiary adrenal insufficiency, the ACTH level will be inappropriately "normal" or low, usually < 10-20 pg/mL. Primary adrenal insufficiency may also be distinguished from secondary or tertiary adrenal insufficiency by measuring the aldosterone response to IV cosyntropin, but experience with this test is less extensive. Normally the peak aldosterone level 30 minutes after IV cosyntropin should be >16 mcg/dL. It has been suggested that the CRH test can be used to distinguish secondary from tertiary adrenal insufficiency, but this distinction is seldom clinically useful.

Further Investigation of the Differential Diagnosis of Primary Adrenal Insufficiency: Once the diagnosis of primary adrenal insufficiency has been made, further testing is necessary to determine the cause. If the patient has manifestations of other autoimmune endocrine deficiencies (hyper- or hypothyroidism, vitiligo, premature ovarian failure) or a family history of such deficiencies, the diagnosis of autoimmune adrenal insufficiency is likely. Screening can be performed using the serum calcium, glucose, free T4, TSH, and anti-thyroid antibodies (and LH and FSH if amenorrhea is present). The gold standard for diagnosing autoimmune adrenal insufficiency is the simultaneous presence of adrenal cortex autoantibody and 21-hydroxylase autoantibody. If only one of these two adrenal autoantibodies is present, then it cannot be assumed that some form of non-autoimmune adrenal insufficiency has been ruled out. If no other endocrine deficiencies are detected and the anti-adrenal antibodies are negative, a CT of the adrenals should be performed. Absent or atrophic adrenals suggest autoimmune disease, but may also be seen months or years after hemorrhage or infection. Also, the possibility of suppression of the axis by exogenous glucocorticoids should be kept in mind – especially inhalers, creams, and intraarticular injections. A clinical history of lung, bone, pelvic-peritoneal, or genitourinary tuberculosis plus adrenal enlargement or calcification makes a diagnosis of tuberculous adrenalitis extremely likely. Bilateral enlargement of the adrenals and/or the presence of adrenal calcium deposits are also consistent with hemorrhage (which can usually be diagnosed non-invasively with current CT and MRI techniques), infection, invasive disease (e.g. lymphoma, sarcoidosis, hemochromatosis, amyloidosis), or metastases. If hemorrhage is ruled out non-invasively, CT-guided needle aspiration should be done for cultures and cytology. Chest x-ray, urine for AFB, PPD, and complement fixation titers for Histoplasmosis can also be done. Serum levels of Very Long Chain Fatty Acids should be measured in young men and boys with idiopathic primary adrenal insufficiency.

Perry et.al. have published an algorithm for the workup of primary adrenal insufficiency in children. In their series, a definite diagnosis could be made in 94.2% of patients. 71.8% had congenital adrenal hyperplasia (51.5% salt-wasting, 5.8% simple virilizing, 12.6% non-classical, and 1.9% due to a 3 beta-hydroxysteroid dehydrogenase deficiency). 12.8% of their children had autoimmune adrenal insufficiency, of which 4.9% had type 1 Autoimmune Polyglandular Syndrome and 7.8% had other forms of autoimmune primary adrenal insufficiency. 3.9% of their patients had adrenoleukodystrophy, but 25% of their non-CAH boys had X-linked Adrenoleukodystrophy. 2.9% of their patients had Wolman’s Syndrome, 1% Triple A Syndrome, 1% Zellweger Syndrome, and 1% X-linked Adrenal Hypoplasia Congenita. 2.9% had unexplained isolated glucocorticoid deficiency and 2.9% had unexplained
glucocorticoid and mineralocorticoid deficiencies.

Their diagnostic algorithm for children begins with checking the 17-hydroxyprogesterone to rule out congenital adrenal hyperplasia. In the right clinical circumstances, screening for 3 beta-hydroxysteroid dehydrogenase deficiency may be indicated. Genetic analysis for mutations in the CYP21 gene is available, but the usual clinical practice is to make this diagnosis biochemically. Mutation analysis is usually reserved for prenatal diagnosis and detection of carriers. If the workup for Congenital Adrenal Hyperplasia is negative they recommend measuring levels of very long chain fatty acids. Genetic testing for Adrenoleukodystrophy is usually not necessary because the finding of elevated very long chain fatty acids is accurate in 99.9% of affected males. However, genetic testing for mutations in the ABCD1 (ALD) gene is indicated for prenatal diagnosis and detection of carriers, since 15% of obligate female carriers will have normal levels of very long chain fatty acids. If CAH and Adrenoleukodystrophy are ruled out they recommend testing for adrenal autoantibodies (this is typically performed by indirect immunofluorescence using monkey adrenal tissue; they remark that the specificity of the diagnosis is improved with the identification of autoantibodies to specific target antigens such as 21-hydroxylase, 17-hydroxylase, side chain cleavage enzyme, and aromatic L- amino acid decarboxylase; however, I have determined that only the autoantibodies against 21-hydroxylase are routinely available in this country). Positive autoantibodies with no other distinguishing features suggest isolated autoimmune primary adrenal insufficiency. The additional presence of autoimmune thyroiditis and type 1 diabetes mellitus suggests Autoimmune Polyglandular Syndrome Type 2 (no genetic testing available). The presence of hypoparathyroidism or mucocutaneous Candidiasis suggests the APECED or Autoimmune Polyglandular Syndrome Type 2 Syndrome. Genetic testing for mutations in the AIRE gene is commercially available, but it costs $995. Other tests are ordered based on the presence of other associated clinical features (note: I am deeply indebted to Dr. Carol Crowe of the MetroHealth Medical Center Department of Genetics for helping me sort out which of these genetic analyses is and is not currently commercially available in this country):

1. Hepatosplenomegaly and adrenal calcifications suggest Wolman Disease (levels of lysosomal acid lipase are measured in peripheral blood leukocytes or cultured skin fibroblasts).

2. Hypogonadism and a family history of affected males suggest X-linked Adrenal Hypoplasia Congenita (FISH – Fluorescence In Situ Hybridization - is used to detect deletions and mutations in the NROB1/DAX1 gene).

3. Achalasia and/or alacrima suggest Triple A Syndrome (genetic testing not currently commercially available).

4. Intrauterine Growth Retardation, genital anomalies, and metaphysical dysplasia suggest IMAGe Syndrome (genetic testing not available).

5. Isolated glucocorticoid deficiency suggests Familial Glucocorticoid Deficiency (testing for mutations in the MC2R or MRAP gene not yet commercially available).

In addition, the finding of unexplained glucocorticoid and mineralocorticoid deficiency mandates re-evaluation at a later stage, particularly with a repeat of the adrenal autoantibodies and another look for associated features typical of the various inherited syndromes.
Further Investigation of the Differential Diagnosis of Secondary or Tertiary Adrenal Insufficiency: Patients who have been diagnosed with secondary or tertiary adrenal insufficiency should undergo dynamic testing for other pituitary hormone deficiencies. MRI should be used to look for a pituitary or hypothalamic tumor. A VDRL, PPD, CXR, and workup for hemochromatosis (Fe/TIBC, ferritin) may be helpful.

**Treatment:**

**Adrenal Crisis:** Treatment of adrenal crisis should not be delayed until tests return if the pre-test index of suspicion is strong. Treatment begins with large volumes of 5% dextrose in normal saline (initially 1 liter per hour) and dexamethasone or hydrocortisone IV (use of dexamethasone will allow you to perform a cosyntropin test while simultaneously treating the patient). In the past it has been written that the starting dose should be dexamethasone 4 mg IV q12-24 hours or hydrocortisone 100 mg IV followed either by 100-200 mg/day in D5W as a continuous IV infusion or 25-50 mg IV q6h, which should continue for the first 24 hours. More recently it has been written that it is unlikely that doses more than 25 mg IV q6h are necessary except when septic shock is suspected, in which case the dose should be 50 mg q6h. If progress is satisfactory, the dose may then be tapered down to an oral maintenance dose over 1-3 days. Intramuscular cortisone acetate should be avoided because of its poor absorption. If there are complications and the patient remains under stress, hydrocortisone should continue at a total daily dose of 100-200 mg/day. No mineralocorticoid is needed initially, because adequate sodium replacement can be achieved with IV normal saline, and because hydrocortisone in high doses has a mineralocorticoid effect of its own. In primary adrenal insufficiency, fludrocortisone can be started when the saline has been stopped and the patient is taking po food and fluids. (Generally, fludrocortisone is not needed until the total daily dose of hydrocortisone drops below about 50 mg/day.) General supportive measures (e.g. correction of hypovolemia and hyperkalemia) should be provided as indicated. It is critical that a search be made for the illness that precipitated the crisis (which might, for example, be a bacterial infection or a myocardial infarction).

**Chronic Adrenal Insufficiency:** The typical treatment regimen calls for hydrocortisone 5-10 mg/m²/day, which is usually about 15-25 mg/day, given as 2/3 in the morning and 1/3 in the early afternoon – e.g. 15 mg in the morning upon awakening and 5 mg about 6 hours later. After ingestion, hydrocortisone peaks rapidly and quite variably in the supraphysiologic range, and then declines rapidly to less than 3.6 mcg/dL after 5-7 hours. Thus, some experts prefer to give 10 mg in the morning and then 5 mg about 4 and 8 hours later. Prednisone and prednisolone have a longer half-life than hydrocortisone and might allow for better control in insulin-dependent diabetics by avoiding the peaks and troughs of hydrocortisone pharmacokinetics. 1 mg of hydrocortisone is considered equivalent to about 0.25 mg of prednisone and 0.2 mg of prednisolone. If prednisone is used the dose should be 2-3 mg at 7-8 AM and 1-2 mg at 2-3 PM.

The glucocorticoid may need to be a bit larger for large individuals, those who metabolize cortisol quickly (especially those taking drugs that speed up cortisol metabolism, such as phenytoin, carbamazepine, oxcarbazepine, topiramate, barbiturates, rifampin, Mitotane, and aminoglutethimide), hyperthyroid patients, and those engaged in heavy manual labor.
Patients taking drugs known to increase cortisol metabolism require a 2-3-fold increase in glucocorticoid dose. The hydrocortisone dose may need to be a little smaller in small individuals and those who metabolize cortisol more slowly (e.g. patients on anti-retrovirals). Once treatment is begun, many subjective complaints resolve within a few days, but it will take longer for strength to return completely to normal. The hyperpigmentation will take weeks to subside.

Measurement of serum cortisol, plasma ACTH, and urinary free cortisol are not reliable ways to determine the appropriateness of the replacement dose. The adequacy of the dose is determined by monitoring for symptoms and signs of underreplacement and overreplacement. Indicators of underreplacement would be weight loss, fatigue, nausea, myalgias, and lack of energy. Indicators of overreplacement would be weight gain, central obesity, striae, osteoporosis, impaired glucose tolerance, and hypertension. In general, it is best to use the smallest dose of glucocorticoid that relieves symptoms of adrenal insufficiency. Osteoporosis has only been reported in patients taking ≥ 30 mg/day of hydrocortisone or ≥ 7.5 mg/day of prednisone. Therefore routine bone density monitoring is not needed in patients on recommended glucocorticoid replacement doses.

Patients with Addison’s disease who also have moderately elevated levels of thyroid autoantibodies and TSH elevations that are less than 10 μU/mL may normalize their TSH levels when glucocorticoid therapy is begun.

Most patients with primary adrenal insufficiency will need mineralocorticoid replacement as well as glucocorticoid replacement, though some do well without it. This is accomplished by the addition of fludrocortisone at a dose of 0.025-2.0 mg/day. Children (in particular neonates and infants) have considerably higher mineralocorticoid requirements than adults and often need additional salt supplementation. Salt intake should be liberal, especially when exercising. Some patients may need to double the dose of fludrocortisone in the summertime (especially if routinely exposed to temperatures > 85 degrees), when perspiration causes excess salt loss. The dose may need to be increased in patients taking phenytoin, Phenobarbital, and carbamazepine. Monitoring for the appropriateness of the dosage should include checking the lying and sitting blood pressure and pulse, watching for development of pedal edema, and checking serum sodium, potassium, and plasma renin activity. Symptoms of postural dizziness should be elicited.

Patients should be given a syringe of hydrocortisone (100 mg Solu-Cortef for injection), to keep at home in case of emergencies (perhaps for the car, work and pocket or purse as well). They should wear a bracelet or necklace identifying them as having adrenal insufficiency. They should be warned to double or triple their replacement dose for a few days when they are ill (e.g. double the dose for 2 days or so during a common cold, triple the dose for more moderate stressful events). Hydrocortisone suppositories are also available. Patients with autoimmune adrenal insufficiency should be screened annually for associated autoimmune disorders with vitamin B-12 levels, fasting glucose, and TSH. In women the regularity of menses should be noted (looking for evidence of premature ovarian failure) and consideration should be given to checking for ovarian autoantibodies if future fertility is an issue.

It has been suggested that women with adrenal insufficiency might benefit from oral replacement of DHEA in doses of 25-50 mg/day. However, study results have been conflicting. Arlt (N Engl J Med 1999), Hunt (J Clin Endo Metab 2000), and Johannsen (J Clin Endo Metab 2002) have documented beneficial effects on quality of life from DHEA supplementation. However, Lovas (J Clin Endo Metab 2003), Van Theil (J Clin Endo Metab 2005), and Dhatariya (Mayo Clin Proc 2008) found no clinically significant effect. In 2008,
Gurnell et al. reported that DHEA supplementation in Addison’s disease reversed ongoing loss of bone mineral density at the femoral neck (but not at other sites), enhanced lean body mass (with no change in fat mass), and improvement in one subscale of the General Health Questionnaire-30, but no significant effect of treatment on fatigue or cognitive or sexual function. In a 2009 meta-analysis, Alkatib et al. reported that DHEA had a small and perhaps clinically trivial effect on Health-Related Quality of Life as well as a small beneficial effect on depression. Effects on anxiety and sexual well-being were not statistically significant. They concluded that the evidence was insufficient to support the routine use of DHEA in women with adrenal insufficiency at this time. It should not be used in patients with a history of breast cancer. The benefits are much less impressive in men than in women. In general it is recommended that DHEA at a dose of 25-50 mg/day be given to women with significantly impaired mood and well-being despite adequate glucocorticoid and mineralocorticoid replacement. The dose should be regulated based on age and sex-adjusted DHEA levels 24 hours after the last dose, aiming for the middle of the normal range. If there has been no obvious benefit after 6 months DHEA should be discontinued. It should be noted that DHEA therapy in the United States is rendered extremely problematic by the lack of product quality control, since DHEA is considered a dietary supplement and is not subject to FDA oversight.

Research indicates that current replacement strategies do not restore patients to a completely normal quality of life. The most common complaints are of fatigue, lack of energy, depression, anxiety, and reduced ability to cope with daily demands. In addition, studies have demonstrated an increased mortality in patients with adrenal insufficiency regardless of the manner of glucocorticoid replacement. There are ongoing attempts to develop forms of glucocorticoid that will allow us to mimic normal physiologic cortisol dynamics more closely.

**Surgery:** It is common practice to give stress doses of glucocorticoids to any surgical candidate who has received supraphysiologic doses of glucocorticoids within the past year. Alternatively, a cosyntropin stimulation test can be done, with coverage given to those with abnormal results. (Significant adrenal suppression is rarely seen from doses of hydrocortisone of <15 mg/m^2^ per day or its equivalent.)

No extra replacement is needed for minor procedures under local anesthesia, including dental work, and for most radiologic procedures. Moderately stressful diagnostic procedures such as endoscopy, barium enema and arteriography can be treated simply with by tripling the usual daily dose. For major surgery (e.g. open heart surgery, IV hydrocortisone 25 mg q6h should be more than sufficient unless one is treating a severe inflammatory process such as septic shock (in which case 50 mg q6h is necessary). If there are no complications, the dose may be decreased by 1/2 each day until you get to the maintenance dose. Cortisone acetate should not be given IM because of poor absorption.

Patients undergoing trans-sphenoidal surgery for non-ACTH-secreting pituitary tumors should have a preoperative rapid cosyntropin test, and should be covered with glucocorticoid if the test is abnormal. According to Inder and Hunt, early postoperative assessment depends on daily clinical assessment and daily 0800 plasma cortisol levels. Levels over 16 μg/dL suggest normal function, and levels < 3.6 μg/dL suggest ACTH deficiency. Patients with levels between 3.6 and 9 may be deficient, and should receive hydrocortisone
replacement until definitive testing is done. This can be as early as 7-10 days postoperatively, but is more conveniently done after 4-6 weeks. Patients with postoperative levels of 9-16 are unlikely to be ACTH deficient, but should be supplemented with glucocorticoid in times of stress until definitive testing. In a recent Meet The Professor syllabus (ENDO 2009), Dr. David M. Cook recommended that patients with large, non-functioning pituitary tumors be replaced with 10 mg of hydrocortisone every morning (more if symptomatic) until 6 weeks after surgery when a cosyntropin stimulation test (preferably with 1 mcg of cosyntropin) can be done. This test will determine if the patient will be persistently in need of hydrocortisone replacement.

Pregnancy: In pregnancy there is a gradual rise in CBG levels, but the dose of hydrocortisone usually does not need to be changed in the first and second trimesters. However, there is normally an increase in free cortisol during the last trimester that requires a 30-50% increase in the hydrocortisone dose. Plasma renin physiologically increases in pregnancy, so the orthostatic changes in pulse and blood pressure, electrolytes, and sometimes urinary sodium excretion will need to be monitored more closely than usual. Progesterone exerts an anti-mineralocorticoid effect, and fludrocortisone doses may need to be adjusted during the last trimester. During delivery patients should receive 100-150 mg of hydrocortisone per 24 hours. After delivery the patient may be tapered to a maintenance dose over 3 days.

HYPOALDOSTERONISM

Hyporeninemic Hypoaldosteronism:

Clinical Manifestations: The most common form of isolated hypoaldosteronism is associated with low plasma renin activity. Cortisol secretion is normal. The plasma renin activity and aldosterone levels do not increase normally in response to postural changes and sodium restriction. The low plasma renin activity appears to be the cause of the low aldosterone secretion, since angiotensin II and ACTH stimulate normal increases in plasma aldosterone. (An occasional patient has subnormal aldosterone responses to these stimuli, raising the possibility of a primary adrenal defect in addition to the abnormally low renin secretion.)

Hyporeninemic hypoaldosteronism presents with unexplained, chronic, mild-moderate hyperkalemia (usually about 5.5-6.5 mEq/L). A mild metabolic acidosis (= Type IV Renal Tubular Acidosis) is seen in less than 70% of cases, and mild-moderate renal insufficiency (creatinine clearance > 15 ml/min) is present in about 80%. A small number of patients will present with muscle weakness or cardiac arrhythmias due to hyperkalemia. The acidosis is due to the hyperkalemia as well as decreased renal hydrogen secretion. Mild-to-moderate hyponatremia is present in half the patients. Most are not dehydrated. In fact, increased extracellular fluid volume and hypertension are common - perhaps due to the renal disease, the fact that cortisol secretion is normal, and other overriding factors.

Etiology: The cause of the low renin secretion is unknown. The typical patient is 50-70 years old and has mild-to-moderate renal insufficiency (which is seen in about 80% of patients with this disorder). This has led to speculation that this may be a primary disorder of the juxtaglomerular apparatus. However, no specific anatomic lesion has ever been identified. The renal insufficiency is usually due to diabetic nephropathy (about half of all patients with this
syndrome are diabetic). It is frequent in tubulointerstitial forms of renal disease, but has been found in virtually all types of renal disease including glomerulonephritis, renal amyloidosis, and the nephropathies associated with multiple myeloma, systemic lupus erythematosus, analgesic abuse, cirrhosis, sickle cell anemia, AIDS, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes), and primary autonomic neuropathy. Transient hyporeninemic hypoaldosteronism can be caused by non-steroidal anti-inflammatory agents, cyclosporine-A, mitomycin-C, and other agents in susceptible individuals.

There are several other theories about the cause of hyporeninemic hypoaldosteronism besides disease in the juxtaglomerular apparatus. A second theory is that the low renin levels are due to volume expansion. (However, the renin and aldosterone responses to prolonged salt restriction and diuretics are usually subnormal.) A third theory is that renin secretion is low due to autonomic insufficiency, with a poor norepinephrine response to posture. (Decreased sensitivity to β-agonists has been reported, raising the possibility of a dual defect in catecholamine production and action.) A fourth theory is that the syndrome is due to secretion of an abnormal renin molecule, or a defect in conversion of pro-renin to renin. Kallikrein levels have been found to be low, and kallikrein promotes conversion of pro-renin to renin. (However, kallikrein levels normalize with mineralocorticoid therapy, suggesting that the deficiency may be a secondary phenomenon.) Another theory is that low levels of PGI2 (=prostacyclin) are responsible. Prostacyclin is a vasodilator and a renin secretagogue. This is consistent with the fact that indomethacin, a cyclo-oxygenase inhibitor, can cause a reversible hyporeninemic hypoaldosteronism. Transforming Growth Factor-β, which may be elevated in diabetes mellitus, inhibits renin release.

**Diagnosis:** The diagnosis of hyporeninemic hypoaldosteronism is made by showing that plasma renin activity and aldosterone secretion do not rise appropriately in response to upright posture and furosemide. The plasma aldosterone-to-plasma renin activity (PAC/PRA) ratio tends to be normal.

**Treatment:** The management of hyporeninemic hypoaldosteronism depends on the severity of the hyperkalemia and the age and medical status of the patient. If the hyperkalemia is mild and there are no EKG changes, the patient may simply be monitored. Dietary potassium can be restricted, and tight control of blood sugar in diabetics will help. Drugs that can aggravate hyperkalemia should be avoided including potassium-sparing diuretics, beta-blockers, cyclo-oxygenase inhibitors (e.g. indomethacin), angiotensin converting enzyme inhibitors and heparin. Oral sodium polystyrene sulfonate can help, but it increases the sodium load and may be contraindicated in patients who cannot tolerate the increased sodium. Oral sodium bicarbonate has been used, but may be hazardous in those with renal failure, congestive heart failure and hypertension due to the increased sodium load. Patients with hypertension, mild renal impairment, and congestive heart failure can respond quite favorably to therapy with diuretics. Fludrocortisone therapy is reserved for patients with severe hyperkalemia and no hypertension or congestive heart failure. The dose is 0.1-0.3 mg/day. In some patients the renal response to mineralocorticoid seems decreased, leading to the need for doses higher than usual. The fludrocortisone can be used in combination with furosemide.

**Hyperreninemic Hypoaldosteronism:** Hyperreninemic hypoaldosteronism is a condition
in which there is an isolated defect in aldosterone synthesis and secretion, with normal cortisol secretion. Plasma renin activity is appropriately elevated. Several disorders can result in hyperreninemic hypoaldosteronism.

**Critical Illness/ICU Hypoaldosteronism:** A dissociation of renin secretion from aldosterone production has been described in critically ill ICU patients – especially those who are septic or hemodynamically compromised. Aldosterone, corticosterone, and 18-hydroxycorticosterone (but not cortisol) levels become suppressed after 48-96 hours of continuous ACTH stimulation, so ACTH-mediated inhibition of 1 beta-hydroxylase and 1 beta-hydroxylase may be the cause of this syndrome. On the other hand, these patients have an increased plasma 18-hydroxycorticosterone/aldosterone ratio, and the aldosterone response to angiotensin II is decreased, so selective inhibition of aldosterone synthase may be involved. These patients are usually not hyperkalemic, and blood pressure levels are no lower in these patients than in similar patients with appropriate aldosterone levels. Aldosterone secretion may be inhibited by atrial natriuretic hormone, cytokines such as tumor necrosis factor, hypoxia, or the effect of chronic exposure to increased ACTH levels. It has also been speculated that this may be an adaptation to serious illness, with shunting of adrenal steroid production away from mineralocorticoid and androgen production toward glucocorticoid synthesis. Patients critically ill with AIDS have been reported to have low DHEA levels and a subnormal response of aldosterone to ACTH. This may simply be a specific example of the decrease in aldosterone secretion seen in other critically ill individuals.

**Pharmacologic Inhibition of Aldosterone Secretion:** Heparin administration can be associated with increased natriuresis with or without hyperkalemia in certain patients. Aldosterone synthesis is suppressed, with a compensatory increase in plasma renin activity. Sometimes the increased renin secretion fails to compensate for the impaired aldosterone synthesis, particularly in patients with an impaired renin-angiotensin-aldosterone axis (such as diabetics). Other drugs that can inhibit aldosterone synthesis in the zona glomerulosa include cyclosporine and calcium channel blockers.

**Congenital Hypoaldosteronism:** This is a rare disorder inherited in an autosomal recessive manner, caused by abnormalities in the enzyme "aldosterone synthase" which catalyzes the last 3 steps of aldosterone synthesis: 11-hydroxylation, 18-hydroxylation, and 18-oxidation. Two forms of this disorder have been described. Type I Aldosterone Synthase Deficiency generally reflects mutations causing a complete inactivation of aldosterone synthase activity, which presents as a defect in the 18-hydroxylation of corticosterone. It is extremely rare. Biochemically there is absence of aldosterone and marked overproduction of corticosterone without a corresponding increase in 18-hydroxycorticosterone. The ratio of 18-hydroxycorticosterone to aldosterone is normal.

In Type II Aldosterone Synthase Deficiency, the clinical picture suggests an inability to convert 18-hydroxycorticosterone to aldosterone. It is inherited as an autosomal recessive trait. It is rare, but is seen with increased frequency in Iranian Jews. Plasma renin is high, and aldosterone is low. Plasma 18-hydroxycorticosterone levels are markedly elevated, and the plasma 18-hydroxycorticosterone/aldosterone ratio is > 5. Also, the urinary ratio of the metabolite of 18-hydroxycorticosterone (which is 18-hydroxytetrahydroaldosterone) to the
metabolite of aldosterone (which is tetrahydroaldosterone) is > 5. In older children, adolescents, and adults, this biochemical profile may be present with no clinical manifestations.

The severity of Aldosterone Synthase Deficiency is inversely related to the age at diagnosis. It can present as a salt-wasting crisis in neonates, growth impairment in children, or as an asymptomatic abnormality in adults (there is one report in the literature of one such patient who did not come to medical attention until developing hyperkalemia after preparation for a barium enema – the patient had a past history of failure to thrive in infancy). Hyponatremia, hyperkalemia, and metabolic acidosis are present. The plasma renin activity is > 2 ng/ml/hr and the PAC/PRA ratio is <2.0. Treatment is with usual replacement doses of Florinef in infancy and early childhood, but therapy doesn’t need to be continued in most cases. Also, spontaneous normalization of growth can occur in untreated patients.

**Removal of an Aldosterone-Secreting Adenoma:** A unilateral aldosterone-secreting adenoma will suppress renin secretion, resulting in atrophy of the normal aldosterone-secreting cells. Unilateral adrenalectomy, therefore, can leave the patient with a temporary hyperreninemic hypoaldosteronism. Severe hyperkalemia and hypotension may last for several days to several weeks after surgery.

**Carcinoma Metastatic to the Adrenal Glands:** Though metastases to the adrenal glands are common, this only occasionally results in hypoaldosteronism.

**Selective Autoimmune Destruction of the Zona Glomerulosa:** Selective autoimmune destruction of the zona glomerulosa has been described. It presents with mild metabolic acidosis and occasionally hyponatremia. In the late stages it can progress to panadrenal insufficiency. Anti-adrenal antibodies may be present. Mucocutaneous Candidiasis and hypoparathyroidism may occur – a form of autoimmune polyglandular syndrome (APS). There is a report of a patient with idiopathic hemochromatosis who had an isolated mineralocorticoid deficiency.

**Isolated Mineralocorticoid Deficiency:** This is a variant of X-linked Congenital Adrenal Hypoplasia, a disease that usually causes glucocorticoid and gonadotropin deficiency as well as mineralocorticoid deficiency. It is caused by mutations in the DAX1 gene, a gene that encodes a protein which is part of a regulatory cascade required for normal gonadal, adrenal, and hypothalamic development. Patients usually have abnormal adrenal gland development characterized by lack of a permanent zone of the adrenal cortex. Apparently some mutations in DAX1 can result in atypical and mild Congenital Adrenal Hypoplasia with normal glucocorticoid and gonadotropin production.

**Pseudohypoaldosteronism:** This is a rare inherited disorder in which the renal tubules are unresponsive to mineralocorticoid. Patients present with renal salt loss, dehydration, hyperkalemia, hyponatremia, metabolic acidosis, and failure to thrive. Renin and aldosterone levels are elevated, and there is no response to exogenous mineralocorticoids. Cortisol levels are normal. Pseudohypoaldosteronism Type 1 has both a multiorgan and a renal subtype. Pseudohypoaldosteronism type 2 is less well understood.

The multiorgan form of Pseudohypoaldosteronism Type 1 is due to loss-of-
function mutations in the amiloride-sensitive epithelial sodium channels in the distal renal tubular cells. It is inherited in an autosomal recessive pattern, and is associated with salt loss from multiple organs (kidneys, sweat and salivary glands, and colonic mucosa). This condition does not improve with age.

A less severe autosomal dominant form that affects only the kidneys is caused by heterozygous inactivating mutations in the gene for the mineralocorticoid receptor. This disorder tends to improve with age, perhaps because of a higher salt intake with increasing age. Patients respond well to salt supplementation, but exogenous mineralocorticoids have no effect.

Since therapy with mineralocorticoid is ineffective, patients are treated with sodium supplementation and potassium-binding resins.

Pseudohypoaldosteronism Type 2 is a non-salt wasting disorder. Patients present with hyperkalemia and hypertension. Hyperchloremic metabolic acidosis and suppressed plasma renin activity are more variable. Inheritance is autosomal dominant. Possible causes include increased sodium reabsorption prior to the site of aldosterone action, a generalized membrane defect impairing potassium movement into cells, and increased chloride reabsorption that impairs potassium secretion. Treatment with furosemide, DDAVP, and sodium bicarbonate has been effective.

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