Defective synthesis of the steroid hormones produced by the adrenal cortex can have profound effects on human development and homeostasis. In 1855 Thomas Addison identified the significance of the "suprarenal capsules" when he reported on the case of a patient who presented with chronic adrenal insufficiency resulting from progressive lesions of the adrenal glands caused by tuberculosis. Adrenal insufficiency is, therefore, referred to as **Addison disease**. In the absence of steroid hormone replacement therapy, Addison disease can rapidly cause death in a little as 1–2 weeks.

In addition to diseases that result from the total absence of adrenocortical function, there are syndromes that result from hypersecretion of adrenocortical hormones (hypercortisolemia). In 1932 Harvey Cushing reported on several cases of adrenocortical hyperplasia that were the result of basophilic adenomas of the anterior pituitary. Hypercortisolemias that manifest due to adrenocortical hyperplasia are referred to as Cushing syndrome, whereas, hypercortisolemias due to excessive anterior pituitary secretion of ACTH are referred to as Cushing disease.

Despite the characterizations of adrenal insufficiency and adrenal hyperplasia, there remained uncertainty about the relationship between adrenocortical hyperfunction and virilism (premature development of male secondary sex characteristics). In 1942 this confusion was resolved by Fuller Albright when he delineated the differences between children with Cushing syndrome and those with adrenogenital syndromes which are more commonly referred to as **congenital adrenal hyperplasias (CAH)**. The CAH are a group of inherited disorders that result from loss-of-function mutations in one of several genes involved in adrenal steroid hormone synthesis. In the virilizing forms of CAH the mutations result in impairment of cortisol production and the consequent accumulation of steroid intermediates proximal to the defective enzyme. All forms of CAH are inherited in an autosomal recessive manner. There are two common and at least three rare forms of CAH that result in virilization. The common forms are caused by defects in either CYP21A2 (21-hydroxylase, also identified as just CYP21 or CYP21B) or CYP11B1 (11β-hydroxylase). The majority of CAH cases (90–95%) are the result of defects in CYP21A2 with a frequency of between 1 in 5,000 and 1 in 15,000. Three rare forms of virilizing CAH result from either defects in 3β-hydroxysteroid dehydrogenase (HSD3B2), placental aromatase or P450-oxidoreductase (POR). An additional CAH is caused by mutations that affect either the 17α-hydroxylase, 17,20-lyase or both activities encoded in the CYP17A1 gene. In individuals harboring CYP17A1 mutations that result in severe loss of enzyme activity there is absent sex steroid hormone production accompanied by hypertension resulting from mineralocorticoid excess.

Introduction to Cushing Syndrome and Cushing Disease

Hypercortisolemia is the hallmark symptom in both Cushing disease and Cushing syndrome. Cushing syndrome is the disorder first described by Harvey Cushing in 1932 in several patients with adrenocortical hyperplasia that were the result of basophilic adenomas of the anterior pituitary. Cushing described this syndrome as patients with truncal (central) adiposity, hypertension, weakness, fatigability,

purplish abdominal striae ("stretch" marks), amenorrhea, edema, glucosuria, osteoporosis, and hirsuitism. Some confusion can result given that the current distinction between Cushing syndrome and Cushing disease is that the former is associated with adrenal dysfunction (most usually due to tumors) resulting in excess cortisol production and secretion, whereas, the latter results from anterior pituitary dysfunction (most usually due to tumors) resulting in excess ACTH secretion. The excess ACTH over stimulates the adrenal glands resulting, secondarily, in excess cortisol secretion. Sometimes Cushing disease is referred to as ACTH-dependent Cushing syndrome. Considering all cases of hypercortisolemia, 80–85% are caused by pituitary corticotroph adenomas resulting in excess ACTH secretion. The other 10–15% of cases result from unilateral benign and malignant adrenal tumors resulting directly in excessive cortisol secretion.

Clinical Features of Cushing Syndrome/Disease

Physical Findings

Central obesity was and continues to be the most common finding in Cushing syndrome. This feature is apparent in approximately 95% of adult patients and in 100% of pediatric patients. In addition to truncal adiposity, Cushing syndrome patients exhibit unique fat accumulations over the face and neck giving the classical "moon" facies and "buffalo hump". In addition to the unique patterns of fat deposition, Cushing syndrome patients have thin extremities (spider appearance) that are due to the effects of cortisol on protein disposition in skeletal muscle. Hypertension is observed in at least 80% of Cushing syndrome patients. This associated hypertension is a major contributing factor to cardiovascular morbidity in this disease. The hypertension in Cushing syndrome results from the effects of glucocorticoids on plasma volume, peripheral vascular resistance, and cardiac output. These latter effects of glucocorticoids are due, in part, to the fact that glucocorticoids also bind and activate the mineralocorticoid receptor in addition to the glucocorticoid receptor.

Although the hypertension usually improves with surgical removal of the precipitating tumor, patients may still require some form of pharmacologic antihypertensive intervention. This therapy may be required only pre-operatively but is required post-operatively as well in some patient. The thiazides and furosemide can worsen the hypokalemia caused by the excess cortisol and, therefore, should be avoided. The renin-angiotensin system is augmented in Cushing syndrome due to the hypercortisolemia and, therefore, ARBs (angiotensin II receptor blockers) and ACE (angiotensin-converting-enzyme) inhibitors are the recommended drugs of choice to treat hypertension in these patients.

Cushing syndrome patients can manifest with virilization due to the excess cortisol and adrenal androgens. Therefore, women often present with amenorrhea combined with hirsutism, acne, signs of virilization (clitoral enlargement, deepening of the voice, male pattern baldness). Male patients frequently present with diminished libido or impotence associated with subnormal testosterone production.

Screening for Cushing Syndrome

The most common, and recommended, initial tests for Cushing syndrome are urinary free cortisol (UFC) at least two times, late night salivary cortisol, at least two measurements, a 1 mg overnight dexamethasone suppression test (DST), or longer low-dose DST (2 mg/day for 48 hr). Sometimes patient will show normal test results but presented with distinctive clinical features highly suggestive of Cushing syndrome. In these cases it is recommended to periodically repeat the tests.

The gold standard screening test for determination of Cushing syndrome is to assay for ACTH and cortisol levels following a dose of dexamethasone. In this test, a failure to see ACTH and cortisol secretion be suppressed is highly indicative of Cushing syndrome. The 1 mg dexamethasone test is usually given between 11pm and midnight (12am) with cortisol levels being measured between 8am and 9am the following morning. Positive cortisol suppression, in this test, is evident if the serum level is less than 1.8 mg/dl in patients with pituitary causes of Cushing syndrome. In patients with adrenal causes of Cushing syndrome, a positive result is evident with cortisol suppression to 5 mg/dl. In patients with underlying psychiatric disorders (depression, anxiety, obsessive-compulsive disorder) and in patients morbid obesity or in alcoholics the recommended test is the 2 days, 2 mg/day DST assay.

Once hypercortisolemia is diagosed, its cause needs to be identified. An ACTH level is the next step to further investigate the source of Cushing syndrome. ACTH levels below 5 pg/ml at two separate occasions support the diagnosis of ACTH-independent Cushing disease. If serum ACTH is more than 15 pg/ml the disease is most likely to be ACTH-dependent Cushing syndrome.

Introduction to Addison Disease

Adrenal insufficiency describes a related group of disorders that are generally divided into two broad categories. Disorders that are due to a primary inability of the adrenal glands to synthesize and secrete hormone constitute the primary adrenal insufficiency syndromes. Disorders of adrenal function that result from inadequate adrenocortiocotropic hormone (ACTH) synthesis or release from the anterior pituitary constitute the secondary adrenal insufficiency syndromes. The major primary adrenal insufficiency syndrome is Addison disease.

Addison disease was first described by Thomas Addison in 1855. Dr. Addison's original description of the disorder listed the characteristic features as....."general languor and debility, remarkable feebleness of the heart’s action, irritability of the stomach, and a peculiar change of color in the skin, occurring in connection with a diseased condition of the suprarenal capsules". In this early description, the diseased condition of the suprarenal capsules was primarily (70-90%) the result of tuberculosis. Addison’s description of the clinical features associated with this form of primary adrenal insufficiency was extremely elegant given that at the time the function of the adrenal glands was unknown.

Following Addison's initial description, much work has been done to understand the underlying biochemistry and physiology behind the symptoms associated with adrenal insufficiency. It is now known that Addison disease results from the inability of the adrenal cortex to synthesize and secrete glucocorticoid (primarily

cortisol) and mineralocorticoid (primarily aldosterone) hormones. Although most of the early cases were the result of infection with Mycobacterium tuberculosis, today the most frequent cause of Addison disease is idiopathic atrophy, most often the result of autoimmune destruction of the cortical tissue of the adrenal glands. Rare instances of Addison disease are associated with adrenoleukodystrophy, tumor metastases, HIV infection, cytomegalovirus (CMV) infection, bilateral hemorrhage, amyloidosis, and sarcoidosis. The consequence of adrenal cortical hormone synthesis failure is increased secretion of ACTH, from anterior pituitary corticotropes, in an effort to stimulate the adrenal glands. In addition, the loss of adrenal cortisol production results in loss of the normal feed-back inhibitory loop that cortisol exerts upon the pituitary corticotrophic cells that secrete ACTH. Primary and secondary adrenal insufficiency share many clinical features, yet have easily distinguishable differences. The associated increase in ACTH secretion in Addison disease contrasts with secondary adrenal insufficiency which is due to ACTH deficiency. In addition, Addison disease is associated with hyperpigmentation. The hyperpigmentation in Addison disease is related to melanocyte stimulation by ACTH and α-melanocyte-stimulating hormone (α-MSH), where ACTH is the more potent stimulator of melanogenesis. Indeed, as discussed in detail in the Gut-Brain Interrelationship page, α-MSH function is more related to control of feeding behaviors than to any role in pigmentation. In secondary adrenal insufficiency syndromes, mineralocorticoid synthesis is essentially normal, whereas, glucocorticoid synthesis is insufficient. The normal mineralocorticoid synthesis in secondary adrenal insufficiency is due to the fact that it is primarily regulated by salt and water metabolism rather than ACTH. Without treatment, adrenal insufficiency can be fatal, hence, early recognition is extremely important.

Clinical Features of Addison Disease

Physical Findings

The characteristic clinical presentation of acute primary adrenal insufficiency includes an insidious onset of asthenia (fatigability and weakness), cutaneous and mucosal pigmentation, agitation, nausea, vomiting, anorexia, weight loss, orthostatic (postural) hypotension (drop in blood pressure upon standing), confusion, circulatory collapse, abdominal pain, and fever. Indeed, one can consider the hallmark features of Addison disease to be asthenia, weight loss, and pigmentation (particularly on sun-exposed skin), as these three symptoms are present in >97% of patients. Addison disease is also associated with a characteristic sequelae of biochemical presentations. These include hyponatremia, hypoglycemia, hyperkalemia, unexplained eosinophilia, and mild prerenal azotemia (accumulation of urea and creatinine in the body). The typical history and clinical findings of chronic primary adrenal insufficiency include a protracted history of malaise, fatigue, anorexia, weight loss, joint and back pain, and darkening of the skin. In addition, patients may crave salt and may develop preferences for salty foods and fluids.

As pointed out above, darkening of the skin is one of the hallmark signs of primary adrenal insufficiency. The hyperpigmentation associated with Addison disease may

be homogeneous or blotchy and occurs in all racial and ethnic groups. In addition, isolated darker areas occur at the palmar creases, flexural areas, sites of friction, recent scars, vermilion border of the lips, and genital skin. Mucosal membranes, in particular the buccal, periodontal, and vaginal mucosa may also show patchy macular areas of increased pigmentation. The cutaneous and mucosal pigmentation increases with age and advancement of the symptoms of Addison disease.
Autoimmune destruction is the most common cause of primary adrenal insufficiency in industrialized countries and may be the sole cause or, in rare instances, be associated with inherited autoimmune polyglandular syndromes. These latter syndromes tend to present either in childhood (type 1), in association with hypoparathyroidism and mucocutaneous candidiasis, or in adulthood (type 2), in association with insulin-dependent diabetes mellitus, autoimmune thyroid disease, and vitiligo (autoimmune destruction of melanocytes). Suspicion of Addison disease should be high in individuals with AIDS as well as other viral disorders such as CMV necrotizing adrenalitis.

Biochemical Findings

Upon suspicion of Addison disease, biochemical testing is needed to confirm the diagnosis of adrenal insufficiency. As the disease advances, serum sodium, chloride, and bicarbonate levels will be reduced while serum potassium levels will be elevated all of which results from insufficient mineralocorticoid (aldosterone). Aldosterone exerts its primary effects through actions on the kidneys but also functions in the colon and sweat glands. The principle effect of aldosterone is to enhance sodium (Na^+) reabsorption in the connecting tubule (CNT) and cortical collecting duct of the nephrons in the kidneys. Within these regions of the nephron aldosterone induces the expression of the Na^+,K^+-ATPase subunit genes (ATP1A1 and ATP1B1), the genes encoding the subunits (SCNN1A, SCNN1B, and SCNN1C) of the epithelial sodium channel (ENaC), and the SLC12A3 gene (encoding the Na^+-Cl^- cotransporter, NCC). The net effect of the induction of these transporter genes, by aldosterone, is enhanced Na^+ reabsorption as a function of the apical membrane localized ENaC and NCC transporters and delivery to the blood via the action of the basolateral membrane localized Na^+,K^+-ATPase. Secondary to the Na^+ uptake is efflux of potassium (K^+) to the tubular lumen. In addition to K^+ excretion, aldosterone enhances the excretion of hydrogen (H^+) ions from the collecting duct which is a compensating action to counter the accumulation of the positive charge imparted by increased Na^+ reabsorption. Therefore, the hyponatremia of Addison disease results from both the loss of sodium to the urine and to the movement of sodium into the intracellular compartment. As sodium moves into the cell, fluid depletion in the vasculature ensues which exacerbates the hypotension of Addison disease. The hyperkalemia, primarily due to loss of aldosterone, is also a result of acidosis and impaired glomerular filtration.

Plasma levels of cortisol and aldosterone are reduced below normal levels. In addition, neither hormone levels rise in response to administration of ACTH as would be expected in a normal individual. Normal cortisol levels in the hypotensive state, due to the absence of adrenal insufficiency, are expected to be in

the range of 18μg/dL (495nmol/L) following administration of cosyntropin (250μg administered IM or IV). In individuals in whom the cosyntropin administration test results in cortisol values greater than 19μg/dL (524nmol/L), Addison disease can be excluded as the cause of associated symptomology. Alternatively, if the cortisol level is less than 3μg/dL (83nmol/L) it is virtually assured that the patient's symptoms are due to Addison disease. Measurement of free cortisol in the urine is not at all useful in the correct diagnosis of Addison disease.

Measurement of plasma ACTH helps to determine if the observed symptoms and biochemical results are due to primary or secondary adrenal insufficiency. With primary insufficiency the values of plasma ACTH will be above the normal range, whereas, in secondary insufficiency the plasma levels will be lower than normal. Identification of hypokalemia in the presence of elevated plasma renin levels signifies a mineralocorticoid deficiency and, therefore, allows for discrimination of primary adrenal insufficiency.

Introduction to Graves Disease

Graves disease is a disorder that was originally described by the Irish physician, Robert James Graves in 1835. His original description referred to the disease as "exophthalmic goiter". Graves disease is now known to be a syndrome that manifests as hyperthyroidism with a diffuse goiter. Specifically, Graves disease is associated with thyrotoxicosis which is defined as a state of thyroid hormone excess but is not synonymous with hyperthyroidism (result of excessive thyroid function). The major causes of thyrotoxicosis are the hyperthyroidism of Graves disease, toxic adenomas, and toxic multinodular goiter. In addition to hyperthyroidism and goiter, Graves disease is associated with eye disease characterized by inflammation and involvement of intra-orbital structures, dermopathy referred to as pretibial myxoedema, and rare involvement of the nails, fingers and long bones known as acropachy.

Graves disease is an autoimmune disease caused by autoantibodies to the thyroid stimulating hormone (TSH) receptor, TSH-R. These antibodies (identified as TSI: TSH-R-stimulating immunoglobulins) bind the the TSH-R on thyroid follicular cells and mimic the receptor activation actions of TSH. The consequences of this hyperactivation of the thyroid are stimulated follicular cell growth, resulting in diffuse thyroid enlargement and increased production of thyroid hormones. With respect to the thyroid hormones, the fraction of triiodothyronine (T3) production relative to thyroxine (T4) is increased.

Graves disease is the most common autoimmune disease in the US affecting 0.5% of the population. Graves disease accounts for 60-80% of all forms of thyrotoxicosis with the prevalence being higher among women than men. Smokers and those individuals with other autoimmune disorders or with a family history of thyroid autoimmunity are more likely to develop the disease than the general population. The disease rarely begins prior to adolescence and typically manifests between 20 and 50 years of age. Across different populations, the rate of the disease can vary dependent upon the intake of iodine with increased prevalence of Graves disease associated with higher iodine intake.

Clinical Features of Graves Disease

Physical Findings

The onset of Graves disease is usually acute, reflecting the sudden production of TSI. Most patients will report the classical symptoms of hyperthyroidism that include weight loss despite increased appetite, heat intolerance, irritability, insomnia, sweatiness, diarrhea, palpitations, muscular weakness and menstrual irregularity. Upon physical examination the classic clinical signs of Graves disease will be diffuse goiter, eye disease, warm smooth skin, hyperreflexia, fine resting tremor, and tachycardia. Each of these symptoms of Graves disease are related to the effects of thyroid overstimulation of metabolism and exacerbation of sympathetic nervous system responses. The sympathomimetic effects include the aforementioned tachycardia as well as hand tremors, anxiety, and gastrointestinal hypermotility. Less common findings include atrial fibrillation and a thyroid bruit reflecting the marked increase in thyroid vascularity. Older presenting patients are more likely to present with depression, weight loss, atrial fibrillation, and congestive heart failure then will be present in younger patients. Although less likely, some Graves disease patients will present with proximal myopathy, cardiomyopathy, malabsorption, hypercalcemia, hepatitis, gynecomastia, and loss of glycemic control in patients with diabetes.

Eye disease affects up to 50% of patients with Graves disease. The pathophysiology of the ocular issues associated with Graves disease are distinct from the sympathomimetic ocular effects of thyroid hormone excess which are identified as thyroid stare, known as the Dalrymple sign (wide open eyes and eyelid spasm). The cardinal features of thyroid eye disease include exophthalmos (abnormal eyeball protrusion), chemosis (conjuntive edema) and when severe, impaired extra-ocular muscle movement. The impaired eye movement is most easily seen during a vertical and lateral gaze test. The consequences of chemosis include infections leading to swollen, congested, watery or gritty eyes. Vision changes also result resulting in loss of visual fields or acuity and diplopia (double vision).

Biochemical Findings

In any patient suspected of hyperthyroidism it is extremely important to perform a comprehensive clinical assessment of disturbances in biochemical processes. To this end, serum TSH is a sensitive index for primary thyroid disease and therefore, the most important initial screening test. Patients who are identified with reduced levels of TSH are likely to have suppression of the hypothalamic-pituitary axis. In these patients it is necessary to subsequently measure for the level of free T3 and T4. In Graves disease associatd hyperthyroidism both of these hormones will be elevated in the serum. Care must be taken in interpreting free thyroid hormone levels as artifacts in their measurements are associated with critical illness, disturbances in binding proteins due to drugs or pregnancy, and to the use of heparin as an anticogulant.

The measurement of serum TSH-receptor antibodies is highly correlated to the confirmation of a diagnosis of Graves disease. In 90% of patients with presumed Graves disease, TSI and TSH-receptor binding immunoglobulins (TBII) are found and are directly related to the disruption in thyroid function. However, routine

measurement of TSI or TBII is unnecessary in patients in whom the diagnosis of Graves disease is confirmed due to thyrotoxicosis with eye changes suggestive of thyroid eye disease. The measurement of TSI and TBII are also useful for assessing the risk of relapse after a course of drug treatment for Graves disease. These drugs include the thionamides, methimazole (MMI), carbimazole, and propylthiouracil (PTU). Measurement of the autoantibodies is also highly useful when assessing the risk of neonatal Graves disease in pregnant women with Graves disease. Other antibodies, including thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies, may be significantly elevated in Graves disease but they are not specific to a diagnosis of the disease. These latter autoantibodies may also be detected in Hashimoto disease (chronic lymphocytic thyroditis resulting in hypothyroidism). Hashimoto disease is the most common form of hypothyroidism in the US.

Genetics of Graves Disease

The majority of autoimmune diseases, including Graves disease, strongly correlate to polymorphic genes in the major histocompatibility complex (MHC). The human MHC is often referred to as the HLA (human leukocyte antigens) region and HLA encoded molecules are central for the function of the immune system. HLA encoded proteins bind fragments of antigens in the form of peptides and present them to T lymphocytes. HLA molecules are divided into HLA class I (HLA-A, B, C) and class II (HLA-DR, DQ, DP). Use of the "shared epitope hypothesis" in the analysis of autoimmune disorders, it has been determined that there is a primary role in the HLA DRB1 locus in the etiology of Graves disease. In Caucasian Graves disease patients increased prevalence of the DRB1*03 DQA1*05 DQB1*02 haplotype is usually observed suggesting that some gene(s) encoded at this locus increase the risk of disease development by 2–3 fold. Direct analysis of the DNA sequence of exon 2 of the HLA-DRB1 gene in 208 Graves disease patients and 149 controls found an associated polymorphism at amino acid position 74. Variants with arginine at position 74 appear to be overrepresented among Graves disease patients. The possibility that DRB1 position 74 is a primary determinant of Graves disease susceptibility is consistent with the results of another study analyzing DRB1, DQB1 and DQA1 loci in 871 Graves disease patients and 621 controls.

Polymorphisms in the protein tyrosine phosphatase-22 (PTPN22) gene, which encodes the lymphoid tyrosine phosphatase (LYP) protein, have been shown to be associated with type 1 diabetes (T1D). Subsequently several of these poymorphisms were associated with increased risk for a number of other autoimmune diseases including Graves disease, rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and autoimmune Addison disease (AAD). Indeed, in many autoimmune diseases PTPN22 represents the second most strongly associated locus after HLA. PTPN22 is involved in limiting the adaptive response to antigen by dephosphorylating and inactivating T cell receptor (TCR) associated kinases and their substrates. In lymphocytes, PTPN22 physically associates with CSK (c-Src kinase). CSK is an important suppressor of the Src family kinases that mediate TCR signaling.

The polymorphism in PTPN22, most highly correlated to Graves disease (as well as other autoimmune disorders), is a SNP (single nucleotide polymorphism) that causes an Arg to Trp substitution at residue 620 (R620W). The R620W variant disrupts the interaction between PTPN22 and CSK leading to increased phosphatase activity, which in turn suppresses TCR signaling more efficiently than the wild-type protein. Association between the PTPN22 R620W polymorphism and Graves disease has been demonstrated in numerous studies among Caucasians. Indeed this variant of PTPN22 is one of the strongest known genetic factors predisposing humans to autoimmune diseases.
Additional loci showing an association with the development of Graves disease include CD40, CTLA4, FCRL3, the thyrotropin receptor (thyroid stimulating hormone receptor, TSHR), and thyroglobulin. CD40 is a costimulatory protein expressed on the surface of antigen presenting cells (APC). The CD40 protein is a receptor of the TNF receptor (TNFR) superfamily. CTLA4 is cytotoxic T-lymphocyte-associated protein 4 (also known as CD152) expressed on the surface of helper T cells. The CTLA4 protein is a member of the immunoglobulin superfamily. FCRL3 is the gene encoding the Fc receptor-like protein 3 which is another member of the immunoglobulin superfamily.