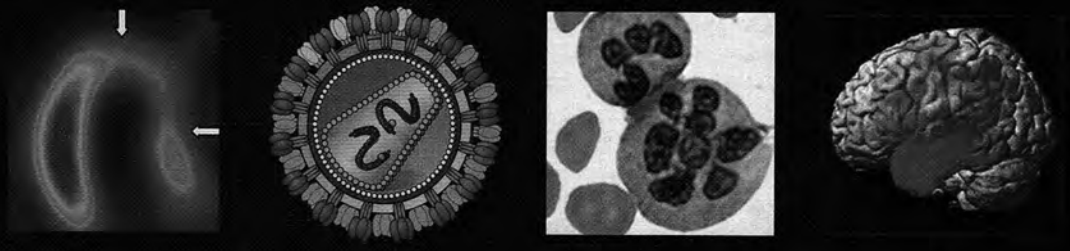
16th Edition

HARRISON'S

PRINCIPLES OF Internal Medicine



Kasper Braunwald Fauci
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CONTENTS

with a 5-year survival of 80 to 90% for low-grade lesions. More invasive or histologically poorly differentiated tumors are more likely to recur locally and metastasize. Metastatic disease is treated with the chemotherapy used in bladder cancer, and the outcome is similar to that of metastatic transitional cell cancer of bladder origin.

FURTHER READING

ADVANCED BLADDER CANCER META-ANALYSIS COLLABORATION: Neoadjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis. Lancet 361:1927, 2003

BORDEN LS JR et al: Bladder cancer. Curr Opin Oncol 15:227, 2003

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81 HYPERPLASTIC AND MALIGNANT DISEASES OF THE PROSTATE

Howard I. Scher

The frequency of both benign and malignant changes in the prostate increase with age. Autopsies of men in the eighth decade of life show hyperplastic changes in >90% and malignant changes in >70% of individuals. The high prevalence of these diseases in an elderly population with competing causes of morbidity and mortality mandates a risk-adapted approach to diagnosis and treatment. This can be achieved by considering these diseases as a series of states. Each state represents a distinct clinical milestone for which intervention(s) may be recommended based on the presence or risk of developing symptoms or death from disease in a given time frame (Fig. 81-1). For benign proliferative disorders, symptoms of urinary frequency, infection, and potential for obstruction are weighed against the side effects and complications of medical or surgical therapy. For prostate malignancies, the risk of developing the disease, symptoms, or death from cancer are balanced against the morbidities of interventions recommended and preexisting comorbid conditions.

In 2004, around 230,000 prostate cancer cases were diagnosed, of whom 29,900 succumbed. The absolute number of prostate cancer deaths has decreased in the past 5 years; this has been attributed by some to the widespread use of detection strategies based on monitoring prostate-specific antigen (PSA). However, screening has not been proven to improve survival in prospective randomized trials. The paradox of management is that although the disease remains the second leading cause of cancer deaths in men, the almost 8:1 ratio in incidence to prostate cancer–specific mortality shows that the majority of men do not die of their disease.

ANATOMY AND PATHOLOGY

The prostate is located in the pelvis and is surrounded by the rectum, the bladder, the periprostatic and dorsal vein complexes that are responsible for erectile function, and the urinary sphincter that is responsible for passive urinary control. The prostate is composed of branching tubuloalveolar glands arranged in lobules and surrounded by a stroma. The acinal unit includes an epithelial compartment made up of epithelial, basal, and neuroendocrine cells and a stromal compartment that includes fibroblasts and smooth-muscle cells. The compartments are separated by a basement membrane. PSA and acid phosphatase (ACP) are produced in the epithelial cells. Both cell types express androgen receptors and depend on androgens for growth. Testosterone, the major circulating androgen, is converted by the enzyme 5-α reductase to dihydrotestosterone in the gland. Changes in prostate size occur during puberty and after the age of 55 in the periurethral portion of the gland. Most cancers develop in the peripheral zone, which can often be palpated by a digital rectal examination (DRE).

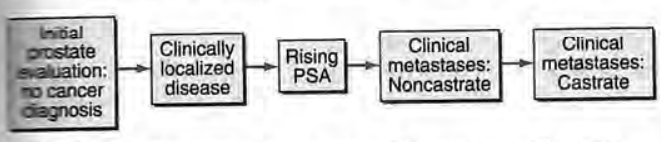

FIGURE 81-1 Clinical states of prostate cancer. PSA, prostate-specific antigen.

Nonmalignant growth occurs predominantly in the transition zone around the urethra.

EPIDEMIOLOGY

The development of a prostate cancer involves a multistep process. Hypermethylation of the GSTP1 gene promoter, leading to a loss of function of a gene that detoxifies carcinogens, is one early change. Epidemiologic studies show that the risk of being diagnosed with prostate cancer increases by a factor of 2 if one first-degree relative is affected and by 4 if two or more are affected. Current estimates are that 40% of early-onset and 5 to 10% of all cancers are hereditary and follow a Mendelian inheritance pattern. Prostate cancer affects ethnic groups differently. Matched for age, the prostates of African-American males have both a greater number of precursor prostatic intraepithelial neoplasia (PIN) lesions and larger tumors than white males, possibly related to the higher levels of testosterone seen in African-American males. These lesions are highly unstable, and typically multifocal. Polymorphic variants of the androgen receptor gene, the cytochrome P450 C17 gene, and the steroid 5α-reductase type II (*SRD5A2*) gene have also been implicated in the variations in incidence. The incidence of autopsy-detected cancers is similar around the world, while the incidence of the clinical disease varies. Thus, environmental factors may play a role. High consumption of dietary fats, such as α-linoleic acid, or polycyclic aromatic hydrocarbons that form when red meats are cooked is believed to increase risk. Similar to breast cancer in Asian women, the risk of prostate cancer in Asian males increases when they move to western environments. Protective factors include the isoflavinoid genistein (which inhibits 5α-reductase), cruciferous vegetables that contain isothiocyanate sulfuraphane, retinoids such as lycopene (in pizza and tomatoes), and inhibitors of cholesterol biosynthesis. The antioxidant α-tocopherol (vitamin E) and selenium may also reduce risk.

DIAGNOSIS AND TREATMENT BY CLINICAL STATE

The clinical states framework considers the risk of morbidity from an enlarging but nonmalignant gland; the probability that a clinically significant cancer is present in an individual with or without urinary symptoms; or, for those with a prostate cancer diagnosis; the probability of developing symptoms or dying from disease. At any point in time, a patient resides in one state and remains there until the disease has progressed to the next state. Applying this paradigm, a patient with localized prostate cancer who has had all cancer removed surgically remains in the state of localized disease as long as the PSA remains undetectable. The time within a state becomes a measure of the impact of an intervention on the natural history of disease, be it benign or malignant in etiology, recognizing that the impact may not be assessable for years. It also allows a distinction between *cure*—the elimination of all cancer cells, the primary therapeutic objective when treating most cancers—and *cancer control*, in which the tempo of the illness is modulated and symptoms controlled until the patient dies of other causes. It is the concept of cancer control that makes the man-

agement of prostate cancer unique. Even when a recurrence is documented, immediate therapy is not always necessary. Rather, as at the time of diagnosis, the need for intervention is based on the tempo of the illness as it unfolds in the individual, relative to the risk:reward ratio of the therapy being considered.

NO CANCER DIAGNOSIS ■ Symptoms The need to pursue a diagnosis of prostate cancer is based on symptoms, an abnormal DRE, or an elevated serum PSA. The urologic history should focus on symptoms of outlet obstruction, continence, potency, or a change in ejaculatory pattern. Benign proliferative disease may produce hesitancy, intermittent voiding, a diminished stream, incomplete emptying, and postvoid leakage. The severity of these symptoms can be quantitated with the self-administered American Urological Association (AUA) *Symptom Index* (Table 81-1) recognizing that the degree of symptoms does not always relate to gland size. Resistance to urine flow reduces bladder compliance, leading to nocturia, urgency, and, ultimately, to retention. Infection, tranquilizing drugs, antihistamines, or alcohol can precipitate urinary retention. Prostatitis often produces pain or induration. Symptoms of metastatic disease include pain secondary to osseous metastases, although many are asymptomatic despite extensive spread. Less common are symptoms related to marrow compromise (myelophthisis), a coagulopathy, or spinal cord compression.

Physical Examination The DRE focuses on the size, consistency, and abnormalities within or beyond the gland. Many cancers occur in the peripheral zone and can be palpated on DRE. Carcinomas are characteristically hard, nodular, and irregular, while induration may be due to benign prostatic hypertrophy (BPH) or to calculi or tumor. Overall, 20 to 25% of men with an abnormal DRE have cancer.

PROSTATE-SPECIFIC ANTIGEN

PSA is a kallikrein-like serine protease that causes liquefaction of seminal coagulum. It is produced by both nonmalignant and malignant epithelial cells. PSA is prostate specific, not prostate cancer specific, and increases may occur from prostatitis, nonmalignant enlargement of the gland (BPH), prostate cancer, and prostate biopsies. The level is not affected by the performance of a DRE. It circulates in the blood as an inactive complex with the protease inhibitors α-$_1$-antichymotrypsin and β_2-macroglobulin and has an estimated half-life in the serum of 2 to 3 days. Levels should be undetectable if the prostate has been removed. PSA immunostaining is used to establish a prostate cancer diagnosis.

PSA testing was approved for early detection in 1994. It is recommend on an annual basis along with a DRE for men over age 50 (with an anticipated survival of >10 years; this includes men up to age 76 years). For African Americans and men with a family history, testing is advised to begin at age 40. The normal range of PSA is 0 to 4 ng/mL. For values >4, the sensitivity for prostate cancer detection is 57 to 79%, the specificity is 59 to 68%, and the positive predictive value is 40 to 49%.

The PSA-based criteria used to recommend a diagnostic prostate biopsy have evolved over time. PSA values may fluctuate for no apparent reason; thus, an isolated abnormal value should be confirmed before proceeding with further testing. These evolving criteria aim to increase the sensitivity of the test for younger men more likely to die of the disease and to reduce the frequency of detecting cancers of low malignant potential in elderly men more likely to die of other causes. Age-specific reference ranges apply a lower "upper" limit of normal for younger males and higher "upper" limit for older individuals. Different thresholds alter sensitivity and specificity of detection. The threshold for performance of a biopsy is now 2.6 ng/mL for men under age 60. Prostate-specific antigen density (PSAD) measurements were developed to correct for the contribution of BPH to the total PSA level. PSAD is calculated by dividing the serum PSA by the estimated prostate weight calculated by transrectal ultrasound (TRUS). Values <0.10 are consistent with BPH, while those >0.15 suggest cancer. *PSA velocity* is the rate of change in PSA levels over time. It is particularly useful for men with values that are rising in the seemingly "normal" range. Rates of rise >0.75 ng/mL per year suggest cancer. As an example, an increase from 2.5 to 3.9 in a 1-year period would warrant further testing. Free and complexed PSA measurements are used when levels are between 4 and 10 ng/mL to decide who needs a biopsy. In cancer, the level of free PSA is lower. The ratios of free to total, complexed to total, and free to complexed PSA have also been used. In one series, specificity improved by 20% using a normal range of free/total >0.15; complexed/total <0.70; and free/complexed >0.25. A diagnostic algorithm based on the DRE and PSA findings is illustrated in Fig. 81-2. In general, a biopsy is recommended if the DRE or PSA are abnormal.

Prostate Biopsy A diagnosis of cancer is established by a TRUS-guided needle biopsy. Direct visualization assures that all areas of gland are sampled. A minimum of six separate cores, three from the right and three from the left, are advised, as is a separate biopsy of the transition zone, if clinically indicated. Performance of a biopsy is not advised in a patient with prostatitis until a course of antibiotics has been administered. The positive predictive value of an abnormal DRE is 21%, while 25% of men with a PSA > 4 ng/mL and an abnormal DRE, and 17% of men with a PSA of 2.5 to 4.0 ng/mL and normal DRE, have cancer. Those with an abnormal PSA and negative biopsy are advised to undergo a repeat biopsy.

TABLE 81-1 AUA System Index

Questions to Be Answered	AUA Symptom Score (Circle 1 Number on Each Line)					
	Not at All	Less than 1 Time in 5	Less than Half the Time	About Half the Time	More than Half the time	Almost Always
Over the past month, how often you have had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
Over the past month, how often have you had to urinate again less than 2 h after you finished urinating?	0	1	2	3	4	5
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	(None)	(1 time)	(2 times)	(3 times)	(4 times)	(5 times)
Sum of 7 circled numbers (AUA Symptom Score): ———						

Note: AUA, American Urological Association.

Source: Barry MJ et al: J Urol 148:1549, 1992. Used with permission.

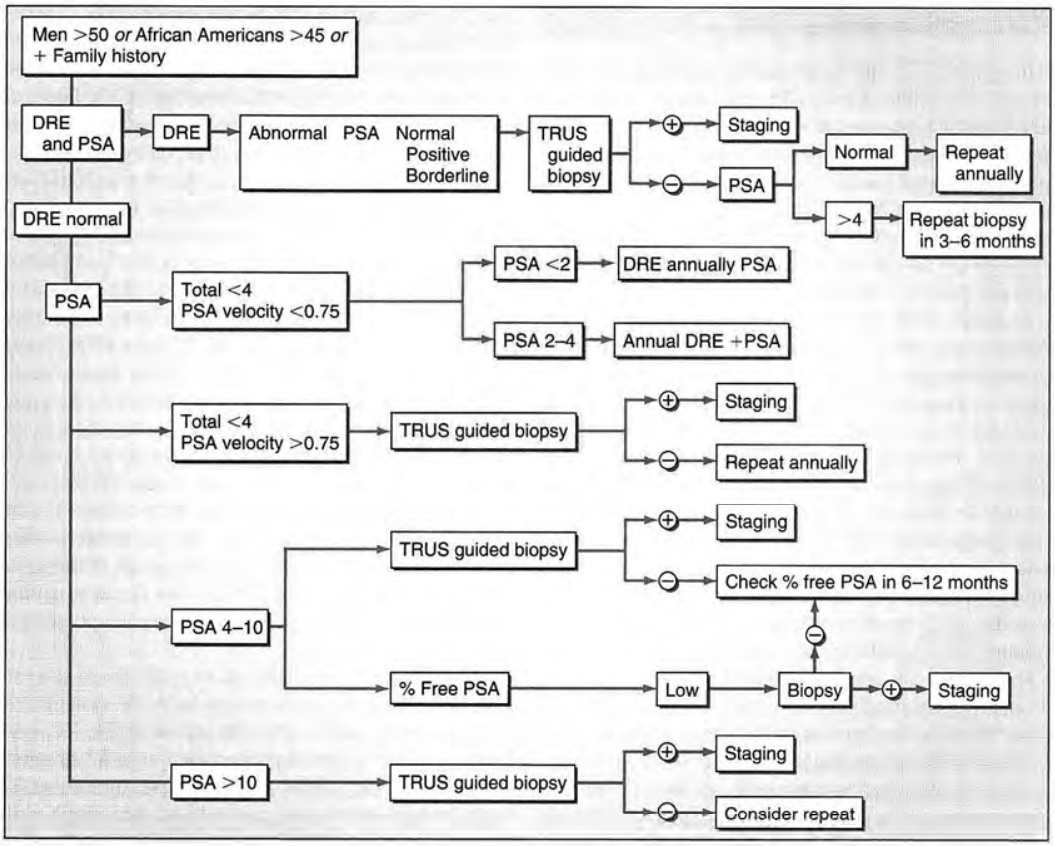

FIGURE 81-2 Algorithm for diagnostic evaluation of men based on digital rectal examination and prostate-specific antigen levels.

Pathology The noninvasive proliferation of epithelial cells within ducts is termed *prostatic intraepithelial neoplasia*. PIN is a precursor of cancer, but not all PIN lesions develop into invasive cancers. Of the cancers identified, >95% are adenocarcinomas; the remaining are squamous, transitional cell tumors, and rarely, carcinosarcomas. Metastases to the prostate are rare, but in some cases, transitional cell tumors of the bladder or colon cancers invade the gland by direct extension. Each core of the biopsy is examined for the presence of cancer, and the amount of cancer present is quantified. A measure of histologic aggressiveness is also assigned using the *Gleason grading system*, in which the dominant and secondary glandular histologic patterns are scored from 1 (well differentiated) to 5 (undifferentiated) and summed to give a total score of 2 to 10 for each tumor. The most poorly differentiated area of tumor (i.e., the area with the highest histologic grade) often determines biologic behavior. The presence or absence of perineural invasion and extracapsular spread are also recorded.

PSA-based detection strategies have changed the clinical spectrum of the disease. Now, 95 to 99% of newly diagnosed cancers are clinically localized, 40% are not palpable, and, of these, 70% are pathologically organ-confined. The downside of widespread use is the detection and treatment of cancers with such a low malignant potential that they would not have shortened survival or produced symptoms during the patient's lifetime. The side effects of treatment, including impotence, incontinence, and bowel dysfunction, are unacceptable for these cases. Formal clinical trials to assess the value of screening on prostate cancer morbidity and mortality are ongoing. Until the results of these studies are available, men are advised to make an informed decision about whether to undergo testing.

Prevention It is difficult to identify individuals who are at risk for developing a cancer that is clinically significant. The Prostate Cancer Prevention Trial is a double-blinded, randomized multicenter trial designed to investigate the ability of finasteride, a 5α-reductase inhibitor, to prevent the development of prostate cancer in men age $\geq$55 years. The prostate cancer detection rate was 18.4% (803 of 4364) for finasteride and 24.4% (1147 of 4692) for placebo-treated men. However, more of the cancers detected in the finasteride group were high-grade [37% (280 of 757) vs. 22% (237 of 1068 cancers) for the placebo]. No effect on survival was detected. Vitamin E and selenium (the SELECT study) are also being tested as preventive agents.

Treatment of Benign Disease Asymptomatic patients do not require treatment regardless of the size of the gland, while those with an inability to urinate, gross hematuria, recurrent infection, or bladder stones may require surgery. Typically, obstruction does not occur and the symptoms remain stable over time. In these cases, uroflowmetry can identify patients with normal flow rates who are unlikely to benefit from treatment and those with high postvoid residuals who may need other interventions. Pressure-flow studies detect primary bladder dysfunction. Cystoscopy is recommended if hematuria is documented and to assess the urinary outflow tract before surgery. Imaging of the upper tracts is advised for patients with hematuria, a history of calculi, or prior urinary tract problems. Therapies such as finasteride, which blocks the conversion of testosterone to dihydrotestosterone, have been shown to decrease prostate size, increase urine flow rates, and improve symptoms. They will also lower baseline PSA levels by 50%, an important consideration when using PSA to guide biopsy recommendations. α-Adrenergic blockers such as terazosin act by relaxing the smooth muscle of the bladder neck and increasing peak urinary flow rates. No data show that these agents influence the progression of the disease. Surgical approaches include a transurethral resection of the prostate (TURP), transurethral incision, or removal of the gland via a retropubic, suprapubic or perineal approach. TULIP (transurethral ultrasound-guided laser-induced prostatectomy), coils, stents, and hyperthermia are also utilized.

PROSTATE CANCER STAGING The TNM staging system includes categories for cancers that are palpable on DRE, those identified solely on the basis of an abnormal PSA (T1c), those that are palpable but clin-

ically confined to the gland (T2), and those that have extended outside of the gland (T3 and T4) (Table 81-2). The assessment of disease extent based on DRE alone is inaccurate with respect to the extent of the disease within the gland, the presence or absence of capsular invasion, involvement of seminal vesicles, and extension of disease to lymph nodes. This led to a modification of the staging system to include the results of imaging studies on the assignment of T stage. Unfortunately, no single test has proven to predict the pathologic stage accurately, be it the presence of organ-confined disease, seminal vesical involvement, or lymph node spread.

TRUS is most frequently used to assess the primary tumor, but no consistent finding predicts cancer with certainty. TRUS is used primarily to direct prostate biopsies. Computed tomography (CT) scans lack sensitivity and specificity to detect extraprostatic extension and are inferior to magnetic resonance imaging (MRI) in visualization of lymph nodes. MRI specificity is improved with an endorectal coil and aids in planning radiation therapy. T1-weighted images demonstrate the periprostatic fat, periprostatic venous plexus, perivesicular tissues, lymph nodes, and bone marrow. T2-weighted images demonstrate the internal architecture of the prostate and seminal vesicles. Most cancers have a low signal, while the normal peripheral zone has a high signal, although the technique lacks sensitivity and specificity.

Radionuclide bone scans are used to evaluate spread to osseous sites. This test is sensitive but relatively nonspecific because areas of increased uptake are not always related to metastatic disease. Healing fractures, arthritis, Paget's disease, and other conditions will also show abnormal uptake. True-positive bone scan results are rare if the PSA <8 ng/mL and uncommon when the PSA $<$ 10 ng/mL unless the tumor is high grade. When the PSA <10 ng/mL, a positive bone scan is usually falsely positive, which in turn, leads to additional low-yield testing.

CLINICALLY LOCALIZED DISEASE Localized prostate cancers are clinically confined to the prostate. Patients with localized disease are managed by radical surgery, radiation therapy, or watchful waiting. Data from the literature do not provide clear evidence for the superiority of any one treatment. Choice of therapy needs consideration of several factors: the presence of symptoms, the probability that the untreated tumor will adversely affect the patient during his lifetime and thus require treatment, and whether the tumor can be cured by single-modality therapy directed at the prostate or requires both local and systemic therapy to achieve cure. As most of the tumors detected are deemed clinically significant, most men undergo treatment.

Comparing the outcomes of various forms of therapy is limited by the lack of prospective trials, referral bias, and differences in the outcomes used. The primary outcomes are cancer control and treatment-related morbidities. These benchmarks of success or failure vary by modality. Often, PSA relapse–free survival is used because an effect on metastatic progression or survival may not be apparent for years. Based on a half-life in the blood of 3 days, PSA should be undetectable in the blood 4 weeks after all prostate tissue has been removed by radical surgery. If PSA remains detectable, the patient is considered to have persistent disease. In contrast, the PSA does not become undetectable after radiation therapy because the remaining nonmalignant elements of the gland continue to produce PSA even if all cancer cells have been eliminated. Similarly, there is no adequate cancer control definition for a patient treated with watchful waiting because PSA levels will continue to rise in the absence of therapy. Other outcomes are the time to objective progression (local or systemic) and cancer-specific and overall survival; however, these outcomes may take years to define.

The more advanced the disease, the lower the probability of local control and the higher the probability of systemic relapse. More important is that within the categories of T1, T2, and T3 disease are tumors with a range of prognoses. Some T3 tumors are curable with therapy directed solely at the prostate, and some T1 lesions have a high probability of systemic relapse that requires the integration of local and systemic therapy to achieve cure. T1c tumors particularly require the use of other factors to predict outcomes and select treatment. Many groups have developed prognostic models based on a combination of the initial T stage, Gleason score, and baseline PSA. Some are based on discrete cut points (PSA <10 or $\geq$ 10; Gleason score of $\leq$6, 7, or $\geq$8). Others are nomograms that use PSA and Gleason score as continuous variables. These algorithms are used to predict disease extent: organ confined vs. nonorgan confined, node negative or positive, and the probability of success using a PSA-based definition of failure specific to the local therapy under consideration. Exactly what cut-off value would lead a patient to accept one form of therapy vs. another is an area of active debate. One nomogram to predict PSA relapse–free survival following radical surgery is illustrated in Fig. 81-2. Specific nomograms have been developed for radical prostatectomy, external-beam radiation therapy, and brachytherapy (seed implantation). These are being refined continually to incorporate other clinical parameters and biologic determinants. Surgical technique, radiation therapy delivery, and criteria for watchful waiting continue to be refined and improved; the year treatment was given affects outcomes independent of other factors. The improvements make treatment decisions a dynamic process.

The frequency of adverse events for the different modalities is highly variable. Of greatest concern to patients are the effects on continence, sexual potency, and bowel function. Part of the variability relates to the definition used for a specific complication and whether the patient or physician is reporting the event. Incontinence figures range from 2% to 47% and impotence rates range from 25% to 89% following radical prostatectomy. The time of the assessment is also important. After surgery, impotence is immediate but may reverse over time, while with radiation therapy, impotence is not immediate but may develop over time.

Radical Retropubic Prostatectomy (RRP) The goal of radical prostatectomy is to excise the cancer completely with a clear margin, to maintain continence by preserving the external sphincter, and to preserve potency by sparing the autonomic nerves in the neurovascular bundle. RRP is advised for patients with a life expectancy of >10 years and is performed using a retropubic, perineal, or laparoscopic approach.

TABLE 81-2 *Comparison of Clinical Stage by the TNM Classification System and the Whitmore-Jewett Staging System*

TNM Stage	Description	Whitmore-Jewett Stage	Description
T1a	Nonpalpable, with 5% or less of resected tissue with cancer	A1	Well differentiated tumor on few chips from 1 lobe
T1b	Nonpalpable, with >5% of resected tissue with cancer	A2	Involvement more diffuse
T1c	Nonpalpable, detected due to elevated serum PSA		
T2a	Palpable, half of one lobe or less	BIN	Palpable, < one lobe, surrounded by normal tissue
T2b	Palpable, > half of one lobe but not both lobes	B1	Palpable, < one lobe
T2c	Palpable, involves both lobes	B2	Palpable, one entire lobe or both lobes
T3a	Palpable, unilateral extracapsular extension	C1	Palpable, outside capsule, not into seminal vesicles
T3b	Palpable, bilateral extracapsular extension		
T3c	Tumor invades seminal vesicle(s)	C2	Palpable, seminal vesicle involved
MI	Distant metastases	D	Metastatic disease

Source: Adapted from FF Schroder et al: TNM classification of prostate cancer. Prostate (Suppl) 4:129, 1992; and American Joint Committee on Cancer, 1992.

Outcomes can be predicted using postoperative nomograms that consider pretreatment factors and the pathologic findings at surgery. PSA failure is defined as a detectable value of 0.2 or 0.4 ng/mL, although the exact definition varies among series. The techniques continue to improve as the ability to localize the tumor within or beyond the prostate are refined with different biopsy algorithms and with imaging. The result is better case selection and surgical planning, which in turn have led to more rapid recovery and higher rates of continence and potency. Factors associated with incontinence include older age, shorter urethra length, surgical technique, preservation of neurovascular bundles, and development of an anastomotic stricture. Surgical experience is also a factor. In one series, 6% of patients had mild stress urinary incontinence (SUI) (requiring 1 pad/day), 2% moderate SUI (>1 pad/day), and 0.3% severe SUI (requiring an artificial urinary sphincter). At 1 year, 92% were completely continent. In contrast, the results in a Medicare population treated at multiple centers showed that at 3, 12, and 24 months following surgery, 58, 35, and 42% wore pads in their underwear, and 24, 11, and 15% reported "a lot" of urine leakage. Factors associated with recovery of erectile function include younger age, quality erections before surgery, and the absence of damage to the neurovascular bundles. Erectile function returns in a median of 4 to 6 months if both bundles are preserved. Potency is reduced by half if at least one nerve bundle is sacrificed. In cases where cancer control requires the removal of both bundles, sural nerve grafts are being explored. Overall, with the availability of drugs such as sildenafil, intraurethral inserts of alprostadil, and intracavernosal injections of vasodilators, many patients recover satisfactory sexual function.

High-risk patients are those with a predicted high probability of failure with surgery alone based on pretreatment factors. In these situations, nomograms and predictive models can only go so far. Exactly what probability of success or failure would lead a physician to recommend and a patient to seek alternative approaches is controversial. For example, it may be appropriate to recommend radical surgery for a younger patient with a low probability of cure. To improve the outcomes of surgery for high-risk patients, neoadjuvant hormonal therapy has been explored. The results of several large trials testing 3 or 8 months of androgen ablation before surgery showed that serum PSA levels decreased by 96%, prostate volumes reduced by 34%, and margin positivity rates declined from 41 to 17%. Unfortunately, hormones did not produce an improvement in PSA relapse–free survival. Thus, neoadjuvant hormonal therapy is not recommended.

Radiation Therapy Radiation therapy is given by external beam, the implantation of radioactive sources into the gland, or a combination of both. Contemporary external beam radiation techniques now use three-dimensional conformal treatment plans to maximize the administered dose to the tumor and to minimize the exposure of the surrounding normal structures. The addition of intensity modulation (IMRT) has allowed further shaping of the isodose curves and the delivery of higher doses to the tumor and a further reduction in normal tissue exposure. These advances have allowed the safe administration of doses >80 Gy, higher local control rates, and fewer side effects. Overall, radiation therapy is associated with a higher frequency of bowel complications (mainly diarrhea) than surgery. Measures of cancer control include the proportion of patients who show a decline in PSA to <0.5 or 1 ng/mL, the proportion with "nonrising" PSA values, or the proportion with a negative biopsy of the prostate 2 years after completion of treatment. PSA relapse is defined as three consecutive rising PSA values from the nadir value, with the time to failure as the midpoint between the nadir and first rising value.

Radiation dose is important. A PSA nadir of <1.0 ng/mL was observed in 90% of patients receiving 75.6 or 81.0 Gy vs. 76 and 56% for those receiving 70.2 Gy and 64.8 Gy, respectively. The positive biopsy rates at 2.5 years were 4% for those treated with 81 Gy, vs. 36 and 27% for those receiving 70.2 or 75.6 Gy. The frequency of rectal complications relates directly to the volume of the anterior rectal wall receiving full-dose treatment. Grade 3 rectal or urinary toxicities were seen in 2.1% of cases at a median dose of 75.6 Gy. Grade 3 urethral strictures requiring dilatation developed in 1% of cases, all of whom had undergone a TURP. Pooled data show that the frequency of grade 3 to 4 toxicities is 6.9 and 3.5%, respectively, for patients who received >70 Gy. The frequency of erectile dysfunction is related to the quality of erections pretreatment, the dose administered, and the time of assessment. The etiology is related to a disruption of the vascular supply and not the nerve fibers.

Neoadjuvant hormone therapy has also been studied in combination with radiation therapy to increase local control rates, decrease the size of the prostate so that the exposure of normal tissues to full-dose radiation is reduced, and decrease the rate of systemic failure. Short-term hormone exposures can reduce toxicities and improve local control rates, but long-term (2 to 3 years) treatment is needed to prolong the time to PSA failure and the development of metastatic disease. The impact on survival has been less clear.

Brachytherapy involves the direct implantation of the prostate with radioactive sources. It is based on the principle that the deposition of radiation energy in tissues decreases exponentially as a function of the square of the distance from the source. The goal is to deliver intensive irradiation to the prostate, minimizing the exposure of the surrounding tissues. Techniques have evolved from intraoperative manual insertion methods to the current standard, in which customized templates based on CT and ultrasonographic assessment of the tumor are used for seed placement based on computer-optimized dosimetry to achieve more homogeneous dose distributions. The implants themselves are now performed transperineally, without an open procedure, with real-time imaging. The result is a marked reduction in local failure rates with fewer complications. In a series of 197 patients followed for a median of 3 years, 5-year actuarial PSA relapse–free survival for patients with pretherapy PSA levels of 0 to 4, 4 to 10, and >10 μg/mL were 98, 90 and 89%, respectively. In a separate report of 201 patients who underwent posttreatment biopsies, 80% were negative, 17% indeterminate, and 3% were positive. The results did not change with longer follow-up. Nevertheless, many physicians feel that implantation is best reserved for patients with good or intermediate prognostic features. The procedure is well tolerated, although most patients experience urinary frequency and urgency that can persist for several months. Incontinence has been seen in 2 to 4% of cases. Higher complication rates are observed in patients who have undergone a prior TURP or who have obstructive symptoms at baseline. Proctitis has been reported in <2% of patients.

Watchful waiting, or deferred therapy, is a policy of no therapeutic intervention(s) until the tumor progresses. Progression can be based on PSA changes, local tumor growth, the development of symptoms, or metastatic disease. The practice evolved from studies of predominantly elderly men with well-differentiated tumors in whom clinically significant progression could not be demonstrated for protracted periods, during which a significant proportion died of intercurrent disease. In a structured literature review of patients treated by radical surgery, a deferred approach, or external beam radiation, the 10-year mean survivals were 93% for radical prostatectomy, 84% for deferred treatment, and 74% for external beam radiation. Risk of progression was related to grade. Men with grade 1 or 2 umors had a 13% risk of death and 19% risk of metastases at 10 years; those with grade 3 tumors had 63 and 74% risks, respectively.

Case selection is critical, and the criteria to select those to whom watchful waiting can be applied safely are under intense study. In a recent prostatectomy series, it was estimated that 10 to 15% of patients had "insignificant" cancers. Given the multifocality of the disease, a concern is the limited ability to predict pathologic findings on the basis of a needle biopsy, even when multiple cores are obtained. Arguing against this approach is the result of a randomized trial of radical prostatectomy vs. watchful waiting from Sweden. With a median follow-up of 6.2 years, men treated by radical surgery had a lower risk of prostate cancer death relative to watchful waiting patients (4.6 vs. 8.9%) and a lower risk of metastatic progression, hazard ratio .63.

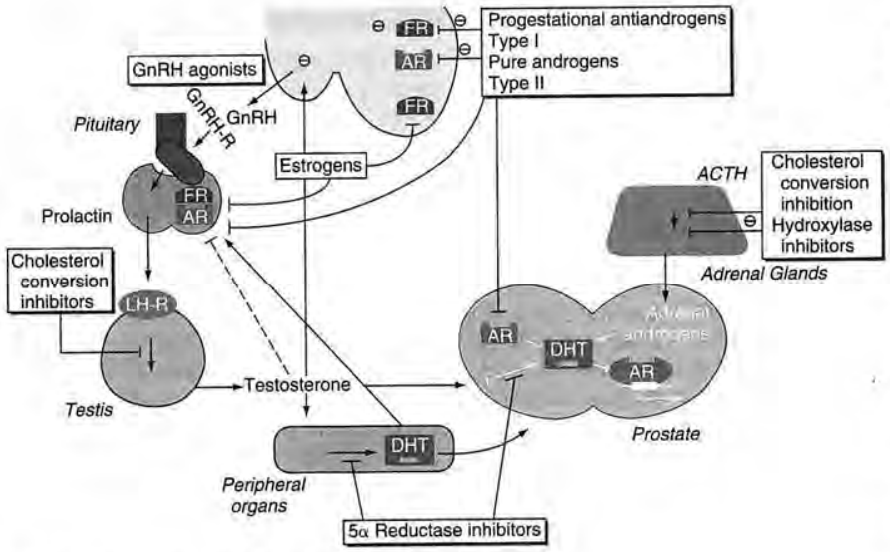

FIGURE 81-3 Sites of action of different hormone therapies.

Nevertheless, it can be anticipated that more patients may be candidates for a deferred approach as PSA testing is applied more widely and earlier.

RISING PSA This state includes patients in whom the sole manifestation of disease is a rising PSA after surgery and/or radiation therapy. By definition, no evidence of disease is found on scan. For these patients the central issue is whether the rise in PSA is the result of persistent disease in the primary site, a systemic recurrence, or both. In theory, disease that persists or has recurred in the primary site may be curable by additional local treatment. For patients who had undergone surgery, the question is whether external beam radiation therapy to the prostate bed can eliminate the disease and lead to an undetectable PSA. For radiation therapy–treated patients, the question is whether a prostatectomy would achieve cure.

The decision to recommend radiation therapy is often made on clinical grounds, as imaging studies such as CT and bone scan are typically uninformative. Some recommend a Prostascint scan: imaging with a radiolabeled antibody to prostate-specific membrane antigen (PSMA), which is highly expressed on prostate epithelial cells. Antibody localization to the prostatic fossa suggests local recurrence; localization to extrapelvic sites predicts failure of radiation therapy. Others recommend that a biopsy of the urethrovesical anastamosis be obtained before considering radiation. Factors that predict for response to salvage radiation are a positive surgical margin, a lower Gleason grade, a long interval from surgery to PSA failure, a slow PSA doubling time, and a low (<0.5 to 1.0 ng/mL) PSA value at the time of treatment. Radiation is generally not recommended if the PSA was persistently elevated after surgery (indicating that disease-free status was not achieved).

For patients with a rising PSA after radiation therapy, a salvage prostatectomy can be considered if the disease was "curable" at the onset, persistent disease has been documented by a biopsy of the prostate, and no metastatic disease is seen on imaging studies. Unfortunately, case selection is poorly defined in most series, and morbidities are significant. As currently performed, virtually all patients are impotent, and ~45% have either total urinary incontinence or stress incontinence. Major bleeding, bladder neck contractures, and rectal injury are not uncommon.

In the majority of cases, the rise in PSA indicates systemic disease. In these cases, the need for treatment should consider the probability of developing clinically detectable disease on scan and in what time frame. That immediate therapy is not required was shown in a series where patients did not receive systemic therapy until metastatic disease was documented. Overall, the median time to metastatic progression was 8 years and 63% of the patients with rising PSA values remained free of metastases at 5 years. Factors associated with progression include Gleason grade, time to recurrence, and PSA doubling times. For those with Gleason grade ≥8 tumors, the probability of metastatic progression was 37, 51, and 71% at 3, 5, and 7 years, respectively. If the time to recurrence was <2 years and PSA doubling time was long (> 10 months), the proportion with metastatic disease was 23, 32, and 53% vs. 47, 69, and 79% if the doubling time was short (< 10 months) during the same time intervals. These models continue to be refined. A difficulty making these predictions is that most patients with a rising PSA receive some form of therapy before the development of metastases.

METASTATIC DISEASE: NONCASTRATE *Metastatic disease noncastrate* refers to patients with tumors visible on an imaging study and noncastrate levels of testosterone. The patient may be newly diagnosed or have recurrent disease after treatment for localized disease. Standard treatment is to block androgen action or decrease androgen production by medical or surgical means. Over 90% of male hormones originate in the testes; <10% are synthesized in the adrenal gland. Surgical orchiectomy is the "gold standard" approach but is least acceptable by patients. Medical therapies can be divided into those that lower testosterone levels, e.g., gonadotropin-releasing hormone (GnRH) agonists and antagonists, estrogens and progestational agents, and the antiandrogens that bind to the androgen receptor but do not signal (Fig. 81-3). Ketoconazole inhibits adrenal androgen synthesis and is used after first-line castration is no longer effective. In this setting, the adrenal glands may contribute up to 40% of the active androgens in the prostate.

GnRH analogues (leuprolide acetate and goserelin acetate) initially produce a rise in luteinizing hormone and follicle-stimulating hormone (FSH), followed by a downregulation of receptors in the pituitary gland, which effects a chemical castration. They were approved on the basis of randomized comparisons showing an improved safety profile (specifically, reduced cardiovascular toxicities) relative to diethylstilbestrol (DES), with equivalent potency. The initial rise in testosterone may result in a clinical flare of the disease. As such, these agents are contraindicated in men with significant obstructive symptoms, cancer-related pain, or spinal cord compromise. Estrogens such as DES also lower testosterone levels but have fallen out of favor due to the risk of vascular complications such as fluid retention, phlebitis, emboli, and stroke.

In contrast, nonsteroidal antiandrogens such as flutamide, bicalutamide, or nilutamide block the binding of androgens to the receptor. Given alone, testosterone levels remain the same or increase. These agents were approved initially to block the flare associated with the initial rise in testosterone that results following GnRH administration. They have also been studied as part of a combined androgen blockade (CAB) or maximal androgen blockade (MAB) and as monotherapy. The concept of CAB was developed to inhibit testicular and adrenal androgens at the outset, and it preoccupied the field for many years. It is achieved clinically by combining an antiandrogen with a GnRH agonist or surgical orchiectomy. Cumulative results of randomized comparisons involving thousands of patients showed no advantage for combining an antiandrogen with surgical orchiectomy, while separate analyses of trials combining an antiandrogen with a GnRH analogue have shown a modest (<10%) survival advantage. Meta-analysis of all combined androgen blockade trials concluded that there was no benefit to the approach. In practice, most patients treated with GnRH analogue therapy receive an antiandrogen for the first 2 to 4 weeks of treatment.

The anti–prostate cancer effects of agents that lower serum testos-

terone levels are similar, and the clinical course is predictable: an initial response, a period of stability in which the cells are dormant and not proliferating, followed by regrowth after a variable period of time as a hormone-independent tumor. Androgen ablation is not curative. Cells that survive castration are present when the disease is first diagnosed. Considered by disease manifestation, PSA levels return to normal in 60 to 70% of cases and measurable disease regression occurs in 50%; while improvements in bone scan occur in 25% of cases, the majority remain stable. Survival is inversely proportional to disease extent. Agents that lower testosterone are associated with an androgen-deprivation syndrome that includes hot flushes, weakness, fatigue, impotence, loss of muscle mass, changes in personality, anemia, depression, and a reduction in bone density. The bone changes can be prevented by treatment with bisphosphonates along with vitamin D and calcium supplementation.

A question often asked is whether antiandrogens, which are associated with fewer hot flashes, less of an effect on libido, less muscle wasting, fewer personality changes, and less bone loss, can be used alone without compromising outcomes. Gynecomastia remains a significant problem but can be alleviated in part with the addition of tamoxifen. Most reported randomized trials suggest that the cancer-specific outcomes are inferior. Even a comparison of bicalutamide, 150 mg (three times the recommended dose of 50 mg), versus surgical castration showed a shorter time to progression and inferior survival for patients with established metastatic disease. Nevertheless, some men may accept the trade-off of a potentially inferior cancer outcome for an improved quality of life.

Another question is whether hormones should be given early, in the adjuvant setting or at the time recurrence is first documented, or late, when metastatic disease or symptoms are manifest. Trials in support of early therapy have often been underpowered relative to the "net benefit" reported or have been criticized on methodologic grounds. In one, although a survival benefit was shown for patients treated with radiation therapy and 3 years of androgen ablation relative to radiation alone, the trial was criticized for the poor outcomes for the control group. Another showing a survival benefit for patients with positive nodes randomized to medical or surgical castration compared to observation ($p = .02$) was criticized because the confidence intervals around the 5- and 8-year survival distributions overlapped between the two groups. A large randomized study comparing early to late hormone treatment (orchiectomy or GnRH analogue) in patients with locally advanced or asymptomatic metastatic disease showed that patients treated early were less likely to progress from M0 to M1 disease, develop pain, and die of prostate cancer. This trial was criticized because therapy was delayed "too long" in the late-treatment group. When patients treated by radical surgery, radiation therapy, or watchful waiting were randomly assigned to receive bicalutamide, 150 mg, or placebo, hormone treatment produced a significant reduction in the proportion of patients who developed osseous metastases at 2 years (9% for bicalutamide; 13.8% for placebo). This result has not gained acceptance in part because too many "good-risk" patients were treated and because no effect on survival was demonstrated. These criticisms are valid; however, the net influence on survival from early hormone intervention is similar to that observed in patients with breast cancer where adjuvant hormonal therapy is routinely given.

Another way to reduce the side effects of androgen ablation is to administer hormones on an intermittent basis. This was proposed as a way to prevent the emergence of castration-resistant cells by "forcing" the cells that survive androgen ablation into a normal differentiation pathway by repleting testosterone. Theoretically, surviving cells that are allowed to proliferate in the presence of androgen will retain sensitivity to androgen ablation. The duration of treatment varies from 2 to 6 months beyond the point of maximal response. Once therapy is stopped, endogenous testosterone levels increase, and the symptoms associated with androgen ablation abate. PSA levels also begin to rise, and, at some level, androgen ablation is restarted. Using this approach, multiple cycles of regression and proliferation have been documented in individual patients. It is unknown whether the intermittent approach increases, decreases, or does not change the overall duration of sensitivity to androgen ablation. A trial to address this question is ongoing.

METASTATIC DISEASE: CASTRATE Castration-resistant disease can be manifest in many ways. For some it is a rise in PSA with no change in radiographs and no new symptoms. In others, it is a rising PSA and progression in bone, with or without symptoms of disease. Still others will show soft tissue disease with or without osseous metastases, and others have a pattern of visceral spread. The prognosis, highly variable, can also be predicted using nomograms designed for this cohort. The important distinction is that despite the failure of first-line hormone treatment, the majority of these tumors remain sensitive to second- and third-line hormonal treatments. Castration resistance does not indicate hormonal resistance. The rising PSA is an indication of continued signaling through the androgen receptor axis.

The manifestations of disease in this patient group hinder the development of drugs and treatment standards because the traditional measures of outcome such as tumor regression do not apply. No PSA-based outcomes are true surrogates for a survival benefit, and assessing changes in osseous disease using bone scans is notoriously inaccurate. It is essential to define therapeutic objectives before initiating treatment, as standards of care have changed on the basis of randomized comparisons that provide clinical benefits without prolonging life. These endpoints include the relief of symptoms and delaying metastases or the time to the development of new symptoms of disease.

The management of these patients requires first that the castrate status be documented. Patients receiving an antiandrogen alone who have elevated levels of serum testosterone should be treated first with a GnRH analogue or orchiectomy and observed for response. Patients on an anti-androgen in combination with a GnRH analogue should have the antiandrogen discontinued, as ~30% will respond to the withdrawal of the antiandrogen. Any response occurs within weeks of stopping flutamide, but may take 8 to 12 weeks with nilutamide and bicalutamide (they have a long terminal half-life). At the time of progression, a different antiandrogen can be given as these agents are not cross-resistant. Other hormones that may be active include estrogens, progestins, ketoconazole, and glucocorticoids. Those who respond to estrogens or progestins should also be evaluated for a withdrawal response at the time of progression. Cytotoxic agents are considered when hormone responses stop.

No chemotherapy regimen has been proven to prolong life in these patients. However, responses to chemotherapy that improve symptom control are not uncommon. Drugs directed at the tumor cell cytoskeleton such estramustine (Emcyt) and a taxane such as paclitaxel or docetaxel can induce responses in ≥50% using measurable disease regression as the endpoint. Seventy percent will show a >50% decline in PSA from baseline. Studies evaluating survival effects are nearly done.

Management of pain is a critical part of therapy. Optimal palliation requires assessing whether the symptoms and metastases are focal or diffuse and whether disease threatens the spinal cord, the cauda equina, or the base of the skull. Neurologic symptoms require emergent evaluation because loss of function may be permanent if not addressed in a timely manner. Single sites of pain or areas of neurologic involvement are best treated with external beam radiation. As the disease is often diffuse, palliation at one site often leads to the emergence of symptoms at another. An important principle of management was established in two randomized trials of mitoxantrone and prednisone vs. prednisone alone. In both studies, mitoxantrone-treated patients had a greater reduction in pain, used fewer narcotics, were more mobile, and had less fatigue. No survival benefit was shown.

Given the bone-dominant nature of prostate cancer spread, bone-directed therapies may be usesful in patients with diffuse disease. Two bone-seeking radioisotopes, ^{89}Sr (metastron) and ^{153}Sm-EDTMP (quadramet), are approved for palliation of pain although they have no effect on PSA or on survival. Fewer patients treated with an isotope

developed new areas of pain or required additional radiation therapy compared to patients receiving external beam radiation therapy alone. Addition of zoledronate to "standard therapy" in patients with castration-resistant disease resulted in fewer skeletal events relative to placebo-treated patients. The bone events included development of new pain, need for radiation therapy, and microfractures. Finally, patients randomly assigned to a combination of ^{89}Sr and doxorubicin after induction chemotherapy had fewer skeletal events and longer survival than patients treated with doxorubicin alone. Confirmatory studies are ongoing.

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82 TESTICULAR CANCER

Robert J. Motzer, George J. Bosl

Primary germ cell tumors (GCTs) of the testis, arising by the malignant transformation of primordial germ cells, constitute 95% of all testicular neoplasms. Infrequently, GCTs arise from an extragonadal site, including the mediastinum, retroperitoneum, and, very rarely, the pineal gland. This disease is notable for the young age of the afflicted patients, the totipotent capacity for differentiation of the tumor cells, and its curability; about 95% of all newly diagnosed patients will be cured. Experience in the management of GCTs leads to improved outcome.

INCIDENCE AND EPIDEMIOLOGY Nearly 9000 new cases of testicular GCT were diagnosed in the United States in 2004; the incidence of this malignancy has increased slowly over the past 40 years. The tumor occurs most frequently in men between the ages of 20 and 40. A testicular mass in a man ≥50 years should be regarded as a lymphoma until proved otherwise. GCT is at least four to five times more common in white than in African-American males, and a higher incidence has been observed in Scandinavia and New Zealand than in the United States.

ETIOLOGY AND GENETICS Cryptorchidism is associated with a severalfold higher risk of GCT. Abdominal cryptorchid testes are at a higher risk than inguinal cryptorchid testes. Orchiopexy should be performed before puberty, if possible. Early orchiopexy reduces the risk of GCT and improves the ability to save the testis. An abdominal cryptorchid testis that cannot be brought into the scrotum should be removed. About 2% of men with GCTs of one testis will develop a primary tumor in the other testis. Testicular feminization syndromes increase the risk of testicular GCT, and Klinefelter's syndrome is associated with mediastinal GCT.

An isochromosome of the short arm of chromosome 12 [i(12p)] is pathognomonic for GCT of all histologic types. Excess 12p copy number either in the form of i(12p) or as increased 12p on aberrantly banded marker chromosomes occurs in nearly all GCTs, but the gene(s) on 12p involved in the pathogenesis are not yet defined.

CLINICAL PRESENTATION A painless testicular mass is pathognomonic for a testicular malignancy. More commonly, patients present with testicular discomfort or swelling suggestive of epididymitis and/or orchitis. In this circumstance, a trial of antibiotics is reasonable. However, if symptoms persist or a residual abnormality remains, then testicular ultrasound examination is indicated.

Ultrasound of the testis is indicated whenever a testicular malignancy is considered and for persistent or painful testicular swelling. If a testicular mass is detected, a radical inguinal orchiectomy should be performed. Because the testis develops from the gonadal ridge, its blood supply and lymphatic drainage originate in the abdomen and descend with the testis into the scrotum. An inguinal approach is taken to avoid breaching anatomic barriers and permitting additional pathways of spread.

Back pain from retroperitoneal metastases is common and must be distinguished from musculoskeletal pain. Dyspnea from pulmonary metastases occurs infrequently. Patients with increased serum levels of human chorionic gonadotropin (hCG) may present with gynecomastia. A delay in diagnosis is associated with a more advanced stage and possibly worse survival.

The staging evaluation for GCT includes a determination of serum levels of α fetoprotein (AFP), hCG, and lactate dehydrogenase (LDH). After orchiectomy, a chest radiograph and a computed tomography (CT) scan of the abdomen and pelvis should be performed. A chest CT scan is required if pulmonary nodules or mediastinal or hilar disease is suspected. Stage I disease is limited to the testis, epididymis, or spermatic cord. Stage II disease is limited to retroperitoneal (regional) lymph nodes. Stage III disease is disease outside the retroperitoneum, involving supradiaphragmatic nodal sites or viscera. The staging may be "clinical"—defined solely by physical examination, blood marker evaluation, and radiographs—or "pathologic"—defined by an operative procedure.

The regional draining lymph nodes for the testis are in the retroperitoneum, and the vascular supply originates from the great vessels (for the right testis) or the renal vessels (for the left testis). As a result, the lymph nodes that are involved first by a right testicular tumor are the interaortocaval lymph nodes just below the renal vessels. For a left testicular tumor, the first involved lymph nodes are lateral to the aorta (para-aortic) and below the left renal vessels. In both cases, further nodal spread is inferior and contralateral and, less commonly, above the renal hilum. Lymphatic involvement can extend cephalad to the retrocrural, posterior mediastinal, and supraclavicular lymph nodes. Treatment is determined by tumor histology (seminoma versus nonseminoma) and clinical stage (Table 82-1).

PATHOLOGY GCTs are divided into nonseminoma and seminoma subtypes. Nonseminomatous GCTs are most frequent in the third decade of life and can display the full spectrum of embryonic and adult cellular differentiation. This entity comprises four histologies: embryonal carcinoma, teratoma, choriocarcinoma, and endodermal sinus (yolk sac) tumor. Choriocarcinoma, consisting of both cytotrophoblasts and syncytiophoblasts, represents malignant trophoblastic differentiation and is invariably associated with secretion of hCG. Endodermal sinus tumor is the malignant counterpart of the fetal yolk sac and is associated with secretion of AFP. Pure embryonal carcinoma may secrete AFP or hCG, or both; this pattern is biochemical evidence of differentiation. Teratoma is composed of somatic cell types derived from two or more germ layers (ectoderm, mesoderm, or endoderm). Each of these histologies may be present alone or in combination with others. Nonseminomatous GCTs tend to metastasize early to sites such as the retroperitoneal lymph nodes and lung parenchyma. One-third of patients present with disease limited to the testis (stage I), one-third with retroperitoneal metastases (stage II), and one-third with more extensive supradiaphragmatic nodal or visceral metastases (stage III).

Seminoma represents about 50% of all GCTs, has a median age in the fourth decade, and generally follows a more indolent clinical course. Most patients (70%) present with stage I disease, about 20% with stage II disease, and 10% with stage III disease; lung or other visceral metastases are rare. Radiation therapy is the treatment of

nancy, and 20% nondiagnostic or yielding insufficient material for diagnosis. Characteristic features of malignancy mandate surgery. A diagnosis of follicular neoplasm also warrants surgery, as benign and malignant lesions cannot be distinguished based on cytopathology or frozen section. The management of patients with benign lesions is more variable. Many authorities advocate TSH suppression, whereas others monitor nodule size without suppression. With either approach, thyroid nodule size should be monitored, either by palpation or ultrasound. Repeat FNA is indicated if a nodule enlarges, and a second biopsy should be performed within 2 to 5 years to confirm the benign status of the nodule.

Nondiagnostic biopsies occur for many reasons, including a fibrotic reaction with relatively few cells available for aspiration, a cystic lesion in which cellular components reside along the cyst margin, or a nodule that may be too small for accurate aspiration. For these reasons, ultrasound-guided FNA is useful when the FNA is repeated. Ultrasound is also increasingly used for initial biopsies in an effort to enhance nodule localization and the accuracy of sampling.

The evaluation of a thyroid nodule is stressful for most patients. They are concerned about the possibility of thyroid cancer, whether verbalized or not. It is constructive, therefore, to review the diagnostic approach and to reassure patients when malignancy is not found. When a suspicious lesion or thyroid cancer is identified, an explanation of the generally favorable prognosis and available treatment options should be provided.

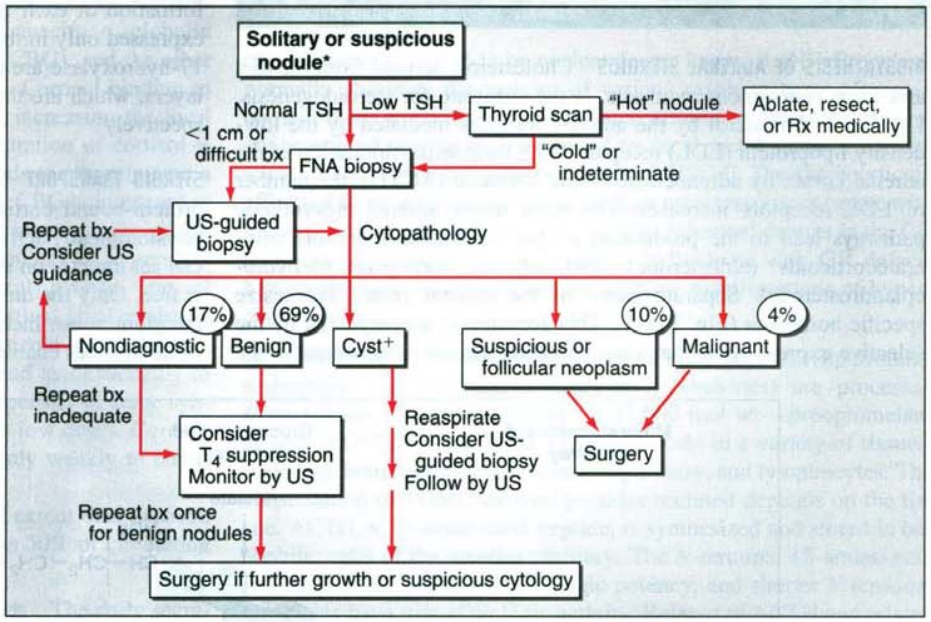

FIGURE 320-13 Approach to the patient with a thyroid nodule. *There are many exceptions to the suggested options. See text and references for details. †About one-third of nodules are cystic or mixed solid-cystic. US, ultrasound; TSH, thyroid-stimulating hormone; FNA, fine-needle aspiration.

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321 DISORDERS OF THE ADRENAL CORTEX

Gordon H. Williams, Robert G. Dluhy

BIOCHEMISTRY AND PHYSIOLOGY

The adrenal cortex produces three major classes of steroids: (1) glucocorticoids, (2) mineralocorticoids, and (3) adrenal androgens. Consequently, normal adrenal function is important for modulating intermediary metabolism and immune responses through glucocorticoids; blood pressure, vascular volume, and electrolytes through mineralocorticoids; and secondary sexual characteristics (in females) through androgens. The adrenal axis plays an important role in the stress response by rapidly increasing cortisol levels. Adrenal disorders include hyperfunction (Cushing's syndrome) and hypofunction (adrenal insufficiency), as well as a variety of genetic abnormalities of steroidogenesis.

STEROID NOMENCLATURE The basic structure of steroids is built upon a five-ring nucleus (Fig. 321-1). The carbon atoms are numbered in a sequence beginning with ring A. Adrenal steroids contain either 19 or 21 carbon atoms. The C_{19} steroids have methyl groups at C-18 and C-19. C_{19} steroids with a ketone group at C-17 are termed *17-ketosteroids*; C_{19} steroids have predominantly androgenic activity. The C_{21} steroids have a 2-carbon side chain (C-20 and C-21) attached at position 17 and methyl groups at C-18 and C-19; C_{21} steroids with a hydroxyl group at position 17 are termed *17-hydroxycorticosteroids*. The C_{21} steroids have either glucocorticoid or mineralocorticoid properties.

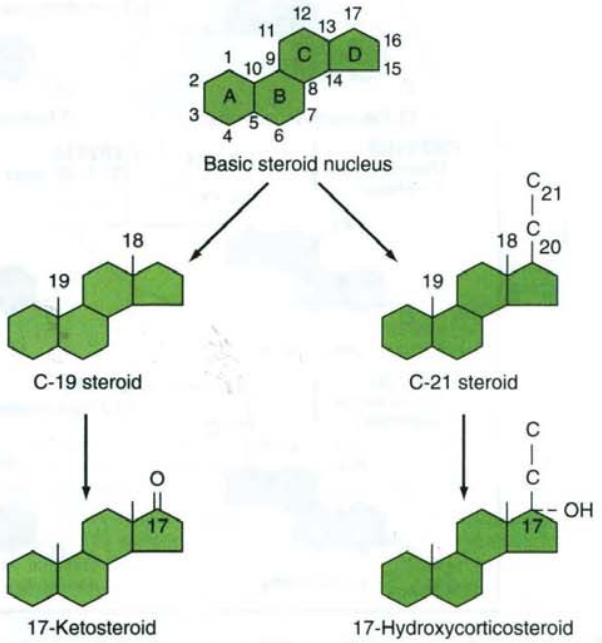

FIGURE 321-1 Basic steroid structure and nomenclature.

BIOSYNTHESIS OF ADRENAL STEROIDS Cholesterol, derived from the diet and from endogenous synthesis, is the substrate for steroidogenesis. Uptake of cholesterol by the adrenal cortex is mediated by the low-density lipoprotein (LDL) receptor. With long-term stimulation of the adrenal cortex by adrenocorticotropic hormone (ACTH), the number of LDL receptors increases. The three major adrenal biosynthetic pathways lead to the production of glucocorticoids (cortisol), mineralocorticoids (aldosterone), and adrenal androgens (dehydroepiandrosterone). Separate zones of the adrenal cortex synthesize specific hormones (Fig. 321-2). This zonation is accompanied by the selective expression of the genes encoding the enzymes unique to the formation of each type of steroid: aldosterone synthase is normally expressed only in the outer (glomerulosa) cell layer, whereas 21- and 17-hydroxylase are expressed in the (inner) faciculata-reticularis cell layers, which are the sites of cortisol and androgen biosynthesis, respectively.

STEROID TRANSPORT Cortisol circulates in the plasma as free cortisol, protein-bound cortisol, and cortisol metabolites. *Free cortisol* is a physiologically active hormone that is not protein-bound and therefore can act directly on tissue sites. Normally, <5% of circulating cortisol is free. Only the unbound cortisol and its metabolites are filterable at the glomerulus. Increased quantities of free steroid are excreted in the urine in states characterized by hypersecretion of cortisol, because the

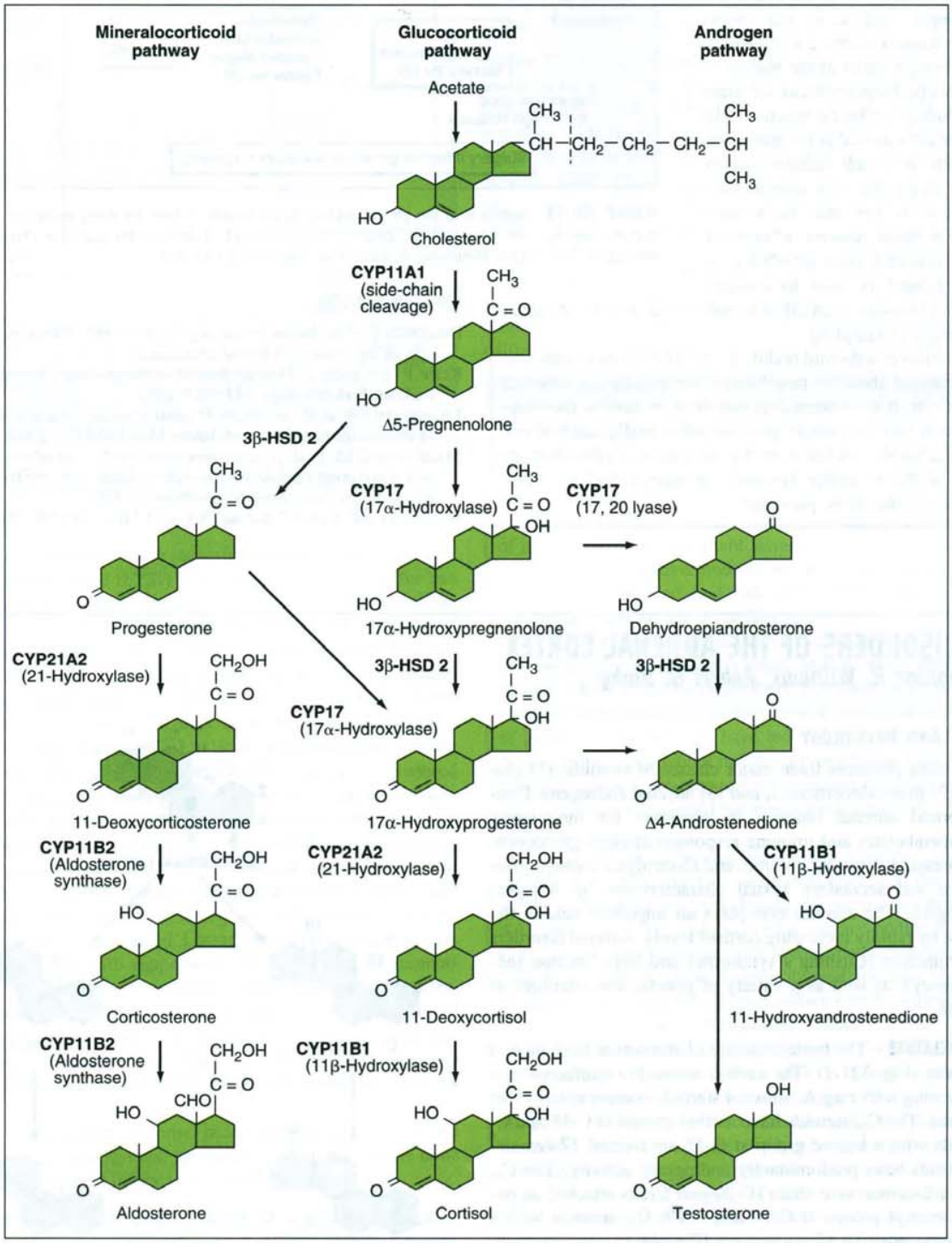

FIGURE 321-2 Biosynthetic pathways for adrenal steroid production; major pathways to mineralocorticoids, glucocorticoids, and androgens. 3β-HSD, 3β-hydroxysteroid dehydrogenase.

unbound fraction of plasma cortisol rises. Plasma has two cortisol-binding systems. One is a high-affinity, low-capacity α_2-globulin termed *transcortin* or *cortisol-binding globulin* (CBG), and the other is a low-affinity, high-capacity protein, *albumin*. Cortisol binding to CBG is reduced in areas of inflammation, thus increasing the local concentration of free cortisol. When the concentration of cortisol is >700 nmol/L (25 μg/dL), part of the excess binds to albumin, and a greater proportion than usual circulates unbound. CBG is increased in high-estrogen states (e.g., pregnancy, oral contraceptive administration). The rise in CBG is accompanied by a parallel rise in *protein-bound cortisol*, with the result that the total plasma cortisol concentration is elevated. However, the free cortisol level probably remains normal, and manifestations of glucocorticoid excess are absent. Most synthetic glucocorticoid analogues bind less efficiently to CBG (~70% binding). This may explain the propensity of some synthetic analogues to produce cushingoid effects at low doses. *Cortisol metabolites* are biologically inactive and bind only weakly to circulating plasma proteins.

Aldosterone is bound to proteins to a smaller extent than cortisol, and an ultrafiltrate of plasma contains as much as 50% of circulating aldosterone.

STEROID METABOLISM AND EXCRETION ■ Glucocorticoids The daily secretion of cortisol ranges between 40 and 80 μmol (15 and 30 mg; 8–10 mg/m^2), with a pronounced circadian cycle. The plasma concentration of cortisol is determined by the rate of secretion, the rate of inactivation, and the rate of excretion of free cortisol. The liver is the major organ responsible for steroid inactivation. A major enzyme regulating cortisol metabolism is 11β-hydroxysteroid dehydrogenase (11β-HSD). There are two isoforms: 11β-HSD I is primarily expressed in the liver and acts as a reductase, converting the inactive cortisone to the active glucocorticoid, cortisol; the 11β-HSD II isoform is expressed in a number of tissues and converts cortisol to the inactive metabolite, cortisone. Mutations in the *11BHSD1* gene are associated with rapid cortisol turnover, leading to activation of the hypothalamic-pituitary-adrenal (HPA) axis and excessive adrenal androgen production in women. In animal models, excess omental expression of 11β-HSD I increases local glucocorticoid production and is associated with central obesity and insulin resistance. The oxidative reaction of 11β-HSD I is increased in hyperthyroidism. Mutations in the *11BHSD2* gene cause the syndrome of *apparent mineralocorticoid excess*, reflecting insufficient inactivation of cortisol in the kidney, allowing inappropriate cortisol activation of the mineralocorticoid receptor (see below).

Mineralocorticoids In individuals with normal salt intake, the average daily secretion of aldosterone ranges between 0.1 and 0.7 μmol (50 and 250 μg). During a single passage through the liver, >75% of circulating aldosterone is normally inactivated by conjugation with glucuronic acid. However, under certain conditions, such as congestive failure, this rate of inactivation is reduced.

Adrenal Androgens The major androgen secreted by the adrenal is dehydroepiandrosterone (DHEA) and its sulfuric acid ester (DHEAS). Approximately 15 to 30 mg of these compounds is secreted daily. Smaller amounts of androstenedione, 11β-hydroxyandrostenedione, and testosterone are secreted. DHEA is the major precursor of the urinary 17-ketosteroids. Two-thirds of the urine 17-ketosteroids in the male are derived from adrenal metabolites, and the remaining one-third comes from testicular androgens. In the female, almost all urine 17-ketosteroids are derived from the adrenal.

Steroids diffuse passively through the cell membrane and bind to intracellular receptors (Chap. 317). Glucocorticoids and mineralocorticoids bind with nearly equal affinity to the mineralocorticoid receptor (MR). However, only glucocorticoids bind to the glucocorticoid receptor (GR). After the steroid binds to the receptor, the steroid-receptor complex is transported to the nucleus, where it binds to specific sites on steroid-regulated genes, altering levels of transcription. Some actions of glucocorticoids (e.g., anti-inflammatory effects) are mediated by GR-mediated inhibition of other transcription factors, such as activating protein-1 (AP-1) or nuclear factor kappa B (NFκB), which normally stimulate the activity of various cytokine genes. Because cortisol binds to the MR with the same affinity as aldosterone, mineralocorticoid specificity is achieved by local metabolism of cortisol to the inactive compound cortisone by 11β-HSD II. The glucocorticoid effects of other steroids, such as high-dose progesterone, correlate with their relative binding affinities for the GR. Inherited defects in the GR cause glucocorticoid resistance states. Individuals with GR defects have high levels of cortisol but do not have manifestations of hypercortisolism.

ACTH PHYSIOLOGY ACTH and a number of other peptides (lipotropins, endorphins, and melanocyte-stimulating hormones) are processed from a larger precursor molecule of 31,000 mol wt—proopiomelanocortin (POMC) (Chap. 318). POMC is made in a variety of tissues, including brain, anterior and posterior pituitary, and lymphocytes. The constellation of POMC-derived peptides secreted depends on the tissue. ACTH, a 39-amino-acid peptide, is synthesized and stored in basophilic cells of the anterior pituitary. The *N*-terminal 18-amino-acid fragment of ACTH has full biologic potency, and shorter *N*-terminal fragments have partial biologic activity. Release of ACTH and related peptides from the anterior pituitary gland is stimulated by corticotropin-releasing hormone (CRH), a 41-amino-acid peptide produced in the median eminence of the hypothalamus (Fig. 321-3). Urocortin, a neuropeptide related to CRH, mimics many of the central effects of CRH (e.g., appetite suppression, anxiety), but its role in ACTH reg-

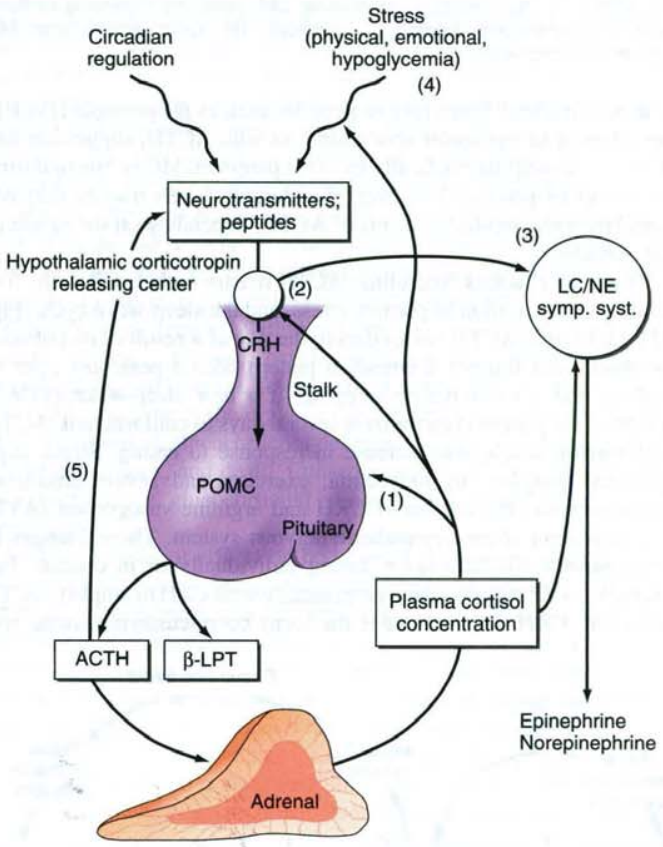

FIGURE 321-3 The hypothalamic-pituitary-adrenal axis. The main sites for feedback control by plasma cortisol are the pituitary gland (1) and the hypothalamic corticotropin-releasing center (2). Feedback control by plasma cortisol also occurs at the locus coeruleus/sympathetic system (3) and may involve higher nerve centers (4) as well. There may also be a short feedback loop involving inhibition of corticotropin-releasing hormone (CRH) by adrenocorticotropic hormone (ACTH) (5). Hypothalamic neurotransmitters influence CRH release; serotoninergic and cholinergic systems stimulate the secretion of CRH and ACTH; α-adrenergic agonists and γ-aminobutyric acid (GABA) probably inhibit CRH release. The opioid peptides β-endorphin and enkephalin inhibit, and vasopressin and angiotensin II augment, the secretion of CRH and ACTH. β-LPT, β-lipotropin; POMC, pro-opiomelanocortin; LC, locus coeruleus; NE, norepinephrine.

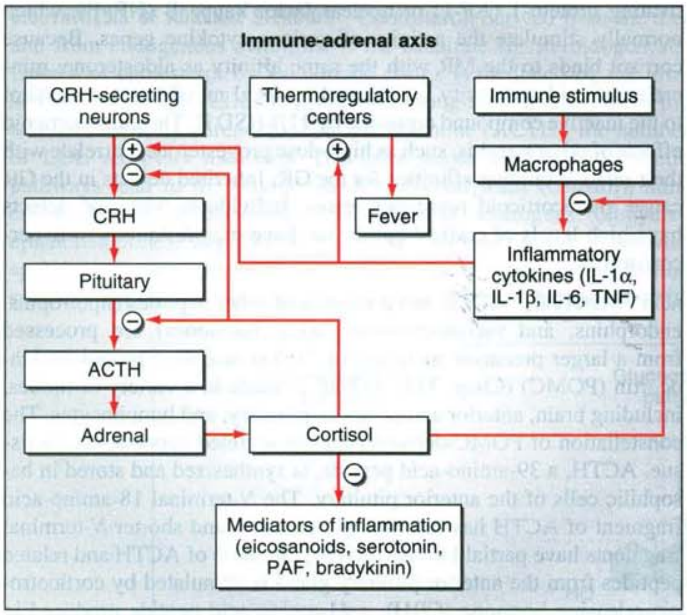

FIGURE 321-4 The immune-adrenal axis. Cortisol has anti-inflammatory properties that include effects on the microvasculature, cellular actions, and the suppression of inflammatory cytokines (the so-called immune-adrenal axis). A stress such as sepsis increases adrenal secretion, and cortisol in turn suppresses the immune response via this system. −, suppression; +, stimulation; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; IL, interleukin; TNF, tumor necrosis factor; PAF, platelet activating factor.

ulation is unclear. Some related peptides such as β-lipotropin (β-LPT) are released in equimolar concentrations with ACTH, suggesting that they are cleaved enzymatically from the parent POMC before or during the secretory process. However, β-endorphin levels may or may not correlate with circulating levels of ACTH, depending on the nature of the stimulus.

The major factors controlling ACTH release include CRH, the free cortisol concentration in plasma, stress, and the sleep-wake cycle (Fig. 321-3). Plasma ACTH varies during the day as a result of its pulsatile secretion, and follows a circadian pattern with a peak just prior to waking and a nadir before sleeping. If a new sleep-wake cycle is adopted, the pattern changes over several days to conform to it. ACTH and cortisol levels also increase in response to eating. Stress (e.g., pyrogens, surgery, hypoglycemia, exercise, and severe emotional trauma) causes the release of CRH and arginine vasopressin (AVP) and activation of the sympathetic nervous system. These changes in turn enhance ACTH release, acting individually or in concert. For example, AVP release acts synergistically with CRH to amplify ACTH secretion; CRH also stimulates the locus coeruleus/sympathetic system. Stress-related secretion of ACTH abolishes the circadian periodicity of ACTH levels but is, in turn, suppressed by prior high-dose glucocorticoid administration. The normal pulsatile, circadian pattern of ACTH release is regulated by CRH; this mechanism is the so-called open feedback loop. CRH secretion, in turn, is influenced by hypothalamic neurotransmitters including the serotoninergic and cholinergic pathways. The immune system also influences the HPA axis (Fig. 321-4). For example, inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL) 1α, IL-1β, and IL-6] produced by monocytes increase ACTH release by stimulating secretion of CRH and/or AVP. Finally, ACTH release is regulated by the level of free cortisol in plasma. Cortisol decreases the responsiveness of pituitary corticotropic cells to CRH; the response of the POMC mRNA to CRH is also inhibited by glucocorticoids. In addition, glucocorticoids inhibit the locus coeruleus/sympathetic system and CRH release. The latter servomechanism establishes the primacy of cortisol in the control of ACTH secretion. The suppression of ACTH secretion that results in adrenal atrophy following *prolonged* glucocorticoid therapy is caused primarily by suppression of hypothalamic CRH release, as exogenous CRH administration in this circumstance produces a rise in plasma ACTH. Cortisol also exerts feedback effects on higher brain centers (hippocampus, reticular system, and septum) and perhaps on the adrenal cortex (Fig. 321-4).

The biologic half-life of ACTH in the circulation is <10 min. The action of ACTH is also rapid; within minutes of its release, the concentration of steroids in the adrenal venous blood increases. ACTH stimulates steroidogenesis via activation of adenyl cyclase. Adenosine-3′,5′-monophosphate (cyclic AMP), in turn, stimulates the synthesis of protein kinase enzymes, thereby resulting in the phosphorylation of proteins that activate steroid biosynthesis.

RENIN-ANGIOTENSIN PHYSIOLOGY Renin is a proteolytic enzyme that is produced and stored in the granules of the juxtaglomerular cells surrounding the afferent arterioles of glomeruli in the kidney. Renin acts on the basic substrate angiotensinogen (a circulating α_2-globulin made in the liver) to form the decapeptide angiotensin I (Fig. 321-5). Angiotensin I is then enzymatically transformed by angiotensin-converting enzyme (ACE), which is present in many tissues (particularly the pulmonary vascular endothelium), to the octapeptide angiotensin II by the removal of the two C-terminal amino acids. Angiotensin II is a potent pressor agent and exerts its action by a direct effect on arteriolar smooth muscle. In addition, angiotensin II stimulates production of aldosterone by the zona glomerulosa of the adrenal cortex; the heptapeptide angiotensin III may also stimulate aldosterone production. The two major classes of angiotensin receptors are termed *AT1* and *AT2*; AT1 may exist as two subtypes α and β. Most of the effects of angiotensins II and III are mediated by the AT1 receptor. Angiotensinases rapidly destroy angiotensin II (half-life, ~1 min), while the half-life of renin is more prolonged (10 to 20 min). In addition to circulating renin-angiotensin, many tissues have a local renin-angiotensin system and the ability to produce angiotensin II. These tissues include the uterus, placenta, vascular tissue, heart, brain, and, particularly, the adrenal cortex and kidney. Although the role of locally generated angiotensin II is not established, it may modulate the growth and function of the adrenal cortex and vascular smooth muscle.

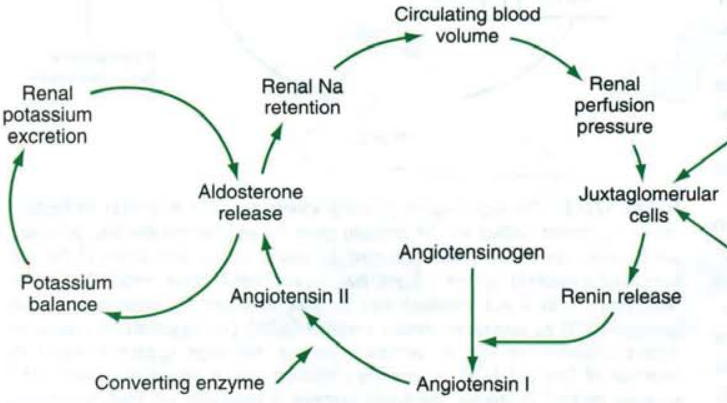

FIGURE 321-5 The interrelationship of the volume and potassium feedback loops on aldosterone secretion. Integration of signals from each loop determines the level of aldosterone secretion.

The amount of renin released reflects the combined effects of four interdependent factors. The *juxtaglomerular cells*, which are specialized myoepithelial cells that cuff the afferent arterioles, act as miniature pressure transducers, sensing renal perfusion pressure and corresponding changes in afferent arteriolar perfusion pressures. For example, a reduction in circulating blood volume leads to a corresponding reduction in renal perfusion pressure and

afferent arteriolar pressure (Fig. 321-5). This change is perceived by the juxtaglomerular cells as a decreased stretch exerted on the afferent arteriolar walls, and the juxtaglomerular cells release more renin into the renal circulation. This results in the formation of angiotensin I, which is converted in the kidney and peripherally to angiotensin II by ACE. Angiotensin II influences sodium homeostasis via two major mechanisms: it changes renal blood flow so as to maintain a constant glomerular filtration rate, thereby changing the filtration fraction of sodium, and it stimulates the adrenal cortex to release aldosterone. Increasing plasma levels of aldosterone enhance renal sodium retention and thus result in expansion of the extracellular fluid volume, which, in turn, dampens the stimulus for renin release. In this context, the renin-angiotensin-aldosterone system regulates volume by modifying renal hemodynamics and tubular sodium transport.

A second control mechanism for renin release is centered in the *macula densa cells*, a group of distal convoluted tubular epithelial cells directly opposed to the juxtaglomerular cells. They may function as chemoreceptors, monitoring the sodium (or chloride) load presented to the distal tubule. Under conditions of increased delivery of filtered sodium to the macula densa, a signal is conveyed to decrease juxtaglomerular cell release of renin, thereby modulating the glomerular filtration rate and the filtered load of sodium.

The *sympathetic nervous system* regulates the release of renin in response to assumption of the upright posture. The mechanism is either a direct effect on the juxtaglomerular cell to increase adenyl cyclase activity or an indirect effect on either the juxtaglomerular or the macula densa cells via vasoconstriction of the afferent arteriole.

Finally, circulating factors influence renin release. Increased dietary intake of potassium decreases renin release, whereas decreased potassium intake increases it. The significance of these effects is unclear. *Angiotensin II* exerts negative feedback control on renin release that is independent of alterations in renal blood flow, blood pressure, or aldosterone secretion. *Atrial natriuretic peptides* also inhibit renin release. Thus, the control of renin release involves both *intrarenal* (pressor receptor and macula densa) and *extrarenal* (sympathetic nervous system, potassium, angiotensin, etc.) mechanisms. Steady-state renin levels reflect all these factors, with the intrarenal mechanism predominating.

GLUCOCORTICOID PHYSIOLOGY The division of adrenal steroids into glucocorticoids and mineralocorticoids is arbitrary in that most glucocorticoids have some mineralocorticoid-like properties. The descriptive term *glucocorticoid* is used for adrenal steroids whose predominant action is on intermediary metabolism. Their overall actions are directed at enhancing the production of the high-energy fuel, glucose, and reducing all other metabolic activity not directly involved in that process. Sustained activation, however, results in a pathophysiologic state, e.g., Cushing's syndrome. The principal glucocorticoid is cortisol (hydrocortisone). The effect of glucocorticoids on intermediary metabolism is mediated by the GR. Physiologic effects of glucocorticoids include the regulation of protein, carbohydrate, lipid, and nucleic acid metabolism. Glucocorticoids raise the blood glucose level by antagonizing the secretion and actions of insulin, thereby inhibiting peripheral glucose uptake, which promotes hepatic glucose synthesis (gluconeogenesis) and hepatic glycogen content. The actions on protein metabolism are mainly catabolic, resulting in an increase in protein breakdown and nitrogen excretion. In large part, these actions reflect a mobilization of glycogenic amino acid precursors from peripheral supporting structures, such as bone, skin, muscle, and connective tissue, due to protein breakdown and inhibition of protein synthesis and amino acid uptake. Hyperaminoacidemia also facilitates gluconeogenesis by stimulating glucagon secretion. Glucocorticoids act directly on the liver to stimulate the synthesis of certain enzymes, such as tyrosine aminotransferase and tryptophan pyrrolase. Glucocorticoids regulate fatty acid mobilization by enhancing the activation of cellular lipase by lipid-mobilizing hormones (e.g., catecholamines and pituitary peptides).

The actions of cortisol on protein and adipose tissue vary in different parts of the body. For example, pharmacologic doses of cortisol can deplete the protein matrix of the vertebral column (trabecular bone), whereas long bones (which are primarily compact bone) are affected only minimally; similarly, peripheral adipose tissue mass decreases, whereas abdominal and interscapular fat expand.

Glucocorticoids have anti-inflammatory properties, which are probably related to effects on the microvasculature and to suppression of inflammatory cytokines. In this sense, glucocorticoids modulate the immune response via the so-called immune-adrenal axis (Fig. 321-4). This "loop" is one mechanism by which a stress, such as sepsis, increases adrenal hormone secretion, and the elevated cortisol level in turn suppresses the immune response. For example, cortisol maintains vascular responsiveness to circulating vasoconstrictors and opposes the increase in capillary permeability during acute inflammation. Glucocorticoids cause a leukocytosis that reflects release from the bone marrow of mature cells as well as inhibition of their egress through the capillary wall. Glucocorticoids produce a depletion of circulating eosinophils and lymphoid tissue, specifically T cells, by causing a redistribution from the circulation into other compartments. Thus, cortisol impairs cell-mediated immunity. Glucocorticoids also inhibit the production and action of the mediators of inflammation, such as the lymphokines and prostaglandins. Glucocorticoids inhibit the production and action of interferon by T lymphocytes and the production of IL-1 and IL-6 by macrophages. The antipyretic action of glucocorticoids may be explained by an effect on IL-1, which appears to be an endogenous pyrogen (Chap. 16). Glucocorticoids also inhibit the production of T cell growth factor (IL-2) by T lymphocytes. Glucocorticoids reverse macrophage activation and antagonize the action of migration-inhibiting factor (MIF), leading to reduced adherence of macrophages to vascular endothelium. Glucocorticoids reduce prostaglandin and leukotriene production by inhibiting the activity of phospholipase A_2, thus blocking release of arachidonic acid from phospholipids. Finally, glucocorticoids inhibit the production and inflammatory effects of bradykinin, platelet-activating factor, and serotonin. It is probably only at pharmacologic dosages that antibody production is reduced and lysosomal membranes are stabilized, the latter effect suppressing the release of acid hydrolases.

Cortisol levels respond within minutes to stress, whether physical (trauma, surgery, exercise), psychological (anxiety, depression), or physiologic (hypoglycemia, fever). The reasons why elevated glucocorticoid levels protect the organism under stress are not understood, but in conditions of glucocorticoid deficiency, such stresses may cause hypotension, shock, and death. Consequently, in individuals with adrenal insufficiency, glucocorticoid administration should be increased during stress.

Cortisol has major effects on body water. It helps regulate the extracellular fluid volume by retarding the migration of water into cells and by promoting renal water excretion, the latter effect mediated by suppression of vasopressin secretion, by an increase in the rate of glomerular filtration, and by a direct action on the renal tubule. The consequence is to prevent water intoxication by increasing solute-free water clearance. Glucocorticoids also have weak mineralocorticoid-like properties, and high doses promote renal tubular sodium reabsorption and increased urine potassium excretion. Glucocorticoids can also influence behavior; emotional disorders may occur with either an excess or a deficit of cortisol. Finally, cortisol suppresses the secretion of pituitary POMC and its derivative peptides (ACTH, β-endorphin, and β-LPT) and the secretion of hypothalamic CRH and vasopressin.

MINERALOCORTICOID PHYSIOLOGY Mineralocorticoids modify function in two classes of cells—epithelial and nonepithelial.

Effects on Epithelia Classically, mineralocorticoids are considered major regulators of extracellular fluid volume and are the major determinants of potassium metabolism. These effects are mediated by the binding of aldosterone to the MR in epithelial cells, primarily the principal cells in the renal cortical collecting duct. Because of its electro-

chemical gradient, sodium passively enters these cells from the urine via epithelial sodium channels located on the luminal membrane and is actively extruded from the cell via the Na/K-activated ATPase ("sodium pump") located on the basolateral membrane. The sodium pump also provides the driving force of potassium loss into the urine through potassium-selective luminal channels, again assisted by the electrochemical gradient for potassium in these cells. Aldosterone stimulates all three of these processes by increasing gene expression directly (for the sodium pump and the potassium channels) or via a complex process (for epithelial sodium channels) to increase both the number and activity of the sodium channels. Water passively follows the transported sodium, thus expanding intra- and extravascular volume.

Because the concentration of hydrogen ion is greater in the lumen than in the cell, hydrogen ion is also actively secreted. Mineralocorticoids also act on the epithelium of the salivary ducts, sweat glands, and gastrointestinal tract to cause reabsorption of sodium in exchange for potassium.

When normal individuals are given aldosterone, an initial period of sodium retention is followed by natriuresis, and sodium balance is reestablished after 3 to 5 days. As a result, edema does not develop. This process is referred to as the *escape phenomenon*, signifying an "escape" by the renal tubules from the sodium-retaining action of aldosterone. While renal hemodynamic factors may play a role in the escape, the level of atrial natriuretic peptide also increases. However, it is important to realize that there is no escape from the potassium-losing effects of mineralocorticoids.

Effect on Nonepithelial Cells The MR has been identified in a number of nonepithelial cells, e.g., neurons in the brain, myocytes, endothelial cells, and vascular smooth-muscle cells. In these cells, the actions of aldosterone differ from those in epithelial cells in several ways:

1. They do not modify sodium-potassium homeostasis.
2. The groups of regulated genes differ, although only a few are known; for example, in nonepithelial cells, aldosterone modifies the expression of several collagen genes and/or genes controlling tissue growth factors, e.g., transforming growth factor (TGF) β and plasminogen activator inhibitor, type 1 (PAI-1).
3. In some of these tissues (e.g., myocardium and brain), the MR is not protected by the 11β-HSD II enzyme. Thus, cortisol rather than aldosterone may be activating the MR. In other tissues (e.g., the vasculature), 11β-HSD II is expressed in a manner similar to that of the kidney. Therefore, aldosterone is activating the MR.
4. Some effects on nonepithelial cells may be via nongenomic mechanisms. These actions are too rapid—occurring within 1 to 2 min and peaking within 5 to 10 min—to be considered genomic, suggesting that they are secondary to activation of a cell-surface receptor. However, no cell-surface MR has been identified, raising the possibility that the same MR is mediating both genomic and nongenomic effects. Rapid, nongenomic effects have also been described for other steroids including estradiol, progesterone, thyroxine, and vitamin D.
5. Some of these tissues—the myocardium and vasculature—may also produce aldosterone, although this theory is controversial.

Regulation of Aldosterone Secretion Three primary mechanisms control adrenal aldosterone secretion: the renin-angiotensin system, potassium, and ACTH (Table 321-1). Whether these are also the primary regulatory mechanisms modifying nonadrenal production is uncertain. The renin-angiotensin system controls extracellular fluid volume via regulation of aldosterone secretion (Fig. 321-5). In effect, the renin-angiotensin system maintains the circulating blood volume constant by causing aldosterone-induced sodium retention during volume deficiency and by decreasing aldosterone-dependent sodium retention when volume is ample. There is an increasing body of evidence indicating that some tissues, in addition to the kidney, produce angiotensin II and may participate in the regulation of aldosterone secretion either from the adrenal or extraadrenal sources. Intriguingly, the adrenal itself is capable of synthesizing angiotensin II. What role(s) the extrarenal production of angiotensin II plays in normal physiology is still largely unknown. However, the tissue renin-angiotensin system is activated in utero in response to growth and development and/or later in life in response to injury.

TABLE 321-1 *Factors Regulating Aldosterone Biosynthesis*

Factor	Effect
Renin-angiotensin system	Stimulation
Sodium ion	Inhibition (?physiologic)
Potassium ion	Stimulation
Neurotransmitters	
Dopamine	Inhibition
Serotonin	Stimulation
Pituitary hormones	
ACTH	Stimulation
Non-ACTH pituitary hormones (e.g., growth hormone)	Permissive (for optimal response to sodium restriction)
β-Endorphin	Stimulation
γ-Melanocyte-stimulating hormone	Permissive
Atrial natriuretic peptide	Inhibition
Ouabain-like factors	Inhibition
Endothelin	Stimulation

Note: ACTH, adrenocorticotropic hormone.

Potassium ion directly stimulates aldosterone secretion, independent of the circulating renin-angiotensin system, which it suppresses (Fig. 321-5). In addition to a direct effect, potassium also modifies aldosterone secretion indirectly by activating the local renin-angiotensin system in the zona glomerulosa. This effect can be blocked by the administration of ACE inhibitors that reduce the local production of angiotensin II and thereby reduce the acute aldosterone response to potassium. An increase in serum potassium of as little as 0.1 mmol/L increases plasma aldosterone levels under certain circumstances. Oral potassium loading therefore increases aldosterone secretion, plasma levels, and excretion.

Physiologic amounts of ACTH stimulate aldosterone secretion acutely, but this action is not sustained unless ACTH is administered in a pulsatile fashion. Most studies relegate ACTH to a minor role in the control of aldosterone. For example, subjects receiving high-dose glucocorticoid therapy, and with presumed complete suppression of ACTH, have normal aldosterone secretion in response to sodium restriction.

Prior dietary intake of both potassium and sodium can alter the magnitude of the aldosterone response to acute stimulation. This effect results from a change in the expression and activity of aldosterone synthase. Increasing potassium intake or decreasing sodium intake sensitizes the response of the glomerulosa cells to acute stimulation by ACTH, angiotensin II, and/or potassium.

Neurotransmitters (dopamine and serotonin) and some peptides, such as atrial natriuretic peptide, γ-melanocyte-stimulating hormone (γ-MSH), and β-endorphin, also participate in the regulation of aldosterone secretion (Table 321-1). Thus, the control of aldosterone secretion involves both stimulatory and inhibitory factors.

ANDROGEN PHYSIOLOGY Androgens regulate male secondary sexual characteristics and can cause virilizing symptoms in women (Chap. 44). Adrenal androgens have a minimal effect in males whose sexual characteristics are predominately determined by gonadal steroids (testosterone). In females, however, several androgen-like effects, e.g., sexual hair, are largely mediated by adrenal androgens. The principal adrenal androgens are DHEA, androstenedione, and 11-hydroxyandrostenedione. DHEA and androstenedione are weak androgens and exert their effects via conversion to the potent androgen testosterone in extraglandular tissues. DHEA also has poorly understood effects on the immune and cardiovascular systems. Adrenal androgen formation is regulated by ACTH, not by gonadotropins. Adrenal androgens are suppressed by exogenous glucocorticoid administration.

LABORATORY EVALUATION OF ADRENOCORTICAL FUNCTION

A basic assumption is that measurements of the plasma or urinary level of a given steroid reflect the rate of adrenal *secretion* of that steroid. However, urine *excretion* values may not truly reflect the secretion rate because of improper collection or altered metabolism. Plasma levels reflect the level of secretion only at the time of measurement. The plasma level (*PL*) depends on two factors: the secretion rate (*SR*) of the hormone and the rate at which it is metabolized, i.e., its metabolic clearance rate (*MCR*). These three factors can be related as follows:

$$PL = \frac{SR}{MCR} \quad \text{or} \quad SR = MCR \times PL$$

BLOOD LEVELS ■ Peptides The plasma levels of ACTH and angiotensin II can be measured by immunoassay techniques. Basal ACTH secretion shows a circadian rhythm, with lower levels in the early evening than in the morning. However, ACTH is secreted in a pulsatile manner, leading to rapid fluctuations superimposed on this circadian rhythm. Angiotensin II levels also vary diurnally and are influenced by dietary sodium and potassium intakes and posture. Both upright posture and sodium restriction elevate angiotensin II levels.

Most clinical determinations of the renin-angiotensin system, however, involve measurements of peripheral *plasma renin activity* (PRA) in which the renin activity is gauged by the generation of angiotensin I during a standardized incubation period. This method depends on the presence of sufficient angiotensinogen in the plasma as substrate. The generated angiotensin I is measured by radioimmunoassay. The PRA depends on the dietary sodium intake and on whether the patient is ambulatory. In normal humans, the PRA shows a diurnal rhythm characterized by peak values in the morning and a nadir in the afternoon. An alternative approach is to measure plasma active renin, which is easier and not dependent on endogenous substrate concentration. PRA and active renin correlate very well on low-sodium diets but less well on high-sodium diets.

Steroids Cortisol and aldosterone are both secreted episodically, and levels vary during the day, with peak values in the morning and low levels in the evening. In addition, the plasma level of aldosterone, but not of cortisol, is increased by dietary potassium loading, by sodium restriction, or by assumption of the upright posture. Measurement of the sulfate conjugate of DHEA may be a useful index of adrenal androgen secretion, as little DHEA sulfate is formed in the gonads and because the half-life of DHEA sulfate is 7 to 9 h. However, DHEA sulfate levels reflect both DHEA production and sulfatase activity.

URINE LEVELS For the assessment of glucocorticoid secretion, the urine 17-hydroxycorticosteroid assay has been replaced by measurement of urinary free cortisol. Elevated levels of urinary free cortisol correlate with states of hypercortisolism, reflecting changes in the levels of unbound, physiologically active circulating cortisol. Normally, the rate of excretion is higher in the daytime (7 A.M. to 7 P.M.) than at night (7 P.M. to 7 A.M.).

Urinary 17-ketosteroids originate in either the adrenal gland or the gonad. In normal women, 90% of urinary 17-ketosteroids is derived from the adrenal, and in men 60 to 70% is of adrenal origin. Urine 17-ketosteroid values are highest in young adults and decline with age.

A carefully timed urine collection is a prerequisite for all excretory determinations. Urinary creatinine should be measured simultaneously to determine the accuracy and adequacy of the collection procedure.

STIMULATION TESTS Stimulation tests are useful in the diagnosis of hormone deficiency states.

Tests of Glucocorticoid Reserve Within minutes after administration of ACTH, cortisol levels increase. This responsiveness can be used as an index of the functional reserve of the adrenal gland for production of cortisol. Under maximal ACTH stimulation, cortisol secretion increases tenfold, to 800 μmol/d (300 mg/d), but maximal stimulation can be achieved only with prolonged ACTH infusions.

A screening test (the so-called rapid ACTH stimulation test) involves the administration of 25 units (0.25 mg) of cosyntropin intravenously or intramuscularly and measurement of plasma cortisol levels before administration and 30 and 60 min after administration, the test can be performed at any time of the day. The most clear-cut criterion for a normal response is a stimulated cortisol level of >500 nmol/L (>18 μg/dL), and the minimal stimulated normal increment of cortisol is >200 nmol/L (>7 μg/dL) above baseline. Severely ill patients with elevated basal cortisol levels may show no further increases following acute ACTH administration.

Tests of Mineralocorticoid Reserve and Stimulation of the Renin-Angiotensin System Stimulation tests use protocols designed to create a programmed volume depletion, such as sodium restriction, diuretic administration, or upright posture. A simple, potent test consists of severe sodium restriction and upright posture. After 3 to 5 days of a 10-mmol/d sodium intake, rates of aldosterone secretion or excretion should increase two- to threefold over the control values. Supine morning plasma aldosterone levels are usually increased three- to sixfold, and they increase a further two- to fourfold in response to 2 to 3 h of upright posture.

When the dietary sodium intake is normal, stimulation testing requires the administration of a potent diuretic, such as 40 to 80 mg furosemide, followed by 2 to 3 h of upright posture. The normal response is a two- to fourfold rise in plasma aldosterone levels.

SUPPRESSION TESTS Suppression tests to document hypersecretion of adrenal hormones involve measurement of the target hormone response after standardized suppression of its tropic hormone.

Tests of Pituitary-Adrenal Suppressibility The ACTH release mechanism is sensitive to the circulating glucocorticoid level. When blood levels of glucocorticoid are increased in normal individuals, less ACTH is released from the anterior pituitary and less steroid is produced by the adrenal gland. The integrity of this feedback mechanism can be tested clinically by giving a glucocorticoid and judging the suppression of ACTH secretion by analysis of urine steroid levels and/or plasma cortisol and ACTH levels. A potent glucocorticoid such as dexamethasone is used, so that the agent can be given in an amount small enough not to contribute significantly to the pool of steroids to be analyzed.

The best *screening* procedure is the overnight dexamethasone suppression test. This involves the measurement of plasma cortisol levels at 8 A.M. following the oral administration of 1 mg dexamethasone the previous midnight. The 8 A.M. value for plasma cortisol in normal individuals should be <140 nmol/L (5 μg/dL).

The definitive test of adrenal suppressibility involves administering 0.5 mg dexamethasone every 6 h for two successive days while collecting urine over a 24-h period for determination of creatinine and free cortisol and/or measuring plasma cortisol levels. In a patient with a normal hypothalamic-pituitary ACTH release mechanism, a fall in the urine free cortisol to <80 nmol/d (30 μg/d) or of plasma cortisol to <140 nmol/L (5 μg/dL) is seen on the second day of administration.

A normal response to either suppression test implies that the glucocorticoid regulation of ACTH and its control of the adrenal glands is physiologically normal. However, an isolated abnormal result, particularly to the overnight suppression test, does not in itself demonstrate pituitary and/or adrenal disease.

Tests of Mineralocorticoid Suppressibility These tests rely on an expansion of extracellular fluid volume, which should decrease circulating plasma renin activity and decrease the secretion and/or excretion of aldosterone. Various tests differ in the rate at which extracellular fluid volume is expanded. One convenient suppression test involves the intravenous infusion of 500 mL/h of normal saline solution for 4 h, which normally suppresses plasma aldosterone levels to <220 pmol/L (<8 ng/dL) from a sodium-restricted diet or to <140 pmol/L (<5 ng/dL) from a normal sodium intake. Alternatively, a high-sodium diet can be administered for 3 days with 0.2 mg fludrocortisone twice daily. Aldosterone excretion is measured on the third day and should be <28 nmol/d (10 μg/d). These tests should not be performed in potassium-

depleted individuals since they carry a risk of precipitating hypokalemia.

TESTS OF PITUITARY-ADRENAL RESPONSIVENESS Stimuli such as insulin-induced hypoglycemia, AVP, and pyrogens induce the release of ACTH from the pituitary by an action on higher neural centers or on the pituitary itself. Insulin-induced hypoglycemia is particularly useful, because it stimulates the release of both growth hormone and ACTH. In this test, regular insulin (0.05 to 0.1 U/kg body weight) is given intravenously as a bolus to reduce the fasting glucose level to at least 50% below basal. The normal cortisol response is a rise to >500 nmol/L (18 μg/dL). Glucose levels must be monitored during insulin-induced hypoglycemia, and it should be terminated by feeding or intravenous glucose, if subjects develop symptoms of hypoglycemia. This test is contraindicated in individuals with coronary artery disease or a seizure disorder.

Metyrapone inhibits 11β-hydroxylase in the adrenal. As a result, the conversion of 11-deoxycortisol (compound S) to cortisol is impaired, causing 11-deoxycortisol to accumulate in the blood and the blood level of cortisol to decrease (Fig. 321-2). The hypothalamic-pituitary axis responds to the declining cortisol blood levels by releasing more ACTH. Note that assessment of the response depends on both an intact hypothalamic-pituitary axis and an intact adrenal gland.

Although modifications of the original metyrapone test have been described, a commonly used protocol involves administering 750 mg of the drug by mouth every 4 h over a 24-h period and comparing the control and postmetyrapone plasma levels of 11-deoxycortisol, cortisol, and ACTH. In normal individuals, plasma 11-deoxycortisol levels should exceed 210 nmol/L (7 μg/dL) and ACTH levels should exceed 17 pmol/L (75 pg/mL) following metyrapone administration. The metyrapone test does not accurately reflect ACTH reserve if subjects are ingesting exogenous glucocorticoids or drugs that accelerate the metabolism of metyrapone (e.g., phenytoin).

A direct and selective test of the pituitary corticotrophs can be achieved with CRH. The bolus injection of ovine CRH (corticorelin ovine triflutate; 1 μg/kg body weight) stimulates secretion of ACTH and β-LPT in normal human subjects within 15 to 60 min. In normal individuals, the mean increment in ACTH is 9 pmol/L (40 pg/mL). However, the magnitude of the ACTH response is less than that produced by insulin-induced hypoglycemia, implying that additional factors (such as vasopressin) augment stress-induced increases in ACTH secretion.

The rapid ACTH test can often distinguish between primary and secondary adrenal insufficiency, because aldosterone secretion is preserved in secondary adrenal failure by the renin-angiotensin system and potassium. Cosyntropin (25 units) is given intravenously or intramuscularly, and plasma cortisol and aldosterone levels are measured before and at 30 and 60 min after administration. The cortisol response is abnormal in both groups, but patients with secondary insufficiency show an increase in aldosterone levels of at least 140 pmol/L (5 ng/dL). No aldosterone response is seen in patients in whom the adrenal cortex is destroyed. Alternatively, ACTH at a physiologic dose (1 μg), the so-called low-dose ACTH test, may be used to detect secondary adrenal insufficiency. An abnormal response is similar to that in the rapid ACTH test. However, levels need to be measured at 30 min, and the ACTH needs to be directly injected intravenously because it can be absorbed by plastic tubing. Because the use of a bolus of exogenous ACTH does not invariably exclude a diagnosis of secondary adrenocortical insufficiency, direct tests of pituitary ACTH reserve (metyrapone test, insulin-induced hypoglycemia) may be required in the appropriate clinical setting.

HYPERFUNCTION OF THE ADRENAL CORTEX

Excess cortisol is associated with Cushing's syndrome; excess aldosterone causes aldosteronism; and excess adrenal androgens cause adrenal virilism. These syndromes do not always occur in the "pure" form but may have overlapping features.

CUSHING'S SYNDROME ■ Etiology Cushing described a syndrome characterized by truncal obesity, hypertension, fatigability and weakness, amenorrhea, hirsutism, purplish abdominal striae, edema, glucosuria, osteoporosis, and a basophilic tumor of the pituitary. As awareness of this syndrome has increased, the diagnosis of Cushing's syndrome has been broadened into the classification shown in Table 321-2. Regardless of etiology, all cases of endogenous Cushing's syndrome are due to increased production of cortisol by the adrenal. In most cases the cause is *bilateral adrenal hyperplasia* due to hypersecretion of pituitary ACTH or ectopic production of ACTH by a nonpituitary source. The incidence of pituitary-dependent adrenal hyperplasia is three times greater in women than in men, and the most frequent age of onset is the third or fourth decade. Most evidence indicates that the primary defect is the de novo development of a pituitary adenoma, as tumors are found in >90% of patients with pituitary-dependent adrenal hyperplasia. Alternatively, the defect may occasionally reside in the hypothalamus or in higher neural centers, leading to release of CRH inappropriate to the level of circulating cortisol. This primary defect leads to hyperstimulation of the pituitary, resulting in hyperplasia or tumor formation. In surgical series, most individuals with hypersecretion of pituitary ACTH are found to have a microadenoma (<10 mm in diameter; 50% are ≤5 mm in diameter), but a pituitary macroadenoma (>10 mm) or diffuse hyperplasia of the corticotrope cells may be found. Traditionally, only an individual who has an ACTH-producing pituitary tumor is defined as having *Cushing's disease*, whereas Cushing's syndrome refers to all causes of excess cortisol: exogenous ACTH tumor, adrenal tumor, pituitary ACTH-secreting tumor, or excessive glucocorticoid treatment.

The *ectopic ACTH syndrome* is caused by nonpituitary tumors that secrete either ACTH and/or CRH and cause bilateral adrenal hyperplasia (Chap. 86). The ectopic production of CRH results in clinical, biochemical, and radiologic features indistinguishable from those caused by hypersecretion of pituitary ACTH. The typical signs and symptoms of Cushing's syndrome may be absent or minimal with ectopic ACTH production, and hypokalemic alkalosis is a prominent manifestation. Most of these cases are associated with the primitive small cell (oat cell) type of bronchogenic carcinoma or with carcinoid tumors of the thymus, pancreas, or ovary; medullary carcinoma of the thyroid; or bronchial adenomas. The onset of Cushing's syndrome may be sudden, particularly in patients with carcinoma of the lung, and this feature accounts in part for the failure of these patients to exhibit the classic manifestations. On the other hand, patients with carcinoid tumors or pheochromocytomas have longer clinical courses and usually exhibit the typical cushingoid features. The ectopic secretion of ACTH is also accompanied by the accumulation of ACTH fragments in plasma and by elevated plasma levels of ACTH precursor molecules.

TABLE 321-2 Causes of Cushing's Syndrome

Adrenal hyperplasia
Secondary to pituitary ACTH overproduction
Pituitary-hypothalamic dysfunction
Pituitary ACTH-producing micro- or macroadenomas
Secondary to ACTH or CRH-producing nonendocrine tumors (bronchogenic carcinoma, carcinoid of the thymus, pancreatic carcinoma, bronchial adenoma)
Adrenal macronodular hyperplasia (including ectopic expression of GIP receptors in the adrenal cortex)
Adrenal micronodular dysplasia
Sporadic
Familial (Carney's syndrome)
Adrenal neoplasia
Adenoma
Carcinoma
Exogenous, iatrogenic causes
Prolonged use of glucocorticoids
Prolonged use of ACTH

Note: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GIP, gastric inhibitory peptide.

Because such tumors may produce large amounts of ACTH, baseline steroid values are usually very high and increased skin pigmentation may be present.

Approximately 20 to 25% of patients with Cushing's syndrome have an adrenal neoplasm. These tumors are usually unilateral, and about half are malignant. Occasionally, patients have biochemical features both of pituitary ACTH excess and of an adrenal adenoma. These individuals may have *nodular hyperplasia* of both adrenal glands, often the result of prolonged ACTH stimulation in the absence of a pituitary adenoma. Two additional entities cause nodular hyperplasia: a familial disorder in children or young adults (so-called pigmented micronodular dysplasia; see below) and an abnormal cortisol response to gastric inhibitory polypeptide or luteinizing hormone, secondary to ectopic expression of receptors for these hormones in the adrenal cortex.

The most common cause of Cushing's syndrome is *iatrogenic* administration of steroids for a variety of reasons. Although the clinical features bear some resemblance to those seen with adrenal tumors, these patients are usually distinguishable on the basis of history and laboratory studies.

Clinical Signs, Symptoms, and Laboratory Findings Many of the signs and symptoms of Cushing's syndrome follow logically from the known action of glucocorticoids (Table 321-3). Catabolic responses in peripheral supportive tissue causes muscle weakness and fatigability, osteoporosis, broad violaceous cutaneous striae, and easy bruisability. The latter signs are secondary to weakening and rupture of collagen fibers in the dermis. Osteoporosis may cause collapse of vertebral bodies and pathologic fractures of other bones. Decreased bone mineralization is particularly pronounced in children. Increased hepatic gluconeogenesis and insulin resistance can cause impaired glucose tolerance. Overt diabetes mellitus occurs in <20% of patients, who probably are individuals with a predisposition to this disorder. Hypercortisolism promotes the deposition of adipose tissue in characteristic sites, notably the upper face (producing the typical "moon" facies), the interscapular area (producing the "buffalo hump"), supraclavicular fat pads, and the mesenteric bed (producing "truncal" obesity) (Fig. 321-6). Rarely, episternal fatty tumors and mediastinal widening secondary to fat accumulation occur. The reason for this peculiar distribution of adipose tissue is not known, but it is associated with insulin resistance and/or elevated insulin levels. The face appears plethoric, even in the absence of any increase in red blood cell concentration. Hypertension is common, and emotional changes may be profound, ranging from irritability and emotional lability to severe depression, confusion, or even frank psychosis. In women, increased levels of adrenal androgens can cause acne, hirsutism, and oligomenorrhea or amenorrhea. Some signs and symptoms in patients with hypercortisolism—i.e., obesity, hypertension, osteoporosis, and diabetes—are nonspecific and therefore are less helpful in diagnosing the condition. On the other hand, easy bruising, typical striae, myopathy, and virilizing signs (although less frequent) are, if present, more suggestive of Cushing's syndrome (Table 321-3).

Except in iatrogenic Cushing's syndrome, plasma and urine cortisol levels are elevated. Occasionally, hypokalemia, hypochloremia, and metabolic alkalosis are present, particularly with ectopic production of ACTH.

Diagnosis The diagnosis of Cushing's syndrome depends on the demonstration of increased cortisol production and failure to suppress cortisol secretion normally when dexamethasone is administered (Chap. 318). Once the diagnosis is established, further testing is designed to determine the etiology (Fig. 321-7 and Table 321-4).

For initial screening, the overnight dexamethasone suppression test is recommended (see above). In difficult cases (e.g., in obese or depressed patients), measurement of a 24-h urine free cortisol can also be used as a screening test. A level >140 nmol/d (50 μg/d) is suggestive of Cushing's syndrome. The definitive diagnosis is then established by failure of urinary cortisol to fall to less than <25 nmol/d (10 μg/d) or of plasma cortisol to fall to <140 nmol/L (5 μg/dL) after a standard low-dose dexamethasone suppression test (0.5 mg every 6 h for 48 h). Owing to circadian variability, plasma cortisol and, to a certain extent, ACTH determinations are not meaningful when performed in isolation, but the absence of the normal fall of plasma cortisol at midnight is consistent with Cushing's syndrome because there is loss of the diurnal cortisol rhythm.

TABLE 321-3 *Frequency of Signs and Symptoms in Cushing's Syndrome*

Sign or Symptom	Percent of Patients
Typical habitus (centripetal obesity)[a]	97
Increased body weight	94
Fatigability and weakness	87
Hypertension (blood pressure >150/90)	82
Hirsutism[a]	80
Amenorrhea	77
Broad violaceous cutaneous striae[a]	67
Personality changes	66
Ecchymoses[a]	65
Proximal myopathy[a]	62
Edema	62
Polyuria, polydipsia	23
Hypertrophy of clitoris	19

[a] Features more specific for Cushing's syndrome.

The task of determining the etiology of Cushing's syndrome is complicated by the fact that all the available tests lack specificity and by the fact that the tumors producing this syndrome are prone to spontaneous and often dramatic changes in hormone secretion (periodic hormonogenesis). No test has a specificity >95%, and it may be necessary to use a combination of tests to arrive at the correct diagnosis.

Plasma ACTH levels can be useful in distinguishing the various causes of Cushing's syndrome, particularly in separating ACTH-dependent from ACTH-independent causes. In general, measurement of plasma ACTH is useful in the diagnosis of ACTH-independent etiologies of the syndrome, since most adrenal tumors cause low or undetectable ACTH levels [<2 pmol/L (10 pg/mL)]. Furthermore, ACTH-secreting pituitary macroadenomas and ACTH-producing nonendocrine tumors usually result in elevated ACTH levels. In the ectopic ACTH syndrome, ACTH levels may be elevated to >110 pmol/L (500 pg/mL), and in most patients the level is >40 pmol/L (200 pg/mL). In Cushing's syndrome as the result of a microadenoma or pituitary-hypothalamic dysfunction, ACTH levels range from 6 to 30 pmol/L (30 to 150 pg/mL) [normal, <14 pmol/L (<60 pg/mL)],

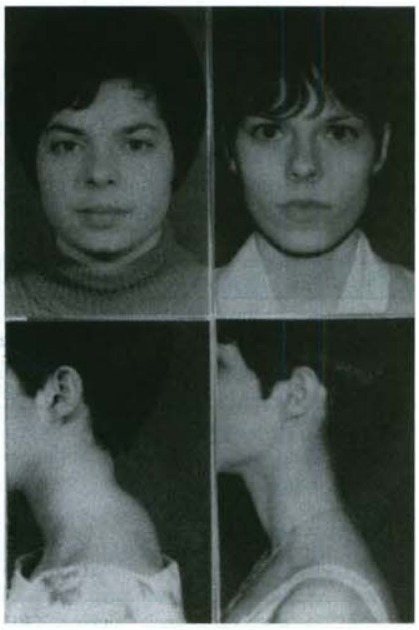

FIGURE 321-6 A woman with Cushing's syndrome due to a right adrenal cortical adenoma. *A*. One month prior to surgery, age 20. *B*. One year after surgery, age 21.

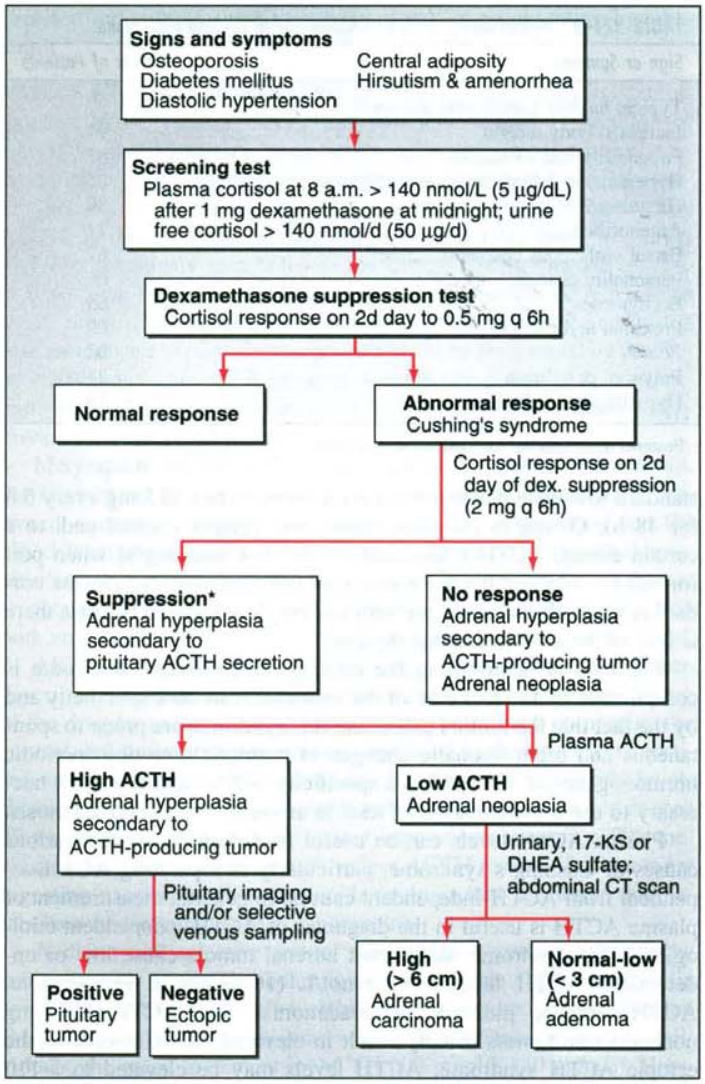

FIGURE 321-7 Diagnostic flowchart for evaluating patients suspected of having Cushing's syndrome. *This group probably includes some patients with pituitary-hypothalamic dysfunction and some with pituitary microadenomas. In some instances, a microadenoma may be visualized by pituitary magnetic resonance scanning. 17-KS, 17-ketosteroids; DHEA, dehydroepiandrosterone; ACTH, adrenocorticotropic hormone; CT, computed tomography.

with half of values falling in the normal range. However, the main problem with the use of ACTH levels in the differential diagnosis of Cushing's syndrome is that ACTH levels may be similar in individuals with hypothalamic-pituitary dysfunction, pituitary microadenomas, ectopic CRH production, and ectopic ACTH production (especially carcinoid tumors) (Table 321-4).

TABLE 321-4 *Diagnostic Tests to Determine the Type of Cushing's Syndrome*

Test	Pituitary Macroadenoma	Pituitary Microadenoma	Ectopic ACTH or CRH Production	Adrenal Tumor
Plasma ACTH level	↑ to ↑↑	N to ↑	↑ to ↑↑↑	↓
Percent who respond to high-dose dexamethasone	<10	95	<10	<10
Percent who respond to CRH	>90	>90	<10	<10

Note: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; N, normal; ↑, elevated; ↓, decreased. See text for definition of a response.

A useful step to distinguish patients with an ACTH-secreting pituitary microadenoma or hypothalamic-pituitary dysfunction from those with other forms of Cushing's syndrome is to determine the response of cortisol output to administration of high-dose dexamethasone (2 mg every 6 h for 2 days). An alternative 8-mg, overnight high-dose dexamethasone test has been developed; however, this test has a lower sensitivity and specificity than the standard test. When the diagnosis of Cushing's syndrome is clear-cut on the basis of baseline urinary and plasma assays, the high-dose dexamethasone suppression test may be used without performing the preliminary low-dose suppression test. The high-dose suppression test provides close to 100% specificity if the criterion used is suppression of urinary free cortisol by >90%. Occasionally, in individuals with bilateral nodular hyperplasia and/or ectopic CRH production, steroid output is also suppressed. Failure of low- and high-dose dexamethasone administration to suppress cortisol production (Table 321-4) can occur in patients with adrenal hyperplasia secondary to an ACTH-secreting pituitary macroadenoma or an ACTH-producing tumor of nonendocrine origin and in those with adrenal neoplasms.

Because of these difficulties, several additional tests have been advocated, such as the metyrapone and CRH infusion tests. The rationale underlying these tests is that steroid hypersecretion by an adrenal tumor or the ectopic production of ACTH will suppress the hypothalamic-pituitary axis so that inhibition of pituitary ACTH release can be demonstrated by either test. Thus, most patients with pituitary-hypothalamic dysfunction and/or a microadenoma have an increase in steroid or ACTH secretion in response to metyrapone or CRH administration, whereas most patients with ectopic ACTH-producing tumors do not. Most pituitary macroadenomas also respond to CRH, but their response to metyrapone is variable. However, false-positive and false-negative CRH tests can occur in patients with ectopic ACTH and pituitary tumors.

The main diagnostic dilemma in Cushing's syndrome is to distinguish those instances due to microadenomas of the pituitary from those due to ectopic sources (e.g., carcinoids or pheochromocytoma) that produce CRH and/or ACTH. The clinical manifestations are similar unless the ectopic tumor produces other symptoms, such as diarrhea and flushing from a carcinoid tumor or episodic hypertension from a pheochromocytoma. Sometimes, one can distinguish between ectopic and pituitary ACTH production by using metyrapone or CRH tests, as noted above. In these situations, computed tomography (CT) of the pituitary gland is usually normal. Magnetic resonance imaging (MRI) with the enhancing agent gadolinium may be better than CT for this purpose but demonstrates pituitary microadenomas in only half of patients with Cushing's disease. Because microadenomas can be detected in up to 10 to 20% of individuals without known pituitary disease, a positive imaging study does not prove that the pituitary is the source of ACTH excess. In those with negative imaging studies, selective petrosal sinus venous sampling for ACTH is now used in many referral centers. ACTH levels are measured at baseline, 2, 5, and 10 min after ovine CRH (1 μ/kg IV) injections. Peak petrosal:peripheral ACTH ratios of >3 confirm the presence of a pituitary ACTH-secreting tumor. In centers where petrosal sinus sampling is performed frequently, it has proved highly sensitive for distinguishing pituitary and nonpituitary sources of ACTH excess. However, the catheterization procedure is technically difficult, and complications have occurred.

The diagnosis of a *cortisol-producing adrenal adenoma* is suggested by low ACTH and disproportionate elevations in baseline urine free cortisol levels with only modest changes in urinary 17-ketosteroids or plasma DHEA sulfate. Adrenal androgen secretion is usually reduced in these patients owing to the cortisol-induced suppression of ACTH and subsequent involution of the androgen-producing zona reticularis.

The diagnosis of *adrenal carcinoma* is suggested by a palpable abdominal mass and by markedly elevated baseline values of both urine 17-ketosteroids and plasma DHEA sulfate. Plasma and urine cortisol levels are variably elevated. Adrenal carcinoma is usually resistant to both ACTH stimulation and dexamethasone suppression. El-

evated adrenal androgen secretion often leads to virilization in the female. Estrogen-producing adrenocortical carcinoma usually presents with gynecomastia in men and dysfunctional uterine bleeding in women. These adrenal tumors secrete increased amounts of androstenedione, which is converted peripherally to the estrogens estrone and estradiol. Adrenal carcinomas that produce Cushing's syndrome are often associated with elevated levels of the intermediates of steroid biosynthesis (especially 11-deoxycortisol), suggesting inefficient conversion of the intermediates to the final product. This feature also accounts for the characteristic increase in 17-ketosteroids. Approximately 20% of adrenal carcinomas are not associated with endocrine syndromes and are presumed to be nonfunctioning or to produce biologically inactive steroid precursors. In addition, the excessive production of steroids is not always clinically evident (e.g., androgens in adult men).

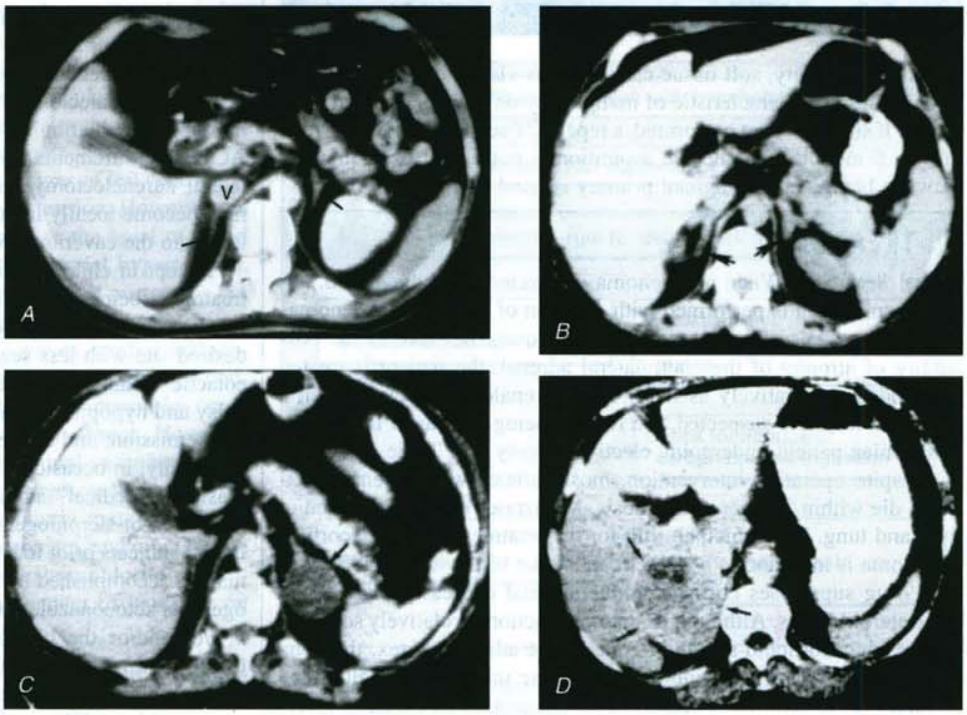

FIGURE 321-8 Computed tomography (CT) is the preferred method for visualizing the adrenal glands (*arrows*). *A*. The normal right adrenal gland is adjacent to the inferior vena cava (V) where it emerges from the liver. Approximately 90% of right adrenal glands appear as linear structures extending posteriorly from the inferior vena cava into the space between the right lobe of the liver and the crus of the diaphragm. The normal left adrenal gland is lateral to the left crus of the diaphragm and below the stomach. Most left adrenal glands are shaped like an inverted V or Y. *B*. Adrenal CT scan of a patient with ectopic ACTH production. Both adrenal glands (*arrows*) are enlarged (compare with *A*). In contrast, only 50% of patients with bilateral adrenal hyperplasia secondary to pituitary ACTH hypersecretion show enlargement of the adrenals when imaged by CT scan. *C*. CT scan of a patient with Cushing's syndrome with biochemical evidence only of cortisol overproduction. The left adrenal has been replaced by a racquet-shaped 2-cm tumor (*arrow*). Attenuation of the tumor is low because of its high lipid content. *D*. CT scan in a patient with Cushing's syndrome and biochemical evidence of an adrenal carcinoma. In contrast to the tumor in *C*, the right-sided mass in this patient is large and has a heterogeneous appearance—usual characteristics of an adrenal carcinoma.

Differential Diagnosis ■ *PSEUDO-CUSHING'S SYNDROME* Problems in diagnosis include patients with obesity, chronic alcoholism, depression, and acute illness of any type. Extreme *obesity* is uncommon in Cushing's syndrome; furthermore, with exogenous obesity, the adiposity is generalized, not truncal. On adrenocortical testing, abnormalities in patients with exogenous obesity are usually modest. Basal urine steroid excretion levels in obese patients are also either normal or slightly elevated, and the diurnal pattern in blood and urine levels is normal. Patients with *chronic alcoholism* and those with *depression* share similar abnormalities in steroid output: modestly elevated urine cortisol, blunted circadian rhythm of cortisol levels, and resistance to suppression using the overnight dexamethasone test. In contrast to alcoholic subjects, depressed patients do not have signs and symptoms of Cushing's syndrome. Following discontinuation of alcohol and/or improvement in the emotional status, results of steroid testing usually return to normal. One or more of three tests have been used to differentiate mild Cushing's syndrome and pseudo-Cushing's syndrome. The serum cortisol level following the standard 2-day low-dose dexamethasone test has very high sensitivity and specificity. Although the CRH test alone is less useful, in combination with the low-dose dexamethasone test, there is nearly complete discrimination between these two conditions. Finally, a midnight cortisol level obtained in awake patients may have similar predictive value as the low-dose dexamethasone test if a cut-off of 210 nmol/L (7.5 μg/dL) is used. Patients with *acute illness* often have abnormal results on laboratory tests and fail to exhibit pituitary-adrenal suppression in response to dexamethasone, since major stress (such as pain or fever) interrupts the normal regulation of ACTH secretion. *Iatrogenic Cushing's syndrome*, induced by the administration of glucocorticoids or other steroids such as megestrol that bind to the glucocorticoid receptor, is indistinguishable by physical findings from endogenous adrenocortical hyperfunction. The distinction can be made, however, by measuring blood or urine cortisol levels in a basal state; in the iatrogenic syndrome these levels are low secondary to suppression of the pituitary-adrenal axis. The severity of iatrogenic Cushing's syndrome is related to the total steroid dose, the biologic half-life of the steroid, and the duration of therapy. Also, individuals taking afternoon and evening doses of glucocorticoids develop Cushing's syndrome more readily and with a smaller total daily dose than do patients taking morning doses only.

Radiologic Evaluation for Cushing's Syndrome The preferred radiologic study for visualizing the adrenals is a CT scan of the abdomen (Fig. 321-8). CT is of value both for localizing adrenal tumors and for diagnosing bilateral hyperplasia. All patients believed to have hypersecretion of pituitary ACTH should have a pituitary MRI scan with gadolinium contrast. Even with this technique, small microadenomas may be undetectable; alternatively, false-positive masses due to cysts or nonsecretory lesions of the normal pituitary may be imaged. In patients with ectopic ACTH production, high-resolution chest CT is a useful first step.

Evaluation of Asymptomatic Adrenal Masses With abdominal CT scanning, many incidental adrenal masses (so-called incidentalomas) are discovered. This is not surprising, since 10 to 20% of subjects at autopsy have adrenocortical adenomas. The first step in evaluating such patients is to determine whether the tumor is functioning by means of appropriate screening tests, e.g., measurement of 24-h urine catecholamines and metabolites and serum potassium and assessment of adrenal cortical function by dexamethasone-suppression testing. However, 90% of incidentalomas are nonfunctioning. If an extra-adrenal malignancy is present, there is a 30 to 50% chance that the adrenal tumor is a metastasis. If the primary tumor is being treated and there are no other metastases, it is prudent to obtain a fine-needle aspirate of the adrenal mass to establish the diagnosis. In the absence of a known malignancy the next step is unclear. The probability of adrenal carcinoma is <0.01%, the vast majority of adrenal masses being benign adenomas. Features suggestive of malignancy include large size (a size > 4 to 6 cm suggests carcinoma); irregular margins;

and inhomogeneity, soft tissue calcifications visible on CT (Fig. 321-8), and findings characteristic of malignancy on a chemical-shift MRI image. If surgery is not performed, a repeat CT scan should be obtained in 3 to 6 months. Fine-needle aspiration is not useful to distinguish between benign and malignant primary adrenal tumors.

Rx TREATMENT

Adrenal Neoplasm When an adenoma or carcinoma is diagnosed, adrenal exploration is performed with excision of the tumor. Adenomas may be resected using laparoscopic techniques. Because of the possibility of atrophy of the contralateral adrenal, the patient is treated pre- and postoperatively as if for total adrenalectomy, even when a unilateral lesion is suspected, the routine being similar to that for an Addisonian patient undergoing elective surgery (see Table 321-8).

Despite operative intervention, most patients with adrenal carcinoma die within 3 years of diagnosis. Metastases occur most often to liver and lung. The principal drug for the treatment of adrenocortical carcinoma is mitotane (*o,p'*-DDD), an isomer of the insecticide DDT. This drug suppresses cortisol production and decreases plasma and urine steroid levels. Although its cytotoxic action is relatively selective for the glucocorticoid-secreting zone of the adrenal cortex, the zona glomerulosa may also be inhibited. Because mitotane also alters the extraadrenal metabolism of cortisol, plasma and urinary cortisol levels must be assessed to titrate the effect. The drug is usually given in divided doses three to four times a day, with the dose increased gradually to tolerability (usually <6 g daily). At higher doses, almost all patients experience side effects, which may be gastrointestinal (anorexia, diarrhea, vomiting) or neuromuscular (lethargy, somnolence, dizziness). All patients treated with mitotane should receive long-term glucocorticoid maintenance therapy, and, in some, mineralocorticoid replacement is appropriate. In approximately one-third of patients, both tumor and metastases regress, but long-term survival is not altered. In many patients, mitotane only inhibits steroidogenesis and does not cause regression of tumor metastases. Osseous metastases are usually refractory to the drug and should be treated with radiation therapy. Mitotane can also be given as adjunctive therapy after surgical resection of an adrenal carcinoma, although there is no evidence that this improves survival. Because of the absence of a long-term benefit with mitotane, alternative chemotherapeutic approaches based on platinum therapy have been used. However, there are no data presently available indicating a prolongation of life.

BILATERAL HYPERPLASIA Patients with hyperplasia usually have a relative or absolute increase in ACTH levels. Since therapy would logically be directed at reducing ACTH levels, the ideal primary treatment for ACTH- or CRH-producing tumors, whether pituitary or ectopic, is surgical removal. Occasionally (particularly with ectopic ACTH production) surgical excision is not possible because the disease is far advanced. In this situation, "medical" or surgical adrenalectomy may correct the hypercortisolism.

Controversy exists as to the proper treatment for bilateral adrenal hyperplasia when the source of the ACTH overproduction is not apparent. In some centers, these patients (especially those who suppress after the administration of a high-dose dexamethasone test) undergo surgical exploration of the pituitary via a transsphenoidal approach in the expectation that a microadenoma will be found (Chap. 318). However, in most circumstances selective petrosal sinus venous sampling is recommended, and the patient is referred to an appropriate center if the procedure is not available locally. If a microadenoma is not found at the time of exploration, total hypophysectomy may be needed. Complications of transsphenoidal surgery include cerebrospinal fluid rhinorrhea, diabetes insipidus, panhypopituitarism, and optic or cranial nerve injuries.

In other centers, total adrenalectomy is the treatment of choice. The cure rate with this procedure is close to 100%. The adverse effects include the certain need for lifelong mineralocorticoid and glucocorticoid replacement and a 10 to 20% probability of a pituitary tumor developing over the next 10 years (Nelson's syndrome; Chap. 318). It is uncertain whether these tumors arise de novo or if they were present prior to adrenalectomy but were too small to be detected. Periodic radiologic evaluation of the pituitary gland by MRI as well as serial ACTH measurements should be performed in all individuals after bilateral adrenalectomy for Cushing's disease. Such pituitary tumors may become locally invasive and impinge on the optic chiasm or extend into the cavernous or sphenoid sinuses.

Except in children, pituitary irradiation is rarely used as primary treatment, being reserved rather for postoperative tumor recurrences. In some centers, high levels of gamma radiation can be focused on the desired site with less scattering to surrounding tissues by using stereotactic techniques. Side effects of radiation include ocular motor palsy and hypopituitarism. There is a long lag time between treatment and remission, and the remission rate is usually <50%.

Finally, in occasional patients in whom a surgical approach is not feasible, "medical" adrenalectomy may be indicated (Table 321-5). Inhibition of steroidogenesis may also be indicated in severely cushingoid subjects prior to surgical intervention. Chemical adrenalectomy may be accomplished by the administration of the inhibitor of steroidogenesis ketoconazole (600 to 1200 mg/d). In addition, mitotane (2 or 3 g/d) and/or the blockers of steroid synthesis aminoglutethimide (1 g/d) and metyrapone (2 or 3 g/d) may be effective either alone or in combination. Mitotane is slow to take effect (weeks). Mifepristone, a competitive inhibitor of the binding of glucocorticoid to its receptor, may be a treatment option. Adrenal insufficiency is a risk with all these agents, and replacement steroids may be required.

ALDOSTERONISM

Aldosteronism is a syndrome associated with hypersecretion of the mineralocorticoid aldosterone. In *primary* aldosteronism the cause for the excessive aldosterone production resides within the adrenal gland; in *secondary* aldosteronism the stimulus is extraadrenal.

Primary Aldosteronism In the original descriptions of excessive and inappropriate aldosterone production, the disease was the result of an *aldosterone-producing adrenal adenoma* (Conn's syndrome). Most cases involve a unilateral adenoma, which is usually small and may occur on either side. Rarely, primary aldosteronism is due to an adrenal carcinoma. Aldosteronism is twice as common in women as in men, usually occurs between the ages of 30 and 50, and is present in ~1% of unselected hypertensive patients. However, the prevalence may be as high as 5%, depending on the criteria and study population. In many patients with clinical and biochemical features of primary aldosteronism, a solitary adenoma is not found at surgery. Instead, these patients have *bilateral cortical nodular hyperplasia*. In the literature, this disease is also termed *idiopathic hyperaldosteronism*, and/or *nodular hyperplasia*. The cause is unknown.

SIGNS AND SYMPTOMS Hypersecretion of aldosterone increases the renal distal tubular exchange of intratubular sodium for secreted potassium and hydrogen ions, with progressive depletion of body potassium and development of hypokalemia. Most patients have diastolic hypertension, which may be very severe, and headaches. The hypertension is probably due to the increased sodium reabsorption and extracellular volume expansion. *Potassium depletion* is responsible for the muscle

TABLE 321-5 Treatment Modalities for Patients with Adrenal Hyperplasia Secondary to Pituitary ACTH Hypersecretion

Treatments to reduce pituitary ACTH production
Transsphenoidal resection of microadenoma
Radiation therapy
Treatments to reduce or eliminate adrenocortical cortisol secretion
Bilateral adrenalectomy
Medical adrenalectomy (metyrapone, mitotane, aminoglutethimide, ketoconazole)[a]

[a] Not curative but effective as long as chronically administered in selected patients.
Note: ACTH, adrenocorticotropic hormone.

weakness and fatigue and is due to the effect of potassium depletion on the muscle cell membrane. The polyuria results from impairment of urinary concentrating ability and is often associated with polydipsia. However, some individuals with mild disease, particularly the bilateral hyperplasia type, may have normal potassium levels and therefore have no symptoms associated with hypokalemia.

Electrocardiographic and roentgenographic signs of left ventricular enlargement are, in part, secondary to the hypertension. However, the left ventricular hypertrophy is disproportionate to the level of blood pressure when compared to individuals with essential hypertension, and regression of the hypertrophy occurs even if blood pressure is not reduced after removal of an aldosteronoma. Electrocardiographic signs of potassium depletion include prominent U waves, cardiac arrhythmias, and premature contractions. In the absence of associated congestive heart failure, renal disease, or preexisting abnormalities (such as thrombophlebitis), edema is characteristically absent. However, structural damage to the cerebral circulation, retinal vasculature, and kidney occurs more frequently than would be predicted based on the level and duration of the hypertension. Proteinuria may occur in as many as 50% of patients with primary aldosteronism, and renal failure occurs in up to 15%. Thus, it is probable that excess aldosterone production induces cardiovascular damage independent of its effect on blood pressure.

LABORATORY FINDINGS Laboratory findings depend on both the duration and the severity of potassium depletion. An overnight concentration test often reveals impaired ability to concentrate the urine, probably secondary to the hypokalemia. Urine pH is neutral to alkaline because of excessive secretion of ammonium and bicarbonate ions to compensate for the metabolic alkalosis.

Hypokalemia may be severe (<3 mmol/L) and reflects body potassium depletion, usually >300 mmol. In mild forms of primary aldosteronism, potassium levels may be normal. *Hypernatremia* is infrequent but may be caused by sodium retention, concomitant water loss from polyuria, and resetting of the osmostat. Metabolic alkalosis and elevation of serum bicarbonate are caused by hydrogen ion loss into the urine and migration into potassium-depleted cells. The alkalosis is perpetuated by potassium deficiency, which increases the capacity of the proximal convoluted tubule to reabsorb filtered bicarbonate. If hypokalemia is severe, serum magnesium levels are also reduced.

DIAGNOSIS The diagnosis is suggested by persistent hypokalemia in a nonedematous patient with a normal sodium intake who is not receiving potassium-wasting diuretics (furosemide, ethacrynic acid, thiazides). If hypokalemia occurs in a hypertensive patient taking a potassium-wasting diuretic, the diuretic should be discontinued and the patient should be given potassium supplements. After 1 to 2 weeks, the potassium level should be remeasured, and if hypokalemia persists, the patient should be evaluated for a mineralocorticoid excess syndrome (Fig. 321-9).

The criteria for the diagnosis of primary aldosteronism are (1) diastolic hypertension without edema, (2) hyposecretion of renin (as judged by low plasma renin activity levels) that fails to increase appropriately during volume depletion (upright posture, sodium depletion), and (3) hypersecretion of aldosterone that does not suppress appropriately in response to volume expansion.

Patients with primary aldosteronism characteristically *do not have edema*, since they exhibit an "escape" phenomenon from the sodium-retaining aspects of mineralocorticoids. Rarely, pretibial edema is present in patients with associated nephropathy and azotemia.

The estimation of plasma renin activity is of limited value in separating patients with primary aldosteronism from those with hypertension of other causes. Although failure of plasma renin activity to rise normally during volume-depletion maneuvers is a criterion for a diagnosis of primary aldosteronism, suppressed renin activity also occurs in ~25% of patients with essential hypertension.

Although a renin measurement alone lacks specificity, the ratio of serum aldosterone to plasma renin activity is a very useful screening test. A high ratio (>30), when aldosterone is expressed as ng/dL and plasma renin activity as ng/mL per hour, strongly suggests autonomy of aldosterone secretion. Aldosterone levels need to be >500 pmol/L (>15 ng/dL) when salt intake is not restricted. In some centers, the aldosterone/plasma renin activity ratio is used as a primary screen test in all normokalemic, difficult-to-control hypertensive patients, in addition to those with hypokalemia. Ultimately, it is necessary to demonstrate a lack of aldosterone suppression to diagnose primary aldosteronism (Fig. 321-9). The autonomy exhibited in these patients refers only to the resistance to suppression of secretion during volume expansion; aldosterone can and does respond in a normal or above-normal fashion to the stimulus of potassium loading or ACTH infusion.

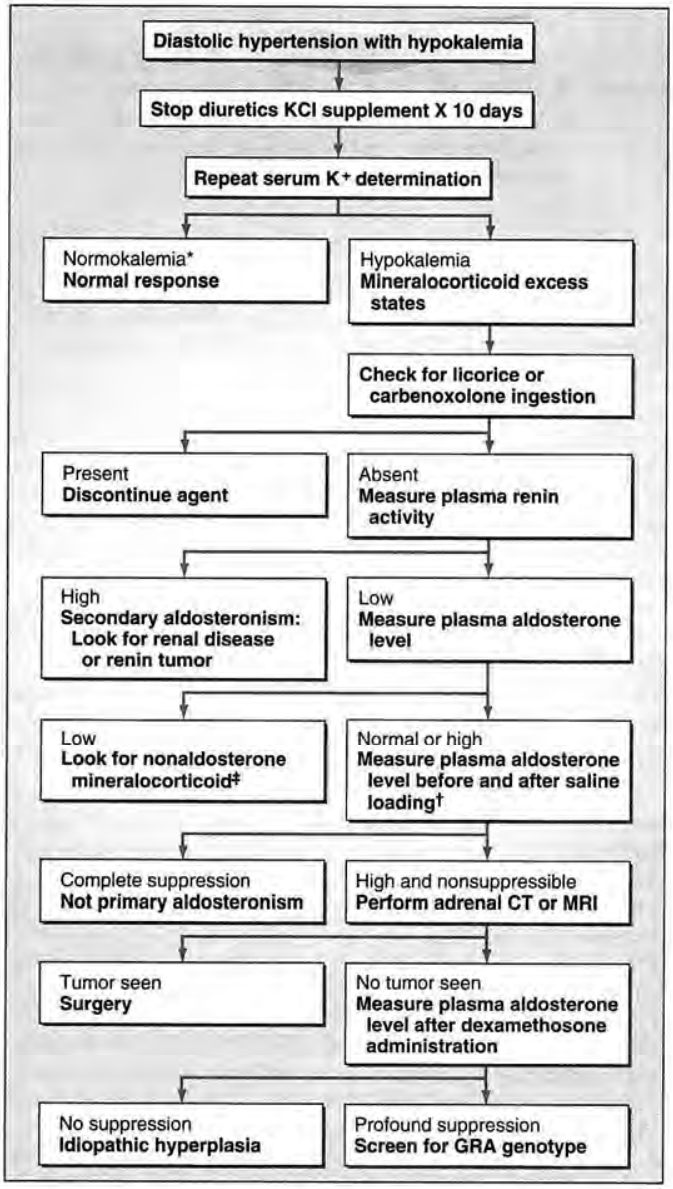

FIGURE 321-9 Diagnostic flowchart for evaluating patients with suspected primary aldosteronism. *Serum K^+ may be normal in some patients with hyperaldosteronism who are taking potassium-sparing diuretics (spironolactone, triamterene) or who have a low sodium intake and a high potassium intake. †This step should not be taken if hypertension is severe (diastolic pressure > 115 mmHg) or if cardiac failure is present. Also, serum potassium levels should be corrected before the infusion of saline solution. Alternative methods that produce comparable suppression of aldosterone secretion include oral sodium loading (200 mmol/d) and the administration of fludrocortisone, 0.2 mg bid, for 3 days. ‡For example, Liddle's syndrome, apparent mineralocorticoid excess syndrome, or a deoxycorticosterone-secreting tumor. (GRA, glucocorticoid-remediable aldosteronism; CT, computed tomography; MRI, magnetic resonance imaging.)

Once hyposecretion of renin and failure of aldosterone secretion suppression are demonstrated, aldosterone-producing adenomas should be localized by abdominal CT scan, using a high-resolution scanner as many aldosteronomas are <1 cm in size. If the CT scan is negative, percutaneous transfemoral bilateral adrenal vein catheterization with adrenal vein sampling may demonstrate a two- to threefold increase in plasma aldosterone concentration on the involved side. In cases of hyperaldosteronism secondary to cortical nodular hyperplasia, no lateralization is found. It is important for samples to be obtained simultaneously if possible and for cortisol levels to be measured to ensure that false localization does not reflect dilution or an ACTH- or stress-induced rise in aldosterone levels. In a patient with an adenoma, the aldosterone/cortisol ratio lateralizes to the side of the lesion.

DIFFERENTIAL DIAGNOSIS Patients with hypertension and hypokalemia may have either primary or secondary hyperaldosteronism (Fig. 321-10). A useful maneuver to distinguish between these conditions is the measurement of plasma renin activity. Secondary hyperaldosteronism in patients with accelerated hypertension is due to elevated plasma renin levels; in contrast, patients with primary aldosteronism have suppressed plasma renin levels. Indeed, in patients with a serum potassium concentration of <2.5 mmol/L, a high ratio of plasma aldosterone to plasma renin activity in a random sample is usually sufficient to establish the diagnosis of primary aldosteronism without additional testing. Ectopic ACTH production should also be considered in patients with hypertension and severe hypokalemia.

Primary aldosteronism must also be distinguished from other *hypermineralocorticoid states*. Nonaldosterone mineralocorticoid states will have suppressed plasma renin activity but low aldosterone levels. The most common problem is to distinguish between hyperaldosteronism due to an adenoma and that due to idiopathic bilateral nodular hyperplasia. This distinction is important because hypertension associated with idiopathic hyperplasia does not usually benefit from bilateral adrenalectomy, whereas hypertension associated with aldosterone-producing tumors is usually improved or cured by removal of the adenoma. Although patients with idiopathic bilateral nodular hyperplasia tend to have less severe hypokalemia, lower aldosterone secretion, and higher plasma renin activity than do patients with primary aldosteronism, differentiation is impossible solely on clinical and/or biochemical grounds. An anomalous postural decrease in plasma aldosterone and elevated plasma 18-hydroxycorticosterone levels are present in most patients with a unilateral lesion. However, these tests are also of limited diagnostic value in the individual patient, because some adenoma patients have an increase in plasma aldosterone with upright posture, so-called renin-responsive aldosteronoma. A definitive diagnosis is best made by radiographic studies, including bilateral adrenal vein catheterization, as noted above.

In a few instances, hypertensive patients with hypokalemic alkalosis have adenomas that secrete deoxycorticosterone. Such patients have reduced plasma renin activity levels, but aldosterone levels are either normal or reduced, suggesting the diagnosis of mineralocorticoid excess due to a hormone other than aldosterone. Several inherited disorders have clinical features similar to those of primary aldosteronism (see below).

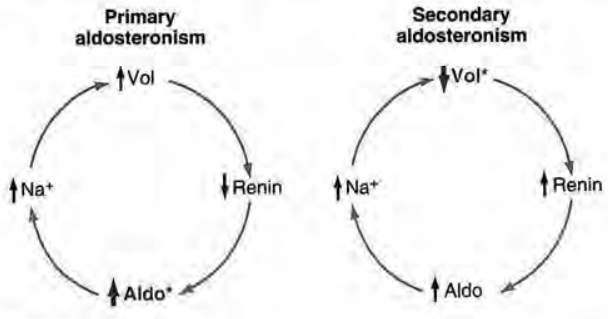

FIGURE 321-10 Responses of the renin-aldosterone volume control loop in primary versus secondary aldosteronism.

℞ TREATMENT

Primary aldosteronism due to an adenoma is usually treated by surgical excision of the adenoma. Where possible a laparoscopic approach is favored. However, dietary sodium restriction and the administration of an aldosterone antagonist—e.g., spironolactone—are effective in many cases. Hypertension and hypokalemia are usually controlled by doses of 25 to 100 mg spironolactone every 8 h. In some patients medical management has been successful for years, but chronic therapy in men is usually limited by side effects of spironolactone such as gynecomastia, decreased libido, and impotence.

When idiopathic bilateral hyperplasia is suspected, surgery is indicated only when significant, symptomatic hypokalemia cannot be controlled with medical therapy, i.e., by spironolactone, triamterene, or amiloride. Hypertension associated with idiopathic hyperplasia is usually not benefited by bilateral adrenalectomy.

Secondary Aldosteronism *Secondary aldosteronism* refers to an appropriately increased production of aldosterone in response to activation of the renin-angiotensin system (Fig. 321-10). The production rate of aldosterone is often higher in patients with secondary aldosteronism than in those with primary aldosteronism. Secondary aldosteronism usually occurs in association with the accelerated phase of hypertension or on the basis of an underlying edema disorder. Secondary aldosteronism in pregnancy is a normal physiologic response to estrogen-induced increases in circulating levels of renin substrate and plasma renin activity and to the anti-aldosterone actions of progestogens.

Secondary aldosteronism in hypertensive states is due either to a primary overproduction of renin (primary reninism) or to an overproduction of renin secondary to a decrease in renal blood flow and/or perfusion pressure (Fig. 321-10). Secondary hypersecretion of renin can be due to a narrowing of one or both of the major renal arteries by atherosclerosis or by fibromuscular hyperplasia. Overproduction of renin from both kidneys also occurs in severe arteriolar nephrosclerosis (malignant hypertension) or with profound renal vasoconstriction (the accelerated phase of hypertension). The secondary aldosteronism is characterized by hypokalemic alkalosis, moderate to severe increases in plasma renin activity, and moderate to marked increases in aldosterone levels.

Secondary aldosteronism with hypertension can also be caused by rare renin-producing tumors (primary reninism). In these patients, the biochemical characteristics are of renal vascular hypertension, but the primary defect is renin secretion by a juxtaglomerular cell tumor. The diagnosis can be made by demonstration of normal renal vasculature and/or demonstration of a space-occupying lesion in the kidney by radiographic techniques and documentation of a unilateral increase in renal vein renin activity. Rarely, these tumors arise in tissues such as the ovary.

Secondary aldosteronism is present in many forms of *edema*. The rate of aldosterone secretion is usually increased in patients with edema caused by either cirrhosis or the nephrotic syndrome. In congestive heart failure, elevated aldosterone secretion varies depending on the severity of cardiac failure. The stimulus for aldosterone release in these conditions appears to be *arterial hypovolemia* and/or hypotension. Thiazides and furosemide often exaggerate secondary aldosteronism via volume depletion; hypokalemia and, on occasion, alkalosis can then become prominent features. On occasion secondary hyperaldosteronism occurs without edema or hypertension (Bartter and Gitelman syndromes, see below).

Aldosterone and Cardiovascular Damage Although many studies have investigated the role of angiotensin II in mediating cardiovascular damage, additional evidence indicates that aldosterone has an important

role that is independent of angiotensin II. Patients with primary aldosteronism (in which angiotensin II levels are usually very low) have a higher incidence of left ventricular hypertrophy (LVH), albuminuria, and stroke than do patients with essential hypertension. Experimental animal models mimicking secondary aldosteronism (angiotensin infusion) or primary aldosteronism (aldosterone infusion) reveal a common pathophysiologic sequence. Within the first few days there is activation of proinflammatory molecules with a histologic picture of perivascular macrophage infiltrate and inflammation, followed by cellular death, fibrosis, and ventricular hypertrophy. These events are prevented if an aldosterone receptor antagonist is used or if adrenalectomy is performed initially. The same pathophysiologic sequence is seen in animals with average aldosterone levels and cardiovascular damage, i.e., diabetes mellitus, or genetic hypertensive rats. Importantly, the level of sodium intake is a critical co-factor. If salt intake is severely restricted, no damage occurs even though the aldosterone levels are markedly elevated. Thus, it is not the level of aldosterone per se that is responsible for the damage, but its level relative to the volume or sodium status of the individual.

Four clinical studies support these experimental results. In the RALES trial, patients with class II/IV heart failure were randomized to standard care or a low dose of the mineralocorticoid receptor antagonist, spironolactone. There was a 30% reduction in all-cause mortality and cardiovascular mortality and hospitalizations after 36 months. Two studies in hypertensive subjects addressed the question of the relative importance of a reduction of angiotensin II formation versus blockade of the MR in mediating cardiovascular damage. Subjects were randomized to eplerenone (an MR antagonist), enalapril (an ACE inhibitor), or both agents. In the first study the subjects had LVH, with the end point being a reduction in LVH. In the second, the subjects had diabetes mellitus and proteinuria, with the end point being a reduction in proteinuria. In both studies all three treatment arms substantially reduced the primary end point; however, the most potent effect occurred in the combination arms of the studies. In the monotherapy LVH arms, the reduction in LVH was similar, while in the proteinuria study, eplerenone produced a greater reduction than did enalapril. The final study was the EPHESUS trial, where individuals who developed congestive heart failure after an acute myocardial infarction were randomized to standard-of-care treatment with or without a small dose of eplerenone. Eplerenone administration produced a significantly greater reduction in mortality (15 to 17%) and in cardiovascular-related hospitalizations than the placebo arm. Thus, these four clinical studies provide strong support to the hypothesis that MR blockade has a significant added advantage over standard-of-care therapy in reducing cardiovascular mortality and surrogate end points. However, regulatory approval is pending.

SYNDROMES OF ADRENAL ANDROGEN EXCESS Adrenal androgen excess results from excess production of DHEA and androstenedione, which are converted to testosterone in extraglandular tissues; elevated testosterone levels account for most of the virilization. Adrenal androgen excess may be associated with the secretion of greater or smaller amounts of other adrenal hormones and may, therefore, present as "pure" syndromes of virilization or as "mixed" syndromes associated with excessive glucocorticoids and Cushing's syndrome. →***For further discussion of hirsutism and virilization, see Chap. 44.***

HYPOFUNCTION OF THE ADRENAL CORTEX

Cases of adrenal insufficiency can be divided into two general categories: (1) those associated with primary inability of the adrenal to elaborate sufficient quantities of hormone, and (2) those associated with a secondary failure due to inadequate ACTH formation or release (Table 321-6).

PRIMARY ADRENOCORTICAL DEFICIENCY (ADDISON'S DISEASE) The original description of Addison's disease—"general languor and debility, feebleness of the heart's action, irritability of the stomach, and a peculiar change of the color of the skin"—summarizes the dominant clinical features. Advanced cases are usually easy to diagnose, but recognition of the early phases can be a real challenge.

TABLE 321-6 Classification of Adrenal Insufficiency

PRIMARY ADRENAL INSUFFICIENCY
Anatomic destruction of gland (chronic or acute)
"Idiopathic" atrophy (autoimmune, adrenoleukodystrophy)
Surgical removal
Infection (tuberculous, fungal, viral—especially in AIDS patients)
Hemorrhage
Invasion: metastatic
Metabolic failure in hormone production
Congenital adrenal hyperplasia
Enzyme inhibitors (metyrapone, ketoconazole, aminoglutethimide)
Cytotoxic agents (mitotane)
ACTH-blocking antibodies
Mutation in ACTH receptor gene
Adrenal hypoplasia congenita
SECONDARY ADRENAL INSUFFICIENCY
Hypopituitarism due to hypothalamic-pituitary disease
Suppression of hypothalamic-pituitary axis
By exogenous steroid
By endogenous steroid from tumor

Note: ACTH, adrenocorticotropic hormone.

Incidence Acquired forms of primary insufficiency are relatively rare, may occur at any age, and affect both sexes equally. Because of the common therapeutic use of steroids, secondary adrenal insufficiency is relatively common.

Etiology and Pathogenesis Addison's disease results from progressive destruction of the adrenals, which must involve >90% of the glands before adrenal insufficiency appears. The adrenal is a frequent site for chronic granulomatous diseases, predominantly tuberculosis but also histoplasmosis, coccidioidomycosis, and cryptococcosis. In early series, tuberculosis was responsible for 70 to 90% of cases, but the most frequent cause now is *idiopathic* atrophy, and an autoimmune mechanism is probably responsible. Rarely, other lesions are encountered, such as adrenoleukodystrophy, bilateral hemorrhage, tumor metastases, HIV, cytomegalovirus (CMV), amyloidosis, adrenomyeloneuropathy, familial adrenal insufficiency, or sarcoidosis.

Although half of patients with idiopathic atrophy have circulating adrenal antibodies, autoimmune destruction is probably secondary to cytotoxic T lymphocytes. Specific adrenal antigens to which autoantibodies may be directed include 21-hydroxylase (CYP21A2) and side chain cleavage enzyme, but the significance of these antibodies in the pathogenesis of adrenal insufficiency is unknown. Some antibodies cause adrenal insufficiency by blocking the binding of ACTH to its receptors. Some patients also have antibodies to thyroid, parathyroid, and/or gonadal tissue (Chap. 330). There is also an increased incidence of chronic lymphocytic thyroiditis, premature ovarian failure, type 1 diabetes mellitus, and hypo- or hyperthyroidism. The presence of two or more of these autoimmune endocrine disorders in the same person defines the polyglandular autoimmune syndrome type II. Additional features include pernicious anemia, vitiligo, alopecia, nontropical sprue, and myasthenia gravis. Within families, multiple generations are affected by one or more of the above diseases. Type II polyglandular syndrome is the result of a mutant gene on chromosome 6 and is associated with the HLA alleles B8 and DR3.

The combination of parathyroid and adrenal insufficiency and chronic mucocutaneous candidiasis constitutes type I polyglandular autoimmune syndrome. Other autoimmune diseases in this disorder include pernicious anemia, chronic active hepatitis, alopecia, primary hypothyroidism, and premature gonadal failure. There is no HLA association; this syndrome is inherited as an autosomal recessive trait. It is caused by mutations in the *a*utoimmune *p*oly*e*ndocrinopathy *c*andidiasis *e*ctodermal *d*ystrophy (APECED) gene located on chromo-

some 21q22.3. The gene encodes a transcription factor thought to be involved in lymphocyte function. The type I syndrome usually presents during childhood, whereas the type II syndrome is usually manifested in adulthood.

Clinical suspicion of adrenal insufficiency should be high in patients with AIDS (Chap. 173). CMV regularly involves the adrenal glands (so-called CMV necrotizing adrenalitis), and involvement with *Mycobacterium avium-intracellulare*, *Cryptococcus*, and Kaposi's sarcoma has been reported. Adrenal insufficiency in AIDS patients may not be manifest, but tests of adrenal reserve frequently give abnormal results. When interpreting tests of adrenocortical function, it is important to remember that medications such as rifampin, phenytoin, ketoconazole, megestrol, and opiates may cause or potentiate adrenal insufficiency. Adrenal hemorrhage and infarction occur in patients on anticoagulants and in those with circulating anticoagulants and hypercoagulable states, such as the antiphospholipid syndrome.

There are several rare genetic causes of adrenal insufficiency that present primarily in infancy and childhood (see below).

Clinical Signs and Symptoms Adrenocortical insufficiency caused by gradual adrenal destruction is characterized by an insidious onset of fatigability, weakness, anorexia, nausea and vomiting, weight loss, cutaneous and mucosal pigmentation, hypotension, and occasionally hypoglycemia (Table 321-7). Depending on the duration and degree of adrenal hypofunction, the manifestations vary from mild chronic fatigue to fulminating shock associated with acute destruction of the glands, as described by Waterhouse and Friderichsen.

Asthenia is the cardinal symptom. Early it may be sporadic, usually most evident at times of stress; as adrenal function becomes more impaired, the patient is continuously fatigued, and bed rest is necessary.

Hyperpigmentation may be striking or absent. It commonly appears as a diffuse brown, tan, or bronze darkening of parts such as the elbows or creases of the hand and of areas that normally are pigmented such as the areolae about the nipples. Bluish-black patches may appear on the mucous membranes. Some patients develop dark freckles, and irregular areas of vitiligo may paradoxically be present. As an early sign, tanning following sun exposure may be persistent.

Arterial hypotension with postural accentuation is frequent, and blood pressure may be in the range of 80/50 or less.

Abnormalities of gastrointestinal function are often the presenting complaint. Symptoms vary from mild anorexia with weight loss to fulminating nausea, vomiting, diarrhea, and ill-defined abdominal pain, which may be so severe as to be confused with an acute abdomen. Patients may have personality changes, usually consisting of excessive irritability and restlessness. Enhancement of the sensory modalities of taste, olfaction, and hearing is reversible with therapy. Axillary and pubic hair may be decreased in women due to loss of adrenal androgens.

Laboratory Findings In the early phase of gradual adrenal destruction, there may be no demonstrable abnormalities in the routine laboratory parameters, but adrenal reserve is decreased—that is, while basal steroid output may be normal, a subnormal increase occurs after stress. Adrenal stimulation with ACTH uncovers abnormalities in this stage of the disease, eliciting a subnormal increase of cortisol levels or no increase at all. In more advanced stages of adrenal destruction, serum sodium, chloride, and bicarbonate levels are reduced, and the serum potassium level is elevated. The hyponatremia is due both to loss of sodium into the urine (due to aldosterone deficiency) and to movement into the intracellular compartment. This extravascular sodium loss depletes extracellular fluid volume and accentuates hypotension. Elevated plasma vasopressin and angiotensin II levels may contribute to the hyponatremia by impairing free water clearance. Hyperkalemia is due to a combination of aldosterone deficiency, impaired glomerular filtration, and acidosis. Basal levels of cortisol and aldosterone are subnormal and fail to increase following ACTH administration. Mild to moderate hypercalcemia occurs in 10 to 20% of patients for unclear reasons. The electrocardiogram may show nonspecific changes, and the electroencephalogram exhibits a generalized reduction and slowing. There may be a normocytic anemia, a relative lymphocytosis, and a moderate eosinophilia.

Diagnosis The diagnosis of adrenal insufficiency should be made only with ACTH stimulation testing to assess adrenal reserve capacity for steroid production (see above for ACTH test protocols). In brief, the best screening test is the cortisol response 60 min after 250 μg of cosyntropin given intramuscularly or intravenously. Cortisol levels should exceed 495 nmol/L (18 μg/dL). If the response is abnormal, then primary and secondary adrenal insufficiency can be distinguished by measuring aldosterone levels from the same blood samples. In secondary, but not primary, adrenal insufficiency the aldosterone increment will be normal [$\geq$150 pmol/l (5 ng/dL)]. Furthermore, in primary adrenal insufficiency, plasma ACTH and associated peptides (β-LPT) are elevated because of loss of the usual cortisol-hypothalamic-pituitary feedback relationship, whereas in secondary adrenal insufficiency, plasma ACTH values are low or "inappropriately" normal (Fig. 321-11).

TABLE 321-7 Frequency of Symptoms and Signs in Adrenal Insufficiency

Sign or Symptom	Percent of Patients
Weakness	99
Pigmentation of skin	98
Weight loss	97
Anorexia, nausea, and vomiting	90
Hypotension (<110/70)	87
Pigmentation of mucous membranes	82
Abdominal pain	34
Salt craving	22
Diarrhea	20
Constipation	19
Syncope	16
Vitiligo	9

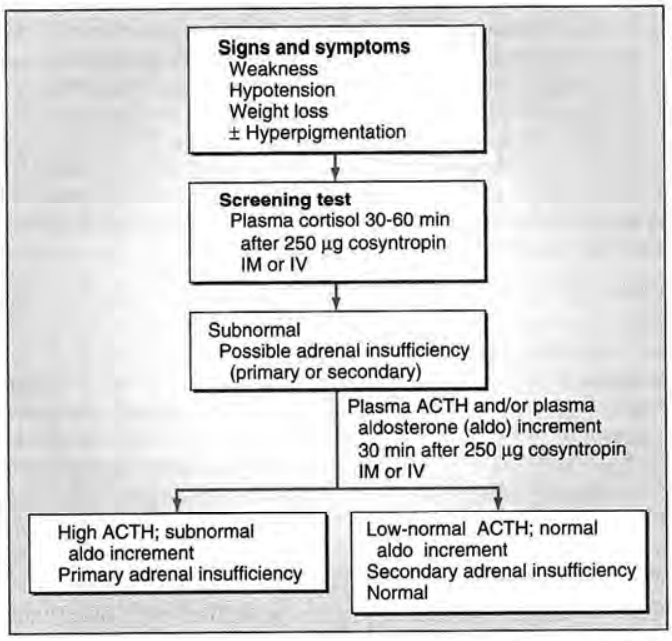

FIGURE 321-11 Diagnostic flowchart for evaluating patients with suspected adrenal insufficiency. Plasma adrenocorticotropic hormone (ACTH) levels are low in secondary adrenal insufficiency. In adrenal insufficiency secondary to pituitary tumors or idiopathic panhypopituitarism, other pituitary hormone deficiencies are present. On the other hand, ACTH deficiency may be isolated, as seen following prolonged use of exogenous glucocorticoids. Because the isolated blood levels obtained in these screening tests may not be definitive, the diagnosis may need to be confirmed by a continuous 24-h ACTH infusion. Normal subjects and patients with secondary adrenal insufficiency may be distinguished by insulin tolerance or metyrapone testing.

Differential Diagnosis Because weakness and fatigue are common, diagnosis of early adrenocortical insufficiency may be difficult. However, the combination of mild gastrointestinal distress, weight loss, anorexia, and a suggestion of increased pigmentation makes it mandatory to perform ACTH stimulation testing to rule out adrenal insufficiency, particularly before steroid treatment is begun. Weight loss is useful in evaluating the significance of weakness and malaise. Racial pigmentation may be a problem, but a *recent* and progressive *increase* in pigmentation is usually reported by the patient with gradual adrenal destruction. Hyperpigmentation is usually absent when adrenal destruction is rapid, as in bilateral adrenal hemorrhage. The fact that hyperpigmentation occurs with other diseases may also present a problem, but the appearance and distribution of pigment in adrenal insufficiency are usually characteristic. When doubt exists, measurement of ACTH levels and testing of adrenal reserve with the infusion of ACTH provide clear-cut differentiation.

TABLE 321-8 Steroid Therapy Schedule for a Patient with Adrenal Insufficiency Undergoing Surgery[a]

	Hydrocortisone Infusion, Continuous, mg/h		Hydrocortisone (Orally)		Fludrocortisone (Orally), 8 A.M.
			8 A.M.	4 P.M.	
Routine daily medication			20	10	0.1
Day before operation			20	10	0.1
Day of operation	10				
Day 1	5–7.5				
Day 2	2.5–5				
Day 3	2.5–5	*or*	40	20	0.1
Day 4	2.5–5	*or*	40	20	0.1
Day 5			40	20	0.1
Day 6			20	20	0.1
Day 7			20	10	0.1

[a] All steroid doses are given in milligrams. An alternative approach is to give 100 mg hydrocortisone as an intravenous bolus injection every 8 h on the day of the operation (see text).

Rx TREATMENT

All patients with adrenal insufficiency should receive specific hormone replacement. These patients require careful education about the disease. Replacement therapy should correct both glucocorticoid and mineralocorticoid deficiencies. Hydrocortisone (cortisol) is the mainstay of treatment. The dose for most adults (depending on size) is 20 to 30 mg/d. Patients are advised to take glucocorticoids with meals or, if that is impractical, with milk or an antacid, because the drugs may increase gastric acidity and exert direct toxic effects on the gastric mucosa. To simulate the normal diurnal adrenal rhythm, two-thirds of the dose is taken in the morning, and the remaining one-third is taken in the late afternoon. Some patients exhibit insomnia, irritability, and mental excitement after initiation of therapy; in these, the dosage should be reduced. Other situations that may necessitate smaller doses are hypertension and diabetes mellitus. Obese individuals and those on anticonvulsive medications may require increased dosages. Measurements of plasma ACTH or cortisol or of urine cortisol levels do not appear to be useful in determining optimal glucocorticoid dosages.

Since the replacement dosage of hydrocortisone does not replace the mineralocorticoid component of the adrenal hormones, mineralocorticoid supplementation is usually needed. This is accomplished by the administration of 0.05 to 0.1 mg fludrocortisone per day by mouth. Patients should also be instructed to maintain an ample intake of sodium (3 to 4 g/d).

The adequacy of mineralocorticoid therapy can be assessed by measurement of blood pressure and serum electrolytes. Blood pressure should be normal and without postural changes; serum sodium, potassium, creatinine, and urea nitrogen levels should also be normal. Measurement of plasma renin levels may also be useful in titrating the dose.

In female patients with adrenal insufficiency, androgen levels are also low. Thus, some physicians believe that daily replacement with 25 to 50 mg of DHEA orally may improve quality of life and bone mineral density.

Complications of glucocorticoid therapy, with the exception of gastritis, are *rare* at the dosages recommended for treatment of adrenal insufficiency. Complications of mineralocorticoid therapy include hypokalemia, hypertension, cardiac enlargement, and even congestive heart failure due to sodium retention. Periodic measurements of body weight, serum potassium level, and blood pressure are useful. All patients with adrenal insufficiency should carry medical identification, should be instructed in the parenteral self-administration of steroids, and should be registered with a medical alerting system.

Special Therapeutic Problems During periods of intercurrent illness, especially in the setting of fever, the dose of hydrocortisone should be doubled. With severe illness it should be increased to 75 to 150 mg/d. When oral administration is not possible, parenteral routes should be employed. Likewise, before surgery or dental extractions, supplemental glucocorticoids should be administered. Patients should also be advised to increase the dose of fludrocortisone and to add salt to their otherwise normal diet during periods of strenuous exercise with sweating, during extremely hot weather, and with gastrointestinal upsets such as diarrhea. A simple strategy is to supplement the diet one to three times daily with salty broth (1 cup of beef or chicken bouillon contains 35 mmol of sodium). For a representative program of steroid therapy for the patient with adrenal insufficiency who is undergoing major surgery, see Table 321-8. This schedule is designed so that on the day of surgery it will mimic the output of cortisol in normal individuals undergoing prolonged major stress (10 mg/h, 250 to 300 mg/d). Thereafter, if the patient is improving and is afebrile, the dose of hydrocortisone is tapered by 20 to 30% daily. Mineralocorticoid administration is unnecessary at hydrocortisone doses >100 mg/d because of the mineralocorticoid effects of hydrocortisone at such dosages.

SECONDARY ADRENOCORTICAL INSUFFICIENCY ACTH deficiency causes *secondary* adrenocortical insufficiency; it may be a selective deficiency, as is seen following prolonged administration of excess glucocorticoids, or it may occur in association with deficiencies of multiple pituitary hormones (panhypopituitarism) (Chap. 318). Patients with secondary adrenocortical hypofunction have many symptoms and signs in common with those having primary disease but are *not hyperpigmented*, since ACTH and related peptide levels are low. In fact, plasma ACTH levels distinguish between primary and secondary adrenal insufficiency, since they are elevated in the former and decreased to absent in the latter. Patients with total pituitary insufficiency have manifestations of multiple hormone deficiencies. An additional feature distinguishing primary adrenocortical insufficiency is the *near-normal level of aldosterone secretion* seen in pituitary and/or isolated ACTH deficiencies (Fig. 321-11). Patients with pituitary insufficiency may have hyponatremia, which can be dilutional or secondary to a subnormal increase in aldosterone secretion in response to severe sodium restriction. However, severe *dehydration*, *hyponatremia*, and *hyperkalemia* are characteristic of severe mineralocorticoid insufficiency and favor a diagnosis of primary adrenocortical insufficiency.

Patients receiving long-term steroid therapy, despite physical findings of Cushing's syndrome, may develop adrenal insufficiency because of prolonged pituitary-hypothalamic suppression and adrenal atrophy secondary to the loss of endogenous ACTH. These patients have two deficits, a loss of adrenal responsiveness to ACTH and a failure of pituitary ACTH release. They are characterized by low blood cortisol and ACTH levels, a low baseline rate of steroid excretion, and abnormal ACTH and metyrapone responses. Most patients with steroid-induced adrenal insufficiency eventually recover normal HPA re-

sponsiveness, but recovery time varies from days to months. The rapid ACTH test provides a convenient assessment of recovery of HPA function. Because the plasma cortisol concentrations after injection of cosyntropin and during insulin-induced hypoglycemia are usually similar, the rapid ACTH test assesses the integrated HPA function (see "Tests of Pituitary-Adrenal Responsiveness," above). Some investigators suggest using the low-dose (1 μg) ACTH test for suspected secondary ACTH deficiency. Additional tests to assess pituitary ACTH reserve include the standard metyrapone and insulin-induced hypoglycemia tests.

Glucocorticoid therapy in patients with secondary adrenocortical insufficiency does not differ from that for the primary disorder. Mineralocorticoid therapy is usually not necessary, as aldosterone secretion is preserved.

ACUTE ADRENOCORTICAL INSUFFICIENCY Acute adrenocortical insufficiency may result from several processes. On the one hand, *adrenal crisis* may be a rapid and overwhelming intensification of chronic adrenal insufficiency, usually precipitated by sepsis or surgical stress. Alternatively, acute hemorrhagic destruction of both adrenal glands can occur in previously well individuals. In children, this event is usually associated with septicemia with *Pseudomonas* or meningococcemia (Waterhouse-Friderichsen syndrome). In adults, anticoagulant therapy or a coagulation disorder may result in bilateral adrenal hemorrhage. Occasionally, bilateral adrenal hemorrhage in the newborn results from birth trauma. Hemorrhage has been observed during pregnancy, following idiopathic adrenal vein thrombosis, and as a complication of venography (e.g., infarction of an adenoma). The third and most frequent cause of acute insufficiency is the rapid withdrawal of steroids from patients with adrenal atrophy owing to chronic steroid administration. Acute adrenocortical insufficiency may also occur in patients with congenital adrenal hyperplasia or those with decreased adrenocortical reserve when they are given drugs capable of inhibiting steroid synthesis (mitotane, ketoconazole) or of increasing steroid metabolism (phenytoin, rifampin).

Adrenal Crisis The long-term survival of patients with adrenocortical insufficiency depends largely on the prevention and treatment of adrenal crisis. Consequently, the occurrence of infection, trauma (including surgery), gastrointestinal upsets, or other stresses necessitates an immediate increase in hormone. In untreated patients, preexisting symptoms are intensified. Nausea, vomiting, and abdominal pain may become intractable. Fever may be severe or absent. Lethargy deepens into somnolence, and hypovolemic vascular collapse ensues. In contrast, patients previously maintained on chronic glucocorticoid therapy may not exhibit dehydration or hypotension until they are in a preterminal state, since mineralocorticoid secretion is usually preserved. In all patients in crisis, a precipitating cause should be sought.

℞ TREATMENT

Treatment is directed primarily toward repletion of circulating glucocorticoids and replacement of the sodium and water deficits. Hence an intravenous infusion of 5% glucose in normal saline solution should be started with a bolus intravenous infusion of 100 mg hydrocortisone followed by a continuous infusion of hydrocortisone at a rate of 10 mg/h. An alternative approach is to administer a 100-mg bolus of hydrocortisone intravenously every 6 h. However, only continuous infusion maintains the plasma cortisol constantly at stress levels [>830 nmol/L (30 μg/dL)]. Effective treatment of hypotension requires glucocorticoid replacement and repletion of sodium and water deficits. If the crisis was preceded by prolonged nausea, vomiting, and dehydration, several liters of saline solution may be required in the first few hours. Vasoconstrictive agents (such as dopamine) may be indicated in extreme conditions as adjuncts to volume replacement. With large doses of steroid, i.e., 100 to 200 mg hydrocortisone, the patient receives a maximal mineralocorticoid effect, and supplementary mineralocorticoid is superfluous. Following improvement, the steroid dosage is tapered over the next few days to maintenance levels, and mineralocorticoid therapy is reinstituted if needed (Table 321-8).

ADRENAL CORTICOL INSUFFICIENCY IN ACUTELY ILL PATIENTS The physiology of the HPA axis is dramatically altered during critical illnesses such as trauma, surgery, sepsis, and shock. In such situations cortisol levels rise four- to sixfold, diurnal variation is abolished, and the unbound fractions of cortisol rise in the circulation and in target tissues. Inadequate cortisol production during critical illness can result in hypotension, reduced systemic vascular resistance, shock, and death.

A major area of controversy in presumably normal individuals is the correlation of clinical outcomes with the cortisol levels measured during critical illness. Subnormal cortisol production during acute severe illness has been termed "functional" or "relative" adrenal insufficiency. Conceptually, the elevated cortisol levels that are observed are viewed as insufficient to control the inflammatory response and maintain blood pressure. If such patients can be identified, treatment with supplementary cortisol could be beneficial.

A level of cortisol in a critically ill patient below which replacement glucocorticoids may improve prognosis is not firmly established, although many have accepted a level of ≤441 nmol/L (15 μg/dL). On the other hand, a random cortisol >938 nmol/L (34 μg/dL) in the setting of critical illness is unlikely to be associated with relative adrenal insufficiency. In patients who have random cortisol levels between 441 and 938 nmol/L (15 and 34 μg/dL), a cosyntropin stimulation test may identify patients with diminished adrenal reserve [increment <255 nmol/L (9 μg/dL)] who may benefit from supplementary cortisol treatment. If the diagnosis of relative or functional adrenal insufficiency is considered in an acutely ill, hypotensive patient, treatment with supplementary cortisol should be initiated promptly following the measurement of a random cortisol level and/or performing a cosyntropin stimulation test. Supplemental cortisol may be particularly beneficial in patients with septic shock where glucocorticoids have been reported to reduce mortality and the duration of vasopressor therapy. Such patients should be treated with 50 to 75 mg of intravenous hydrocortisone every 6 h as bolus treatment or the same amount as a continuous infusion. Treatment can be terminated if the cortisol levels obtained at the outset are normal. On the other hand, those patients with abnormal testing should be treated for 1 week and then tapered. In surviving patients, adrenal function should be reevaluated after resolution of the critical illness.

HYPOALDOSTERONISM

Isolated aldosterone deficiency accompanied by normal cortisol production occurs in association with hyporeninism, as an inherited biosynthetic defect, postoperatively following removal of aldosterone-secreting adenomas, during protracted heparin administration, in pretectal disease of the nervous system, and in severe postural hypotension.

The feature common to all forms of hypoaldosteronism is the inability to increase aldosterone secretion appropriately in response to salt restriction. Most patients have unexplained hyperkalemia, which is often exacerbated by restriction of dietary sodium intake. In severe cases, urine sodium wastage occurs at a normal salt intake, whereas in milder forms, excessive loss of urine sodium occurs only with salt restriction.

Most cases of isolated hypoaldosteronism occur in patients with a deficiency in renin production (so-called hyporeninemic hypoaldosteronism), most commonly in adults with diabetes mellitus and mild renal failure and in whom hyperkalemia and metabolic acidosis are out of proportion to the degree of renal impairment. Plasma renin levels fail to rise normally following sodium restriction and postural changes. The pathogenesis is uncertain. Possibilities include renal disease (the most likely), autonomic neuropathy, extracellular fluid volume expansion, and defective conversion of renin precursors to active renin. Aldosterone levels also fail to rise normally after salt restriction and volume contraction; this effect is probably related to the hyporeninism, since biosynthetic defects in aldosterone secretion usually can-

not be demonstrated. In these patients, aldosterone secretion increases promptly after ACTH stimulation, but it is uncertain whether the magnitude of the response is normal. On the other hand, the level of aldosterone appears to be subnormal in relationship to the hyperkalemia.

Hypoaldosteronism can also be associated with high renin levels and low or elevated levels of aldosterone (see below). Severely ill patients may also have hyperreninemic hypoaldosteronism; such patients have a high mortality rate (80%). Hyperkalemia is not present. Possible explanations for the hypoaldosteronism include adrenal necrosis (uncommon) or a shift in steroidogenesis from mineralocorticoids to glucocorticoids, possibly related to prolonged ACTH stimulation.

Before the diagnosis of isolated hypoaldosteronism is considered for a patient with hyperkalemia, "pseudohyperkalemia" (e.g., hemolysis, thrombocytosis) should be excluded by measuring the *plasma* potassium level. The next step is to demonstrate a normal cortisol response to ACTH stimulation. Then, the response of renin and aldosterone levels to stimulation (upright posture, sodium restriction) should be measured. Low renin and aldosterone levels establish the diagnosis of hyporeninemic hypoaldosteronism. A combination of high renin levels and low aldosterone levels is consistent with an aldosterone biosynthetic defect or a selective unresponsiveness to angiotensin II. Finally, there is a condition that clinically and biochemically mimics hypoaldosteronism with elevated renin levels. However, the aldosterone levels are not low but high—so-called pseudohypoaldosteronism. This inherited condition is caused by a mutation in the epithelial sodium channel (see below).

℞ TREATMENT

The treatment is to replace the mineralocorticoid deficiency. For practical purposes, the oral administration of 0.05 to 0.15 mg fludrocortisone daily should restore electrolyte balance if salt intake is adequate (e.g., 150 to 200 mmol/d). However, patients with hyporeninemic hypoaldosteronism may require higher doses of mineralocorticoid to correct hyperkalemia. This need poses a potential risk in patients with hypertension, mild renal insufficiency, or congestive heart failure. An alternative approach is to reduce salt intake and to administer furosemide, which can ameliorate acidosis and hyperkalemia. Occasionally, a combination of these two approaches is efficacious.

GENETIC CONSIDERATIONS **Glucocorticoid Diseases** ■ *CONGENITAL ADRENAL HYPERPLASIA* Congenital adrenal hyperplasia (CAH) is the consequence of recessive mutations that cause one of several distinct enzymatic defects (see below). Because cortisol is the principal adrenal steroid regulating ACTH elaboration and because ACTH stimulates adrenal growth and function, a block in cortisol synthesis may result in the enhanced secretion of adrenal androgens and/or mineralocorticoids depending on the site of the enzyme block. In severe congenital virilizing hyperplasia, the adrenal output of cortisol may be so compromised as to cause adrenal deficiency despite adrenal hyperplasia.

CAH is the most common adrenal disorder of infancy and childhood (Chap. 328). Partial enzyme deficiencies can be expressed after adolescence, predominantly in women with hirsutism and oligomenorrhea but minimal virilization. Late-onset adrenal hyperplasia may account for 5 to 25% of cases of hirsutism and oligomenorrhea in women, depending on the population.

Etiology Enzymatic defects have been described in 21-hydroxylase (CYP21A2), 17α-hydroxylase/17,20-lyase (CYP17), 11β-hydroxylase (CYP11B1), and in (3β-HSD2) (Fig. 321-2). Although the genes encoding these enzymes have been cloned, the diagnosis of specific enzyme deficiencies with genetic techniques is not practical because of the large number of different deletions and missense mutations. CYP21A2 deficiency is closely linked to the HLA-B locus of chromosome 6 so that HLA typing and/or DNA polymorphism can be used to detect the heterozygous carriers and to diagnose affected individuals in some families (Chap. 296). The clinical expression in the different disorders is variable, ranging from virilization of the female (CYP2/A2) to feminization of the male (3β-HSD2) (Chap. 328).

Adrenal virilization in the female at birth is associated with ambiguous external genitalia (*female pseudohermaphroditism*). Virilization begins after the fifth month of intrauterine development. At birth there may be enlargement of the clitoris, partial or complete fusion of the labia, and sometimes a urogenital sinus in the female. If the labial fusion is nearly complete, the female infant has external genitalia resembling a penis with hypospadias. In the *postnatal* period, CAH is associated with virilization in the female and isosexual precocity in the male. The excessive androgen levels result in accelerated growth, so that bone age exceeds chronologic age. Because epiphyseal closure occurs early, growth stops, but truncal development continues, the characteristic appearance being a short child with a well-developed trunk.

The most common form of CAH (95% of cases) is a result of impairment of CYP21A2. In addition to cortisol deficiency, aldosterone secretion is decreased in approximately one-third of the patients. Thus, with CYP21A2 deficiency, adrenal virilization occurs with or without a salt-losing tendency due to aldosterone deficiency (Fig. 321-2).

CYP11B1 deficiency causes a "hypertensive" variant of CAH. Hypertension and hypokalemia occur because of the impaired conversion of 11-deoxycorticosterone to corticosterone, resulting in the accumulation of 11-deoxycorticosterone, a potent mineralocorticoid. The degree of hypertension is variable. Steroid precursors are shunted into the androgen pathway.

CYP17 deficiency is characterized by hypogonadism, hypokalemia, and hypertension. This rare disorder causes decreased production of cortisol and shunting of precursors into the mineralocorticoid pathway with hypokalemic alkalosis, hypertension, and suppressed plasma renin activity. Usually, 11-deoxycorticosterone production is elevated. Because CYP17 hydroxylation is required for biosynthesis of both adrenal androgens and gonadal testosterone and estrogen, this defect is associated with sexual immaturity, high urinary gonadotropin levels, and low urinary 17-ketosteroid excretion. Female patients have primary amenorrhea and lack of development of secondary sexual characteristics. Because of deficient androgen production, male patients have either ambiguous external genitalia or a female phenotype (*male pseudohermaphroditism*). Exogenous glucocorticoids can correct the hypertensive syndrome, and treatment with appropriate gonadal steroids results in sexual maturation.

With 3β-HSD2 deficiency, conversion of pregnenolone to progesterone is impaired, so that the synthesis of both cortisol and aldosterone is blocked, with shunting into the adrenal androgen pathway via 17α-hydroxypregnenolone and DHEA. Because DHEA is a weak androgen, and because this enzyme deficiency is also present in the gonad, the genitalia of the male fetus may be incompletely virilized or feminized. Conversely, in the female, overproduction of DHEA may produce partial virilization.

Diagnosis The diagnosis of CAH should be considered in infants having episodes of acute adrenal insufficiency or salt-wasting or hypertension. The diagnosis is further suggested by the finding of hypertrophy of the clitoris, fused labia, or a urogenital sinus in the female or of isosexual precocity in the male. In infants and children with a CYP21A2 defect, increased urine 17-ketosteroid excretion and increased plasma DHEA sulfate levels are typically associated with an increase in the blood levels of 17-hydroxyprogesterone and the excretion of its urinary metabolite pregnanetriol. Demonstration of elevated levels of 17-hydroxyprogesterone in amniotic fluid at 14 to 16 weeks of gestation allows prenatal detection of affected female infants.

The diagnosis of a *salt-losing form* of CAH due to defects in CYP21A2 is suggested by episodes of acute adrenal insufficiency with hyponatremia, hyperkalemia, dehydration, and vomiting. These infants and children often crave salt and have laboratory findings indicating deficits in both cortisol and aldosterone secretion.

With the *hypertensive form* of CAH due to CYP11B1 deficiency, 11-deoxycorticosterone and 11-deoxycortisol accumulate. The diagnosis is confirmed by demonstrating increased levels of 11-deoxycortisol in the blood or increased amounts of tetrahydro-11-deoxycortisol in the urine. Elevation of 17-hydroxyprogesterone levels does not imply a coexisting CYP21A2 deficiency.

Very high levels of urine DHEA with low levels of pregnanetriol and of cortisol metabolites in urine are characteristic of children with 3β-HSD2 deficiency. Marked salt-wasting may also occur.

Adults with *late-onset adrenal hyperplasia* (partial deficiency of CYP21A2, CYP11B1, or 3β-HSD2) are characterized by normal or moderately elevated levels of urinary 17-ketosteroids and plasma DHEA sulfate. A high basal level of a precursor of cortisol biosynthesis (such as 17-hydroxyprogesterone, 17-hydroxypregnenolone, or 11-deoxycortisol), or elevation of such a precursor after ACTH stimulation, confirms the diagnosis of a partial deficiency. Measurement of steroid precursors 60 min after bolus administration of ACTH is usually sufficient. Adrenal androgen output is easily suppressed by the standard low-dose (2 mg) dexamethasone test.

℞ TREATMENT

Therapy in CAH patients consists of daily administration of glucocorticoids to suppress pituitary ACTH secretion. Because of its low cost and intermediate half-life, prednisone is the drug of choice except in infants, in whom hydrocortisone is usually used. In adults with late-onset adrenal hyperplasia, the smallest single bedtime dose of a long- or intermediate-acting glucocorticoid that suppresses pituitary ACTH secretion should be administered. The amount of steroid required by children with CAH is approximately 1 to 1.5 times the normal cortisol production rate of 27 to 35 μmol (10 to 13 mg) of cortisol per square meter of body surface per day and is given in divided doses two or three times per day. The dosage schedule is governed by repetitive analysis of the urinary 17-ketosteroids, plasma DHEA sulfate, and/or precursors of cortisol biosynthesis. Skeletal growth and maturation must also be monitored closely, as overtreatment with glucocorticoid replacement therapy retards linear growth.

Receptor Mutations *Isolated glucocorticoid deficiency* is a rare autosomal recessive disease secondary to a mutation in the ACTH receptor. Usually mineralocorticoid function is normal. Adrenal insufficiency is manifest within the first 2 years of life as hyperpigmentation, convulsions, and/or frequent episodes of hypoglycemia. In some patients the adrenal insufficiency is associated with achalasia and alacrima—Allgrove's, or triple A, syndrome. However, in some triple A syndrome patients, no mutation in the ACTH receptor has been identified, suggesting that a distinct genetic abnormality causes this syndrome. *Adrenal hypoplasia congenita* is a rare X-linked disorder caused by a mutation in the *DAX1* gene. This gene encodes an orphan nuclear receptor that plays an important role in the development of the adrenal cortex and also the hypothalamic-pituitary-gonadal axis. Thus, patients present with signs and symptoms secondary to deficiencies of all three major adrenal steroids—cortisol, aldosterone, and adrenal androgens—as well as gonadotropin deficiency. Finally a rare cause of hypercortisolism without cushingoid stigmata is *primary cortisol resistance* due to mutations in the glucocorticoid receptor. The resistance is incomplete because patients do not exhibit signs of adrenal insufficiency.

Miscellaneous Conditions Adrenoleukodystrophy causes severe demyelination and early death in children, and adrenomyeloneuropathy is associated with a mixed motor and sensory neuropathy with spastic paraplegia in adults; both disorders are associated with elevated circulating levels of very long chain fatty acids and cause adrenal insufficiency. Autosomal recessive mutations in the *st*eroidogenic *a*cute *r*egulatory (STAR) protein gene cause congenital lipoid adrenal hyperplasia (Chap. 328), which is characterized by adrenal insufficiency and defective gonadal steroidogenesis. Because STAR mediates cholesterol transport into the mitochondrion, mutations in the protein cause massive lipid accumulation in steroidogenic cells, ultimately leading to cell toxicity.

MINERALOCORTICOID DISEASES Some forms of CAH have a mineralocorticoid component (see above). Others are caused by a mutation in other enzymes or ion channels important in mediating or mimicking aldosterone's action.

Hypermineralocorticoidism ■ *LOW PLASMA RENIN ACTIVITY* Rarely, hypermineralocorticoidism is due to a defect in cortisol biosynthesis, specifically 11- or 17-hydroxylation. ACTH levels are increased, with a resultant increase in the production of the mineralocorticoid 11-deoxycorticosterone. Hypertension and hypokalemia can be corrected by glucocorticoid administration. The definitive diagnosis is made by demonstrating an elevation of precursors of cortisol biosynthesis in the blood or urine or by direct demonstration of the genetic defect.

Glucocorticoid administration can also ameliorate hypertension or produce normotension even though a hydroxylase deficiency cannot be identified (Fig. 321-9). These patients have normal to slightly elevated aldosterone levels that do not suppress in response to saline but do suppress in response to 2 days of dexamethasone (2 mg/d). The condition is inherited as an autosomal dominant trait and is termed *glucocorticoid-remediable aldosteronism* (GRA). This entity is secondary to a chimeric gene duplication whereby the 11-β hydroxylase gene promoter (which is under the control of ACTH) is fused to the aldosterone synthase coding sequence. Thus, aldosterone synthase activity is ectopically expressed in the zona fasciculata and is regulated by ACTH, in a fashion similar to the regulation of cortisol secretion. Screening for this defect is best performed by assessing the presence or absence of the chimeric gene. Because the abnormal gene may be present in the absence of hypokalemia, its frequency as a cause of hypertension is unknown. Individuals with suppressed plasma renin levels and juvenile-onset hypertension or a history of early-onset hypertension in first-degree relatives should be screened for this disorder. Early hemorrhagic stroke also occurs in GRA-affected individuals.

GRA documented by genetic analysis may be treated with glucocorticoid administration or antimineralocorticoids, i.e., spironolactone, triamterene, or amiloride. Glucocorticoids should be used only in small doses to avoid inducing iatrogenic Cushing's syndrome. A combination approach is often necessary.

HIGH PLASMA RENIN ACTIVITY *Bartter syndrome* is characterized by severe hyperaldosteronism (hypokalemic alkalosis) with moderate to marked increases in renin activity and hypercalciuria, but normal blood pressure and no edema; this disorder usually begins in childhood. Renal biopsy shows juxtaglomerular hyperplasia. Bartter syndrome is caused by a mutation in the renal Na-K-2Cl co-transporter gene. The pathogenesis involves a defect in the renal conservation of sodium or chloride. The renal loss of sodium is thought to stimulate renin secretion and aldosterone production. Hyperaldosteronism produces potassium depletion, and hypokalemia further elevates prostaglandin production and plasma renin activity. In some cases, the hypokalemia may be potentiated by a defect in renal conservation of potassium.

Gitelman syndrome is an autosomal recessive trait characterized by renal salt wasting and as a result, as in Bartter syndrome, activation of the renin-angiotensin-aldosterone system. As a consequence affected individuals have low blood pressure, low serum potassium, low serum magnesium, and high serum bicarbonate. In contrast to Bartter syndrome, urinary calcium excretion is reduced. Gitelman syndrome results from loss-of-function mutations of the renal thiazide-sensitive Na-Cl co-transporter.

Increased Mineralocorticoid Action *Liddle syndrome* is a rare autosomal dominant disorder that mimicks hyperaldosteronism. The defect is in the genes encoding the β or η subunits of the epithelial sodium channel. Both renin and aldosterone levels are low, owing to the constitutively activated sodium channel and the resulting excess sodium reabsorption in the renal tubule.

TABLE 321-9 A Checklist for Use Prior to the Administration of Glucocorticoids in Pharmacologic Doses

Presence of tuberculosis or other chronic infection (chest x-ray, tuberculin test)
Evidence of glucose intolerance or history of gestational diabetes mellitus
Evidence of preexisting osteoporosis (bone density assessment in organ transplant recipients or postmenopausal patients)
History of peptic ulcer, gastritis, or esophagitis (stool guaiac test)
Evidence of hypertension or cardiovascular disease
History of psychological disorders

A rare autosomal recessive cause of hypokalemia and hypertension is 11β-HSD II deficiency, in which cortisol cannot be converted to cortisone and hence binds to the MR and acts as a mineralocorticoid. This condition, also termed *apparent mineralocorticoid excess syndrome*, is caused by a defect in the gene encoding the renal isoform of this enzyme, 11β-HSD II. Patients can be identified either by documenting an increased ratio of cortisol to cortisone in the urine or by genetic analysis. Patients with the 11β-HSD deficiency syndrome can be treated with small doses of dexamethasone, which suppresses ACTH and endogenous cortisol production but binds less well to the mineralocorticoid receptor than does cortisol.

The ingestion of candies or chewing tobacco containing certain forms of licorice produces a syndrome that mimics primary aldosteronism. The component of such agents that causes sodium retention is glycyrrhizinic acid, which inhibits 11β-HSD II and hence allows cortisol to act as a mineralocorticoid. The diagnosis is established or excluded by a careful history.

Decreased Mineralocorticoid Production or Action In patients with a deficiency in aldosterone biosynthesis, the transformation of corticosterone into aldosterone is impaired, owing to a mutation in the aldosterone synthase (CYP11B2) gene. These patients have low to absent aldosterone secretion, elevated plasma renin levels, and elevated levels of the intermediates of aldosterone biosynthesis (corticosterone and 18-hydroxycorticosterone).

Pseudohypoaldosteronism type I (PHA-I) is an autosomal recessive disorder that is seen in the neonatal period and is characterized by salt wasting, hypotension, hyperkalemia, and high renin and aldosterone levels. In contrast to the gain-of-function mutations in the epithelial sodium channel in Liddle syndrome, mutations in PHA-I result in loss of epithelial sodium channel function.

PHARMACOLOGIC CLINICAL USES OF ADRENAL STEROIDS

The widespread use of glucocorticoids emphasizes the need for a thorough understanding of the metabolic effects of these agents. Before adrenal hormone therapy is instituted, the expected gains should be weighed against undesirable effects. Several important questions should be addressed before initiating therapy. First, how serious is the disorder (the more serious, the greater the likelihood that the risk/benefit ratio will be positive)? Second, how long will therapy be required (the longer the therapy, the greater the risk of adverse side effects)? Third, does the individual have preexisting conditions that glucocorticoids may exacerbate (Table 321-9)? If so, then a careful risk/benefit assessment is required to ensure that the ratio is favorable given the increased likelihood of harm by steroids in these patients. Supplementary measures to minimize undesirable metabolic effects are shown in Table 321-10. Fourth, which preparation is best?

THERAPEUTIC CONSIDERATIONS The following considerations should be taken into account in deciding which steroid preparation to use:

1. *The biologic half-life.* The rationale behind alternate-day therapy is to decrease the metabolic effects of the steroids for a significant part of each 48 h period while still producing a pharmacologic effect durable enough to be effective. Too long a half-life would defeat the first purpose, and too short a half-life would defeat the second. In general, the more potent the steroid, the longer its biologic half-life.

TABLE 321-10 Supplementary Measures to Minimize Undesirable Metabolic Effects of Glucocorticoids

Monitor caloric intake to prevent weight gain.
Restrict sodium intake to prevent edema and minimize hypertension and potassium loss.
Provide supplementary potassium if necessary.
Provide antacid, H_2 receptor antagonist, and/or H^+,K^+-ATPase inhibitor therapy.
Institute alternate-day steroid schedule if possible. Patients receiving steroid therapy over a prolonged period should be protected by an appropriate increase in hormone level during periods of acute stress. A rule of thumb is to *double* the maintenance dose.
Minimize osteopenia by
Administering gonadal hormone replacement therapy: 0.625–1.25 mg conjugated estrogens given cyclically with progesterone, unless the uterus is absent; testosterone replacement for hypogonadal men
Ensuring high calcium intake (should be approximately 1200 mg/d)
Administering supplemental vitamin D if blood levels of calciferol or $1,25(OH)_2$ vitamin D are reduced
Administering bisphosphonate prophylactically, orally or parenterally, in high-risk patients

2. *The mineralocorticoid effects of the steroid.* Most synthetic steroids have less mineralocorticoid effect than hydrocortisone (Table 321-11).
3. *The biologically active form of the steroid.* Cortisone and prednisone have to be converted to biologically active metabolites before anti-inflammatory effects can occur. Because of this, in a condition for which steroids are known to be effective and when an adequate dose has been given without response, one should consider substituting hydrocortisone or prednisolone for cortisone or prednisone.
4. *The cost of the medication.* This is a serious consideration if chronic administration is planned. Prednisone is the least expensive of available steroid preparations.
5. *The type of formulation.* Topical steroids have the distinct advantage over oral steroids in reducing the likelihood of systemic side effects. In addition, some inhaled steroids have been designed to minimize side effects by increasing their hepatic inactivation if they are swallowed (Chap. 236). However, all topical steroids can be absorbed into the systemic circulation.

TABLE 321-11 Glucocorticoid Preparations

Commonly Used Name[a]	Estimated Potency[b]	
	Glucocorticoid	Mineralocorticoid
SHORT-ACTING		
Hydrocortisone	1	1
Cortisone	0.8	0.8
INTERMEDIATE-ACTING		
Prednisone	4	0.25
Prednisolone	4	0.25
Methylprednisolone	5	<0.01
Triamcinolone	5	<0.01
LONG-ACTING		
Paramethasone	10	<0.01
Betamethasone	25	<0.01
Dexamethasone	30–40	<0.01

[a] The steroids are divided into three groups according to the duration of biologic activity. Short-acting preparations have a biologic half-life <12 h; long-acting, >48 h; and intermediate, between 12 and 36 h. Triamcinolone has the longest half-life of the intermediate-acting preparations.

[b] Relative milligram comparisons with hydrocortisone, setting the glucocorticoid and mineralocorticoid properties of hydrocortisone as 1. Sodium retention is insignificant for commonly employed doses of methylprednisolone, triamcinolone, paramethasone, betamethasone, and dexamethasone.

ALTERNATE-DAY STEROID THERAPY The most effective way to minimize the cushingoid effects of glucocorticoids is to administer the total 48-h dose as a *single* dose of *intermediate-acting steroid* in the morning, *every other day*. If symptoms of the underlying disorder can be controlled by this technique, it offers distinct advantages. Three considerations deserve mention: (1) The alternate-day schedule may be approached through transition schedules that allow the patient to adjust gradually; (2) supplementary nonsteroid medications may be needed on the "off" day to minimize symptoms of the underlying disorder; and (3) many symptoms that occur during the off day (e.g., fatigue, joint pain, muscle stiffness or tenderness, and fever) may represent relative adrenal insufficiency rather than exacerbation of the underlying disease.

The alternate-day approach capitalizes on the fact that cortisol secretion and plasma levels normally are highest in the early morning and lowest in the evening. The normal pattern is mimicked by administering an intermediate-acting steroid in the morning (7 to 8 A.M.) (Table 321-11).

Initially, the steroid regimen often requires daily or more frequent doses of steroid to achieve the desired anti-inflammatory or immunity-suppressing action. *Only after this desired effect is achieved is an attempt made to switch to an alternate-day program.* A number of schedules can be used for transferring from a daily to an alternate-day program. The key points to be considered are flexibility in arranging a program and the use of supportive measures on the off day. One may attempt a gradual transition to the alternate-day schedule rather than an abrupt changeover. One approach is to keep the steroid dose constant on one day and gradually reduce it on the alternate day. Alternatively, the steroid dose can be increased on one day and reduced on the alternate day. In any case, it is important to anticipate that some increase in pain or discomfort may occur in the 36 to 48 h following the last dose.

WITHDRAWAL OF GLUCOCORTICOIDS FOLLOWING LONG-TERM USE It is possible to reduce a daily steroid dose gradually and eventually to discontinue it, but under most circumstances withdrawal of steroids should be initiated by first implementing an alternate-day schedule. Patients who have been on an alternate-day program for a month or more experience less difficulty during termination regimens. The dosage is gradually reduced and finally discontinued after a replacement dosage has been reached (e.g., 5 to 7.5 mg prednisone). Complications rarely ensue unless undue stress is experienced, and patients should understand that for ≥1 year after withdrawal from long-term high-dose steroid therapy, supplementary hormone should be given in the event of a serious infection, operation, or injury. A useful strategy in patients with symptoms of adrenal insufficiency on a tapering regimen is to measure plasma cortisol levels prior to the steroid dose. A level <140 nmol/L (5 μg/dL) indicates suppression of the pituitary-adrenal axis and implies that a more cautious tapering of steroids is indicated.

In patients on high-dose daily steroid therapy, it is advised to reduce dosage to ~20 mg prednisone daily as a single morning dose before beginning the transition to alternate-day therapy. If a patient cannot tolerate an alternate-day program, consideration should be given to the possibility that the patient has developed primary adrenal insufficiency.

FURTHER READING

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322 PHEOCHROMOCYTOMA

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Pheochromocytomas produce, store, and secrete catecholamines. They are usually derived from the adrenal medulla but may develop from chromaffin cells in or about sympathetic ganglia (extraadrenal pheochromocytomas or paragangliomas). Related tumors that secrete catecholamines and produce similar clinical syndromes include chemodectomas derived from the carotid body and ganglioneuromas derived from the postganglionic sympathetic neurons.

The clinical features are due predominantly to the release of catecholamines and, to a lesser extent, to the secretion of other substances. Hypertension is the most common sign, and hypertensive paroxysms or crises, often spectacular and alarming, occur in over half the cases.

Pheochromocytoma occurs in approximately 0.1% of the hypertensive population but is, nevertheless, an important correctable cause of high blood pressure. Indeed, it is usually curable if diagnosed and treated, but it may be fatal if undiagnosed or mistreated. Postmortem series indicate that most pheochromocytomas are unsuspected clinically, even when the tumor is related to the fatal outcome.

PATHOLOGY ■ Location and Morphology In adults, approximately 80% of pheochromocytomas are unilateral and solitary, 10% are bilateral, and 10% are extraadrenal. In children, a fourth of tumors are bilateral, and an additional fourth are extraadrenal. Solitary lesions inexplicably favor the right side. Although pheochromocytomas may grow to large size (>3 kg), most weigh <100 g and are <10 cm in diameter. Pheochromocytomas are highly vascular.

The tumors are made up of large, polyhedral, pleomorphic chromaffin cells. Fewer than 10% of these tumors are malignant. As with several other endocrine tumors, malignancy cannot be determined from the histologic appearance; tumors that contain large numbers of aneuploid or tetraploid cells, as determined by flow cytometry, are more likely to recur. Local invasion of surrounding tissues or distant metastases indicate malignancy.

EXTRAADRENAL PHEOCHROMOCYTOMAS Extraadrenal pheochromocytomas usually weigh 20 to 40 g and are <5 cm in diameter. Most are located within the abdomen in association with the celiac, superior mesenteric, and inferior mesenteric ganglia. Approximately 10% are in the thorax, 1% are within the urinary bladder, and <3% are in the neck, usually in association with the sympathetic ganglia or the extracranial branches of the ninth or tenth cranial nerves.

Catecholamine Synthesis, Storage, and Release Pheochromocytomas synthesize and store catecholamines by processes resembling those of the normal adrenal medulla. Little is known about the mechanisms of catecholamine release from pheochromocytomas, but changes in blood flow and necrosis within the tumor may be the cause in some instances. These tumors are not innervated, and catecholamine release does not result from neural stimulation. Pheochromocytomas also store and secrete a variety of peptides, including endogenous opioids, adrenomedullin, endothelin, erythropoietin, parathyroid hormone–related protein, neuropeptide Y, and chromagranin A. These peptides contribute to the clinical manifestations in selected cases, as noted below.

EPINEPHRINE, NOREPINEPHRINE, AND DOPAMINE Most pheochromocytomas produce both norepinephrine and epinephrine, and the percentage of norepinephrine is usually greater than in the normal adrenal. Most extraadrenal pheochromocytomas secrete norepinephrine exclusively. Rarely, pheochromocytomas produce epinephrine alone, particularly in association with multiple endocrine neoplasia (MEN). Although