16th Edition

HARRISON'S PRINCIPLES OF Internal Medicine

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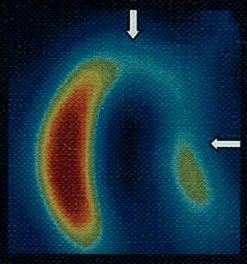

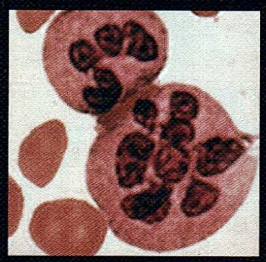
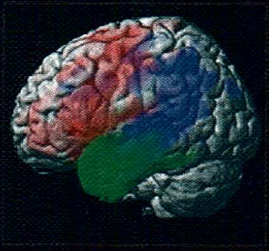

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Outcomes can be predicted using postoperative nomograms that consider pretreatment factors and the pathologic findings at surgery. PSA failure is defined as a detectable value of 0.2 or 0.4 ng/mL, although the exact definition varies among series. 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 tumors 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.

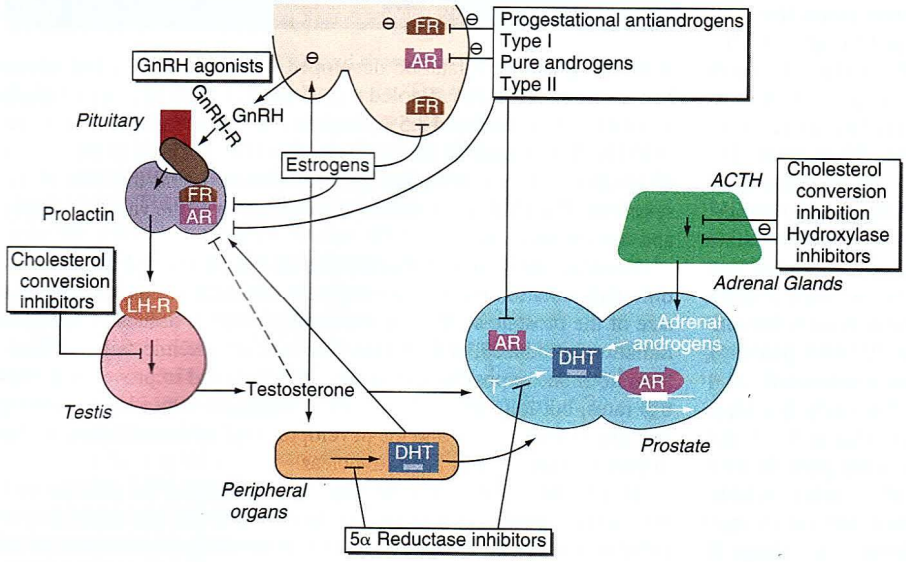

FIGURE 81-3 Sites of action of different hormone therapies.

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 as with progression include Gleason gra to recurrence, and PSA doubling ti those with Gleason grade ≥8 tumors, ability of metastatic progression was and 71% at 3, 5, and 7 years, respect the time to recurrence was <2 years doubling time was long (> 10 mon proportion with metastatic disease wa and 53% vs. 47, 69, and 79% if the time was short (< 10 months) during time intervals. These models continue fined. A difficulty making these predi that most patients with a rising PSA some form of therapy before the deve of metastases.

METASTATIC DISEASE: NONCASTRATE *disease noncastrate* refers to patients mors visible on an imaging study and trate levels of testosterone. The patien newly diagnosed or have recurrent dis treatment for localized disease. Stand ment is to block androgen action or decrease androgen produ medical or surgical means. Over 90% of male hormones or the testes; <10% are synthesized in the adrenal gland. S chiectomy is the "gold standard" approach but is least acce patients. Medical therapies can be divided into those that l tosterone levels, e.g., gonadotropin-releasing hormone (Gn nists and antagonists, estrogens and progestational agents, a tiandrogens that bind to the androgen receptor but do not s 81-3). Ketoconazole inhibits adrenal androgen synthesis a after first-line castration is no longer effective. In this setti renal glands may contribute up to 40% of the active androg prostate.

GnRH analogues (leuprolide acetate and goserelin acetat produce a rise in luteinizing hormone and follicle-stimulatin (FSH), followed by a downregulation of receptors in the gland, which effects a chemical castration. They were appro basis of randomized comparisons showing an improved saf (specifically, reduced cardiovascular toxicities) relative to d bestrol (DES), with equivalent potency. The initial rise in te may result in a clinical flare of the disease. As such, these contraindicated in men with significant obstructive sympto related pain, or spinal cord compromise. Estrogens such as lower testosterone levels but have fallen out of favor due of vascular complications such as fluid retention, phlebi and stroke.

In contrast, nonsteroidal antiandrogens such as flutam tamide, or nilutamide block the binding of androgens to t Given alone, testosterone levels remain the same or incre agents were approved initially to block the flare associat initial rise in testosterone that results following GnRH a They have also been studied as part of a combined andro (CAB) or maximal androgen blockade (MAB) and as m The concept of CAB was developed to inhibit testicular androgens at the outset, and it preoccupied the field for It is achieved clinically by combining an antiandrogen w agonist or surgical orchiectomy. Cumulative results of comparisons involving thousands of patients showed no combining an antiandrogen with surgical orchiectomy, w analyses of trials combining an antiandrogen with a Gn have shown a modest (<10%) survival advantage. Me all combined androgen blockade trials concluded that benefit to the approach. In practice, most patients treat analogue therapy receive an antiandrogen for the first 2 treatment.

The anti–prostate cancer effects of agents that lower

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

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 ba oid output may be normal, a subnormal increase occurs afte Adrenal stimulation with ACTH uncovers abnormalities in th of the disease, eliciting a subnormal increase of cortisol leve increase at all. In more advanced stages of adrenal destruction sodium, chloride, and bicarbonate levels are reduced, and the potassium level is elevated. The hyponatremia is due both to sodium into the urine (due to aldosterone deficiency) and to mo into the intracellular compartment. This extravascular sodium pletes extracellular fluid volume and accentuates hypotensio vated plasma vasopressin and angiotensin II levels may contri the hyponatremia by impairing free water clearance. Hyperkal due to a combination of aldosterone deficiency, impaired glo filtration, and acidosis. Basal levels of cortisol and aldoster subnormal and fail to increase following ACTH administratio to moderate hypercalcemia occurs in 10 to 20% of patients for reasons. The electrocardiogram may show nonspecific chang the electroencephalogram exhibits a generalized reduction an ing. There may be a normocytic anemia, a relative lymphocyto a moderate eosinophilia.

Diagnosis The diagnosis of adrenal insufficiency should be ma with ACTH stimulation testing to assess adrenal reserve capa steroid production (see above for ACTH test protocols). In br best screening test is the cortisol response 60 min after 250 cosyntropin given intramuscularly or intravenously. Cortisol should exceed 495 nmol/L (18 μg/dL). If the response is ab then primary and secondary adrenal insufficiency can be disting by measuring aldosterone levels from the same blood samples. ondary, but not primary, adrenal insufficiency the aldosterone ment will be normal [≥150 pmol/l (5 ng/dL)]. Furthermore, in p adrenal insufficiency, plasma ACTH and associated peptides (are elevated because of loss of the usual cortisol-hypothalami tary feedback relationship, whereas in secondary adrenal insuffi plasma ACTH values are low or "inappropriately" norma 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

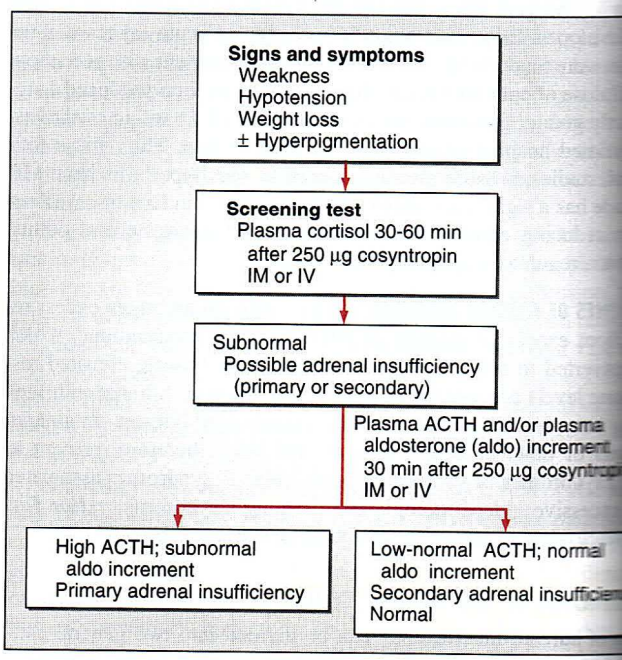

FIGURE 321-11 Diagnostic flowchart for evaluating patients with suspected insufficiency. Plasma adrenocorticotropic hormone (ACTH) levels are low in se adrenal insufficiency. In adrenal insufficiency secondary to pituitary tumors pathic panhypopituitarism, other pituitary hormone deficiencies are present.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

Diagnosis Because weakness and fatigue are common, diagnosis of adrenocortical insufficiency may be difficult. However, the combination of gastrointestinal distress, weight loss, anorexia, and a suggestion of increased pigmentation makes it mandatory to perform ACTH stimulation tests to rule out adrenal insufficiency, preferably before steroid treatment is started. Weight loss is useful in evaluating the significance of weakness and fatigue. Racial pigmentation may be a problem, but a *recent* and progressive increase in pigmentation is usually recognized by the patient with gradual advancement. 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. 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 usually make clear-cut differentiation.

TREATMENT

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 mg/d. Patients are advised to take glucocorticoids with meals or, if that is impractical, with milk or an antacid, because the drugs may decrease 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 emotional excitement after initiation of therapy; in these, the dosage should be reduced. Other situations that may necessitate smaller doses include hypertension and diabetes mellitus. Obese individuals and those taking 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 dosage.

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 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 often 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.

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

	Hydrocortisone Infusion, Continuous, mg/h		Hydrocortisone (Orally) 8 A.M.	Hydrocortisone (Orally) 4 P.M.	Fludrocortisone (Orally), 8 A.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).

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 100 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 deficiency in renin production (so-called hyporeninemic hypoaldosteronism), most commonly in adults with diabetes mellitus and 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

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 duc 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.