PRINCIPLES AND PRACTICE OF ENDOCRINOLOGY AND METABOLISM

THIRD EDITION

Kenneth L. Becker, Editor

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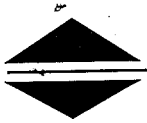

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tions causing steroid 21-hydroxylase deficiency. Proc Natl Acad Sci U S A 1988; 85:4436.
70. Owerbach D, Crawford YM, Draznin MB. Direct analysis of CYP21B genes in 21-hydroxylase deficiency using polymerase chain reaction amplification. Mol Endocrinol 1990; 4:125.
71. Mornet E, Crete P, Kuttenn F, et al. Distribution of deletions and seven point mutations on CYP21B genes in three clinical forms of steroid 21-hydroxylase deficiency. Am J Hum Genet 1991; 48:79.
72. Higashi Y, Hiromasa T, Tanae A, et al. Effects of individual mutations in the P-450(C21) pseudogene on the P-450(C21) activity and their distribution in the patient genomes of congenital steroid 21-hydroxylase deficiency. J Biochem 1991; 109:638.
73. Speiser PW, Dupont J, Zhu D, et al. Disease expression and molecular genotype in congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Invest 1992; 90:584.
74. Wedell A, Thilén A, Ritzén EM, et al. Mutational spectrum of the steroid 21-hydroxylase gene in Sweden: implications for genetic diagnosis and association with disease manifestation. J Clin Endocrinol Metab 1994; 78:1145.
75. Higashi Y, Tanae A, Inoue H, et al. Aberrant splicing and missense mutations cause steroid 21-hydroxylase [P-450(C21)] deficiency in humans: possible gene conversion products. Proc Natl Acad Sci U S A 1988; 85:7486.
76. Tusie-Luna MT, Traktman P, White PC. Determination of functional effects of mutations in the steroid 21-hydroxylase gene (CYP21) using recombinant vaccinia virus. J Biol Chem 1990; 265:20916.
77. Tusie-Luna MT, Speiser PW, Dumic M, et al. A mutation (Pro-30 to Leu) in CYP21 represents a potential nonclassic steroid 21-hydroxylase deficiency allele. Mol Endocrinol 1991; 5:685.
78. Higashi Y, Hiromasa T, Tanae A, et al. Effects of individual mutations in the P-450(C21) pseudogene on the P-450(C21) activity and their distribution in the patient genomes of congenital steroid 21-hydroxylase deficiency. J Biochem (Tokyo) 1991; 109:638.
79. Dickerman Z, Grant DR, Faiman C, Winter JSD. Intraadrenal steroid concentrations in man: zonal differences and developmental changes. J Clin Endocrinol Metab 1984; 59:1031.
80. Nikoshkov A, Lajic S, Vlamis-Gardikas A, et al. Naturally occurring mutants of human steroid 21-hydroxylase (P450c21) pinpoint residues important for enzyme activity and stability. J Biol Chem 1998; 273:6163.
81. Mornet E, Dupont J, Vitek A, White PC. Characterization of two genes encoding human steroid 11β-hydroxylase (P-450 11β). J Biol Chem 1989; 264:20961.
82. Chua SC, Szabo P, Vitek A, et al. Cloning of cDNA encoding steroid 11β-hydroxylase (P450c11). Proc Natl Acad Sci U S A 1987; 84:7193.
83. Kawamoto T, Mitsuuchi Y, Toda K, et al. Cloning of cDNA and genomic DNA for human cytochrome $P\text{-}450_{11}\beta$. FEBS Lett 1990; 269:345.
84. Kawamoto T, Mitsuuchi Y, Ohnishi T, et al. Cloning and expression of a cDNA for human cytochrome P-450aldos as related to primary aldosteronism. Biochem Biophys Res Commun 1990; 173:309.
85. Curnow KM, Tusie-Luna MT, Pascoe L, et al. The product of the CYP11B2 gene is required for aldosterone biosynthesis in the human adrenal cortex. Mol Endocrinol 1991; 5:1513.
86. White PC, Pascoe L, Curnow KM, et al. Molecular biology of 11β-hydroxylase and 11β-hydroxysteroid dehydrogenase enzymes. J Steroid Biochem Mol Biol 1992; 43:827.
87. Curnow KM, Slutsker L, Vitek J, et al. Mutations in the CYP11B1 gene causing congenital adrenal hyperplasia and hypertension cluster in exons 6, 7, and 8. Proc Natl Acad Sci U S A 1993; 90:4552.
88. White PC, Dupont J, New MI, et al. A mutation in CYP11B1 (Arg-448→His) associated with steroid 11β-hydroxylase deficiency in Jews of Moroccan origin. J Clin Invest 1991; 87:1664.
89. Naiki Y, Kawamoto T, Mitsuuchi Y, et al. A nonsense mutation (TGG116TAG[Stop]) in CYP11B1 causes steroid 11β-hydroxylase deficiency. J Clin Endocrinol Metab 1993; 77:1677.
90. Helmberg A, Ausserer B, Kofler R. Frame shift by insertion of 2 basepairs in codon 394 of CYP11B1 causes congenital adrenal hyperplasia due to steroid 11 beta-hydroxylase deficiency. J Clin Endocrinol Metab 1992; 75:1278.
91. Nakagawa Y, Yamada M, Ogawa H, Igarashi Y. Missense mutation in CYP11B1 (CGA[Arg-384]→GGA[Gly]) causes steroid 11 beta-hydroxylase deficiency. Eur J Endocrinol 1995; 132:286.
92. Yang LX, Toda K, Miyahara K, et al. Classic steroid 11 beta-hydroxylase deficiency caused by a C→G transversion in exon 7 of CYP11B1. Biochem Biophys Res Commun 1995; 216:723.
93. Geley S, Kapelari K, Johrer K, et al. CYP11B1 mutations causing congenital adrenal hyperplasia due to 11 beta-hydroxylase deficiency. J Clin Endocrinol Metab 1996; 81:2896.
94. Merke DP, Tajima T, Chhabra A, et al. Novel CYP11B1 mutations in congenital adrenal hyperplasia due to steroid 11 beta-hydroxylase deficiency. J Clin Endocrinol Metab 1998; 83:270.
95. Joehrer K, Geley S, Strasser-Wozak EM, et al. CYP11B1 mutations causing non-classic adrenal hyperplasia due to 11 beta-hydroxylase deficiency. Hum Mol Genet 1997; 6:1829.
96. Matteson KJ, Picado-Leonard J, Chung B-C, et al. Assignment of the gene for adrenal P450c17 (steroid 17α-hydroxylase/17,20-lyase) to human chromosome 10. J Clin Endocrinol Metab 1986; 63:789.
97. Chung B-C, Picado-Leonard J, Haniu M, et al. Cytochrome P450c17 (steroid 17α-hydroxylase/17,20-lyase): cloning of human adrenal and testis cDNAs indicates the same gene is expressed in both tissues. Proc Natl Acad Sci U S A 1987; 84:407.
98. Suzuki Y, Nagashima T, Nomura Y, et al. A. A new compound heterozygous mutation (W17X, 436 + 5G→T) in the cytochrome P450c17 gene causes 17 alpha-hydroxylase/17,20-lyase deficiency. J Clin Endocrinol Metab 1998; 83:199.
99. Lachance Y, Luu-The V, Labrie C, et al. Characterization of human 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4 isomerase gene and its expression in mammalian cells. J Biol Chem 1990; 265:20469.
100. Lorence MC, Corbin CJ, Kamimura N, et al. Structural analysis of the gene encoding human 3β-hydroxysteroid dehydrogenase/$\Delta^{5\to4}$-isomerase. Mol Endocrinol 1990; 4:1850.
101. Lachance Y, Luu-The V, Verreault H, et al. Structure of the human type II 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4 isomerase (3β-HSD) gene: adrenal and gonadal specificity. DNA Cell Biol 1991; 10:701.
102. Berube D, Luu-The V, Lachance Y, et al. Assignment of the human 3β-HSD gene to the p13 band of chromosome 1. Cytogenet Cell Genet 1989; 52:199.
102a. McCartin S, Russell AJ, Fisher RA, et al. Phenotypic variability and origins of mutations, in the gene encoding 3β-hydroxysteroid dehydrogenase type II. Mol Endocrinol 2000; 24:75.
103. Rheaume E, Simard J, Morel Y, et al. Congenital adrenal hyperplasia due to point mutations in the type II 3β-hydroxysteroid dehydrogenase gene. Nature 1992; 1:239.
104. Chang YT, Kappy MS, Iwamoto K, et al. Mutations in the type II 3 beta-hydroxysteroid dehydrogenase (3 beta-HSD) gene in a patient with classic salt-wasting 3 beta-HSD deficiency congenital adrenal hyperplasia. Pediatr Res 1993; 34:698.
105. Simard J, Rheaume E, Sanchez R, et al. Molecular basis of congenital adrenal hyperplasia due to 3β-hydroxysteroid dehydrogenase deficiency. Mol Endocrinol 1993; 7:716.
106. Sakkal-Alkaddour H, Zhang L, Yang X, et al. Studies of 3 beta-hydroxysteroid dehydrogenase genes in infants and children manifesting premature pubarche and increased adrenocorticotropin-stimulated delta 5-steroid levels. J Clin Endocrinol Metab 1996; 81:3961.
107. Chung BC, Matteson KJ, Voutilainen R, et al. Human cholesterol side-chain cleavage enzyme, P450scc: cDNA cloning, assignment of the gene to chromosome 15, and expression in the placenta. Proc Natl Acad Sci U S A 1986; 83:8962.
108. Lin D, Gitelman SE, Saenger P, Miller WL. Normal genes for the cholesterol side chain cleavage enzyme, P450ssc, in congenital lipoid adrenal hyperplasia. J Clin Invest 1991; 88:1955.
109. Miller WL. Congenital lipoid adrenal hyperplasia: the human gene knockout for the steroidogenic acute regulatory protein. J Mol Endocrinol 1997; 19:227.
110. Ulick S, Wang JZ, Morton DH. The biochemical phenotypes of two inborn errors in the biosynthesis of aldosterone. J Clin Endocrinol Metab 1992; 74:1415.
111. Harada N, Ogawa H, Shozu M, Yamada K. Genetic studies to characterize the origin of the mutation in placental aromatase deficiency. Am J Hum Genet 1992; 51:666.
112. Ito Y, Fisher CR, Conte FA, et al. Molecular basis of aromatase deficiency in an adult female with sexual infantilism and polycystic ovaries. Proc Natl Acad Sci U S A 1993; 90:11673.
113. Simpson ER, Zhao Y, Agarwal VR, et al. Aromatase expression in health and disease. Recent Prog Horm Res 1997; 52:185.
114. Eckstein B, Cohen S, Farkas A, Rosler A. The nature of the defect in familial male pseudohermaphroditism in Arabs of Gaza. J Clin Endocrinol Metab 1989; 68:477.
115. Rosler A, Belanger A, Labrie F. Mechanisms of androgen production in male pseudohermaphroditism due to 17 beta-hydroxysteroid dehydrogenase deficiency. J Clin Endocrinol Metab 1992; 75:773.
116. Castro-Magana M, Angulo M, Uy J. Male hypogonadism with gynecomastia caused by late-onset deficiency of testicular 17-ketosteroid reductase. N Engl J Med 1993; 328:1297.
117. Pang S, Softness B, Sweeney WJ, New MI. Hirsutism, polycystic ovarian disease, and ovarian 17-ketosteroid reductase deficiency. N Engl J Med 1987; 316:1295.
118. Andersson S, Moghrabi N. Physiology and molecular genetics of 17 beta-hydroxysteroid dehydrogenases. Steroids 1997; 62:143.
119. Moghrabi N, Hughes IA, Dunaif A, Andersson S. Deleterious missense mutations and silent polymorphism in the human 17beta-hydroxysteroid dehydrogenase 3 gene (HSD17B3). J Clin Endocrinol Metab 1998; 83:2855.
120. Nyckoff JA, Seely EW, Hurwitz S, et al. Glucocorticoid-remediable aldosteronism and pregnancy. Hypertension 2000; 35:668.

CHAPTER 78

CORTICOSTEROID THERAPY

LLOYD AXELROD

This chapter examines the risks associated with the use of glucocorticoids and of mineralocorticoids for various illnesses, and provides guidelines for the administration of these commonly prescribed substances.

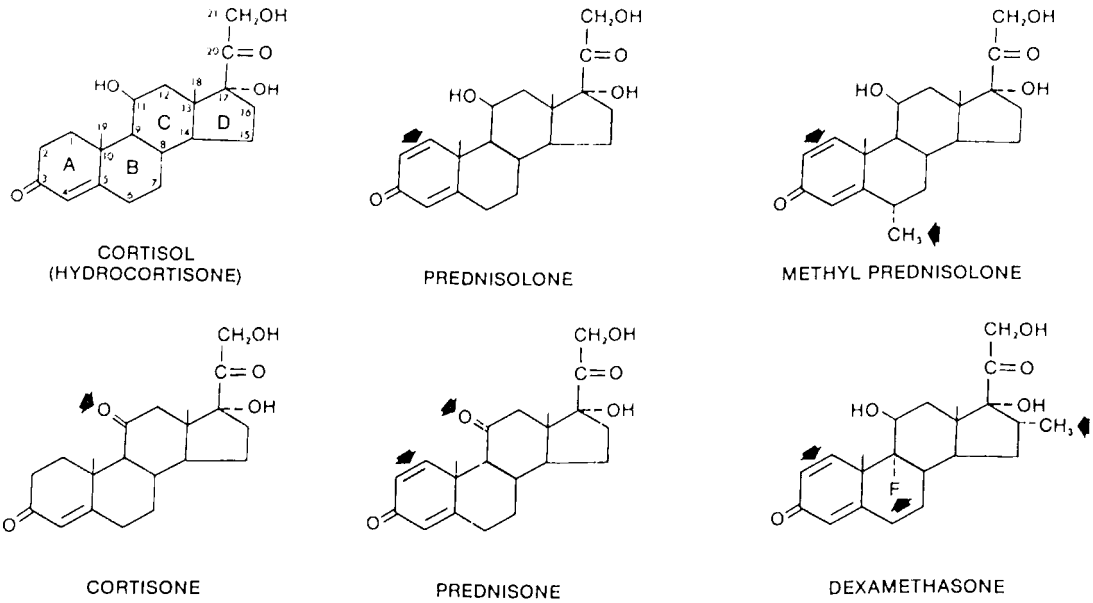


FIGURE 78-1. The structures of commonly used glucocorticoids. In the depiction of cortisol, the 21 carbon atoms of the glucocorticoid skeleton are indicated by numbers and the four rings are designated by letters. The *arrows* indicate the structural differences between cortisol and each of the other molecules. (From Axelrod L. Glucocorticoid therapy. Medicine [Baltimore] 1976; 55:39, and Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. Textbook of rheumatology, 4th ed. Philadelphia: WB Saunders, 1993:779.)

GLUCOCORTICOIDS

STRUCTURE OF COMMONLY USED GLUCOCORTICOIDS

Figure 78-1 indicates the structures of several commonly used glucocorticoids.[1,2] *Cortisol (hydrocortisone)* is the principal circulating glucocorticoid in humans.

Glucocorticoid activity requires a hydroxyl group at carbon 11 of the steroid molecule. Cortisone and prednisone are 11-keto compounds. Consequently, they lack glucocorticoid activity until they are converted in vivo to cortisol and prednisolone, the corresponding 11-hydroxyl compounds.[3,4] This conversion occurs predominantly in the liver. Thus, topical application of cortisone is ineffective in the treatment of dermatologic diseases that respond to topical application of cortisol.[4] Similarly, the antiinflammatory action of cortisone delivered by intraarticular injection is minimal compared with the effect of cortisol administered in the same manner.[3] Cortisone and prednisone are used only for systemic therapy. All glucocorticoid preparations marketed for topical or local use are 11-hydroxyl compounds, which obviates the need for biotransformation.

PHARMACODYNAMICS

HALF-LIFE, POTENCY, AND DURATION OF ACTION

The important differences among the systemically used glucocorticoid compounds are duration of action, relative glucocorticoid potency, and relative mineralocorticoid potency (Table 78-1).[1,2] The commonly used glucocorticoids are classified as *short-acting, intermediate-acting,* and *long-acting* on the basis of the duration of corticotropin (ACTH) suppression after a single dose, equivalent in antiinflammatory activity to 50 mg of prednisone (Table 78-1).[5] The relative potencies of the glucocorticoids correlate with their affinities for the intracellular glucocorticoid receptor.[6] The observed potency of a glucocorticoid, however, is determined not only by the intrinsic biologic potency, but also by the duration of action.[6,7] Consequently, the relative potency of two glucocorticoids varies as a function of the time interval between the administration of the two steroids and the determination of the potency. In particular, failure to account for the duration of action may lead to a marked underestimation of the potency of dexamethasone.[7]

The correlation between the *circulating half-life* ($T_{1/2}$) of a glucocorticoid and its *potency* is weak. The $T_{1/2}$ of cortisol in the circulation is in the range of 80 to 115 minutes.[1] The $T_{1/2}$s of other commonly used agents are cortisone, 0.5 hours; prednisone, 3.4 to 3.8 hours; prednisolone, 2.1 to 3.5 hours; methylprednisolone, 1.3 to 3.1 hours; and dexamethasone 1.8 to 4.7 hours.[1,7,8] Prednisolone and dexamethasone have comparable circulating $T_{1/2}$s, but dexamethasone is clearly more potent. Similarly, the correlation between the circulating $T_{1/2}$ of a glucocorticoid and its *duration of action* is poor. The many actions of glucocorticoids do not have an equal duration, and the duration of action may be a function of the dose.

The duration of ACTH suppression is not simply a function of the level of antiinflammatory activity, because variations in the duration of ACTH suppression are achieved by doses of glucocorticoids with comparable antiinflammatory activity. The duration of ACTH suppression produced by an individual glucocorticoid, however, probably is dose related.[5]

TABLE 78-1.
Commonly Used Glucocorticoids

Duration of Action*	Glucocorticoid Potency†	Equivalent Glucocorticoid Dose (mg)	Mineralocorticoid Activity
SHORT-ACTING			
Cortisol (hydrocortisone)	1	20	Yes‡
Cortisone	0.8	25	Yes‡
Prednisone	4	5	No
Prednisolone	4	5	No
Methylprednisolone	5	4	No
INTERMEDIATE-ACTING			
Triamcinolone	5	4	No
LONG-ACTING			
Betamethasone	25	0.60	No
Dexamethasone	30	0.75	No

*The classification by duration of action is based on Harter JG. Corticosteroids. NY State J Med 1966;66:827.

†The values given for glucocorticoid potency are relative. Cortisol is arbitrarily assigned a value of 1.

‡Mineralocorticoid effects are dose related. At doses close to or within the basal physiologic range for glucocorticoid activity, no such effect may be detectable.

(Data from Axelrod L. Glucocorticoid therapy. Medicine [Baltimore] 1976;55:39; Axelrod L. Adrenal corticosteroids. In: Miller RR, Greenblatt DJ, eds. Handbook of drug therapy. New York: Elsevier North-Holland, 1979:809; and Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. Textbook of rheumatology, 4th ed. Philadelphia: WB Saunders, 1993:779.)

In short, the slight differences in the circulating $T_{1/2}$s of the glucocorticoids contrast with their marked differences in potency and duration of ACTH suppression. Thus, the duration of action of a glucocorticoid is not determined by its presence in the circulation. This is consistent with the mechanism of action of steroid hormones. A steroid molecule binds to a specific intracellular receptor protein (see Chap. 4). This steroid-receptor complex modifies the process of transcription by which RNA is transcribed from the DNA template. This process alters the rate of synthesis of specific proteins. The steroid thereby modifies the phenotypic expression of the genetic information. Thus, the glucocorticoid *continues* to act inside the cell after it has disappeared from the circulation. Moreover, the events initiated by the glucocorticoid may continue to occur, or a product of these events (such as a specific protein) may be present after the disappearance of the glucocorticoid.

BIOAVAILABILITY, ABSORPTION, AND BIOTRANSFORMATION

Normally, a person's plasma cortisol level is much lower after the oral administration of cortisone than after an equal dose of cortisol.[9] Consequently, although oral cortisone may be adequate replacement therapy in chronic adrenal insufficiency, the oral form of this agent should not be used when larger, pharmacologic effects are sought. Comparable plasma prednisolone levels are achieved in normal persons after equivalent oral doses of prednisone and prednisolone.[8,10] After the administration of either of these corticosteroids, however, there is wide variation in individual prednisolone concentrations, which may reflect variability in absorption.[8]

In contrast to the marked rises that follow the intramuscular injection of hydrocortisone, plasma cortisol levels rise little or not at all after an intramuscular injection of cortisone acetate. When it is given intramuscularly, cortisone acetate does not provide adequate plasma cortisol levels and offers no advantage over hydrocortisone delivered by the same route. The explanation for the failure of intramuscular cortisone acetate to provide adequate plasma cortisol levels is unknown. It may reflect poor absorption from the site of injection. Alternatively, intramuscular cortisone acetate, which reaches the liver through the systemic circulation, may be metabolically inactivated before it can be converted to cortisol in the liver, in contrast to oral cortisone acetate, which reaches the liver through the portal circulation.

PLASMA TRANSPORT PROTEINS

In normal humans, circadian fluctuations occur in the capacity of corticosteroid-binding globulin (transcortin) to bind cortisol and prednisolone. Patients who have been treated with prednisone for a prolonged period have no diurnal variation in the binding capacity of corticosteroid-binding globulin for cortisol or prednisolone, and both capacities are reduced in comparison with normal persons. Thus, long-term glucocorticoid therapy not only alters the endogenous secretion of steroids, but also affects the transport of some glucocorticoids in the circulation. This may explain why the disappearance of prednisolone is more rapid in those persons who have previously received glucocorticoids.

GLUCOCORTICOID THERAPY IN THE PRESENCE OF LIVER DISEASE

Plasma cortisol levels are normal in patients with hepatic disease. Although the clearance of cortisol is reduced in patients with cirrhosis, the hypothalamic-pituitary-adrenal (HPA) homeostatic mechanism remains intact. Consequently, the decreased rate of metabolism is accompanied by decreased synthesis of cortisol (see Chap. 205).

The conversion of prednisone to prednisolone is impaired in patients with active liver disease.[11] This is largely offset by a decreased rate of elimination of prednisolone from the plasma in these patients.[11] In patients with liver disease, the plasma availability of prednisolone is quite variable after oral doses of either prednisone or prednisolone.[12] This is further complicated by the lower percentage of plasma prednisolone that is bound to protein in patients with active liver disease; the unbound fraction is inversely related to the serum albumin concentration. An increased frequency of prednisone side effects is observed at low serum albumin levels.[12] Both these findings may reflect impaired hepatic function. Because the impairment of conversion of prednisone to prednisolone is quantitatively small in the presence of liver disease and is offset by a decreased rate of clearance of prednisolone, and because of the marked variability in plasma prednisolone levels after the administration of either corticosteroid, there is no clear mandate to use prednisolone rather than prednisone in patients with active liver disease or cirrhosis.[8] If prednisone or prednisolone is used, however, a somewhat lower than usual dose should be given if the serum albumin level is low.[8]

GLUCOCORTICOID THERAPY AND THE NEPHROTIC SYNDROME

When hypoalbuminemia is caused by the nephrotic syndrome, the fraction of prednisolone that is protein bound is decreased. The unbound fraction is inversely related to the serum albumin concentration. The unbound prednisolone concentration remains normal, however.[13,14] Because the pharmacologic effect is determined by the unbound concentration, altered prednisolone kinetics do not explain the increased frequency of prednisolone-related side effects in these patients.

GLUCOCORTICOID THERAPY AND HYPERTHYROIDISM

The bioavailability of prednisolone after an oral dose of prednisone is reduced in patients with hyperthyroidism because of decreased absorption of prednisone and increased hepatic clearance of prednisolone.[15]

GLUCOCORTICOIDS DURING PREGNANCY

Glucocorticoid therapy is well tolerated in pregnancy.[16] Glucocorticoids cross the placenta, but there is no compelling evidence that this produces clinically significant HPA suppression or Cushing syndrome in neonates,[16] although subnormal responsiveness to exogenous ACTH may occur. Similarly, there is no evidence that glucocorticoids increase the incidence of congenital defects in humans.[16] Glucocorticoids do appear to decrease the birth weight of full-term infants; the long-term consequences of this are unknown. Because the concentrations of prednisone and prednisolone in breast milk are low, the administration of these drugs to the mother of a nursing infant is unlikely to produce deleterious effects in the infant.

GLUCOCORTICOID THERAPY AND AGE

The clearance of prednisolone and methylprednisolone decreases with age.[17,18] Despite the higher prednisolone levels seen in elderly subjects compared with young subjects after comparable doses, endogenous plasma cortisol levels are suppressed to a lesser extent in the elderly.[17] These findings may be associated with an increased incidence of side effects and suggest the need to use smaller doses in the elderly than in young patients.

DRUG INTERACTIONS

The concomitant use of medications can alter the effectiveness of glucocorticoids; the reverse also is true.[19]

EFFECTS OF OTHER MEDICATIONS ON GLUCOCORTICOIDS

The metabolism of glucocorticoids is accelerated by substances that induce hepatic microsomal enzyme activity, such as pheny-

toin, barbiturates, and rifampin. The administration of these medications can increase the corticosteroid requirements of patients with adrenal insufficiency or lead to deterioration in the conditions of patients whose underlying disorders are well controlled by glucocorticoid therapy. These substances should be avoided in patients receiving corticosteroids. Diazepam does not alter the metabolism of glucocorticoids and is preferable to barbiturates in this setting. If drugs that induce hepatic microsomal enzyme activity must be used in patients taking corticosteroids, an increase in the required dose of corticosteroids should be anticipated.

Conversely, ketoconazole increases the bioavailability of large doses of prednisolone (0.8 mg/kg) because of inhibition of hepatic microsomal enzyme activity.[20] Oral contraceptive use decreases the clearance of prednisone and increases its bioavailability.[21]

The bioavailability of prednisone is decreased by antacids in doses comparable to those used clinically.[22] The bioavailability of prednisolone is not impaired by sucralfate, H_2-receptor blockade, or cholestyramine.

EFFECTS OF GLUCOCORTICOIDS ON OTHER MEDICATIONS

The concurrent administration of a glucocorticoid and a salicylate may reduce the serum salicylate level. Conversely, reduction of the corticosteroid dose during the administration of a fixed dose of salicylate may lead to a higher and possibly toxic serum salicylate level. This interaction may reflect the induction of salicylate metabolism by glucocorticoids.[23]

Glucocorticoids may increase the required dose of insulin or oral hypoglycemic agents, antihypertensive drugs, or glaucoma medications. They also may alter the required dose of sedative-hypnotic or antidepressant therapy. Digitalis toxicity can result from hypokalemia caused by glucocorticoids, as from hypokalemia of any cause. Glucocorticoids can reverse the neuromuscular blockade induced by pancuronium.

CONSIDERATIONS BEFORE INITIATING THE USE OF GLUCOCORTICOIDS AS PHARMACOLOGIC AGENTS

Cushing syndrome (see Chap. 75) is a life-threatening disorder. The 5-year mortality was higher than 50% at the beginning of the era of glucocorticoid and ACTH therapy.[24] Infection and cardiovascular complications were frequent causes of death. High-dose exogenous glucocorticoid therapy is similarly hazardous.

Table 78-2 summarizes the important questions to consider before initiating glucocorticoid therapy.[25] These questions enable the physician to assess the potential risks that must be weighed against the possible benefits of treatment. The more severe the underlying disorder, the more readily can systemic glucocorticoid therapy be justified. Thus, corticosteroids are commonly used in patients with severe forms of systemic lupus erythematosus, sarcoidosis, active vasculitis, asthma, chronic active hepatitis, transplantation rejection, pemphigus, or diseases of comparable severity. Generally, systemic corticosteroids should not be administered to patients with mild rheumatoid arthritis or mild bronchial asthma; such patients should receive more conservative therapy first. Although these patients may experience symptomatic relief from glucocorticoids, it may prove difficult to withdraw the drugs. Consequently, they may unnecessarily experience Cushing syndrome and HPA suppression.

DURATION OF THERAPY

The anticipated duration of glucocorticoid therapy is another critical issue. The use of glucocorticoids for 1 to 2 weeks for a condition such as poison ivy or allergic rhinitis is unlikely to be associated with serious side effects in the absence of a contraindication. An exception to this rule is a corticosteroid-induced psychosis. This complication may occur after only a few days of high-dose glucocorticoid therapy, even in patients with no previous history of psychiatric disease (see Chap. 201).[26,27] Because the risk of so many complications is related to the dose and duration of therapy, the smallest possible dose should be prescribed for the shortest possible period. If hypoalbuminemia is present, the dose should be reduced. If long-term treatment is indicated, the use of an alternate-day schedule should be considered.

TABLE 78-2.
Considerations before the Use of Glucocorticoids as Pharmacologic Agents

1. How serious is the underlying disorder?
2. How long will therapy be required?
3. What is the anticipated effective corticosteroid dose?
4. Is the patient predisposed to any of the potential hazards of glucocorticoid therapy?
   - Diabetes mellitus
   - Osteoporosis
   - Peptic ulcer, gastritis, or esophagitis
   - Tuberculosis or other chronic infections
   - Hypertension and cardiovascular disease
   - Psychological difficulties
5. Which glucocorticoid preparation should be used?
6. Have other modes of therapy been used to minimize the glucocorticoid dosage and to minimize the side effects of glucocorticoid therapy?
7. Is an alternate-day regimen indicated?

(Modified from Thorn GW. Clinical considerations in the use of corticosteroids. N Engl J Med 1966; 274:775.)

LOCAL USE

A local corticosteroid preparation should be used whenever possible because systemic effects are minimal when these substances are administered correctly. Examples include topical therapy in dermatologic disorders, corticosteroid aerosols in bronchial asthma and allergic rhinitis, and corticosteroid enemas in ulcerative proctitis. Systemic absorption of inhaled glucocorticoids leading to Cushing syndrome and HPA suppression is a rare occurrence when these agents are administered correctly at prescribed doses.[28,29] The intraarticular injection of corticosteroids may be of value in carefully selected patients if strict aseptic techniques are used and if frequent injections are avoided.

SELECTING A SYSTEMIC PREPARATION

Agents with little or no mineralocorticoid activity should be used when a glucocorticoid is prescribed for pharmacologic purposes. If the dosage is to be tapered over a few days, a long-acting agent may be impractical. For alternate-day therapy, a short-acting agent that generally does not cause sodium retention (e.g., prednisone, prednisolone, or methylprednisolone) should be used. There is no indication for glucocorticoid conjugates designed to achieve a prolonged duration of action (several days or several weeks) after a single intramuscular injection. The bioavailability of such preparations cannot be regulated precisely, the duration of action cannot be estimated reliably, and it is not possible to taper the dosage rapidly in the event of an adverse reaction such as a corticosteroid-induced psychosis. The use of such preparations may cause HPA suppression more frequently than do comparable doses of the same glucocorticoid given orally. The use of supplemental medications to minimize the systemic corticosteroid dose and to reduce the side effects of systemic glucocorticoids should always be considered. In asthma, for example, treatment should include inhaled glucocorticoids and bronchodilators, such as β-adrenergic agonists and theophylline, and may include cromolyn.

EFFECTS OF EXOGENOUS GLUCOCORTICOIDS

ANTIINFLAMMATORY AND IMMUNOSUPPRESSIVE EFFECTS

Endogenous glucocorticoids protect the organism from damage caused by its own defense reactions and the products of these reac-

tions during stress.[30,30a] Consequently, the use of glucocorticoids as antiinflammatory and immunosuppressive agents represents an application of the physiologic effects of glucocorticoids to the treatment of disease.[30] Glucocorticoids have many effects on inflammatory and immune responses, which are described in this section.

Glucocorticoids inhibit synthesis of almost all known cytokines and of several cell surface molecules required for immune function.[31–33] When an immune stimulus such as tumor necrosis factor binds to its receptor, nuclear factor kappa B (NF-κB) moves to the nucleus, where it activates many immunoregulatory genes. This activation of NF-κB involves the degradation of its cytoplasmic inhibitor IκBα and the translocation of NF-κB to the nucleus. Glucocorticoids are potent inhibitors of NF-κB activation. This inhibition is mediated by the induction of the IκBα inhibitory protein, which traps activated NF-κB in inactive cytoplasmic complexes.[31–33] This reduction in NF-κB activity appears to explain the ability of glucocorticoids to inhibit the production of cytokines and cell surface molecules and to suppress the immune response.

Influence on Blood Cells and on the Microvasculature. Glucocorticoid effects on inflammatory and immune phenomena include effects on leukocyte movement, leukocyte function, and humoral factors (Table 78-3). In general, glucocorticoids have a greater effect on leukocyte traffic than on function, and more effect on cellular than on humoral processes.[34,35] Glucocorticoids alter the traffic of all the major leukocyte populations in the circulation (see Chap. 212).

Probably the most important antiinflammatory effect of glucocorticoids is the ability to inhibit the recruitment of neutrophils and monocyte-macrophages to an inflammatory site.[35] Corticosteroids modify the increased capillary and membrane permeability that occurs in an area of inflammation. By decreasing the dilation of the microvasculature and the increased capillary permeability that occur during an inflammatory response, the exudation of fluid and the formation of edema may be reduced, and the migration of leukocytes may be impaired.[2,35,36] The decrease in the accumulation of inflammatory cells is also related to decreased adherence of inflammatory cells to the vascular endothelium. It is not possible to determine the relative contributions of the direct vascular effect, the effect on inflammatory cell adherence to the vascular wall, and the effect on chemotaxis to the reduction in inflammation caused by glucocorticoids.

Glucocorticoids have multiple effects on leukocyte function.[35] Corticosteroids suppress cutaneous delayed hypersensitivity responses. Monocyte-macrophage traffic and function are sensitive to glucocorticoids (see Table 78-3). Glucocorticoids in divided daily doses depress the bactericidal activity of monocytes. The sensitivity of monocytes to glucocorticoids may explain the effectiveness of these agents in many granulomatous diseases because the monocyte is the principal cell involved in granuloma formation.[35] Although neutrophil traffic is sensitive to glucocorticoids, neutrophil function appears to be relatively resistant to these agents.[35] Whereas most in vivo studies of neutrophil phagocytosis have found no evidence for impairment of phagocytosis or bacterial killing,[35] other studies suggest that glucocorticoids induce a generalized phagocytic defect affecting both granulocytes and monocytes.

Glucocorticoid therapy retards the disappearance of sensitized erythrocytes, platelets, and artificial particles from the circulation.[35] This may account for the efficacy of glucocorticoids in the treatment of idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia.

Influence on Arachidonic Acid Derivatives. Glucocorticoids inhibit prostaglandin (PG) and leukotriene synthesis by inhibiting the release of arachidonic acid from phospholipids.[37] This inhibition of arachidonic acid release appears to be mediated by the induction of lipocortins, a family of related proteins that inhibit phospholipase A_2, which is an enzyme that liberates arachidonic acid from phospholipids (see Chap. 172).[38,39] This mechanism is distinct from the mechanism of action of the nonsteroidal antiinflammatory agents, such as salicylates and indomethacin, which inhibit the cyclooxygenase that converts arachidonic acid to the cyclic endoperoxide intermediates in the PG synthetic pathway; in some tissues, glucocorticoids inhibit cyclooxygenase activity. Thus, the glucocorticoids and the nonsteroidal antiinflammatory agents exert their antiinflammatory effects at two distinct but adjacent loci in the synthetic pathway of arachidonic acid metabolism. Glucocorticoids and nonsteroidal antiinflammatory agents have different spectra of antiinflammatory effects. Some of the therapeutic effects of corticosteroids that are not produced by the nonsteroidal agents may be related to the inhibition of leukotriene formation.[37]

TABLE 78-3.
Effects of Glucocorticoids on Inflammatory and Immune Responses in Humans

EFFECTS ON LEUKOCYTE MOVEMENT
Lymphocytes
Circulating lymphocytopenia 4–6 hours after drug administration, secondary to redistribution of cells to other lymphoid compartments
Depletion of recirculating lymphocytes
Selective depletion of T lymphocytes more than B lymphocytes
Monocyte-Macrophages
Circulating monocytopenia 4–6 hours after drug administration, probably secondary to redistribution
Inhibition of accumulation of monocyte-macrophages at inflammatory sites
Neutrophils
Circulating neutrophilia
Accelerated release of neutrophils from the bone marrow
Blockade of accumulation of neutrophils at inflammatory sites
Eosinophils
Circulating eosinopenia, probably secondary to redistribution
Decreased migration of eosinophils into immediate hypersensitivity skin test sites
EFFECTS ON LEUKOCYTE FUNCTION
Lymphocytes
Suppression of delayed hypersensitivity skin testing by inhibition of recruitment of monocyte-macrophages
Suppression of lymphocyte proliferation to antigens more easily than proliferation to mitogens
Suppression of mixed leukocyte reaction proliferation
Suppression of T lymphocyte–mediated cytotoxicity (at high concentrations in vitro)
No effect on antibody-dependent cell-mediated cytotoxicity
Suppression of spontaneous (natural) cytotoxicity
Regulatory effects on helper and suppressor cell populations
Monocyte-Macrophages
Suppression of cutaneous delayed hypersensitivity by inhibition of lymphokine effect on the macrophage
Blockade of Fc receptor binding and function
Depression of bactericidal activity
Possible decrease in monocyte chemotaxis
Neutrophils
Possibly no effect on phagocytic and bactericidal capability (controversial)
Increase in antibody-dependent cellular cytotoxicity
Probable decrease in lysosomal release but little effect on lysosomal membrane stabilization at pharmacologic concentrations
Inhibition of chemotaxis only by suprapharmacologic concentrations
EFFECTS ON HUMORAL FACTORS
Mild decrease in immunoglobulin levels
Decreased reticuloendothelial clearance of antibody-coated cells
Decreased synthesis of prostaglandins and leukotrienes
Inhibition of plasminogen activator release
Potentiation of the actions of catecholamines
Antagonism of histamine-induced vasodilation

(Adapted from Parrillo JE, Fauci AS. Mechanisms of glucocorticoid action on immune processes. Annu Rev Pharmacol Toxicol 1979;19:179.)

TABLE 78-4.
Adverse Reactions to Glucocorticoids

OPHTHALMIC
Posterior subcapsular cataracts, increased intraocular pressure and glaucoma, exophthalmos
CARDIOVASCULAR
Hypertension
Congestive heart failure in predisposed patients
GASTROINTESTINAL
Peptic ulcer disease, pancreatitis
ENDOCRINE-METABOLIC
Truncal obesity, moon facies, supraclavicular fat deposition, posterior cervical fat deposition (buffalo hump), mediastinal widening (lipomatosis), hepatomegaly caused by fatty liver
Acne, hirsutism or virilism, erectile dysfunction, menstrual irregularities
Suppression of growth in children
Hyperglycemia; diabetic ketoacidosis; hyperosmolar, nonketotic diabetic coma; hyperlipoproteinemia
Negative balance of nitrogen, potassium, and calcium
Sodium retention, hypokalemia, metabolic alkalosis
Secondary adrenal insufficiency
MUSCULOSKELETAL
Myopathy
Osteoporosis, vertebral compression fractures, spontaneous fractures
Aseptic necrosis of femoral and humeral heads and other bones
NEUROPSYCHIATRIC
Convulsions
Benign intracranial hypertension (pseudotumor cerebri)
Alterations in mood or personality
Psychosis
DERMATOLOGIC
Facial erythema, thin fragile skin, petechiae and ecchymoses, violaceous striae, impaired wound healing
IMMUNE, INFECTIOUS
Suppression of delayed hypersensitivity
Neutrophilia, monocytopenia, lymphocytopenia, decreased inflammatory responses
Susceptibility to infections

(Data from Axelrod L. Adrenal corticosteroids. In: Miller RR, Greenblatt DJ, eds. Handbook of drug therapy. New York: Elsevier North-Holland, 1979:809; and Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. Textbook of rheumatology, 4th ed. Philadelphia: WB Saunders, 1993:779.)

SIDE EFFECTS

The side effects of glucocorticoids include the diverse manifestations of Cushing syndrome and HPA suppression (Table 78-4).[40] Iatrogenic Cushing syndrome differs from endogenous Cushing syndrome in several respects: hypertension, acne, menstrual disturbances, male erectile dysfunction, hirsutism or virilism, striae, purpura, and plethora are more common in endogenous Cushing syndrome; benign intracranial hypertension, glaucoma, posterior subcapsular cataract, pancreatitis, and aseptic necrosis of bone are virtually unique to iatrogenic Cushing syndrome; and obesity, psychiatric symptoms, and poor wound healing have nearly equal frequency in both.[40,41] These differences may be explained as follows. When Cushing syndrome is caused by exogenous glucocorticoids, ACTH secretion is suppressed. In spontaneous, ACTH-dependent Cushing syndrome, the elevated ACTH output causes bilateral adrenal hyperplasia. In the former circumstance, the secretion of adrenocortical androgens and mineralocorticoids is not increased. Conversely, when ACTH output is elevated, the secretion of adrenal androgens and mineralocorticoids may be increased.[1] The augmented secretion of adrenal androgens may account for the higher prevalence of virilism, acne, and menstrual irregularities in the endogenous form of Cushing syndrome, and the enhanced production of mineralocorticoids may explain the higher prevalence of hypertension.[1]

Some of the complications that are virtually unique to iatrogenic Cushing syndrome arise after the prolonged use of large doses of glucocorticoids. Examples are benign intracranial hypertension, posterior subcapsular cataract, and aseptic necrosis of bone.[1]

Although the association of glucocorticoid therapy and peptic ulcer disease is controversial,[42–47] glucocorticoids appear to increase the risk of peptic ulcer disease and also gastrointestinal hemorrhage (see Chap. 204).[45,46] The magnitude of the association between glucocorticoid therapy and these complications is small and is related to the total dose and duration of therapy.[42,45] The risk of peptic ulcer disease and related gastrointestinal problems is increased by the concurrent use of glucocorticoids and nonsteroidal antiinflammatory drugs.[48,49]

Glucocorticoid therapy, especially daily therapy, may suppress the immune response to skin tests for tuberculosis. When possible, tuberculin skin testing is advisable before the initiation of glucocorticoid therapy. Routine isoniazid prophylaxis probably is not indicated for corticosteroid-treated patients, even for those with positive tuberculin skin test results.[50]

At similar doses, some patients respond to and experience side effects of glucocorticoids more readily than do others. Variations in responsiveness to glucocorticoids may be a consequence of drug interactions or of variations in the severity of the underlying disease. Alterations in bioavailability probably do not account for variations in the therapeutic response to glucocorticoids. In patients who experience side effects, the metabolic clearance rate of prednisolone and the volume of distribution are lower[10,51] and the circulating $T_{1/2}$ is longer[51] than in those who do not experience side effects. Impaired renal function may contribute to a decrease in the clearance of prednisolone and an increase in the prevalence of cushingoid features.[52] Patients who have a cushingoid habitus while taking prednisone have higher endogenous plasma cortisol levels than do those without this complication, perhaps because of resistance of the HPA axis to suppression by exogenous glucocorticoids.[53]

Variations in the effectiveness of corticosteroids may be the result of altered cellular responsiveness to the drugs.[54–57] In patients with primary open-angle glaucoma, exogenous glucocorticoids produce a more pronounced rise of intraocular pressure[54]; a greater suppression of the 8:00 a.m. plasma cortisol level when dexamethasone, 0.25 mg, is administered the previous evening at 11:00 p.m.[56]; and greater suppression of phytohemagglutinin-induced lymphocyte transformation[55,57] than in normal persons. Primary open-angle glaucoma is relatively common. These findings suggest that a distinct subpopulation of patients are hyperresponsive to glucocorticoids and that this sensitivity is genetically determined (see Chap. 215).

PREVENTION OF SIDE EFFECTS

Increasingly, the issues of concern to physicians and patients with respect to glucocorticoid therapy are not only HPA suppression but long-term complications such as glucocorticoid-induced osteoporosis and *Pneumocystis carinii* pneumonia. Of course, the risk of many complications can be reduced by the use of the *lowest possible dose of a glucocorticoid for the shortest possible period*, by the use of *regional or topical* rather than systemic steroids, and by the use of *alternate-day corticosteroid therapy*. In addition, *pharmacologic interventions* to prevent specific complications such as bone disease and *P. carinii* pneumonia are now widely used.

Osteoporosis. The majority of patients who receive long-term glucocorticoid therapy will develop low bone mineral density. By some estimates, more than one-fourth of these patients will sustain osteoporotic fractures.[58] The prevalence of vertebral fractures in asthmatic patients on glucocorticoid therapy for at least a year is 11%.[58] Patients with rheumatoid arthritis who are treated with glucocorticoids have an increased incidence of fractures of the hips, ribs, spine, legs, ankles, and feet.[58] Skeletal wasting occurs most rapidly during the first year

of therapy. Trabecular bone is affected more than cortical bone. The effects on the skeleton are related to the cumulative dose and duration of treatment.[58] Alternate-day glucocorticoid therapy does not reduce the risk of osteopenia. Inhaled steroids have been associated with bone loss.

The pathogenesis of glucocorticoid-induced osteoporosis involves several different mechanisms.[58] Glucocorticoids decrease intestinal absorption of calcium and phosphate by vitamin D-independent mechanisms. Urinary calcium excretion is increased, possibly as a result of direct effects on renal tubular calcium reabsorption. These changes may lead to secondary hyperparathyroidism in at least some patients. Glucocorticoids reduce sex hormone production. This may be a direct effect by decreasing gonadal hormone release. It may also be indirect by reducing ACTH secretion and adrenal androgen production. Also, inhibition of luteinizing hormone secretion can result in decreased estrogen and testosterone production by the gonads. Glucocorticoids also have an inhibitory effect on the proliferation of osteoblasts, attachment of osteoblasts to matrix, and the synthesis of type I collagen and noncollagenous proteins by osteoblasts.

The evaluation of a patient should emphasize medical risk factors for osteoporosis, including inadequate dietary calcium and vitamin D intake, alcohol consumption, smoking, menopause, and any history of infertility or impotence suggesting hypogonadism in males. Attention should also be devoted to the possible presence of thyrotoxicosis, overtreatment with thyroid medication, renal osteodystrophy, multiple myeloma, osteomalacia, or primary hyperparathyroidism. When appropriate, laboratory studies should be ordered for evaluation of these disorders. When glucocorticoid therapy will be administered for more than a few months, it is reasonable to obtain a baseline measurement of bone mineral density using dual energy x-ray absorptiometry.

In general, all patients should receive calcium and vitamin D supplementation to correct any nutritional deficiency. Calcium therapy alone is associated with rapid rates of spinal bone loss and offers only partial protection from this loss. There is no evidence that the combination of calcium and vitamin D completely prevents bone loss caused by glucocorticoids.[59] Calcitriol and bisphosphonates, specifically alendronate and etidronate, are effective in the prevention of bone loss.[60–63] If calcitriol is used, careful follow-up determinations of serum calcium levels is necessary. Hypogonadotropic men should receive testosterone therapy; hormone replacement therapy should be considered for postmenopausal women. Patients should be educated about the risks and the consequences of osteoporosis and the factors in their own lives that may contribute. Because glucocorticoids also affect muscle mass and function, patients should be advised about exercises for maintaining muscle strength.

***Pneumocystis carinii* Pneumonia.** Glucocorticoids predispose patients to infections of many varieties. Until recently, prophylaxis against infections for patients treated with glucocorticoids was limited to patients receiving transplantation of organs, who also receive other forms of immunosuppression. Currently, prophylaxis for patients with other disorders who are treated with glucocorticoids is being used, particularly for *P. carinii* pneumonia.[64,65]

In a series of 116 patients without acquired immunodeficiency syndrome (AIDS) who experienced a first episode of *P. carinii* pneumonia between 1985 and 1991, 105 (90.5%) had received glucocorticoids within 1 month before the diagnosis of *P. carinii* pneumonia was established.[64] The median daily dose was equivalent to 30 mg prednisone; 25% of the patients had received as little as 16 mg daily. The median duration of glucocorticoid therapy was 12 weeks before the development of the pneumonia. In 25% of the patients, *P. carinii* pneumonia developed after 8 weeks or less of glucocorticoid therapy. However, the attack rate in patients with primary or metastatic central nervous system tumors who received glucocorticoid therapy was 1.3% and may be lower in other conditions.[65] Also, prophylactic therapy may produce side effects.

Some physicians recommend prophylaxis (e.g., with trimethoprim-sulfa, one double-strength tablet a day) for patients with impaired immune competence conferred by chemotherapy, transplantation, or an inflammatory disorder who have received prednisone 20 mg or more per day for more than 1 month. No controlled studies with such prophylaxis in steroid-treated patients are available. Among patients undergoing bone marrow or organ transplantation at the Mayo Clinic from 1989 to 1995, no cases of *P. carinii* pneumonia were detected in those who received adequate chemoprophylaxis.

WITHDRAWAL FROM GLUCOCORTICOIDS

The symptoms associated with glucocorticoid withdrawal include anorexia, myalgia, nausea, emesis, lethargy, headache, fever, desquamation, arthralgia, weight loss, and postural hypotension. Many of these symptoms can occur with normal plasma glucocorticoid levels and in patients with normal responsiveness to conventional tests of the HPA system.[66,67] These patients may have abnormal responses to a more sensitive test using 1 μg of α-1-24 ACTH rather than the conventional 250-μg dose.[68,69] Because glucocorticoids inhibit PG production and because many of the features of the corticosteroid withdrawal syndrome can be produced by PGs such as PGE_2 and PGI_2, this syndrome may be caused by a sudden increase in PG production after the withdrawal of exogenous corticosteroids. The corticosteroid withdrawal syndrome may contribute to psychologic dependence on glucocorticoid treatment and to difficulties in withdrawing such therapy.

SUPPRESSION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL SYSTEM

DEVELOPMENT OF HYPOTHALAMIC-PITUITARY-ADRENAL SUPPRESSION

Few well-documented cases of acute adrenocortical insufficiency have been reported after prolonged glucocorticoid therapy and none have been reported after ACTH therapy.[1] After the introduction of ACTH and glucocorticoids into clinical practice in the late 1940s, patients were described in whom shock was attributed to adrenocortical insufficiency induced by these agents, but biochemical evidence of adrenocortical insufficiency was not available to substantiate the diagnosis.[1] Prolonged hypotension, or even an apparent response of hypotension to intravenous hydrocortisone, is not a reliable means of assessing adrenocortical function. It must be demonstrated simultaneously that the plasma cortisol level is lower than the values found in normal persons experiencing a comparable degree of stress. When testing for plasma cortisol levels became available in the early 1960s, three cases were described in which these criteria were met. The paucity of reports may reflect the fact that acute adrenocortical insufficiency after glucocorticoid therapy is uncommon in properly treated patients, and that physicians may be reluctant to report such events.

The minimal duration of glucocorticoid therapy that can produce HPA suppression must be ascertained from studies of adrenocortical weight and adrenocortical responsiveness to provocative tests.[1,2] Any patient who has received a glucocorticoid in dosages equivalent to 20 to 30 mg per day of prednisone for more than 5 days should be suspected of having HPA suppression.[1,2] If the dosages are closer to but above the physiologic range, 1 month is probably the minimal interval.[1,2]

The stress of general anesthesia and surgery is not hazardous to patients who have received only replacement doses (no more than 25 mg hydrocortisone, 5 mg prednisone, 4 mg triamcinolone, or 0.75 mg dexamethasone), provided the corticosteroid is given early in the day. If doses of this size are given late in the day, suppression may occur as a result of inhibition of the diurnal surge of ACTH release.

TABLE 78-5.
Assessment of Hypothalamic-Pituitary-Adrenal (HPA) Function in Patients Treated with Glucocorticoids

METHOD
Withhold exogenous corticosteroids for 24 hr
Give cosyntropin [synthetic α1-24 ACTH] 250 μg as intravenous bolus or intramuscular injection
Obtain plasma cortisol level 30 or 60 min after administration of ACTH
Performance of the test in the morning is customary but not essential
INTERPRETATION
Normal response: Plasma cortisol level >18 μg/dL at 30 or 60 minutes after ACTH administration

Note: Traditional recommendations also specify an increment above baseline of 7 μg/dL at 30 minutes or 11 μg/dL at 60 minutes and a doubling of the baseline value at 60 minutes. These end-points are valid in normal, unstressed subjects but are frequently misleading in ill patients with a normal HPA axis, in whom stress may raise the baseline plasma cortisol level by an increase in *endogenous* ACTH levels.

(From Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. Textbook of rheumatology, 4th ed. Philadelphia: WB Saunders, 1993:779.)

ASSESSMENT OF HYPOTHALAMIC-PITUITARY-ADRENAL FUNCTION

When HPA suppression is suspected, the physician may wish to assess the integrity of the HPA system. A test of HPA reserve is indicated only when the result will modify therapy. In practice, this applies to patients who may need an increase in the corticosteroid dosage to cover a stressful event (such as general anesthesia and surgery) and to patients in whom withdrawal of glucocorticoid therapy is contemplated. In the latter group, a test of the HPA axis usually is indicated only when the glucocorticoid dosage has been reduced to replacement levels, for example, 5 mg prednisone daily (or an equivalent dosage of another glucocorticoid). In stable patients receiving prolonged glucocorticoid therapeutic regimens, frequent tests of HPA reserve function are not indicated. For example, it is not necessary to test before each reduction in dosage during tapering of the steroid regimen. The responsiveness of the HPA system may change as corticosteroid therapy continues, and repeated testing is costly.

The short ACTH test is a useful guide to the presence or absence of HPA suppression in patients treated with glucocorticoids (Table 78-5). Although this test assesses directly only the adrenocortical response to ACTH, it is an effective measure of the integrity of the HPA axis. *Because hypothalamic-pituitary function returns before adrenocortical function during recovery from HPA suppression, a normal adrenocortical response to ACTH in this setting implies that hypothalamic-pituitary function also is normal.* This rationale is supported by direct observation. Thus, the maximal response of the plasma cortisol level to ACTH corresponds to the maximal plasma cortisol level observed during the induction of general anesthesia and surgery in patients who have received glucocorticoid therapy.[1,2] A normal response to ACTH before surgery is unlikely to be followed by markedly impaired secretion of cortisol during anesthesia and surgery in corticosteroid-treated patients. An abnormal response to ACTH is a necessary but not a sufficient condition for the diagnosis of adrenal insufficiency in glucocorticoid-treated patients who undergo surgery; some patients with an abnormal response to ACTH tolerate surgery without glucocorticoid treatment.[70] Moreover, hypotension in the operative or postoperative period in patients who have been treated previously with glucocorticoid therapy is often a result of other causes, such as volume depletion and reactions to anesthetic medication. The hypotension often responds to treatment of these factors.

Other tests of HPA function generally are not indicated. The *low-dose (1 μg) short ACTH test* is more sensitive than the conventional-dose ACTH test in patients who have been treated with glucocorticoids.[68,68a] The conventional dose of ACTH used in the short ACTH test (and other ACTH tests) produces circulating ACTH levels that are far above the physiologic range. These supraphysiologic levels may produce a normal plasma cortisol level in patients with partial adrenocortical insufficiency. Nevertheless, the low-dose short ACTH test has not yet replaced the conventional-dose short ACTH test. The *lower limit* of the normal range for the low-dose ACTH test has *not* yet been defined.[69] Also, there are *no* commercially available preparations of ACTH available for direct use in the low-dose short ACTH test. The injection for the low-dose short ACTH test must be prepared by dilution, which is a source of *inconvenience and possible error.* Insulin-induced hypoglycemia may be hazardous (especially in patients with cardiac or neurologic disease), and the symptoms may be uncomfortable. This procedure is more time-consuming and more costly than the ACTH test because more cortisol values must be determined. The measurement of plasma cortisol levels before and after the administration of corticotropin-releasing hormone also has been recommended.[71] This test also is longer and more expensive than the ACTH test and has not been compared to a physiologic stress such as anesthesia and surgery. It offers no clear advantage over the ACTH test.

CORTICOTROPIN AND THE HYPOTHALAMIC-PITUITARY-ADRENAL SYSTEM

Pharmacologic doses of ACTH cause elevated cortisol secretory rates and increased plasma cortisol levels. The elevated plasma cortisol levels might be expected to suppress ACTH release. Actually, there is no evidence of clinically significant hypothalamic-pituitary suppression in patients who have received ACTH therapy.[1] The failure of ACTH to suppress HPA function is not explained by the dose of ACTH used, the frequency of injection, the time of administration, or the plasma cortisol pattern after ACTH administration. Alternatively, it is possible that the hyperplastic and overactive adrenal cortex that results from ACTH therapy compensates for hypothalamic or pituitary suppression. Although threshold adrenocortical sensitivity to ACTH is not changed in patients who have received daily ACTH therapy, there may be altered adrenocortical responsiveness to ACTH in the physiologic range. Moreover, the normal response of the plasma cortisol level in patients treated with ACTH may be preserved, at least in part, because ACTH treatment reduces the rate of ACTH secretion but not the total amount secreted, whereas glucocorticoids reduce both the rate of secretion and the total amount secreted.[72]

RECOVERY FROM HYPOTHALAMIC-PITUITARY-ADRENAL SUPPRESSION

During the recovery from HPA suppression, hypothalamic-pituitary function returns before adrenocortical function.[1,2,73] Twelve months must elapse after the withdrawal of large doses of glucocorticoids given for a prolonged period before HPA function, including responsiveness to stress, returns to normal.[1,2,73] Conversely, recovery from HPA suppression that has been induced by a brief course of corticosteroids (i.e., 25 mg prednisone twice daily for 5 days) occurs within 5 days.[74] Patients with mild suppression of the HPA axis (i.e., normal basal plasma and urine corticosteroid levels but diminished responses to ACTH and insulin-induced hypoglycemia) resume normal HPA function more rapidly than do those with severe depression of the HPA axis (i.e., low basal plasma and urine corticosteroid levels and diminished responses to ACTH and insulin-induced hypoglycemia). The time course of recovery correlates with the total duration of previous glucocorticoid therapy and the total previous corticosteroid dose. Nevertheless, in an individual patient, it is not possible to predict the duration of recovery from a course of glucocorticoid therapy at supraphysiologic doses lasting more than a few weeks. Consequently, persistence of HPA suppression should be suspected for 12 months after such treatment. The recovery interval after suppression of the contralateral adrenal cortex by the products

of an adrenocortical tumor may exceed 12 months. The recovery from HPA suppression that is induced by exogenous glucocorticoids may be more rapid in children than in adults.

WITHDRAWAL OF PATIENTS FROM GLUCOCORTICOID THERAPY

RISKS OF WITHDRAWAL

The decision to discontinue glucocorticoid therapy provokes apprehension among physicians. The deleterious consequences of such an action include precipitation of adrenocortical insufficiency, development of the corticosteroid withdrawal syndrome, or exacerbation of the underlying disease. Adrenocortical insufficiency after the withdrawal of glucocorticoids is justly feared. The likelihood of precipitating the underlying disease depends on the activity and natural history of the illness in question. When there is any possibility that the underlying illness will flare up, the glucocorticoid should be withdrawn gradually, over an interval of weeks to months, with frequent reassessment of the patient.

TREATMENT OF PATIENTS WITH HYPOTHALAMIC-PITUITARY-ADRENAL SUPPRESSION

No proven means exists for hastening a return to normal HPA function once inhibition has resulted from glucocorticoid therapy. The use of ACTH does not prevent or reverse the development of glucocorticoid-induced adrenal insufficiency. Conversion to an alternate-day schedule permits but does not accelerate recovery. In children, alternate-day glucocorticoid therapy actually may delay recovery.

The recovery from corticosteroid-induced adrenal insufficiency is time dependent and spontaneous. The rate of recovery is determined not only by the doses given when the corticosteroids are being tapered, but also by the doses administered during the initial phase of treatment, before tapering is commenced. During the course of recovery, small doses of hydrocortisone (10–20 mg) or prednisone (2.5–5.0 mg) given in the morning may alleviate the withdrawal symptoms. Recovery of HPA function still occurs when small doses of glucocorticoids are administered in the morning. The possibility cannot be excluded, however, that small doses of glucocorticoids given in the morning retard the rate of recovery from HPA suppression.

ALTERNATE-DAY GLUCOCORTICOID THERAPY

Alternate-day glucocorticoid therapy is defined as the administration of a short-acting glucocorticoid with no appreciable mineralocorticoid effect (i.e., prednisone, prednisolone, or methylprednisolone) once every 48 hours in the morning, at about 8:00 a.m. The purpose of this approach is to minimize the adverse effects of glucocorticoids while retaining the therapeutic benefits. The original basis for this schedule was the hypothesis that the antiinflammatory effects of glucocorticoids persist longer than do the undesirable metabolic effects.[75–77] This hypothesis is *not* supported by observations of the duration of corticosteroid effects. A second hypothesis emphasizes that intermittent rather than continuous administration produces a cyclic, although not diurnal, pattern of glucocorticoid levels in the circulation and within the target cells that simulates the normal diurnal cycle.[34] This may prevent the development of Cushing syndrome and HPA suppression while providing therapeutic benefit. Because the full expression of a disease frequently occurs only when the level of inflammatory activity is elevated over a protracted period, the intermittent administration of a glucocorticoid may be sufficient to shorten the interval during which the disorder develops without interruption and thereby to prevent the level of disease activity from becoming apparent clinically (Fig. 78-2).[34] The duration of action of the glucocorticoid is important here. The selection of prednisone, prednisolone, and methylprednisolone as the agents of choice

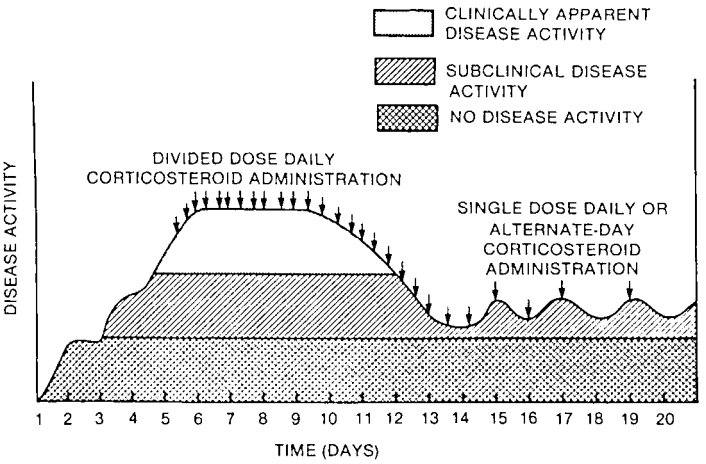


FIGURE 78-2. The effect of glucocorticoid administration on the activity of the underlying disease. A divided daily dosage schedule may be necessary initially in some disorders. When the disease is controlled, or from the start of therapy in certain diseases, alternate-day therapy may be effective. (From Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med 1976; 84:304.)

for alternate-day therapy and of 48 hours as the appropriate interval between doses has an empiric basis. It has been found that intervals of 36, 24, and 12 hours were accompanied by adrenal suppression, and that an interval of 72 hours was therapeutically ineffective when prednisone (and, occasionally, triamcinolone) was used.[77] An interval of 48 hours is optimal.

ALTERNATE-DAY GLUCOCORTICOID THERAPY AND MANIFESTATIONS OF CUSHING SYNDROME

An alternate-day regimen can prevent or ameliorate the manifestations of Cushing syndrome.[1,2] The susceptibility to infections that characterizes Cushing syndrome may be alleviated. Patients have been described in whom refractory infections appeared to clear after conversion from daily to alternate-day regimens. In addition, there is a low frequency of infections in patients receiving alternate-day therapy. Children treated with alternate-day steroid therapy regain or retain tonsillar and peripheral lymphoid tissue. The available information strongly suggests that alternate-day regimens are associated with a lower incidence of infections than are daily regimens, but it does not firmly establish this point.

Host defense mechanisms have been studied in patients receiving alternate-day therapy. Patients maintained on such schedules who have been studied on the days they do not take the medication have normal blood neutrophil and monocyte counts, normal cutaneous inflammatory responses, and normal neutrophil $T_{1/2}$s. Patients receiving daily therapy, however, demonstrate neutrophilia, monocytopenia, decreased cutaneous neutrophil and monocyte inflammatory responses, and prolongation of the neutrophil $T_{1/2}$. Patients studied on the days they do not receive treatment do not have the lymphocytopenia observed in patients who receive daily therapy. Monocyte cellular function is normal in patients receiving alternate-day treatment at 4 hours and at 24 hours after a dose. Intermittently normal leukocyte kinetics, preservation of delayed hypersensitivity, and preservation of monocyte cellular function may explain the apparently reduced susceptibility to infection of patients receiving alternate-day therapy.[78–80]

EFFECTS OF ALTERNATE-DAY GLUCOCORTICOID THERAPY ON HYPOTHALAMIC-PITUITARY-ADRENAL RESPONSIVENESS

Patients receiving alternate-day glucocorticoid therapy may have some suppression of basal corticosteroid levels, but they have normal or nearly normal responsiveness to provocative

tests such as the corticotropin-releasing hormone stimulation test, the ACTH stimulation test, insulin-induced hypoglycemia, and the metyrapone test.[1,2,81] They have less suppression of HPA function than do patients receiving daily therapy.

EFFECTS OF ALTERNATE-DAY THERAPY ON THE UNDERLYING DISEASE

Alternate-day glucocorticoid therapy is as effective, or nearly as effective, in controlling diverse disorders as daily therapy in divided doses.[1,2] This approach has provided apparent benefit in patients with the following disorders: childhood nephrotic syndrome, adult nephrotic syndrome, membranous nephropathy, renal transplantation, mesangiocapillary glomerulonephritis, lupus nephritis, ulcerative colitis, rheumatoid arthritis, acute rheumatic fever, myasthenia gravis, Duchenne muscular dystrophy, dermatomyositis, idiopathic polyneuropathy, asthma, Sjögren syndrome, sarcoidosis, alopecia areata and other chronic dermatoses, and pemphigus vulgaris. Prospective, controlled studies demonstrate the efficacy of alternate-day therapy in membranous nephropathy and renal transplantation. The role of alternate-day therapy in giant cell arteritis is controversial.[82–84]

USE OF ALTERNATE-DAY THERAPY

Because alternate-day therapy can *prevent or ameliorate the manifestations of Cushing syndrome, can avert or permit recovery from HPA suppression, and is as effective (or nearly as effective) as continuous therapy,* patients for whom long-term glucocorticoid administration is indicated should be placed on such programs whenever possible. Nevertheless, physicians sometimes are reluctant to use alternate-day schedules, often because of an unsuccessful experience. Many efforts fail because of lack of familiarity with the indications for and use of such therapy.

The benefits of alternate-day glucocorticoid therapy are demonstrable only when corticosteroids are used for a *prolonged* period. There is no reason to use an alternate-day schedule when the anticipated duration of therapy is less than several weeks.

Alternate-day therapy may not be necessary or appropriate during the initial stages of therapy or during exacerbation of the underlying disease. Nevertheless, patients with many chronic disorders have been treated with an alternate-day regimen as initial therapy with apparent benefit.[1,2] In patients with rheumatoid arthritis, it appears to be easier to establish treatment with alternate-day corticosteroids than to convert from daily therapy. Physicians treating recipients of renal transplants initially use daily therapy and then convert to an alternate-day schedule.

Alternate-day therapy may be hazardous in the presence of adrenocortical insufficiency of any cause because patients are unprotected against glucocorticoid insufficiency during the last 12 hours of the 48-hour cycle. In patients who have been taking glucocorticoids for more than a brief period, or in those who may have adrenal insufficiency on another basis, the adequacy of HPA function should be determined before the initiation of an alternate-day program. It may be possible to surmount this obstacle by giving a small dose of a short-acting glucocorticoid (i.e., 10 mg hydrocortisone) in the afternoon of the second day; this approach has not been studied systematically.

Alternate-day glucocorticoid therapy may fail to prevent or ameliorate the manifestations of Cushing syndrome or HPA suppression if a short-acting glucocorticoid is not used, or if it is used incorrectly. For example, the use of prednisone four times a day on alternate days may be less successful than the use of the same total dose once every 48 hours.

An abrupt alteration from daily to alternate-day therapy should be avoided. First, the prolonged use of daily-dose glucocorticoids may have caused HPA suppression. In addition, patients with normal HPA function may experience withdrawal symptoms and have an exacerbation of the underlying disease.

No program of conversion from continuous therapy to alternate-day therapy has been shown to be optimal. One approach is to reduce the frequency of drug administration until the total dose for each day is given in the morning, and then to increase the dosage gradually on the first day of each 2-day period and to decrease the dosage on the second day. Another approach is to double the dosage on the first day of each 2-day cycle, to give this as a single morning dose if possible, and then to taper the dosage gradually on the second day.[85] It is not clear how often changes in dosage should be made with any approach. This depends on many variables, including the underlying disease involved, the duration of previous glucocorticoid therapy, the personality of the patient, and the physician's ability to use adjunctive therapy. Nonetheless, the conversion should be made as quickly as the patient can tolerate it. If adrenal insufficiency, the corticosteroid withdrawal syndrome, or an exacerbation of the underlying disease develops, the previously effective regimen should be reinstituted and then tapered more gradually. Occasionally, it is necessary to resume full daily dosages temporarily. An absolute change of dosage represents a larger percentage change in dosage at small total daily doses than at large total daily doses. Changes in the dosage should be about 10 mg prednisone (or equivalent) at total daily doses of more than 30 mg, 5 mg at total doses of more than 20 mg, and 2.5 mg at lower doses. The interval between changes in the dosage may be as short as 1 day or as long as many weeks.

Optimal results from alternate-day glucocorticoid therapy may not be achieved because of failure to use supplemental therapy for the underlying disorder. Conservative (nonglucocorticoid) therapy often is used until a glucocorticoid is initiated, at which time these less toxic therapeutic measures are ignored. Adjunctive therapeutic measures may facilitate the use of the lowest possible corticosteroid dose. With alternate-day therapy, these measures especially should be used during the end of the second day, when symptoms may be prominent. Supplemental therapy may be especially helpful in disorders in which patients are likely to experience symptoms of the disease on the day off therapy, such as asthma and rheumatoid arthritis. In illnesses in which disabling symptoms are less likely to appear on the alternate day, such as the childhood nephrotic syndrome, less difficulty may be encountered.

Alternate-day therapy may fail because of failure to inform patients about the purposes of this regimen. Because glucocorticoids may induce euphoria, patients may be reluctant to accept modification of a schedule of frequent doses. A careful explanation about the risks of glucocorticoid excess, attuned to patients' intellectual and emotional ability to comprehend, enhances the prospects of success.

DAILY SINGLE-DOSE GLUCOCORTICOID THERAPY

Sometimes, alternate-day therapy fails because patients experience symptoms of the underlying disease during the last few hours of the second day. In these situations, single-dose glucocorticoid therapy may be of value.[1,2] This regimen appears to be as effective as divided daily doses in controlling such underlying diseases as rheumatoid arthritis, systemic lupus erythematosus, polyarteritis, and proctocolitis. In giant cell arteritis, a daily dose in the morning is nearly as effective as daily therapy in divided doses.[82] Daily single-dose therapy reduces the likelihood that HPA suppression will develop. The manifestations of Cushing syndrome, however, probably are not prevented or ameliorated by a daily single-dose regimen.

GLUCOCORTICOIDS OR CORTICOTROPIN?

Disorders that respond to glucocorticoid therapy also respond to ACTH therapy if the adrenal cortex is normal. There is no evidence, however, that ACTH is superior to glucocorticoids for the treatment of any disorder when comparable doses are

used.[1,2,86] Hydrocortisone and ACTH, given intravenously in pharmacologically equivalent doses (determined by plasma cortisol levels and urinary corticosteroid excretion rates), are equally effective in the treatment of inflammatory bowel disease.[87] Similarly, there is no apparent difference in the effectiveness of prednisone and ACTH for the treatment of infantile spasms.[88] Because ACTH does not appear to offer any therapeutic advantage, glucocorticoids are preferable for therapeutic purposes: they can be administered orally, the dose can be regulated precisely, their effectiveness does not depend on adrenocortical responsiveness (an important consideration in patients who have been treated with glucocorticoids), and they produce a lower frequency of certain side effects such as acne, hypertension, and increased pigmentation.[1,2] If alternate-day therapy cannot be used, ACTH might appear to be preferable because it does not suppress the HPA axis. This benefit usually is outweighed by the advantages of glucocorticoids and by the fact that daily injections of ACTH are not superior to single daily doses of short-acting glucocorticoids; in both cases, HPA suppression is unlikely to result, but Cushing syndrome is not prevented. In life-threatening situations, glucocorticoids are indicated because maximal blood levels are obtained immediately after intravenous administration, whereas with ACTH infusion, the plasma cortisol level rises to a plateau over several hours. The principal indication for ACTH continues to be the assessment of adrenocortical function.

DOSAGE

ANTIINFLAMMATORY OR IMMUNOSUPPRESSIVE THERAPY

The glucocorticoid dosage required for antiinflammatory or immunosuppressive therapy is variable, and depends on the disease under treatment. In general, the dosage ranges from just above that needed for long-term replacement therapy up to 60 to 80 mg prednisone or its equivalent daily. Although much larger dosages sometimes are recommended for diseases such as asthma, systemic lupus erythematosus, and cerebral edema, controlled studies have not established the need for such large amounts of medication. The role of massive doses of corticosteroids in asthma is controversial.[89,90] Most studies report no advantage of high-dose therapy (e.g., more than 60–80 mg prednisone per day). Many physicians use intravenous pulse therapy (e.g., 1 g per day of methylprednisolone intravenously for 3 consecutive days) for severe manifestations of systemic lupus erythematosus, rapidly progressive glomerulonephritis, or other entities. There are no controlled studies that compare the results of pulse therapy with 60 to 80 mg per day of prednisone, however. Thus, the superiority of pulse therapy has not been demonstrated.[91,92]

When alternate-day therapy is used, the dosage is variable and depends on the disease under treatment. It may range from just above that needed for long-term replacement therapy to 150 mg prednisone every other day.

PERIOPERATIVE MANAGEMENT

Traditional doses of glucocorticoids recommended for perioperative coverage in patients treated with steroids (e.g., 100 mg hydrocortisone intravenously every 8 hours or 20 mg methylprednisolone intravenously every 8 hours on the day of surgery, with a gradual taper over subsequent days) are arbitrary and have no empirical basis.[70] A study in cynomolgus monkeys explored the doses required to prevent postoperative hypotension.[93] Bilateral adrenalectomies were performed in the experimental animals, and replacement doses of glucocorticoids were given for 4 months. The animals were then divided into three groups, given normal, one-tenth normal, or 10 times the normal replacement doses of glucocorticoids. A cholecystectomy was performed on each animal under these conditions. The animals that received one-tenth normal replacement doses had an increased mortality rate, decreased peripheral vascular resistance, and hypotension. The group that received normal replacement doses of glucocorticoids had no more hypotension or postoperative complications than did the group receiving 10 times the replacement dose. A double-blind study in patients provided similar results.[94] The investigators studied patients who had taken at least 7.5 mg prednisone a day for several months and had an abnormal response to an ACTH test. All patients received their usual daily dose of prednisone on the day of surgery. One group of 12 patients received perioperative injections of saline. The other group of 6 patients received hydrocortisone in the saline. There was no significant difference in outcome between the groups in this small study. It appears that patients with secondary adrenal insufficiency resulting from glucocorticoid therapy do not experience hypotension or tachycardia when given only their usual daily dose of steroids for surgical procedures such as joint replacements and abdominal operations.

Based on an analysis of the literature, an interdisciplinary group suggests the use of variable doses, depending on the magnitude of the surgical stress.[70] For *minor surgical stress* (e.g., an inguinal herniorrhaphy), the glucocorticoid target dose would be 25 mg hydrocortisone or equivalent. For *moderate surgical stress* (e.g., a lower extremity revascularization or total joint replacement), the target would be 50 to 75 mg hydrocortisone or equivalent. This might constitute continuation of the patient's usual dose of prednisone (i.e., 10 mg a day) and 50 mg hydrocortisone intravenously intraoperatively. For *major surgical stress* (e.g., esophagogastrectomy or cardiopulmonary bypass), the patient might receive his or her usual steroid dose (e.g., 40 mg prednisone or the parental equivalent preoperatively within 2 hours of surgery) and 50 mg hydrocortisone intravenously every 8 hours after the initial dose for the first 48 to 72 hours. Corticosteroid therapy should not be tapered inadvertently to a dosage below that known to control the underlying disease.

In patients with primary adrenocortical insufficiency, hydrocortisone has the advantage of having mineralocorticoid as well as glucocorticoid activity at high dosages. At dosages less than 100 mg per day, it is necessary to use a mineralocorticoid agent in addition to hydrocortisone; fludrocortisone can be used when patients can take oral medications. Parenteral mineralocorticoid preparations such as desoxycorticosterone acetate are no longer available commercially in the United States.

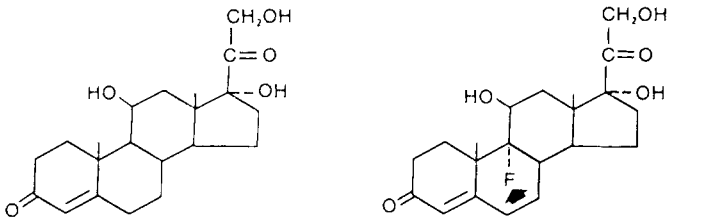
DRUG INTERACTIONS

If patients also must take a hepatic microsomal enzyme inducer, the metabolism of the glucocorticoid will be accelerated and larger daily dosages may be needed. The treatment of adrenocortical insufficiency is considered in Chapter 76.

MINERALOCORTICOIDS

PHARMACOLOGY

Mineralocorticoids are 21-carbon steroids characterized by their effects on fluid and electrolyte balance. They promote renal sodium reabsorption and potassium excretion (see Chap. 79). Mineralocorticoid deficiency (see Chap. 81) causes hyponatremia, volume depletion, hypotension, hyperkalemia, and a hyperchloremic metabolic acidosis. Mineralocorticoid excess (see Chap. 80) is associated with the retention of sodium and water, hypertension, potassium depletion, hypokalemia, and a metabolic alkalosis. The excessive secretion or administration of a mineralocorticoid causes sodium retention, with consequent fluid retention and weight gain. Patients retain several hundred milliequivalents of sodium and gain several kilograms of weight. If mineralocorticoid excess persists, *mineralocorticoid escape* occurs; further sodium retention and weight gain do not



CORTISOL (HYDROCORTISONE) FLUDROCORTISONE (9α-FLUOROHYDROCORTISONE)

FIGURE 78-3. Structure of the mineralocorticoid fludrocortisone. The *arrow* indicates the structural difference between this synthetic steroid and cortisol.

occur. During this escape phenomenon, urinary sodium excretion increases until patients come into balance, and urinary sodium excretion again reflects sodium intake. Thus, patients with mineralocorticoid excess often do not retain sufficient fluid for peripheral edema to develop (although it occasionally does) unless there is another cause for edema such as hypoalbuminemia or right ventricular failure. Therefore, the absence of edema does not exclude the possibility of mineralocorticoid excess.

Aldosterone is the principal mineralocorticoid in humans. Desoxycorticosterone, corticosterone, and cortisol (hydrocortisone) also are secreted in amounts sufficient to cause salt retention in certain pathologic situations.

AGENTS USED CLINICALLY

The agents with mineralocorticoid action that are used clinically are hydrocortisone and fludrocortisone (9α-fluorohydrocortisone, Florinef [Apothecon, a Bristol-Meyers Squibb Co., Princeton, NJ]; Fig. 78-3). When hydrocortisone is given in large dosages (e.g., 100 mg per day or more), a mineralocorticoid effect may be anticipated. Aldosterone is not used clinically, although it is a potent mineralocorticoid and is essentially devoid of glucocorticoid effect. It would be of limited value because of its brief duration of action.

Fludrocortisone is available only for oral therapy. The presence of the fluorine atom in the 9α position enhances the mineralocorticoid potency of hydrocortisone. The enhanced mineralocorticoid potency of 9α-fluorohydrocortisone is explained by impaired renal conversion of this molecule to 9α-fluorocortisone by 11-hydroxysteroid dehydrogenase, in contrast to the rapid conversion of cortisol to cortisone.[95] At recommended dosages, fludrocortisone is an effective mineralocorticoid, but it is essentially free of glucocorticoid activity. Its duration of action is ~12 to 24 hours.[96-99]

If patients also need large dosages of a glucocorticoid, hydrocortisone can be used alone. A dosage of 100 mg per day or more provides mineralocorticoid activity.[96-98] Experimentally, it was found that fludrocortisone, 1 mg per day orally, is equivalent in mineralocorticoid activity to aldosterone, 1 mg per day in four divided intramuscular doses.[98,99]

No mineralocorticoid by itself can increase the sodium stores of sodium-depleted patients. The effectiveness of a mineralocorticoid hormone depends on substrate availability; patients with mineralocorticoid deficiency not only need the hormone, they also need salt and water. Both hormonal therapy and proper fluid and electrolyte administration are necessary to achieve an optimal clinical response.

DRUG INTERACTIONS

Mineralocorticoid activity is antagonized by spironolactone; the latter has no effect in patients with hypoaldosteronism. Amiloride (Midamor), a potassium-sparing diuretic agent that acts even in the absence of aldosterone, can reduce the effects of a mineralocorticoid on sodium and potassium balance.

Anything that promotes salt loss, such as a diuretic medication, impairs mineralocorticoid efficacy. For patients who ordinarily need a diuretic (e.g., for the treatment of hypertension or fluid retention), the desired effect may be achieved by modifying the dosage of mineralocorticoid, the intake of salt, or both. Medications that alter sweating or promote vomiting or diarrhea may affect salt balance and therefore change the effectiveness of a mineralocorticoid.

INDICATIONS

Mineralocorticoid therapy is indicated for primary adrenocortical insufficiency; isolated hypoaldosteronism; salt-losing forms of congenital adrenal hyperplasia; and chronic orthostatic hypotension caused by autonomic insufficiency (multiple systems atrophy [e.g., the Shy-Drager syndrome], idiopathic orthostatic hypotension, and diabetic autonomic neuropathy).

DOSAGE

The usual dosage of fludrocortisone is 0.1 mg daily, but may range from 0.1 mg on alternate days to 0.2 mg daily. Generally, the starting dosage is 0.1 mg daily, with adjustments made according to clinical response. Orthostatic vital signs are of great value in assessing the adequacy of mineralocorticoid replacement therapy. A marked rise in the heart rate or a fall in blood pressure on standing may precede other manifestations of mineralocorticoid deficiency.

REFERENCES

1. Axelrod L. Glucocorticoid therapy. Medicine (Baltimore) 1976; 55:39.
2. Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, eds. Textbook of rheumatology, 4th ed. Philadelphia: WB Saunders, 1993.
3. Hollander JL, Brown EM Jr, Jessar RA, Brown CY. Hydrocortisone and cortisone injected into arthritic joints. JAMA 1951; 147:1629.
4. Robinson RCV, Robinson HM Jr. Topical treatment of dermatoses with steroids. South Med J 1956; 49:260.
5. Harter JG. Corticosteroids: their physiologic use in allergic disease. NY State J Med 1966; 66:827.
6. Ballard PL, Carter JP, Graham BS, Baxter JD. A radioreceptor assay for evaluation of the plasma glucocorticoid activity of natural and synthetic steroids in man. J Clin Endocrinol Metab 1975; 41:290.
7. Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids: effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med 1977; 63:200.
8. Pickup ME. Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet 1979; 4:111.
9. Jenkins JS, Sampson PA. Conversion of cortisone to cortisol and prednisone to prednisolone. BMJ 1967; 2:205.
10. Gambertoglio JG, Amend WJC Jr, Benet LZ. Pharmacokinetics and bioavailability of prednisone and prednisolone in healthy volunteers and patients: a review. J Pharmacokinet Biopharm 1980; 8:1.
11. Davis M, Williams R, Chakraborty J, et al. Prednisone or prednisolone for the treatment of chronic active hepatitis? A comparison of plasma availability. Br J Clin Pharmacol 1978; 5:501.
12. Lewis GP, Jusko WJ, Burke CW, et al. Prednisone side effects and serum-protein levels, a collaborative study. Lancet 1971; 2:778.
13. Frey FJ, Frey BM. Altered prednisolone kinetics in patients with the nephrotic syndrome. Nephron 1982; 32:45.
14. Gatti G, Perucca E, Frigo GM, et al. Pharmacokinetics of prednisone and its metabolite prednisolone in children with nephrotic syndrome during the active phase and in remission. Br J Clin Pharmacol 1984; 17:423.
15. Frey FJ, Horber FF, Frey BM. Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. Clin Pharmacol Ther 1988; 44:510.
16. Schatz M, Patterson R, Zeitz S, et al. Corticosteroid therapy for the pregnant asthmatic patient. JAMA 1975; 233:804.
17. Stuck AE, Frey BM, Frey FJ. Kinetics of prednisolone and endogenous cortisol suppression in the elderly. Clin Pharmacol Ther 1988; 43:354.
18. Tornatore KM, Logue G, Venuto RC, Davis PJ. Pharmacokinetics of methylprednisolone in elderly and young healthy males. J Am Geriatr Soc 1994; 42:1118.
19. Jubiz W, Meikle AW. Alterations of glucocorticoid actions by other drugs and disease states. Drugs 1979; 18:113.
20. Zürcher RM, Frey BM, Frey FJ. Impact of ketoconazole on the metabolism of prednisolone. Clin Pharmacol Ther 1989; 45:366.

21. Legler UF, Benet LZ. Marked alterations in dose-dependent prednisolone kinetics in women taking oral contraceptives. Clin Pharmacol Ther 1986; 39:425.
22. Uribe M, Casian C, Rojas S, et al. Decreased bioavailability of prednisone due to antacids in patients with chronic active liver disease and in healthy volunteers. Gastroenterology 1981; 80:661.
23. Graham GG, Champion GD, Day RO, Paull PD. Patterns of plasma concentrations and urinary excretion of salicylate in rheumatoid arthritis. Clin Pharmacol Ther 1977; 22:410.
24. Plotz CM, Knowlton AI, Ragan C. The natural history of Cushing's syndrome. Am J Med 1952; 13:597.
25. Thorn GW. Clinical considerations in the use of corticosteroids. N Engl J Med 1966; 274:775.
26. Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther 1972; 13:694.
27. Perry PJ, Tsuang MT, Hwang MH. Prednisolone psychosis: clinical observations. Drug Intell Clin Pharm 1984; 18:603.
28. Hollman GA, Allen DB. Overt glucocorticoid excess due to inhaled corticosteroid therapy. Pediatrics 1988; 81:452.
29. Stead RJ, Cooke NJ. Adverse effects of inhaled corticosteroids. BMJ 1989; 298:403.
30. Munck A, Guyre PM. Glucocorticoid physiology and homeostasis in relation to anti-inflammatory actions. In: Schleimer RP, Claman HN, Oronsky A, eds. Anti-inflammatory steroid action: basic and clinical aspects. San Diego: Academic Press, 1989.

30a. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000; 27:55.

31. Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS Jr. Role of transcriptional activation of IκBα in mediation of immunosuppression by glucocorticoids. Science 1995; 270:283.
32. Auphan N, DiDonato JA, Rosette C, et al. Immunosuppression by glucocorticoids: inhibition of NF-κB activity through induction of IκB synthesis. Science 1995; 270:286.
33. Marx J. How the glucocorticoids suppress immunity. Science 1995; 270:232.
34. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med 1976; 84:304.
35. Parrillo JE, Fauci AS. Mechanisms of glucocorticoid action on immune processes. Annu Rev Pharmacol Toxicol 1979; 19:179.
36. Cupps TR, Fauci AS. Corticosteroid-mediated immunoregulation in man. Immunol Rev 1982; 65:133.
37. Samuelsson B. Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. Science 1983; 220:568.
38. DiRosa M, Flower RJ, Hirata F, et al. Anti-phospholipase proteins. Prostaglandins 1984; 28:441.
39. Parente L, DiRosa M, Flower RJ, et al. Relationship between the anti-phospholipase and anti-inflammatory effects of glucocorticoid-induced proteins. Eur J Pharmacol 1984; 99:233.
40. Axelrod L. Side effects of glucocorticoid therapy. In: Schleimer RP, Claman H, Oronsky A, eds. Antiinflammatory steroid action: basic and clinical aspects. San Diego: Academic Press, 1989.
41. Ragan C. Corticotropin, cortisone and related steroids in clinical medicine: practical considerations. Bull NY Acad Med 1953; 29:355.
42. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294:473.
43. Langman MJS, Cooke AR. Gastric and duodenal ulcer and their associated diseases. Lancet 1976; 1:680.
44. Jick H, Porter J. Drug-induced gastrointestinal bleeding. Lancet 1978; 2:87.
45. Messer J, Reitman D, Sacks HS, et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983; 309:21.
46. Spiro HM. Is the steroid ulcer a myth? N Engl J Med 1983; 309:45.
47. Conn HO, Poynard T. Adrenocorticosteroid administration and peptic ulcer: a critical analysis. J Chronic Dis 1985; 38:457.
48. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114:735.
49. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 1991; 115:787.
50. Schatz M, Patterson R, Kloner R, Falk J. The prevalence of tuberculosis and positive tuberculin skin tests in a steroid-treated asthmatic population. Ann Intern Med 1976; 84:261.
51. Kozower M, Veatch L, Kaplan MM. Decreased clearance of prednisolone, a factor in the development of corticosteroid side effects. J Clin Endocrinol Metab 1974; 38:407.
52. Bergrem H, Jervell J, Flatmark A. Prednisolone pharmacokinetics in cushingoid and non-cushingoid kidney transplant patients. Kidney Int 1985; 27:459.
53. Frey FJ, Amend WJC Jr, Lozada F, et al. Endogenous hydrocortisone, a possible factor contributing to the genesis of cushingoid habitus in patients on prednisone. J Clin Endocrinol Metab 1981; 53:1076.
54. Becker B. Intraocular pressure response to topical corticosteroids. Invest Ophthalmol 1965; 4:198.
55. Bigger JF, Palmberg PF, Becker B. Increased cellular sensitivity to glucocorticoids in primary open angle glaucoma. Invest Ophthalmol 1972; 11:832.
56. Becker B, Podos SM, Asseff CF, Cooper DG. Plasma cortisol suppression in glaucoma. Am J Ophthalmol 1973; 75:73.
57. Becker B, Shin DH, Palmberg PF, Waltman SR. HLA antigens and corticosteroid response. Science 1976; 194:1427.
58. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 1996; 39:1791.
59. Sambrook PN. Calcium and vitamin D therapy in corticosteroid bone loss: what is the evidence? J Rheumatol 1996; 23:963.
60. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. N Engl J Med 1993; 328:1747.
61. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 1997; 337:382.
62. Reid IR. Preventing glucocorticoid-induced osteoporosis. N Engl J Med 1997; 337:420.
63. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998; 339:292.
64. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illnesses and prior corticosteroid therapy. Mayo Clin Proc 1996; 71:5.
65. Sepkowitz KA. *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome: who should receive prophylaxis? Mayo Clin Proc 1996:71:102.
66. Amatruda TT Jr, Hollingsworth DR, D'Esopo ND, et al. A study of the mechanism of the steroid withdrawal syndrome: evidence for integrity of the hypothalamic-pituitary-adrenal system. J Clin Endocrinol Metab 1960; 20:339.
67. Amatruda TT Jr, Hurst MM, D'Esopo ND. Certain endocrine and metabolic facets of the steroid withdrawal syndrome. J Clin Endocrinol Metab 1965; 25:1207.
68. Dickstein G, Shechner C, Nicholson WE, et al. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low-dose test. J Clin Endocrinol Metab 1991; 72:773.

68a. Henzen C, Suter A, Lerch E, et al. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. Lancet 2000; 355:542.

69. Streeten DHP. Shortcomings in the low-dose (1 μg) ACTH test for the diagnosis of ACTH deficiency states. J Clin Endocrinol Metab 1999; 84:835.
70. Salem M, Tainsh RE Jr, Bromberg J, et al. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994; 219:416.
71. Schlaghecke R, Kornely E, Santen RT, Ridderskamp P. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. N Engl J Med 1992; 326:226.
72. Daly JR, Fletcher MR, Glass D, et al. Comparison of effects of long-term corticotrophin and corticosteroid treatment on responses of plasma growth hormone, ACTH, and corticosteroid to hypoglycaemia. BMJ 1974; 2:521.
73. Graber AL, Ney RL, Nicholson WE, et al. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. J Clin Endocrinol Metab 1965; 25:11.
74. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med 1979; 66:910.
75. Haugen HN, Reddy WJ, Harter JG. Intermittent steroid therapy in bronchial asthma. Nord Med 1960; 63:15.
76. Reichling GH, Kligman AM. Alternate-day corticosteroid therapy. Arch Dermatol 1961; 83:980.
77. Harter JG, Reddy WJ, Thorn GW. Studies on an intermittent corticosteroid dosage regimen. N Engl J Med 1963; 269:591.
78. MacGregor RR, Sheagren JN, Lipsett MB, Wolff SM. Alternate-day prednisone therapy: evaluation of delayed hypersensitivity responses, control of disease and steroid side effects. N Engl J Med 1969; 280:1427.
79. Dale DC, Fauci AS, Wolff SM. Alternate-day prednisone: leukocyte kinetics and susceptibility to infections. N Engl J Med 1974; 291:1154.
80. Fauci AS, Dale DC. Alternate-day therapy and human lymphocyte subpopulations. J Clin Invest 1975; 55:22.
81. Schürmeyer TH, Tsokos GC, Avgerinos PC, et al. Pituitary-adrenal responsiveness to corticotropin-releasing hormone in patients receiving chronic, alternate day glucocorticoid therapy. J Clin Endocrinol Metab 1985; 61:22.
82. Hunder GG, Sheps SG, Allen GL, Joyce JW. Daily and alternate day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. Ann Intern Med 1975; 82:613.
83. Abruzzo JL. Alternate-day prednisone therapy. Ann Intern Med 1975; 82:714.
84. Bengtsson B-A, Malmvall B-E. An alternate-day corticosteroid regimen in maintenance therapy of giant cell arteritis. Acta Med Scand 1981; 209:347.
85. Fauci AS. Alternate-day corticosteroid therapy. Am J Med 1978; 64:729.
86. Allander E. ACTH or corticosteroids? A critical review of results and possibilities in the treatment of severe chronic disease. Acta Rheum Scand 1969; 15:277.
87. Kaplan HP, Portnoy B, Binder HJ, et al. A controlled evaluation of intravenous adrenocorticotropic hormone and hydrocortisone in the treatment of acute colitis. Gastroenterology 1975; 69:91.
88. Hrachovy RA, Frost JD Jr, Kellaway P, Zion TE. Double-blind study of ACTH vs prednisone therapy in infantile spasms. J Pediatr 1983; 103:641.
89. Editorial. Steroids in acute severe asthma. Lancet 1992; 340:1384.
90. McFadden ER Jr. Dosages of corticosteroids in asthma. Am Rev Respir Dis 1993; 147:1306.
91. Elenbaas J. Steroid pulse therapy in systemic lupus erythematosus. Drug Intell Clin Pharm 1983; 17:342.
92. Kurki P, ed. High dose intravenous corticosteroid therapy of systemic lupus erythematosus and primary crescenteric rapidly progressive glomerulonephritis. Proceedings of a symposium. Scand J Rheumatol 1984; Suppl 54:1.

93. Udelsman R, Ramp J, Gallucci WT, et al. Adaptation during surgical stress: a reevaluation of the role of glucocorticoids. J Clin Invest 1986; 77:1377.
94. Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery 1997; 121:123.
95. Oelkers W, Buchen S, Diederich S, et al. Impaired renal 11β-oxidation of 9α-fluorocortisol: an explanation for its mineralocorticoid potency. J Clin Endocrinol Metab 1994; 78:928.
96. Goldfein A, Laidlaw JC, Haydar NA, et al. Fluorohydrocortisone and chlorohydrocortisone, highly potent derivatives of compound F. N Engl J Med 1955; 252:415.
97. Renold AE, Haydar NA, Reddy WJ, et al. Biological effects of fluorinated derivatives of hydrocortisone and progesterone in man. Ann NY Acad Sci 1955; 61:582.
98. Thorn GW, Renold AE, Morse WI, et al. Highly potent adrenal cortical steroids; structure and biological activity. Ann Intern Med 1955; 43:979.
99. Thorn GW, Sheppard RH, Morse WI, et al. Comparative action of aldosterone and 9-alpha-fluorohydrocortisone in man. Ann NY Acad Sci 1955; 61:609.

CHAPTER 79

RENIN-ANGIOTENSIN SYSTEM AND ALDOSTERONE

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THE RENIN-ANGIOTENSIN SYSTEM

ANGIOTENSINOGEN

Angiotensinogen (AGT), also termed *renin substrate*, is the precursor for the angiotensin peptides, which include *angiotensin (A)-I, II, III, and IV, and* A_{1-7}. Levels of this peptide, which can be rate-limiting for the *renin-angiotensin system*, are produced mainly in the liver, where its precursor *preproangiotensinogen* is synthesized and glycosylated in the hepatocytes; nonetheless, there is evidence of production in other tissues as well (e.g., the heart, blood vessels, kidney, and adipocytes).

In the circulation, AGT, with a half-life of 16 hours, is cleaved by renin (~10%) and/or other enzymes to release A-I (Fig. 79-1). In many tissues not expressing renin, AGT can be cleaved by enzymes other than renin (e.g., cathepsin G, tonin, and chymase). The extent to which AGT is glycosylated may influence the kinetics of renin in the circulation. Indeed, this has been hypothesized in a proposed, separate, brain-AGT system.

There is one copy of the AGT gene in the mammalian genome, which is ~11,800 base pairs (bp) in length.[1,2] This gene has 5 exons that encode for the protein, separated by 4 introns. Exon 1 codes for the 5'-nontranslated region, whereas exon 2 contains the signal peptide and coding regions. AGT is secreted constitutively from hepatocytes; however, several factors (e.g., glucocorticoids, estrogens, thyroid hormone, insulin, and A-II) may exert a positive feedback.[3,4]

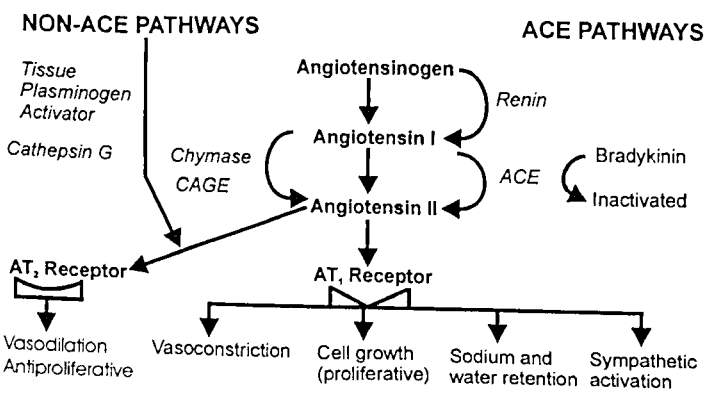

FIGURE 79-1. Angiotensinogen and angiotensin I and II pathways and their role in vascular and fluid homeostasis via angiotensin II receptors (AT_1 and AT_2). (*CAGE*, chymotrypsin-like angiotensin-generating enzyme.)

RELATIONSHIP TO HYPERTENSION

A high molecular-weight form of AGT, which is released during pregnancy, may play a role in *pregnancy-induced hypertension*. In adipose tissue, there is a form of AGT that is increased by insulin and decreased by 3-adrenergic blockade and that possibly contributes to *obesity-related hypertension*. Moreover, AGT may play a role in certain other forms of hypertension, as observed in glucocorticoid excess states (e.g., Cushing syndrome) and thyroid disorders.[1-4] Interestingly, antisense nucleotide sequences that have been used to block AGT mRNA can reduce blood pressure. In spontaneously hypertensive rats, central nervous system (CNS) administration of antisense sequences against the mRNA encoding AGT lowers blood pressure.[5] Furthermore, rats made transgenic with human AGT develop hypertension because AGT is expressed in the blood vessel wall.[6,7] Thus, there is ample documentation for a role of AGT in experimental hypertension.

Further documentation for a role of AGT in hypertension is as follows: Epidemiologic studies have shown a relationship between plasma AGT and human hypertension.[8,9] Polymorphisms of the AGT gene have been linked to familial hypertension, renal disease, and cardiovascular risk factors.[9] Increased levels of AGT are associated with essential hypertension, and an M235T polymorphism in the AGT gene is associated with nephropathy in type 2 diabetics.[10] The AGT M235T molecular variant—threonine substituted for methionine at amino acid 235—is associated by linkage analysis with essential hypertension, especially in whites.[11,12] Subjects bearing the 235 allele have higher levels of AGT (i.e., a 20% increase in homozygous subjects [TT] and a 10% increase in heterozygous subjects [MT]) compared with homozygous (MM) individuals. This linkage of AGT variants to hypertension is population-dependent (i.e., strong in whites, weak in Mexican Americans[13] and the Chinese[14]). AGT mutations probably play a significant but modest role in blood pressure variation. All of these findings suggest that the renin-AGT reaction kinetics are increased by AGT variants, leading to more A-II production, which in turn may increase vascular resistance and growth. In turn, vascular injury induces AGT gene expression in the vascular media and neointima, suggesting that the renin-angiotensin system participates in myointimal proliferation.[15] Finally, gene knock-out mice for AGT develop hypotension with polyuria when challenged with a high-salt diet.[16]

RENIN SYNTHESIS AND RELEASE

Renin, an aspartyl proteolytic enzyme, catalyzes the rate-limiting cleavage of AGT (between the leucine at position 10 and the valine at position 11) to form the *decapeptide A-I*, which is further converted by angiotensin-converting enzyme I (ACE-I) to the *octapeptide, A-II*. It is the plasma renin activity that is accepted as an index of the renin-angiotensin system, because it is difficult to measure other components (e.g., A-II).

Renin synthesis begins with the formation of *preprorenin* in the *juxtaglomerular (JG) cells* of the kidney.[17,18] This precursor is transported into the rough endoplasmic reticulum (Fig. 79-2), where it is cleaved to form a 23-amino-acid inactive form (*prorenin*), which is passed through the Golgi apparatus, glycosylated, and deposited in lysosomal granules.[18] Here it is cleaved by cathepsin B to form *renin*, which can be secreted in response to various stimuli.[18] Basally, there is a low rate of renin release, and this is increased several-fold in response to stimuli.