CHAPTER

4 PRINCIPLES OF THERAPEUTICS

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THERAPY AS A SCIENCE

Over a century ago Claude Bernard formalized criteria for gathering valid information in experimental medicine. However, application of these criteria to therapeutics and to the process of making decisions about therapeutics has, until recently, been slow and inconsistent. At a time when the diagnostic aspects of medicine had become scientifically sophisticated, therapeutic decisions were often made on the basis of impressions and traditions. Historically, the absence of accurate data on the effects of drugs in man was due in large part to ethical standards of human experimentation. "Experimentation" in human beings was precluded, and it was not generally conceded that every treatment by any physician should be designed and in some sense recorded as an experiment.

Although there must always be ethical concern about experimentation in man, principles have been defined, and there are no longer ethical restraints on the gathering of either experimental or observational data on the efficacy and toxicity of drugs in adults. Furthermore, it should now be considered absolutely unethical to use the *art* as opposed to the *science* of therapeutics on any patient who directly (the adult or child) or indirectly (the fetus) receives drugs for therapeutic purposes. Observational (nonexperimental) techniques that can greatly add to our knowledge of the effects of drugs can be applied to all populations (Sheiner and Benet, 1985; Whiting *et al.*, 1986). The fact that such observational techniques have largely been applied in a nonsystematic fashion has led us to rely on a relative paucity of information about many drugs. Therapeutics must now be dominated by objective evaluation of an adequate base of factual knowledge.

Conceptual Barriers to Therapeutics as a Science. The most important barrier that inhibited the development of therapeutics as a science seems to have been the belief that multiple variables in diseases and in the effects of drugs are uncontrollable. If this were true, the scientific method would not be applicable to the study of pharmacotherapy. In fact, therapeutics is the aspect of patient care that is most amenable to the acquisition of useful data, since it involves an intervention and provides an opportunity to observe a response. It is now appreciated that clinical phenomena can be defined, described, and quantified with some precision. The approach to complex clinical data has been artfully discussed by Feinstein (1983).

Another barrier to the realization of therapeutics as a science was overreliance on traditional diagnostic labels for disease. This encouraged the physician to think of a disease as static rather than dynamic, to view patients with the same "label" as a homogeneous rather than a heterogeneous population, and to consider a disease as an entity even when information about pathogenesis was not available. If diseases are not considered to be dynamic, "standard" therapies in "standard" doses will be the order of the day; decisions will be reflexive. Needed instead is an attitude that makes the physician responsible for recognition of and compensation for changes that occur in pathophysiology as the underlying process evolves. For example, the term *myocardial infarction* refers to localized destruction of myocardial cells caused by interruption of the blood supply; however, decisions about therapy must take into account a variety of autonomic, hemodynamic, and electrophysiological variables that change as a function of time, size, and location of the infarction. Failure to take all such variables into

account while planning a therapeutic maneuver may result in ineffective therapy in some patients while exposing others to avoidable toxicity. If groups of patients are in reality heterogeneous and receive alternative treatments, true differences in efficacy or toxicity between therapies may go unrecognized. A diagnosis or label of a disease or syndrome usually indicates a spectrum of possible causes and outcomes. Therapeutic experiments that fail to match groups for the known variables that affect prognosis yield uninterpretable data.

A third conceptual barrier was the incorrect notion that data derived empirically are useless because they are not generated by application of the scientific method. Empiricism is often defined as the practice of medicine founded on mere experience, without the aid of science or a knowledge of principles. The connotations of this definition are misleading; empirical observations need not be scientifically unsound. In fact, concepts of therapeutics have been greatly advanced by the clinical observer who makes careful and controlled observations on the outcome of a therapeutic intervention. The results, even when the mechanisms of disease and their interactions with the effects of drugs are not understood, are nevertheless often crucial to appropriate therapeutic decisions. Frequently, the initial suggestion that a drug may be efficacious in one condition arises from careful, empirical observations that are made while the drug is being used for another purpose. Examples of valid empirical observations that have resulted in new uses of drugs include the use of penicillamine to treat arthritis, lidocaine to treat cardiac arrhythmias, and propranolol and clonidine to treat hypertension. Conversely, empiricism, when not coupled with appropriate observational methods and statistical techniques, often results in findings that are inadequate or invalid.

Clinical Trials. Application of the scientific method to experimental therapeutics is exemplified by a well-designed and well-executed clinical trial. Clinical trials form the basis for therapeutic decisions by all physicians, and it is therefore essential that they be able to evaluate the results and conclusions of such trials critically. To maximize the likelihood that useful information will result from the experiment, the objectives of the study must be defined, homogeneous populations of patients must be selected, appropriate control groups must be found, meaningful and sensitive indices of drug effects must be chosen for observation, and the observations must be converted into data and then into valid conclusions (Feinstein, 1977). The *sine qua non* of any clinical trial is its controls. Many different types of controls may be used, and the term *controlled study* is not synonymous with *randomized double-blind technique*. Selection of a proper control group is as critical to the eventual utility of an experiment as the selection of the experimental group. Although the randomized, double-blind controlled trial is the most effective design for distributing bias and unknown variables between the "treatment" and the "control" groups, it is not necessarily the optimal design for all studies. It may be impossible to use this design to study disorders that occur rarely, disorders in patients who cannot, by regulation or ethics or both, be studied (*e.g.*, children, women of childbearing age, fetuses, or some patients with psychiatric diseases), or disorders with a uniformly fatal outcome (*e.g.*, rabies, where historical controls can be used).

There are several requirements in the design of clinical trials to test the relative effects of alternative therapies. (1) *Specific outcomes* of therapy that are clinically relevant and quantifiable must be measured. (2) The *accuracy of diagnosis* and the *severity of the disease* must be comparable in the groups being contrasted; otherwise, false-positive and false-negative errors may occur. (3) The *dosages* of the drugs must be chosen and individualized in a manner that allows relative efficacy to be compared at equivalent toxicities or allows relative toxicities to be compared at equivalent efficacies. (4) *Placebo effects*, which occur in a large percentage of patients, can confound many studies—particularly those that involve subjective responses; controls must take this into account. However, subjective assessments are important in determining whether a therapy improves the patient's well-being. In fact, quality of life can be assessed by the experimental subject and can be objectively tabulated and incorporated into evaluation of a therapy (Williams, 1987). (5) *Compliance* with the experimental regimens should be assessed before subjects are assigned to experimental or control groups. The drug-taking behavior

of the subjects should be reassessed during the course of the trial. Noncompliance, even if randomly distributed between both groups, may cause falsely low estimates of the true potential benefits or toxicity of a particular treatment. (6) *Sample size* should be estimated prior to beginning a clinical trial and must be taken into account in interpreting the results of the trial. Depending upon such factors as the overall prognosis of the disease and the anticipated improvement in outcome or toxicity from the new treatment, very large numbers of subjects may be needed; otherwise, the possibility of a false-negative result is high (*i.e.*, no statistically significant differences between the two treatments will be found, even though differences actually exist) (Young *et al.*, 1983; Simon, 1986). (7) *Ethical considerations* may be major determinants of the types of controls that can be used and must be evaluated explicitly (Rosner, 1987; Rothman, 1987). For example, in therapeutic trials that involve life-threatening diseases for which there is already an effective therapy, the use of a placebo is unethical, and new treatments must be compared with "standard" therapies.

The results of clinical trials of new therapeutic agents or of old agents for new indications may have severe limitations in terms of what can be expected of drugs when they are used in an office practice. The selection of the patients for experimental trials usually eliminates those with coexisting diseases, and such trials usually assess the effect of only one or two drugs, not the many that might be given to or taken by the same patient under the care of a physician. Clinical trials are usually performed with relatively small numbers of patients for periods of time that may be shorter than are necessary in practice, and compliance may be better controlled than it can be in practice. These factors lead to several inescapable conclusions:

1) Even if the result of a valid clinical trial of a drug is thoroughly understood, the physician can only develop a hypothesis about what the drug might do to a particular patient, and there can be no assurance that what occurred in other patients will be seen. In effect, the physician uses the results of a clinical trial to establish an experiment in each patient. The detection of anticipated and unanticipated effects and the determination of whether or not they are due to the drug(s) being used are important responsibilities of the physician during the supervision of a therapeutic regimen. If an effect of a drug is not seen in a clinical trial, it may still be revealed in the setting of clinical practice. About one half or more of both useful and adverse effects of drugs that were not recognized in the initial formal trials were subsequently discovered and reported by practicing physicians.

2) If an anticipated effect of a drug has not occurred in a patient, this does not mean that the effect cannot occur in that patient or in others. Many factors in the individual patient may contribute to lack of efficacy of a drug. They include, for example, misdiagnosis, poor compliance by the patient to the regimen, poor choice of dosage or dosage intervals, coincidental development of an undiagnosed separate illness that influences the outcome, the use of other agents that interact with primary drugs to nullify or alter their effects, undetected genetic or environmental variables that modify the disease or the pharmacological actions of the drug, or unknown therapy by another physician who is caring for the same patient. Of equal importance, even when a regimen appears to be efficacious and innocuous, a physician should not attribute all improvement to the therapeutic regimen chosen, nor should a physician assume that a deteriorating condition reflects only the natural course of the disease. Similarly, if an anticipated untoward or toxic effect is not seen in a particular patient, it can still occur in others. Physicians who use only their own experience with a drug to make decisions about its use unduly expose their patients to unjustifiable risk or unrealized efficacy. For example, simply because a doctor has not seen a case of chloramphenicol-induced aplastic anemia in his own practice does not mean that such a disaster may not occur; the drug should still be used for the proper indications.

3) Rational therapy is therapy based on the use of observations that have been evaluated critically. It is no less crucial to have a scientific approach to the treatment of an individual patient than to use this approach when investigating drugs in a research setting. In both instances, it is the patient who benefits. Such an approach can be formalized in the practice setting by performing randomized, controlled trials in individual patients who have stable clinical symptomatology. With this strategy a specific ther-

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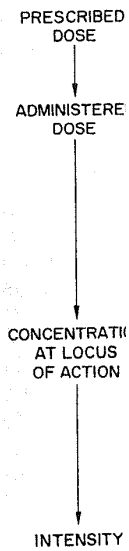

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apy of uncertain efficacy can be compared with a placebo or alternative therapy in a double-blind design with well-defined end points that are tailored to the individual patient. The outcome of such a trial is immediately relevant to the particular patient, although it may not apply to all other patients (Guyatt *et al.*, 1986).

INDIVIDUALIZATION OF DRUG THERAPY

As has been implied above, therapy as a science does not apply simply to the evaluation and testing of new, investigational drugs in animals and man. It applies with equal importance to the treatment of each patient as an individual. Therapists of every type have long recognized and acknowledged that individual patients show wide variability in response to the same drug or treatment method. Progress has been made in identifying the sources of variability (Vesell, 1986). Important factors are presented in Figure 4–1; the basic principles that underlie these sources of variability have been presented in Chapters 1 and 2.

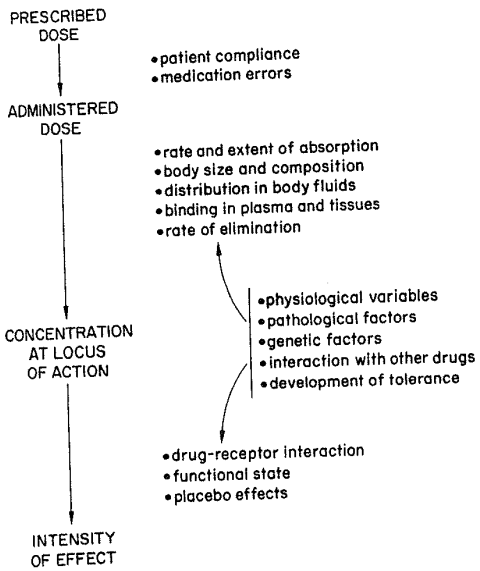


Figure 4–1. *Factors that determine the relationship between prescribed drug dosage and drug effect.* (Modified from Koch-Weser, 1972.)

The following discussion relates to the strategies that have been developed to deal with variability in the clinical setting. (*See also* Appendix II.)

Pharmacokinetic Considerations

Interpatient and intrapatient variation in disposition of a drug must be taken into account in choosing a drug regimen. For a given drug, there may be wide variation in its pharmacokinetic properties among individuals. For some drugs, this variability may account for one half or more of the total variation in eventual response. The relative importance of the many factors that contribute to these differences depends in part on the drug itself and on its usual route of elimination. Drugs that are excreted primarily unchanged by the kidney tend to have smaller differences in disposition among patients with similar renal function than do drugs that are inactivated by metabolism. Of drugs that are extensively metabolized, those with high metabolic clearance and large first-pass elimination have marked differences in bioavailability, whereas those with slower biotransformation tend to have the largest variation in elimination rates between individuals. Studies in identical and nonidentical twins have revealed that genotype is a very important determinant of differences in the rates of metabolism (Penno and Vesell, 1983). For many drugs, physiological and pathological variations in organ function are major determinants of their rate of disposition. For example, the clearance of digoxin and gentamicin is related to the rate of glomerular filtration, whereas that of lidocaine and propranolol is primarily dependent on the rate of hepatic blood flow. The effect of aging and diseases that involve the kidneys or liver is to impair elimination and to increase the variability in the disposition of drugs. In such settings, measurements of concentrations of drugs in biological fluids can be used to assist in the individualization of drug therapy (Spector *et al.*, 1988). Since old age and renal or hepatic diseases may also affect the responsiveness of target tissues (*e.g.*, the brain), the physician should be alert to the possibility of a shift in the range of therapeutic concentrations.

A test should not be performed simply because an assay is available. More assays of drugs are available than are generally useful. Determinations of concentrations of drug in blood, serum, or plasma are particularly useful when well-defined criteria are fulfilled. (1) There must be a demonstrated relationship between the concentration of the drug in plasma and the eventual therapeutic effect that is desired and/or the toxic effect that must be avoided. (2) There should be substantial interpatient variability in disposition of the drug (and small intrapatient variation). Otherwise, concentrations of drug in plasma could be predicted adequately from dose alone. (3) It should be difficult to monitor intended or unintended effects of the drug. Whenever clinical effects or minor toxicity are easily measured (*e.g.*, the effect of a drug on blood pressure), such assessments should be preferred in the decision to make any necessary adjustment of dosage of the drug. However, the effects of some drugs in certain settings are not easily monitored. For example, the effect of Li^+ on manic–depressive psychosis may be delayed and difficult to quantify. For some drugs, the initial manifestation of toxicity may be serious (*e.g.*, digitalis-induced arrhythmias or theophylline-induced seizures). The same concepts apply to a number of agents used for cancer chemotherapy. Other drugs (*e.g.*, antiarrhythmic agents) produce toxic effects that mimic symptoms or signs of the disease being treated. Many drugs are used for prophylaxis of an intermittent, potentially dangerous event; examples include anticonvulsants and antiarrhythmic agents. In each of these situations, titration of drug dosage may be aided by measurements of concentrations of the drug in blood. (4) The concentration of drug required to produce therapeutic effects should be close to the value that causes substantial toxicity (*see* below). If this circumstance does not apply, patients could simply be given the largest dose known to be necessary to treat a disorder, as is commonly done with penicillin. However, if there is an overlap in the concentration–response relationship for desirable and undesirable effects of the drug, as is true for theophylline, determinations of concentration of drug in plasma may allow the dose to be optimized. All four of the above-described criteria should be met if the measurement of drug concentrations is to be of significant value in the adjustment of dosage. Knowledge of concentrations of drugs in plasma or urine is also particularly useful for detection of therapeutic failures that are due to lack of patient compliance with a medical regimen or for identification of patients with unexpected extremes in the rate of drug disposition.

Assay of drugs to assist the physician in achieving a desired concentration of drug in blood or plasma (*i.e.*, "targeting" the dose) is an example of the use of an *intermediate end point of therapy*. An intermediate end point is defined as a specific goal of treatment that is used in place of the ultimate clinical goal, which may be difficult to assess. The concept of intermediate end points, including concentrations of drugs, as a guide to individualization of therapy can also be applied in other ways; one is to provide an indication for a change in the choice of drug therapy. Measurements of concentrations of drugs in plasma and/or measurements of one or more pharmacological effects of the drug can provide an indication of probable lack of efficacy. Other issues of importance with regard to the measurement and interpretation of drug concentrations are discussed in Chapter 1 and Appendix II.

PHARMACODYNAMIC CONSIDERATIONS

Considerable interindividual variation in the response to drugs remains after the concentration of the drug in plasma has been adjusted to a target value; for some drugs this pharmacodynamic variability accounts for much of the total variation in responsiveness between patients. As discussed in Chapter 2, the relationship between the concentration of a drug and the magnitude of the observed response may be complex, even when responses are measured in simplified systems *in vitro*, although typical sigmoidal concentration–effect curves are usually seen (Figure 2–6). When drugs are administered to patients, however, there is no single characteristic relationship between the drug concentration in plasma and the measured effect; the concentration–

effect curve may be concave upward, concave downward, linear, or sigmoid. Moreover, the concentration–effect relationship may be distorted if the response being measured is a composite of several effects, such as the change in blood pressure produced by a combination of cardiac, vascular, and reflex effects. However, such a composite concentration–effect curve can often be resolved into simpler curves for each of its components. These simplified concentration–effect relationships, regardless of their exact shape, can be viewed as having four characteristic variables: potency, slope, maximal efficacy, and individual variation. These are illustrated in Figure 4–2 for the common sigmoid log dose–effect curve.

Potency. The location of the concentration–effect curve along the *concentration axis* is an expression of the potency of a drug. Although often related to the dose of a drug required to produce an effect, potency is more properly related to the concentration of the drug in plasma in order to approximate more closely the situation in isolated systems *in vitro* and to avoid the complicating factors of pharmacokinetic variables. Although potency obviously affects drug dosage, potency *per se* is relatively unimportant in the clinical use of drugs as long as the required dose can be given conveniently. There is no justification for the view that more potent drugs are superior therapeutic agents. However, if the drug is to be administered by transdermal absorption, a highly potent drug is required, since the capacity of the skin to absorb drugs is limited.

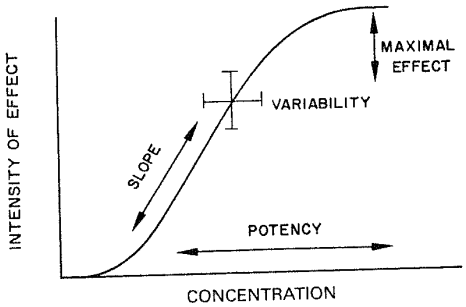


Figure 4–2. *The log dose-effect relationship.*

Representative log dose-effect curve, illustrating its four characterizing variables (*see* text for explanation).

Maximal Efficacy. The maximal effect that can be produced by a drug is its *maximal efficacy* or, simply, *efficacy*. As discussed in Chapter 2, maximal efficacy is determined by the properties of the drug and its receptor–effector system and is reflected in the plateau of the concentration–effect curve. In clinical use, however, a drug's dosage may be limited by undesired effects, and the true maximal efficacy of the drug may not be achievable. Efficacy of a drug is clearly a major characteristic—of much more clinical importance than is potency; furthermore, the two properties are not related and should not be confused. For instance, although some thiazide diuretics have similar or greater potency than the loop diuretic furosemide, the maximal efficacy of furosemide is considerably greater.

Slope. The slope of the concentration–effect curve reflects the mechanism of action of a drug, including the shape of the curve that describes drug binding to its receptor (*see* Chapter 2). The steepness of the curve dictates the range of doses that are useful for achieving a clinical effect. Aside from this fact, the slope of the concentration–effect curve has more theoretical than practical usefulness.

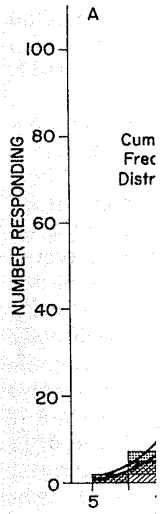
Biological Variability. Different individuals vary in the magnitude of their response to the same concentration of a single drug or to similar drugs when the appropriate correction has been made for differences in potency, maximal efficacy, and slope. In fact, a single individual may not always respond in the same way to the same concentration of drug. A concentration–effect curve applies only to a single individual at one time or to an average individual. The intersecting brackets in Figure 4–2 indicate that an effect of varying intensity will occur in different individuals at a specified concentration of a drug or that a range of concentrations is required to produce an effect of specified intensity in all of the patients.

Specific terms are used to refer to individuals who are unusually sensitive or resistant to a drug and to describe those in whom the drug produces a qualitatively different effect. The mechanisms of these unusual effects are described in general in this chapter and are discussed for individual drugs throughout this textbook. If a drug produces an effect at a very low dosage, the individual is said to be *hyperreactive*. (*Hypersensitivity* usually refers to effects associated with drug allergy, and *supersensitivity* is used to describe the increased sensitivity that results from denervation or long-term treatment with a receptor antagonist.) Individuals who are resistant to drug effect are said to be *hyporeactive*. *Tolerance* connotes hyporeactivity acquired as a result of exposure to the drug, and if tolerance develops rapidly, it is called *tachyphylaxis*. *Idiosyncrasy* is a term that describes an unusual effect of the drug, irrespective of intensity or dosage, that occurs in a small percentage of the population. However, because this term is often confused with drug allergy and because it conveys no useful information, it should probably be abandoned in favor of simple descriptions of the effect and terms that refer to the underlying mechanisms, which are often genetic or immunological.

Attempts have been made to define and measure individual "sensitivity" to drugs in the clinical setting, and progress has been made in understanding some of the determinants of sensitivity to drugs that act at specific receptors. For example, responsiveness to β-adrenergic receptor agonists may change because of disease (*e.g.*, thyrotoxicosis) or because of prior administration of either β-adrenergic agonists or antagonists that can cause changes in the concentration of the β-adrenergic receptor and/or coupling of the receptor to its effector systems (Bristow *et al.*, 1982; Stiles *et al.*, 1984). Resistance of tumors to the antineoplastic agent methotrexate may occur because of gene amplification and subsequent synthesis of large quantities of the receptor for the cytotoxic action of this drug, dihydrofolate reductase (Brown *et al.*, 1983). Receptors are not static components of the cell; they are in a dynamic state that is influenced by both endogenous and exogenous factors (*see* Chapters 2 and 5).

Concentration–Percent Curve. The concentration of a drug that produces a specified effect in a single patient is termed the *individual effective concentration*. This is a *quantal* response, since the defined effect is either present or absent. Individual effective concentrations are usually log-normally distributed, which means that a normal variation curve is the result of plotting the logarithms of the concentration against the frequency of patients achieving the defined effect (Figure 4–3A). A cumulative frequency distribution of individuals achieving the defined effect as a function of drug concentration is the *concentration–percent curve* or the *quantal concentration–effect curve*. This curve resembles the sigmoid shape of the graded concentration–effect curve discussed above (Figure 4–2), but the slope of the concentration–percent curve is an expression of the pharmacodynamic variability in the population rather than an expression of the concentration range from a threshold to a maximal effect in the individual patient.

The dose of a drug required to produce a specified effect in 50% of the population is the *median effective dose*, abbreviated as the ED_{50} (Figure 4–3B). In preclinical studies of drugs, the *median lethal dose*, as determined in experimental animals, is abbreviated as LD_{50}. The ratio of the LD_{50} to the ED_{50} is an indication of the *therapeutic index*, which is a statement of how *selective* the drug is in producing its desired effects. In clinical studies, the dose, or preferably the concentration, of a drug required to produce toxic effects can be compared to the concentration required for the therapeutic effects in the population in order to evaluate the clinical therapeutic index. However, since pharmacodynamic variation in the population may be marked, the concentration or dose of drug required to produce a therapeutic effect in most of the population will usually overlap the concentration required to produce toxicity in some of the population, even though the drug's therapeutic index may be large. Also, the concentration–percent curves for efficacy and toxicity need not be parallel, adding yet



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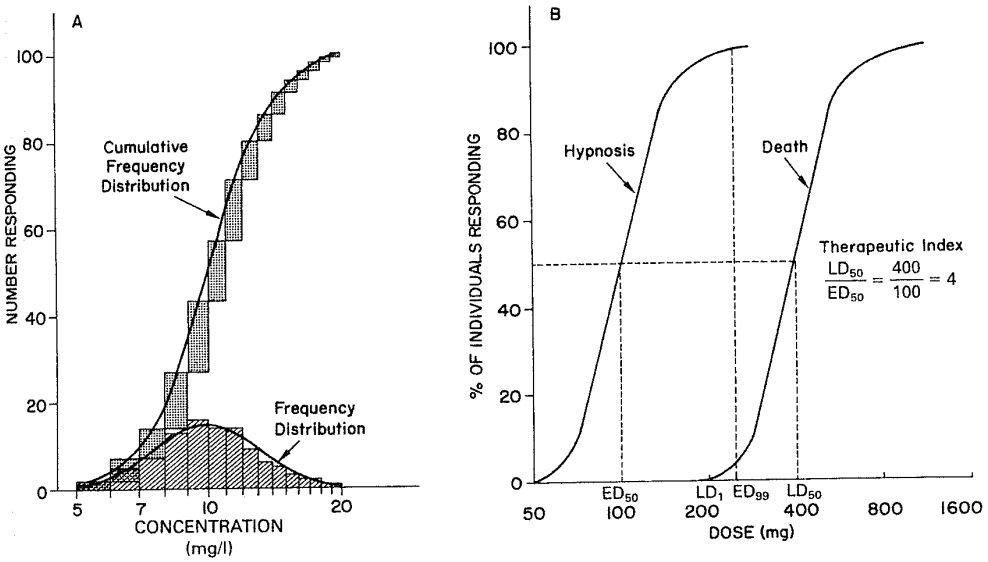

Figure 4–3. *Frequency distribution curves and quantal dose-effect curves.*

A. An experiment was performed on 100 subjects and the effective concentration to produce a quantal response was determined for each individual. The number of subjects who required each dose is plotted, giving a lognormal frequency distribution (bars with diagonal lines). The stippled bars demonstrate that the normal frequency distribution, when summated, yields the cumulative frequency distribution—a sigmoidal curve that is a quantal concentration–effect curve.

B. Quantal Dose-Effect Curves. Animals were injected with varying doses of a sedative–hypnotic, and the responses determined and plotted (*see* text for additional explanation).

another complexity to the determination of the therapeutic index in patients. Finally, *no drug produces a single effect*, and, depending on the effect being measured, the therapeutic index for a drug will vary. For example, much less codeine is required for cough suppression than for control of pain in 50% of the population, and thus the margin of safety, selectivity, or therapeutic index of codeine is much greater as an antitussive than as an analgesic.

Other Factors That Affect Therapeutic Outcome

The variation in pharmacokinetic and pharmacodynamic parameters that accounts for much of the need to individualize therapy has been discussed. Other factors, listed in Figure 4–1, should also be considered as potential determinants of success or failure of therapy. The following presentation serves as an introduction to these subjects, some of which are also discussed elsewhere in this textbook.

Drug–Drug Interactions. The use of several drugs is often essential to obtain a desired therapeutic objective or to treat coexisting diseases. Examples abound, and the choice of drugs to be employed concurrently can be based on sound pharmacological principles. In the treatment of hypertension, a single drug is effective in only a modest percentage of patients. In the treatment of heart failure, the concurrent use of a diuretic with a vasodilator and/or a cardiac glycoside is often essential to achieve an adequate cardiac output and to keep the patient free from edema. Multiple-drug therapy is the norm in cancer chemotherapy and for the treatment of certain infectious diseases. The goals in these cases are usually to improve efficacy and to delay the emergence of malignant cells or of microorganisms that are resistant to the effects of

available drugs. When physicians use several drugs concurrently, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and, if so, how to take advantage of the interaction if it leads to improvement in efficacy or how to avoid the consequences of an interaction if they are adverse.

A *potential drug interaction* refers to the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone.

The frequency of significant beneficial or adverse drug interactions is unknown. Surveys that include data obtained *in vitro*, in animals, and in case reports tend to predict a frequency of interactions that is higher than actually occurs. While such reports have contributed to skepticism about the overall importance of drug interactions, there certainly are a number of potential interactions of clinical importance, and the physician must be alert to the possibility of their occurrence (McInnes and Brodie, 1988). Estimates of the incidence of clinical drug–drug interactions range from 3 to 5% in patients taking a few drugs to 20% in patients who are receiving 10 to 20 drugs. Because most hospitalized patients receive at least six drugs, the scope of the problem is clearly significant (Steel *et al.*, 1981). Recognition of beneficial effects and recognition and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed, a mental set to attribute unusual events to drugs rather than to disease, and adequate observation of the patient. Automated monitoring of prescription orders in the hospital or outpatient pharmacy may decrease the physician's need to memorize potential interactions. Nevertheless, knowledge of likely mechanisms of drug interactions is the only way the clinician can be prepared to analyze new findings systematically. It is incumbent upon the physician to be familiar with the basic principles of drug–drug interactions in planning a therapeutic regimen. Such reactions are discussed for individual drugs throughout this textbook. (*See also* Hansten, 1985; Rizack and Hillman, 1987; Tatro, 1988.)

Interactions may be either pharmacokinetic (alteration of the absorption, distribution, or disposition of one drug by another) or pharmacodynamic (*e.g.*, interactions between agonists and antagonists at drug receptors). The most important adverse drug–drug interactions occur with drugs that have easily recognizable toxicity and a low therapeutic index, such that relatively small changes in drug effect can have significant adverse consequences. Additionally, drug–drug interactions can be important if the disease being controlled with the drug is serious or potentially fatal if untreated and if therapeutic end points are clearly defined. Thus, major interactions have involved oral anticoagulants, oral hypoglycemics, antibiotics, antiepileptics, antiarrhythmics, and cardiac glycosides.

Pharmacokinetic Drug Interactions. Drugs may interact at any point during their absorption, distribution, metabolism, or excretion; the result may be an increase or decrease in the concentration of drug at the site of action. Since individuals vary in their rate of disposition of any given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant.

The delivery of drug into the circulation may be altered by physicochemical interactions that occur prior to absorption. For example, drugs may interact in an intravenous solution to produce an insoluble precipitate that may or may not be obvious. In the gut, drugs may chelate with metal ions or adsorb to medicinal resins. Thus, Ca^{2+} and other metallic cations contained in antacids are chelated by tetracycline, and the complex is not absorbed. Cholestyramine adsorbs and inhibits the absorption of thyroxine, cardiac glycosides, warfarin, corticosteroids, and probably other drugs. The rate and sometimes the extent of absorption can be affected by drugs that reduce gastric motility, but this is usually of little clinical consequence. Interactions within the gut may be indirect and complex. Antibiotics that alter the gastrointestinal flora can reduce the rate of bacterial synthesis of vitamin K such that the effect of oral anticoagulants, which compete with vitamin K, will be enhanced. If a drug is metabolized by the gastrointestinal microorganisms, antibiotic therapy may result in an increase in the absorption of the drug, as has been demonstrated for some patients receiving digoxin (Lindenbaum *et al.*, 1981).

Many drugs are extensively bound to plasma albumin (acidic drugs) or α_1-acid glycoprotein (basic drugs). In general, only unbound drug is free to exert an effect or to be distributed to the tissues. Thus, displacement of one drug from its binding site by another might be expected to result in a change in drug effects. Although such binding/displacement interactions occur, they are rarely of clinical significance. This is because the displaced drug distributes rapidly into the tissues; the larger the apparent volume of distribution of the drug, the less is the rise in the concentration of free drug in the plasma. Furthermore, following the displacement, more free drug is available for metabolism and excretion. Thus, the body's clearance processes eventually reduce the free drug concentration to that which existed prior to the drug-displacement interaction. As a result, the effect of such an interaction is usually small, transient, and frequently unrecognized. However, the relationship of free drug to the total (bound plus free) drug is changed, and the interpretation of plasma drug assays that measure total drug concentration must be altered.

A few drugs are actively transported to their site of action. For instance, the antihypertensive drugs guanethidine and guanadrel cause inhibition of sympathetic function after being transported into adrenergic neurons by the norepinephrine uptake mechanism. Inhibition of this neuronal uptake system by tricyclic antidepressants and some sympathomimetic amines will inhibit the sympathetic blockade and reduce the antihypertensive effects of guanethidine and guanadrel.

Interactions involving drug metabolism can increase or decrease the amount of drug available for action by inhibition or induction of metabolism, respectively. Inhibition of metabolism is usually more predictable than induction, which is influenced by genetic differences between patients. Examples of drugs that inhibit the metabolism of others include inhibitors of some isozymes of cytochrome P_{450} (cimetidine, amiodarone, phenylbutazone, isoniazid, sodium valproate, and erythromycin), xanthine oxidase (allopurinol), and monoamine oxidase (MAO) inhibitors. Drugs that accelerate the metabolism of other agents include barbiturates, rifampin, phenytoin, carbamazepine, chronic smoking, and certain chlorinated hydrocarbons. The effects of enzyme induction are most obvious when drugs are given orally, because all of the absorbed compound must pass through the liver prior to reaching the systemic circulation. Therefore, even for drugs that have a systemic clearance that is mainly dependent on hepatic blood flow (*e.g.*, propranolol), the amount of drug that escapes metabolism on the first pass will be influenced by enzyme induction. Examples of drugs that are affected by enzyme inducers are oral anticoagulants, quinidine, corticosteroids, low-dose estrogen contraceptives, theophylline, mexiletine, methadone, and some β-adrenergic blocking agents.

The ability of one drug to inhibit the renal excretion of another is dependent on an interaction at active transport sites. Many of the reported interactions occur at the anion transport site, where, for example, probenecid inhibits the excretion of penicillin to cause the desirable effects of elevated plasma concentrations of the antibiotic and a longer half-life. Similarly, the renal elimination of methotrexate is inhibited by probenecid, salicylates, and phenylbutazone, but in this case methotrexate toxicity may result from the interaction. Interactions at the transport site for basic drugs include the inhibition of excretion of procainamide by cimetidine and amiodarone. An interaction at an unknown tubular site causes inhibition of the excretion of digoxin by quinidine, verapamil, and amiodarone. Finally, the excretion of Li^+ can be affected by drugs that alter the ability of the proximal renal tubule to reabsorb Na^+. Thus, clearance of Li^+ is reduced and concentrations of Li^+ in plasma are increased by diuretics that cause volume depletion and by nonsteroidal antiinflammatory drugs that enhance proximal tubular reabsorption of Na^+.

Pharmacodynamic Interactions. There are numerous examples of drugs that interact at a common receptor site or that have additive or inhibitory effects due to actions at different sites in an organ. Such interactions are described throughout this textbook. Frequently overlooked is the multiplicity of effects of many drugs. Thus, phenothiazines are effective α-adrenergic antagonists; many antihistamines and tricyclic antidepressants are potent inhibitors of muscarinic receptors. These "minor" actions of drugs may be the cause of drug interactions.

Other interactions of an apparently pharmacodynamic nature are poorly understood or are mediated indirectly. Halogenated hydrocarbons, including many general anesthetics, sensitize the myocardium to the arrhythmogenic actions of catecholamines. This effect may result from an action on the pathway that leads from adrenergic receptor to effector, but the details are unclear. The striking interaction between meperidine and monoamine oxidase inhibitors to produce seizures and hyperpyrexia may be related to excessive amounts of an excitatory neurotransmitter, but the mechanism has not been elucidated.

One drug may alter the normal internal milieu, thereby augmenting or diminishing the effect of another agent. A well-known example of such an interaction is the enhancement of the toxic effects of digoxin as a result of diuretic-induced hypokalemia.

Summary. Drug–drug interactions are only one of the many factors discussed in this chapter that can alter the patient's response to therapy. The major task of the physician is to determine if an interaction

has occurred and the magnitude of its effect. When unexpected effects are seen, a drug interaction should be suspected. Careful drug histories are important because patients may take over-the-counter drugs, may take drugs prescribed by another physician, or may take drugs prescribed for another patient. Care must be exercised when major changes are made in a drug regimen, and drugs that are not necessary should be discontinued. When an interaction is discovered, the interacting drugs may often be used effectively with adjustment of dosage or other therapeutic modifications.

Fixed-Dose Combinations. The concomitant use of two or more drugs adds to the complexity of individualization of drug therapy. The dose of each drug should be adjusted to achieve optimal benefit. Thus, patient compliance is essential, yet more difficult to achieve. To obviate the latter problem many fixed-dose drug combinations are marketed. The use of such combinations is advantageous only if the ratio of the fixed doses corresponds to the needs of the individual patient.

In the United States, a fixed-dose combination of drugs must be approved by the Food and Drug Administration (FDA) before it can be marketed, even though the individual drugs are available for concurrent use. To be approved, certain conditions must be met. The two drugs must act to achieve a better therapeutic response than either drug alone (*e.g.*, many antihypertensive drug combinations); or one drug must act to reduce the incidence of adverse effects caused by the other (*e.g.*, a diuretic that promotes the urinary excretion of K^+ combined with a K^+-sparing diuretic).

Placebo Effects. The net effect of drug therapy is the sum of the pharmacological effects of the drug and the nonspecific placebo effects associated with the therapeutic effort. Although identified specifically with administration of an inert substance in the guise of medication, placebo effects are associated with the taking of any drug, active as well as inert.

Placebo effects result from the physician–patient relationship, the significance of the therapeutic effort to the patient, and the mental set imparted by the therapeutic setting and by the physician. They vary significantly in different individuals and in any one patient at different times. Placebo effects are commonly manifested as alterations of mood, other subjective effects, and objective effects that are under autonomic or voluntary control. They may be favorable or unfavorable relative to the therapeutic objectives. Exploited to advantage, placebo effects can significantly supplement pharmacological effects and can represent the difference between success and failure of therapy (Brody, 1982).

A placebo (in this context, better termed *dummy medication*) is an indispensable element of the controlled clinical trial. In contrast, a placebo has only a limited role in the routine practice of medicine. Although the inert medication may be an effective vehicle for a placebo effect, the physician–patient relationship is generally preferable. Relief or lack of relief of symptoms upon administration of a placebo is not a reliable basis for determining whether the symptoms have a "psychogenic" or "somatic" origin.

Tolerance. Tolerance may be acquired to the effects of many drugs, especially the opioids, various central nervous system (CNS) depressants, and organic nitrates. When this occurs, *cross-tolerance* may develop to the effects of pharmacologically related drugs, particularly those acting at the same receptor site, and drug dosage must be increased to maintain a given therapeutic effect. Since tolerance does not usually develop equally to all effects of a drug, the therapeutic index may decrease. However, there are also examples of the development of tolerance to the undesired effects of a drug and a resultant increase in its therapeutic index (*e.g.*, tolerance to sedation produced by phenobarbital when used as an anticonvulsant).

The mechanisms involved in the development of tolerance are only partially understood. In animals, tolerance often occurs as the result of induced synthesis of the hepatic microsomal enzymes involved in drug biotransformation; the possible significance of this *drug-disposition* or *pharmacokinetic tolerance* during chronic medication in man is an area of continuing investigation. The most important factor in the development of tolerance to the opioids, barbiturates, ethanol, and organic nitrates is some type of cellular adaptation referred to as *pharmaco-*

dynamic tolerance; multiple mechanisms are involved. Tachyphylaxis, such as that to histamine-releasing agents and to the sympathomimetic amines that act indirectly by releasing norepinephrine, has been attributed to depletion of available mediator, but other mechanisms may also contribute. The subject of tolerance is discussed in more detail in Chapter 22.

Genetic Factors. Genetic factors are the major determinants of the normal variability of drug effects and are responsible for a number of striking quantitative and qualitative differences in pharmacological activity (Vesell, 1986). Many of the genetically determined *quantitative* differences in drug response are due to polygenic influences on drug metabolism, which result in a more or less normal distribution of rates of drug clearance across the population. Recently, however, there has been an increasing number of drugs whose metabolic clearances segregate into distinct groups because the drug biotransformation is controlled by a single gene.

Metabolic processes that are under monogenic control include (1) N-acetyltransferase-catalyzed N-acetylation of isoniazid, procainamide, hydralazine, dapsone, sulfamethazine, sulfasalazine, and some potential carcinogenic amines (Horai and Ishizaki, 1987); (2) cytochrome P_{450}-catalyzed oxidation of several β-adrenergic receptor blocking agents, encainide, propafenone, tricyclic antidepressants, phenformin, and dextromethorphan (Clark, 1985; Gonzalez, *et al.*, 1988); (3) several methyltransferase-catalyzed methylations of thiopurines (mercaptopurine, thioguanine, and azathioprine), aliphatic thiol-containing drugs (captopril and penicillamine), catecholamines, and possibly histamine (Weinshilboum, 1988); and (4) plasma cholinesterase-catalyzed hydrolysis of succinylcholine. The quantitative differences in drug response in patients with these genetically determined differences in drug metabolism are due to greater or lesser amounts of active compound in the body, whether this be the parent drug or an active metabolite.

Genetically determined *qualitative* differences in drug effect occur when a known minor toxic property of a drug assumes an exaggerated importance due to a genetic defect in the ability to avoid the toxicity. For example, individuals who are deficient in glucose-6-phosphate dehydrogenase activity are unable to cope with the oxidative stress produced by some drugs, resulting in drug-induced hemolysis.

The objectives of *pharmacogenetics* include not only identification of differences in drug effects that have a genetic basis but also development of simple methods by which susceptible individuals can be recognized before the drug is administered.

Approach to Individualization

After it has been determined that pharmacotherapy is necessary to modify the symptoms or outcome of a disease, the therapist is faced with two types of decisions: the first is qualitative (the initial choice of a specific drug) and the second quantitative (the initial dosage regimen). Optimal treatment will result only when the physician is aware of the sources of variation in response to drugs, and when the dosage regimen is designed on the basis of the best available data about the diagnosis, severity and stage of the disease, presence of concurrent diseases or drug treatment, and predefined goals of acceptable efficacy and limits of acceptable toxicity. If objectively assessable expectations of drug therapy are not set before therapy is initiated, therapy is likely to be ineffective and continued longer than necessary, unless an obvious adverse effect occurs.

In most clinical settings, the decision about the choice of drug is substantially influenced by the confidence the physician has in the accuracy of his diagnosis and estimates of the extent and severity of disease. Based on the best available information, the physician must decide on an initial drug from a group of reasonable alternatives. The extent of this evaluation is itself dependent on many factors, including a cost–benefit analysis of diagnostic tests, and this must be based on the availability and specificity of alternative therapies (Pauker and Kassirer, 1987). The initial dosage regimen is determined by estimation, if possible, of the pharmacokinetic properties of the drug in the individual patient. The estimate must be based on an appreciation of the variables that are most likely to affect the disposition of the particular drug. These variables have been discussed above (*see* Figure 4–1 and Appendix II). Subsequent adjustments may be aided in some instances by measurement of drug concentrations but must ultimately be

based on whether the regimen is efficacious, either without adverse effects or at an acceptable level of toxicity.

It has been stated above that every therapeutic plan is and should be treated as an experiment. As such, most of the considerations that were specified in the discussion of clinical trials must be applied to individual patients. Of utmost importance is the definition of specific goals of treatment and the means to assess whether these goals are being achieved. Whenever possible, the objective end point should be related as closely as possible to the clinical goals of therapy (*e.g.*, shrinkage of a tumor or eradication of an infection). Many clinical goals are, however, difficult to assess (*e.g.*, the prevention of cardiovascular complications associated with hypertension and diabetes). In such cases it is necessary to set intermediate end points to therapy, such as a reduction in blood pressure or the concentration of glucose in plasma. These intermediate end points are based on demonstrated or assumed correlations with the ultimate clinical benefit. In many cases, such as reduction of the concentration of cholesterol in plasma by drugs or the elimination of asymptomatic ventricular arrhythmias, the link between the intermediate goal and the ultimate goal is controversial.

Certain general considerations apply to the individualization of a drug regimen and the concept of intermediate end points. The value or utility of the regimen obviously needs to be assessed at intervals during the course of therapy. The utility of a regimen can be defined as the benefit it produces plus the dangers of not treating the disease minus the sum of the adverse effects of therapy. Another common expression of the usefulness of a regimen is its ratio of risks to benefits (representing a balance between the efficacious and toxic effects of the drug). A definitive evaluation of the utility of a drug is not easy; nevertheless, some sense of the value of a regimen must be established in the minds of the physician and the patient. Knowledge of the usefulness of a given regimen may be a critical determinant of protracted compliance by the patient to a long-term regimen or logical discontinuation by the physician of a marginally efficacious and risky therapy. It must be remembered that the physician, the patient, and the patient's family may have disparate opinions of the utility of a therapeutic regimen. In one study of antihypertensive therapy where all patients were judged to be improved by the physician, only 48% of the patients considered themselves improved and 8% felt worse. Relatives thought that only 1% of the patients were improved and that 99% had evidence of adverse effects of therapy (Jachuck *et al.*, 1982).

DRUG REGULATION AND DEVELOPMENT

Drug Regulation

The history of drug regulation in the United States reflects the growing involvement of governments in most countries to ensure some degree of efficacy and safety in marketed medicinal agents. The first act, the Federal Food and Drug Act of 1906, was concerned with the interstate transport of adulterated or misbranded foods and drugs. There were no obligations to establish drug efficacy and safety. The federal act was amended in 1938, following the deaths of about 100 children that resulted from the marketing of a solution of sulfanilamide in diethylene glycol, an excellent but highly toxic solvent. The amended act, the enforcement of which was entrusted to the FDA, was primarily concerned with the truthful labeling and safety of drugs. Toxicity studies were required, as well as approval of a new drug application (NDA), before a drug could be promoted and distributed. However, no proof of efficacy was required, and extravagant claims for therapeutic indications were commonly made. Drugs could go from the laboratory to clinical testing without approval by the FDA.

In this relatively relaxed atmosphere, research in basic and clinical pharmacology burgeoned in both industrial and academic laboratories. The result was a flow of new drugs, called "wonder drugs" by the lay press, for the treatment of both infectious and organic disease. Because efficacy was not rigorously defined, a number of therapeutic claims could not be supported by data. The risk-to-benefit ratio was seldom mentioned, but it emerged in dramatic fashion early in the 1960s. At that time thalidomide, a hypnotic with no obvious advantage over other drugs in its class, was introduced in the European market. After a short period, it became apparent that the incidence of a relatively rare birth defect, phocomelia, was increasing. It soon reached epidemic proportions, and retrospective epidemiological research firmly established the causative agent to be thalidomide taken early in the course of pregnancy. The reaction to the dramatic demonstration of the teratogenicity of a needless drug was

worldwide. In the United States it resulted in the Harris–Kefauver Amendments to the Food, Drug, and Cosmetic Act in 1962.

The Harris–Kefauver Amendments are sound legislation. They require sufficient pharmacological and toxicological research in animals before a drug can be tested in man. The data from such studies must be submitted to the FDA in the form of an application for an investigational new drug (IND) before clinical studies can begin. Three phases of clinical testing (*see* below) have evolved to provide the data that are used to support a new drug application. For drugs introduced after 1962, proof of efficacy is required, as is documentation of relative safety in terms of the risk-to-benefit ratio for the disease entity to be treated. The 1962 amendments also required manufacturers to provide data to support the claims of efficacy for all drugs marketed between 1938 and 1962.

The provisions of the Harris–Kefauver amendments have greatly increased the time and the cost required to market a new drug. Moreover, although the law requires action on the part of the FDA within a period of 6 months, an NDA may be returned to the applicant for additional basic or clinical research, so that the period actually required for approval of an NDA is on the order of 2 to 3 years. The total time of drug development from the time of filing of an IND application to final approval averages 8 to 9 years (Kaitin *et al.*, 1987). The result has been an increase in the inherent tension that exists between the FDA, which is motivated to protect the public health, and the drug developers, who are motivated to market effective and profitable drug products. Additionally, medical practitioners have criticized the FDA for delaying the approval of new drugs, whereas some consumer groups demand the recall of drugs that may play an important part in the therapeutic regimen of appropriately selected patients. In this climate, the FDA has the difficult task of balancing the requirement to ensure the safety of new drugs with the needs of society for useful medications to be made available in a timely manner. This dilemma has been brought into sharp focus recently by the demands of patients with acquired immunodeficiency syndrome (AIDS) for new and effective therapies. In response to the needs of patients with AIDS and other life-threatening illnesses, the FDA is moving on several fronts (Young *et al.*, 1988). First, the FDA has initiated new "treatment" IND regulations that allow patients with life-threatening diseases for which there is no satisfactory alternative treatment to receive drugs for therapy prior to general marketing if there is limited evidence of drug efficacy without unreasonable toxicity (Figure 4–4). Second, the agency has established a priority review system for potentially useful AIDS-related drugs to assure that the review process is expedited. Finally, the FDA is attempting to be involved more actively in drug development in order to facilitate the approval of drugs designed to treat life-threatening and severely debilitating diseases. By working with the pharmaceutical industry throughout the period of clinical drug development instead of involving themselves only at the end of this process, the FDA hopes to reduce the time from submission of an IND application to the approval of an NDA. This streamlining process will be accomplished by the interactive design of well-planned, focused clinical studies. Sufficient data should then be available earlier in the development process to allow a risk–benefit analysis and a possible decision for approval. In some cases this system may reduce or obviate the need for phase-3 testing prior to approval. Coupled with this expedited development process will be the requirement, when appropriate, for postmarketing studies to answer remaining issues of risks, benefits, and optimal uses of the drug (*Federal Register,* 1988). This new initiative by the FDA is based on the assumption that society is more willing to accept unknown risks from drugs used to treat life-threatening or debilitating diseases. As long as the patient's safety can be reasonably ensured, the new plans to accelerate the drug-development process should prove beneficial to patients with such illnesses.

A seemingly contradictory directive to the FDA is also contained in the Food, Drug, and Cosmetic Act—that is, the FDA cannot interfere with the practice of medicine. Thus, once the efficacy of a new agent has been proven in the context of acceptable toxicity, the drug can be marketed. The physician is then allowed to determine its most appropriate use. However, physicians must realize that new drugs are inherently more risky because of the relatively small amount of data about their effects. Yet there is no practical way to increase knowledge about a drug before it is marketed. A systematic method for postmarketing surveillance is an indispensable requirement for early optimization of drug use.

Before a drug can be marketed, a package insert for use by physicians must be prepared. This is a cooperative effort between the FDA and the pharmaceutical company. The insert usually contains basic pharmacological information, as well as essential clinical information in regard to approved indications, contraindications, precautions, warnings, adverse reactions, usual dosage, and available preparations. Promotional materials cannot deviate from information contained in the insert.

DRUG DEVELOPMENT

Except for concern about the so-called drug lag (Kennedy, 1978) and governmental interference with the practice of medicine, the average physician has not considered it important to understand the process of drug development. Yet an appreciation of this process is necessary if the therapist wishes to have the ability to estimate the risk-to-benefit ratio of a drug and to realize the limitations of the data that support the efficacy and safety of a marketed product.

By the time an IND application has been initiated and a drug reaches the stage of testing in man, its pharmacokinetic, pharmacodynamic, and toxic properties have been evaluated *in vitro* and in several species of animals in accordance with regulations and guidelines published by the FDA. Although the value of many requirements for

Figure 4–4. *The phases of drug development in the United States.* (Sources: Smith, 1978; Kaitin *et al.*, 1987; Young *et al.*, 1988.)

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preclinical testing is self-evident, such as those that screen for direct toxicity to organs and characterize dose-related effects, the value of others is controversial, particularly because of the well-known interspecies variation in the effects of drugs. Interestingly, although many of the preclinical tests have not been convincingly shown to predict effects that are eventually observed in man, the risk of cautious testing of a new drug is surprisingly low.

Trials of drugs in man in the United States are generally conducted in three phases that must be completed before an NDA can be submitted to the FDA for review; these are outlined in Figure 4–4. Although assessment of risk is a major objective of such testing, this is far more difficult than is the determination of whether a drug is efficacious for a selected clinical condition. Usually about 500 to 3000 carefully selected patients receive a new drug during phase-3 clinical trials. At most, only a few hundred are treated for more than 3 to 6 months, regardless of the likely duration of therapy that will be required in practice. Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase-3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are only detectable after the drug is used broadly. The same can be more convincingly stated about most of the effects of drugs on children or the fetus, where premarketing experimental studies are restricted. It is for these reasons that many countries, including the United States, have established systematic methods for the surveillance of the effects of drugs after they have been approved for distribution (Joint Commission on Prescription Drug Use, 1980; Venning, 1983; Strom, 1987a; *see also* below).

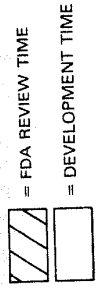

Figure 4–4. *The phases of drug development in the United States.* (Sources: Smith, 1978; Kaitin *et al.*, 1987; Young *et al.*, 1988.)

ADVERSE DRUG REACTIONS AND DRUG TOXICITY

Any drug, no matter how trivial its therapeutic actions, has the potential to do harm. Adverse reactions are a cost of modern medical therapy. Although the mandate of the FDA is to ensure that drugs are safe and effective, both of these terms are relative. The anticipated benefit from any therapeutic decision must be balanced by the potential risks. Patients, to a greater extent than physicians, are unaware of the limitations of the premarketing phase of drug development in defining even relatively common risks of new drugs. Since only a few thousand patients are exposed to experimental drugs in more or less controlled and well-defined circumstances during drug development, adverse drug effects that occur as frequently as 1 in 1000 patients may not be detected prior to marketing. Postmarketing surveillance of drug usage is thus imperative to detect infrequent but significant adverse effects.

Several strategies exist to detect adverse reactions after marketing of a drug, but debate continues about the most efficient and effective method. Formal approaches for estimation of the magnitude of an adverse drug effect are the follow-up or "cohort" study of patients who are receiving a particular drug and the "case–control" study, where the potential for a drug to cause a particular disease is assessed. Cohort studies can estimate the incidence of an adverse reaction, but they cannot, for practical reasons, discover rare events. To have any significant advantage over the premarketing studies, a cohort study must follow at least 10,000 patients who are receiving the drug in order to detect with 95% confidence one event that occurs at a rate of 1 in 3300, and the event can be attributed to the drug only if it does not occur spontaneously in the control population. If the adverse event occurs spontaneously in the control population, substantially more patients and controls must be followed to establish the drug as the cause of the event (Rawlins, 1984; Strom, 1987a). Case–control studies, on the other hand, can discover rare drug-induced events. However, it may be difficult to establish the appropriate control group (Feinstein and Horwitz, 1988), and a case–control study cannot establish the incidence of an adverse drug effect. Furthermore, the suspicion of a drug as a causative factor in a disease must be the impetus for the initiation of such case–control studies.

The magnitude of the problem of adverse reactions to marketed drugs is difficult to quantify. It has been estimated that 3 to 5% of all hospitalizations can be attributed to adverse drug reactions, resulting in 300,000 hospitalizations annually in the United States. Once hospitalized, patients have about a 30% chance of an untoward event related to drug therapy, and the risk attributable to each course of drug therapy is about 5%. The chance of a life-threatening drug reaction is about 3% per patient in the hospital and about 0.4% per each course of

therapy (Jick, 1984). On a university medical service where severely ill patients and patients with complicated courses of disease are treated, adverse reactions to drugs were found to be the most common cause of iatrogenic disease (Steel *et al.*, 1981).

Because of the shortcomings of both cohort and case–control studies, other approaches must be used. Spontaneous reporting of adverse reactions has proven to be an effective way to generate an early signal that a drug may be causing an adverse event (Rawlins, 1988; Rossi *et al.*, 1988). It is the only practical way to detect rare events, events that occur after prolonged use of drug, adverse effects that are delayed in appearance, and many drug–drug interactions (Edlavitch, 1988). In the past few years considerable effort has gone into improving the reporting system in the United States, and the number of reports has increased recently (Faich *et al.*, 1988). Still, the voluntary reporting system in the United States is deficient when compared with the legally mandated systems of the United Kingdom, Canada, New Zealand, Denmark, and Sweden (Rogers *et al.*, 1988). Most physicians feel that detecting adverse reactions is a professional obligation, but relatively few actually report such reactions. Over 40% of physicians are not aware that the FDA has a reporting system for adverse drug reactions, even though the system has been repeatedly publicized in major medical journals.

The most important spontaneous reports are those that describe serious reactions, whether they have been described previously or not. Reports on newly marketed drugs are the most significant, even though the physician may not be able to attribute a causal role to a particular drug. The major use of this system is to provide early warning signals of unexpected adverse effects that can then be investigated by more formal techniques. However, the system also serves to monitor changes in the nature or frequency of adverse drug reactions due to aging of the population, changes in the disease itself, or the introduction of new, concurrent therapies. The primary sources for the reports are responsible, alert physicians; other potentially useful sources are nurses, pharmacists, and students in these disciplines. In addition, hospital based pharmacy and therapeutics committees and quality assurance committees frequently are charged with monitoring adverse drug reactions in hospitalized patients, and reports from these committees should be forwarded to the FDA (Edlavitch, 1988). The simple, one-page forms for reporting are now readily available as the last page of the *Physicians' Desk Reference* and *AMA Drug Evaluations* and are mailed to all physicians at least yearly as part of the FDA "Drug Bulletin." Additionally, physicians may contact the pharmaceutical manufacturer and/or write to the Office of Epidemiology and Biostatistics (HFN-700), Center for Drug Evaluation and Research, Food and Drug Administration, Parklawn Building, Rockville, MD 20857 (Faich *et al.*, 1988).

As with drug interactions, classification of adverse effects of drugs according to information about their causes provides a framework for the transfer of principles to the clinical setting. Such classification appears in Chapter 3. In addition, the clinician obviously also needs to know the frequencies and types of untoward effects caused by each individual drug prescribed; such information is presented throughout this textbook.

GUIDE TO THE "THERAPEUTIC JUNGLE"

The flood of new drugs in recent years has provided many dramatic improvements in therapy, but it has also created a number of problems of equal magnitude. Not the least of these is the "therapeutic jungle," the term used to refer to the combination of the overwhelming number of drugs, the confusion over nomenclature, and the associated uncertainty of the status of many of these drugs. A reduction in the marketing of close congeners and drug mixtures and an improvement in the quality of advertising are important ingredients in the remedy for the "therapeutic jungle." However, physicians can also contribute to the remedy by employing nonproprietary rather than proprietary names whenever appropriate, by using prototypes both as an instructional device and in clinical practice, by

adopting a properly critical attitude toward new drugs, and by knowing and making use of reliable sources of pharmacological information. Most important, they should develop a "way of thinking about drugs" based upon pharmacological principles.

Drug Nomenclature. The existence of many names for each drug, even when reduced to a minimum, has led to a lamentable and confusing situation in drug nomenclature. In addition to its formal *chemical* name, a new drug is usually assigned a *code* name by the pharmaceutical manufacturer. If the drug appears promising and the manufacturer wishes to place it on the market, a *United States Adopted Name* (USAN) is selected by the USAN Council, which is jointly sponsored by the American Medical Association, the American Pharmaceutical Association, and the United States Pharmacopeial Convention, Inc. This *nonproprietary* name is often referred to as the *generic* name. This term has become entrenched, but by definition it should be more properly reserved to designate a chemical or pharmacological class of drugs, such as sulfonamides or sympathomimetics. If the drug is eventually admitted to *The United States Pharmacopeia* (*see* below), the USAN becomes the *official* name. However, the nonproprietary name and the official name of an older drug may differ. Subsequently, the drug will also be assigned a *proprietary* name or *trademark* by the manufacturer. If the drug is marketed by more than one company, it may have several proprietary names. If mixtures of the drug with other agents are marketed, each such mixture may also have a separate proprietary name.

There is increasing worldwide adoption of the same name for each therapeutic substance. For newer drugs, the USAN is usually adopted for the nonproprietary name in other countries, but this is not true for older drugs. International agreement on drug names is mediated through the World Health Organization and the pertinent health agencies of the cooperating countries.

One area of continued confusion and ambiguity is the designation of the stereochemical composition in the name of a drug. The nonproprietary names usually give no indication of the drug's stereochemistry, except for a few drugs such as levodopa and dextroamphetamine. Even the chemical names cited by the USAN Council are often ambiguous. Physicians and other medical scientists are frequently ignorant about drug stereoisomerism and are likely to remain so until the system of nonproprietary nomenclature incorporates stereoisomeric information (Gal, 1988).

The nonproprietary or official name of a drug should be used whenever possible, and such a practice has been adopted in this textbook. The use of the nonproprietary name is clearly less confusing when the drug is available under multiple proprietary names and when the nonproprietary name more readily identifies the drug with its pharmacological class. The best argument for the proprietary name is that it is frequently more easily pronounced and remembered as a result of advertising. For purposes of identification, representative proprietary names, designated by SMALLCAP TYPE, appear throughout the text in chapter sections dealing with preparations as well as in the index. This list is far from complete, since the number of proprietary names for a single drug may be large and since proprietary names differ from country to country.

The Drug Price Competition and Patent Term Restoration Act of 1984 allows more generic versions of brand-name drugs to be approved for marketing. When the physician prescribes drugs, the question arises as to whether the nonproprietary name or a proprietary name should be employed. In practically all states, a pharmacist may substitute a preparation that is equivalent unless the physician indicates "no substitution" on the prescription. Likewise, if the nonproprietary name of a drug is employed, the physician can specify the manufacturer. In view of the discussion above on the individualization of drug therapy, it is understandable why a physician who has carefully adjusted the dose of a drug to a patient's individual requirements for chronic therapy may be reluctant to surrender control over the source of the drug that the patient receives (Strom, 1987b).

Based on a number of considerations, such as the frequency of use of a drug that is only available from a single manufacturer, the cost of filling a prescription, and

the mark-up of the pharmacist, it appears as though the overall savings to society of prescribing the least expensive nonproprietary preparation is about 5% (*see* Trout and Lee, 1981). Of course, savings in individual situations can be very much greater. On the other hand, the lower wholesale cost of the nonproprietary preparation is sometimes not passed on to the consumer (Bloom *et al.*, 1986). More importantly, prescribing by nonproprietary name could result in the patient receiving a preparation of inferior quality or of uncertain bioavailability, and therapeutic failures due to decreased bioavailability have been reported (Strom, 1987b). To address this issue, the FDA has established standards for bioavailability and compiled information about the interchangeability of drug products; unfortunately, data on therapeutic equivalence based on clinical studies do not exist for most of these products (*Approved Prescription Drug Products with Therapeutic Evaluations,* 1987). In spite of this limitation, potential cost savings to the individual patient and simplification of the "therapeutic jungle" dictate that nonproprietary names be used when prescribing, except for drugs with a low therapeutic index and known differences in bioavailability among marketed products (*Medical Letter,* 1986).

Use of Prototypes. It is obviously crucial for the physician to be thoroughly familiar with the pharmacological properties of a drug before it is administered. It follows that the patient will benefit if the physician avoids the temptation to choose from many different drugs for the patient's regimen. A physician's needs for therapeutic agents can usually be satisfied by thorough knowledge of one or two drugs in each therapeutic category. Inevitably, a small number of drugs can be used more effectively. When the clinical setting calls for a drug that the physician uses infrequently, he or she should feel obligated to learn about its effects, to use great caution in its administration, and to apply appropriate procedures in monitoring its effects.

For teaching purposes in this textbook, the confusion created by the welter of similar drugs is reduced by restricting major attention to prototypes in each pharmacological class. Focusing on the representative drugs results in better characterization of a class as a whole, and thereby permits sharper recognition of the occasional member that possesses unique properties. A teaching prototype is often the agent most likely to be employed in clinical use, but this is not always true. A particular drug may be retained as the prototype, even though a new congener is clinically superior, either because more is known about the older drug or because it is more illustrative for the entire class of agents.

Attitude toward New Drugs. A reasonable attitude toward new drugs is summarized by the adage that advises the physician to be "neither the first to use a new drug nor the last to discard the old." Only a minor fraction of new drugs represents a significant therapeutic advance. The limitation of information about toxicity and efficacy at the time of release of a drug has been emphasized above, and this is particularly pertinent to comparisons with older agents in the same therapeutic class. Nevertheless, the important advances in therapeutics in the last 50 years emphasize the obligation to keep abreast of significant advances in pharmacotherapy.

SOURCES OF DRUG INFORMATION

The physician's need for objective, concise, and well-organized information on drugs is obvious. Among the available sources are textbooks of pharmacology and therapeutics, leading medical journals, drug compendia, professional seminars and meetings, and advertising. Despite this cornucopia of information, responsible medical spokesmen insist that most practicing physicians are unable to extract the objective and unbiased data required for the practice of rational therapeutics (*see* Task Force, 1969).

Depending on their aim and scope, pharmacology textbooks provide (in varying proportions) basic pharmacological principles, critical appraisal of useful categories of therapeutic agents, and detailed descriptions of individual drugs or prototypes that serve as standards of reference for assess-

ing new drugs. In addition, pharmacodynamics and pathological physiology are correlated. Therapeutics is considered in virtually all textbooks of medicine, but often superficially. For obvious reasons, textbooks cannot contain information on the most recently introduced drugs.

The source of information described as most often used by physicians in an industry survey is the *Physicians' Desk Reference* (PDR). The brand-name manufacturers whose products appear support this book. No comparative data on efficacy, safety, or cost are included. The information is identical to that contained in drug package inserts, which are largely based on the results of phase-3 testing; its primary value is thus in learning what indications for use of a drug have been approved by the FDA.

There are, however, several inexpensive, unbiased sources of information on the clinical uses of drugs that are preferable to the industry-supported PDR. All recognize that the physician's legitimate use of a drug in a particular patient is not limited by FDA-approved labeling in the package insert. *The United States Pharmacopeia Dispensing Information* (USPDI), first published in 1980, comes in two volumes. One, *Drug Information for the Health Care Provider*, consists of drug monographs that contain practical, clinically significant information aimed at minimizing the risks and enhancing the benefits of drugs. Monographs are developed by USP staff and are reviewed by advisory panels and other reviewers. The *Advice for the Patient* volume is intended to reinforce, in lay language, the oral consultation provided by the therapist, and this may be provided to the patient in written form. It is planned that the volumes will be published frequently. The *American Hospital Formulary Service* (AHFS), published by the American Society of Hospital Pharmacists, is a collection of monographs that are kept current by periodic supplements. The monographs are written on a single drug; there are also general discussions of drugs that are included in a defined class. *AMA Drug Evaluations*, compiled by the American Medical Association Department of Drugs in cooperation with the American Society for Clinical Pharmacology and Therapeutics, includes general information on the use of drugs in special settings (*e.g.*, pediatrics, geriatrics, renal insufficiency, *etc.*) and reflects the consensus of a panel on the effective clinical use of therapeutic agents. *Facts and Comparisons* (Olin, 1988), published by a division of J. B. Lippincott Company, is also organized by pharmacological classes and is updated monthly. Information in monographs is presented in a standard format and incorporates FDA-approved information, which is supplemented with current data obtained from the biomedical literature. A useful feature is the comprehensive list of preparations with a "Cost Index," an index of the average wholesale price for equivalent quantities of similar or identical drugs.

Industry promotion, in the form of direct-mail brochures, journal advertising, displays, professional courtesies, or the detail person or pharmaceutical representative, is intended to be persuasive rather than educational. The pharmaceutical industry cannot, should not, and indeed does not purport to be responsible for the education of physicians in the use of drugs.

Over 1500 medical journals are published regularly in the United States. However, of the two to three dozen medical publications with circulations in excess of 70,000 copies, the great majority are sent to physicians free of charge and paid for by the industry. In addition, special supplements of some peer-reviewed journals are entirely supported by a single drug manufacturer whose product is prominently featured and favorably described. Objective journals, which are not supported by drug manufacturers, include *Clinical Pharmacology and Therapeutics*, which is devoted to original articles that evaluate the actions and effects of drugs in man, and *Drugs*, which publishes timely reviews of individual drugs and drug classes. The *New England Journal of Medicine*, *Annals of Internal Medicine*, *Journal of the American Medical Association*, *Archives of Internal Medicine*, *British Medical Journal*, *Lancet*, and *Postgraduate Medicine* offer timely therapeutic reports and reviews. Three publications deserve special emphasis here because they exemplify effective attempts to provide objective drug information in easily assimilable form.

These are *The Medical Letter, Clin-Alert,* and *Rational Drug Therapy. The Medical Letter* provides summaries of scientific reports and consultants' evaluations of the safety, efficacy, and rationale for use of a drug. *Clin-Alert* consists mainly of abstracts from the literature on drugs. *Rational Drug Therapy* presents a monthly review article on groups of drugs or on the management of specific conditions.

The United States Pharmacopeia (USP) and *The National Formulary* (NF) were recognized as "official compendia" by the Federal Food and Drug Act of 1906. The approved therapeutic agents used in medical practice in the United States are described and defined with respect to source, chemistry, physical properties, tests for identity and purity, assay, and storage. The two official compendia are now published in a single volume.

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CHAPTER

60 ADRENOCORTICOTROPIC HORMONE; ADRENOCORTICAL STEROIDS AND THEIR SYNTHETIC ANALOGS; INHIBITORS OF THE SYNTHESIS AND ACTIONS OF ADRENOCORTICAL HORMONES

Robert C. Haynes, Jr.

Adrenocorticotropic hormone (ACTH, corticotropin) and the steroids of the adrenal cortex are considered together in this chapter because the primary physiological and pharmacological effects of ACTH result from the secretion of adrenocortical steroids. Biologically active synthetic analogs of the adrenocorticosteroids are also included, as are substances that alter the pattern of secretion of the adrenal cortex by inhibiting certain biosynthetic reactions. Synthetic steroids that inhibit the action of glucocorticoids are discussed here; agents that inhibit the action of aldosterone are presented in Chapter 28.

History. The physiological significance of the adrenals began to be appreciated when Addison (1855) described the clinical syndrome resulting from destructive disease of the adrenal glands. His observations interested the physiologist Brown-Séquard (1856), who did the pioneer experiments on the effects of adrenalectomy and concluded that the adrenal glands are essential to life.

By the third decade of this century it was generally recognized that the cortex rather than the medulla is the life-maintaining portion of the gland. The complex nature of adrenocortical deficiency was dramatized in the 1930s by the partisan character of research groups oriented to study either the imbalance of electrolytes or the defects in carbohydrate metabolism present in the deficient state. Renal loss of Na^+ was convincingly demonstrated to be a characteristic of adrenocortical insufficiency by Harrop and associates (1933) as well as by Loeb and coworkers (1933). Equally convincing was the demonstration of a depletion of carbohydrate stores (Cori and Cori, 1927). Furthermore, hypoglycemia could be corrected by adrenocortical extracts (Britton and Silvette, 1931). Glucose and glycogen, formed under the influence of the adrenal cortex during fasting, appeared to be derived from tissue protein (Long *et al.*, 1940). From these studies emerged the concepts of two types of adrenocortical hormones. The mineralocorticoids primarily regulate electrolyte homeostasis, and the glucocorticoids are hormones concerned with carbohydrate metabolism. This concept of the dichotomy of "salt" and "sugar" hormones (mineralocorticoids and glucocorticoids) has proved useful and survives at the present time in a modified form.

In 1932, the neurosurgeon Cushing described the syndrome of hypercorticism, which bears his name (Cushing, 1932). The cases Cushing described were those of "pituitary basophilism," recognized subsequently as being a condition characterized by hypersecretion of ACTH. The symptom complex is now known to result from excessive plasma concentrations of adrenocortical hormones, regardless of whether they originate endogenously or as the consequence of therapeutic intervention.

The preparation of adrenocortical extracts with a reasonable degree of activity was first accomplished in 1930. By 1942, organic chemists had isolated, crystallized, and elucidated the structures of 28 steroids from the adrenal cortex (Reichstein and Shoppee, 1943). Five of these compounds—cortisol (hydrocortisone), cortisone, corticosterone, 11-dehydrocorticosterone, and 11-desoxycorticosterone—were demonstrated to be biologically active. Another decade passed before the principal mineralocorticoid was discovered. Deming and Luetscher (1950) found that extracts of urine from patients with edema induced Na^+ retention and K^+ excretion in adrenalectomized rats. The definitive evidence for the source of the active material was provided by Tait and coworkers (1952), who purified the compound with this activity from adrenocortical extracts. The substance was crystallized, the structure was established, and the hormone named *aldosterone* (Simpson *et al.*, 1954).

In this same era the role of the adenohypophysis was being elucidated by other investigators. The classical studies of Foster and Smith (1926) established the fact that hypophysectomy results in atrophy of the adrenal cortex. By 1933, it had been demonstrated that cell-free extracts of the anterior pituitary had a stimulating effect upon the adrenal cortex of the hypophysectomized animal. Further chemical fractionation of such extracts led to the isolation of a hormone, ACTH, that acted selectively to cause chemical and morphological changes in the adrenal cortex (*see* Astwood *et al.*,

1952), and its structure was established by Bell and coworkers (1956). The rate of release of ACTH from the adenohypophysis was shown to be determined by the balance of the inhibitory effects of the hormones of the adrenal cortex (Ingle *et al.*, 1938) and the excitatory effects of the nervous system.

A detailed analysis of the morphology of the adrenal cortex had suggested to Swann (1940) and to Deane and Greep (1946) that the zona glomerulosa of the adrenal cortex functions relatively independently of the pituitary. Following hypophysectomy, the zona glomerulosa thickens, whereas the fasciculata shrinks markedly and the reticularis disappears almost entirely. These morphological observations, together with the fact that the hypophysectomized rat, in contrast to the adrenalectomized animal, can survive without salt therapy, prompted Swann as well as Deane and Greep to assign to the zona glomerulosa the specific function of autonomously elaborating a hormone regulating electrolyte balance. This hormone is now known to be aldosterone.

In 1949, Hench and coworkers announced the dramatic effects of cortisone and ACTH in the treatment of rheumatoid arthritis. As early as 1929, Hench had been impressed by the fact that arthritic patients, when pregnant or jaundiced, experienced a temporary remission; he believed that a metabolite was responsible for the remission. The possibility that the antirheumatic substance might be an adrenocortical hormone was entertained, and as soon as cortisone was available in sufficient quantity it was tested in a case of acute rheumatoid arthritis. Fortunately, an adequate dose was employed and the response was dramatic. Thereafter, the salutary effects of ACTH were also demonstrated (Hench *et al.*, 1949). Soon, therapeutic applications were extended to other diseases, with results to be presented later in this chapter. The impact upon the medical world can be appreciated from the fact that, in the year following the first published report of the efficacy of cortisone in the treatment of rheumatoid arthritis, the Nobel Prize in Medicine was jointly awarded to Kendall and Reichstein, who were responsible for much of the basic chemical research that led to the synthesis of the steroid, and to Hench, whose contribution has just been described.

ADRENOCORTICOTROPIC HORMONE

Chemistry. The structure of human ACTH, a peptide of 39 amino acid residues, is shown in Figure 60–1. Loss of one amino acid from the amino-terminal end of the molecule by hydrolytic cleavage results in complete loss of biological activity. In contrast, a number of amino acids may be split off the carboxyl-terminal end with no effect on potency. A 20-amino acid peptide (sequence 1 through 20, Figure 60–1) retains the activity of the parent hormone. The structure–activity relationship of ACTH has been reviewed by Otsuka and Inouye (1975). The structural relationships between ACTH, endorphins, lipotropins, and the melanocyte-stimulating hormones are discussed in Chapter 56.

Actions on the Adrenal Cortex. ACTH stimulates the human adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. In the absence of the adenohypophysis, the adrenal cortex undergoes atrophy and the rates of secretion of cortisol and corticosterone, which are markedly reduced, do not respond to otherwise-effective stimuli. Although ACTH can stimulate secretion of aldosterone, the rate of secretion is relatively independent of the adenohypophysis, which explains the nearly normal electrolyte balance in the hypophysectomized animal. The zona glomerulosa is the least affected by atrophic changes that follow hypophysectomy, and it is the glomerulosa that is mainly responsible for the elaboration of aldosterone.

Prolonged administration of large doses of ACTH induces hyperplasia and hypertrophy of the adrenal cortex with continuous high output of cortisol, corticosterone, and androgens.

Mechanism of Action. ACTH acts to stimulate the synthesis of adrenocortical hormones. It is believed that the diffusion of preformed hormones from the cortical cells into the circulation is not affected by ACTH. ACTH, as do many other hormones, controls its target tissue through the agency of cyclic AMP. Thus, ACTH reacts with its specific receptor on the adrenal cell plasma membrane. The activity of adenylyl cyclase is stimulated and both the rate of formation and the concentration of cy-

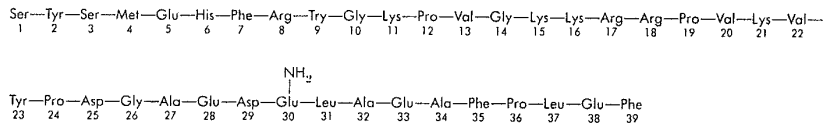

Figure 60–1. *Amino acid sequence of human ACTH.*

Ovine, porcine, and bovine ACTHs differ from human ACTH only at amino acid positions 25, 31, and 33.

clic AMP is increased in adrenocortical cells. Cyclic AMP has been shown to stimulate steroidogenesis (Haynes *et al.*, 1959) and to maintain the weight of the adrenal gland after hypophysectomy (Ney, 1969). Therefore, it is believed that cyclic AMP mediates both the acute and long-term effects of ACTH on the adrenal cortex.

The principal metabolic site at which steroidogenesis is regulated by the cyclic nucleotide is the oxidative cleavage of the side chain of cholesterol, the reaction that results in the formation of pregnenolone (Figure 60–2). Although this step is rate-limiting in the sequence of reactions that leads to the formation of adrenal steroid hormones, it is now generally accepted that the availability of cholesterol is the factor that limits the rate in intact mitochondria (Kahnt *et al.*, 1974). The enzyme that catalyzes the cleavage of cholesterol's side chain is localized to the inner membrane of mitochondria in the adrenal, and ACTH acts in several ways to provide the substrate at this site. ACTH, via cyclic AMP–dependent phosphorylation, activates the cholesterol esterase that hydrolyzes esterified cholesterol within the cell (Beckett and Boyd, 1975; Pittman and Steinberg, 1977), and ACTH stimulates cholesterol uptake from plasma lipoproteins (Koper *et al.*, 1985). However, the most important mechanism is the facilitation of the transfer of cholesterol from the outer to the inner mitochondrial membrane. This transfer is thought to be mediated by a carrier protein that has an extremely short half-life, such that inhibitors of protein synthesis block steroidogenesis and its stimulation by ACTH almost immediately. The exact mechanism by which ACTH accelerates intramitochondrial transfer of cholesterol remains unknown.

The trophic effects of ACTH on the adrenal cortex are most evident in the induction of the enzymes of steroidogenesis. This effect results from the enhanced transcription of specific genes that encode the individual enzymes (Simpson and Waterman, 1988). The regulation of the adrenal cortex by ACTH has been reviewed by Privalle and colleagues (1987).

Extraadrenal Effects of ACTH. Large doses of ACTH given to adrenalectomized animals cause a number of metabolic changes, including ketosis, lipolysis, hypoglycemia (early after administration), and resistance to insulin (late after administration). These extraadrenal effects are of doubtful physiological significance, because of the large doses that are required.

Natural and synthetic corticotropins darken the isolated skin of the frog; this is not surprising since the amino acid sequence, 1 through 13, is identical with that of the melanocyte-stimulating hormone, α-MSH. Large doses of highly purified α-MSH and ACTH have been demonstrated to darken the skin of adrenalectomized human subjects. The hyperpigmentation of the skin that occurs in Addison's disease is thought to result from the high concentrations of ACTH that circulate in this condition (Thody, 1977; *see* Chapter 56).

Regulation of the Secretion of ACTH. The fluctuations in the rates of secretion of cortisol, corticosterone, and, to some extent, aldosterone are determined by the fluctuations in the release of ACTH from the adenohypophysis. The adenohypophysis, in turn, is under the influence of the nervous system and negative-feedback control exerted by corticosteroids (*see* Dallman *et al.*, 1987).

Nervous System: The Final Common Path. Stimuli that induce release of ACTH travel by neural paths converging on the median eminence of the hypothalamus. The functional link between the median eminence and the adenohypophysis, the final common path, is vascular. In response to an appropriate stimulus, corticotropin-releasing factor (CRF), a peptide of 41 amino acid residues, is elaborated at neuronal endings in the median eminence and transported in the hypophyseal-portal vessels to the adenohypophysis, where it stimulates the synthesis and secretion of ACTH. The effects of CRF are mediated by activation of adenylyl cyclase and the cyclic AMP–dependent protein kinase (Aquilera *et al.*, 1983). The isolation and synthesis of ovine CRF were reported by Vale and coworkers (1981), and the structure of human CRF was determined shortly thereafter (Shibahara *et al.*, 1983). CRF increases the concentrations of ACTH and cortisol in plasma when given intravenously to man. Intravenous injection of 100 μg of CRF results in an exaggerated response in patients with Cushing's syndrome caused by pituitary hyperfunction or ectopic CRF production. This test is thus useful in determining the cause of the disease and helps to rule out ectopic production of ACTH or functional tumors of the adrenal cortex as responsible (Müller *et al.*, 1987).

ACTH is synthesized in basophilic cells of the adenohypophysis and, like many other peptide hormones, it is derived from a larger precursor; the prohormone is a glycoprotein of about 30,000 molecular weight. The precursor of ACTH includes the sequences of MSH, the lipotropins, and the endorphins. In man, the role of these three groups of active peptides remains conjectural. The complex processing of the prohormone to ACTH, β-lipotropin, and other peptides has been studied extensively (*see* Imura, 1987).

Negative Feedback of the Corticosteroids (Cortisol and Corticosterone). Administration of certain corticosteroids suppresses the secretion of ACTH, reduces the store of ACTH in the adenohypophysis, and induces morphological changes (hyalinization of the basophilic cells) suggestive of functional impairment of the adenohypophysis. The adrenal cortex itself undergoes atrophy. In contrast, adrenalectomized animals and patients with Addison's disease have abnormally high concentrations of ACTH in the blood even under optimal

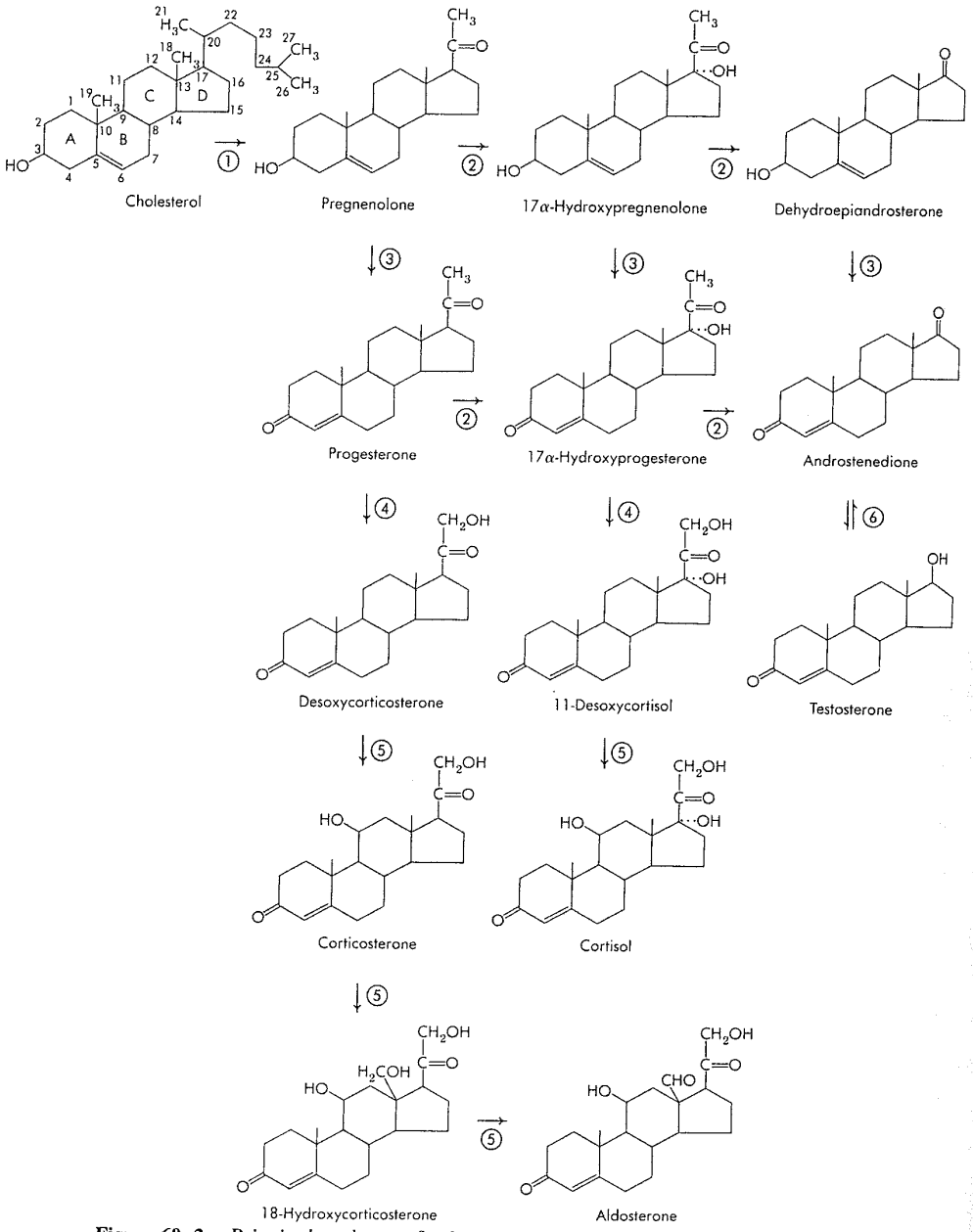

Figure 60–2. *Principal pathways for biosynthesis of adrenocorticosteroids and adrenal androgens.*

Reaction 1 is catalyzed by the cholesterol side chain–cleavage complex (cytochrome $P_{450,scc}$), reaction 2 by cytochrome $P_{450,C17}$, reaction 3 by 3β-hydroxysteroid dehydrogenase, reaction 4 by cytochrome $P_{450,C21}$, reaction 5 by cytochrome $P_{450,C11}$, and reaction 6 by 17-hydroxysteroid dehydrogenase.

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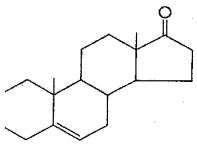

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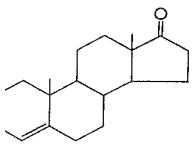

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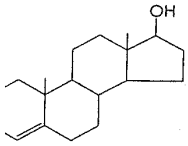

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environmental conditions. When a stimulus is applied to an adrenalectomized animal, the concentration of ACTH reaches even higher levels. These observations point out the important inhibitory role of the corticosteroids and clearly demonstrate that ACTH release remains under control of the nervous system in the absence of corticosteroid feedback. Secretion of ACTH at any instant is determined by the balance of neural excitatory and corticosteroid inhibitory effects.

Mechanism of Feedback by Corticosteroids. Binding of glucocorticoids has been detected in the pituitary, hypothalamus, and other areas of the brain (McEwen, 1979); however, the link between such binding and inhibition of secretion of ACTH has not been completely elucidated. There is evidence of control at both hypothalamic and hypophyseal sites. Nakanishi and coworkers (1977) demonstrated that glucocorticoids cause a decrease in the level of mRNA for ACTH in the pituitary, indicating that a degree of control is exerted at the level of transcription. Treatment of rats with glucocorticoids for a few days decreases the number of CRF receptors in the pituitary but not in the brain (Hauger *et al.*, 1987). This effect, together with inhibition of synthesis, may account in part for the "slow feedback" phase of glucocorticoid inhibition of ACTH secretion. It does not explain the "fast feedback" phase of inhibition that develops within seconds or minutes during a rise in circulating glucocorticoids. It is possible that these rapid effects are mediated by receptors for glucocorticoids on the surface of certain cells, analogous to those thought to mediate the actions of steroidal anesthetic agents (*see* Chapter 17). Feedback regulation of ACTH secretion has been reviewed by Keller-Wood and Dallman (1984).

Examples of Effective Stimuli of Secretion. A number of conditions have been demonstrated to stimulate adrenocortical secretion in man. These include the agonal state, severe infections, surgery, parturition, cold, exercise, and emotional stress. Stressful stimuli override the normal negative-feedback control mechanisms, and plasma concentrations of adrenocortical steroids can be elevated within a few minutes of the initiation of an appropriate stimulus.

Diurnal Cycles in Adrenocortical Activity. The rate of secretion of cortisol by the adrenal cortex of a normal human subject under optimal conditions is about 20 to 30 mg per day. However, the rate is not steady and exhibits rhythmic fluctuations; concentrations of adrenocortical steroids in plasma are relatively high in the early-morning hours, decline during the day, and reach a minimum during the evening. Plasma concentrations of ACTH are higher at 6 A.M. than at 6 P.M. The diurnal patterns of glucocorticoids and ACTH are not observed in patients with Cushing's disease, and this factor is considered in the diagnosis of the disorder.

Absorption and Fate. ACTH is readily absorbed from parenteral sites. The hormone rapidly disappears from the circulation following its intravenous administration; in man, the half-life in plasma is about 15 minutes because of rapid enzymatic hydrolysis.

Bioassay. The USP has adopted the Third International Standard for Corticotropin (Bangham *et al.*, 1962) as the reference standard in the United States. Potency is based on an assay in hypophysectomized rats in which depletion of adrenal ascorbic acid is measured after subcutaneous administration of the ACTH. Except for the synthetic product, cosyntropin, all commercial preparations are now described in these units only.

Preparations, Dosage, and Routes of Administration. *Corticotropin for injection* (ACTH) is available as a lyophilized powder (ACTHAR) for subcutaneous, intramuscular, or intravenous use. The preparation is derived from the pituitaries of mammals used for food. Maximal adrenocortical secretion is obtained in adults with a total dose of 25 USP units infused intravenously for 8 hours.

Repository corticotropin injection (H.P. ACTHAR GEL) is administered either intramuscularly or subcutaneously. It is a highly purified ACTH in gelatin solution. Typical doses are 40 to 80 units, given every 1 to 3 days. *Corticotropin zinc hydroxide suspension* (CORTROPHIN-ZINC) is a preparation of purified corticotropin adsorbed on zinc hydroxide, intended for intramuscular injection. Again, usual doses are 40 to 80 units every 1 to 3 days.

Cosyntropin (CORTROSYN) is a synthetic peptide corresponding to amino acid residues 1 to 24 of human ACTH. This preparation, approved for diagnostic purposes, is given intramuscularly or intravenously in a dose of 0.25 mg.

Therapeutic Uses and Diagnostic Applications of ACTH. At the present time, the most important use of ACTH is as a diagnostic agent in adrenal insufficiency. For this purpose, ACTH is administered and the concentration of cortisol in plasma is determined. A normal increase in plasma cortisol rules out primary adrenocortical failure. In the absence of an acute response, prolonged or repeated administration of ACTH may be required to stimulate an adrenal that has become atrophic because of lack of normal stimulation from ACTH. In cases of pituitary insufficiency, prolonged treatment can be expected to elicit a rise in plasma cortisol concentration.

Therapeutic uses of ACTH have included the treatment of secondary adrenocortical insufficiency and nonendocrine disorders that are responsive to glucocorticoids. However, therapy with ACTH is less predictable and much less convenient than is that with appropriate steroids. Furthermore, ACTH stimulates secretion of mineralocorticoids and, therefore, may cause acute retention of salt and water. ACTH would obviously be of no value in the treatment of primary adrenocortical failure. Furthermore, there is no substantial evidence that therapeutic goals can be attained with

ACTH in secondary adrenocortical insufficiency that cannot be attained with appropriate doses of currently available steroids. It must be kept in mind, however, that ACTH and corticosteroids are not pharmacologically equivalent. Treatment with ACTH exposes the tissues to a mixture of glucocorticoids, mineralocorticoids, and androgens, in contrast to the conventional, contemporary practice of administering a single glucocorticoid. It has been reported that patients treated for prolonged periods of time with ACTH do not develop dermal atrophy, in contrast to those treated with corticosteroids. This finding has been tentatively attributed to a protective action of androgens against the inhibitory effects of glucocorticoids on fibroblasts (Harvey and Grahame, 1973).

Clinical Toxicity of ACTH. The toxicity of ACTH, aside from rare hypersensitivity reactions, is entirely attributable to the increased rate of secretion of adrenocorticosteroids (*see* below). The synthetic ACTH peptides are thought to be less antigenic than is the parent molecule. ACTH, purified from pituitaries of animals, contains significant amounts of vasopressin, and life-threatening hyponatremia can result from its administration (Sheeler and Schumacher, 1979). For this reason cosyntropin, which contains no vasopressin, is preferred. ACTH causes more Na^+ retention, a greater degree of hypokalemic alkalosis, and more acne than do the synthetic congeners of cortisol.

ADRENOCORTICAL STEROIDS

The adrenal cortex synthesizes two classes of steroids: the corticosteroids (glucocorticoids and mineralocorticoids), with 21 carbon atoms, and the androgens, with 19. The major corticosteroids (cortisol, corticosterone, and aldosterone) are shown together with the androgens (dehydroepiandrosterone, androstenedione, and testosterone) in Figure 60–2.

Adrenocorticosteroid Biosynthesis. Cholesterol is an obligatory intermediate in the biosynthesis of corticosteroids. Although the adrenal cortex synthesizes cholesterol from acetate by processes similar to those occurring in liver, the greater part of the cholesterol (60 to 80%) utilized for corticosteroidogenesis comes from exogenous sources, both at rest and following administration of ACTH. Adrenocortical cells thus have large numbers of receptors that mediate the uptake of low-density lipoprotein, the predominant source of cholesterol (*see* Chapter 36). Cholesterol is enzymatically converted to 21-carbon corticosteroids and 19-carbon weak androgens by a series of steps presented in simplified form in Figure 60–2. Most of the reactions are catalyzed by mixed-function oxidases that contain cytochrome P_{450} and require NADPH and molecular oxygen.

In addition to other androgens, the adrenal cortex secretes testosterone; however, about half the plasma testosterone of normal women is derived from androstenedione at an extraadrenal site.

Table 60–1. TYPICAL RATES OF SECRETION AND PLASMA CONCENTRATIONS OF THE MAJOR BIOLOGICALLY ACTIVE CORTICOSTEROIDS IN MAN

		CORTISOL	ALDOSTERONE
Rate of secretion under optimal conditions, mg/day (μmol/day)		20 (55)	0.125 (0.35)
Concentrations in peripheral plasma of man, μg/dl (nM)	8 A.M.	16 (440)	0.01 (0.28)
	4 P.M.	4 (110)	

Adrenocorticosteroids are not stored in the adrenals. The amounts of corticosteroids found in adrenal tissue are insufficient to maintain normal rates of secretion for more than a few minutes in the absence of continuing biosynthesis. For this reason, the rate of biosynthesis is tantamount to the rate of secretion. Table 60–1 shows typical rates of secretion of the physiologically most important corticosteroids in man—cortisol and aldosterone—as well as their approximate concentrations in peripheral plasma. The mechanism of control of steroidogenesis by ACTH has been discussed above, and the regulation of aldosterone synthesis by renin and angiotensin is described in Chapter 31.

PHYSIOLOGICAL FUNCTIONS AND PHARMACOLOGICAL EFFECTS

The effects of the corticosteroids are numerous and widespread. They influence carbohydrate, protein, and lipid metabolism; electrolyte and water balance; and the functions of the cardiovascular system, the kidney, skeletal muscle, the nervous system, and other organs and tissues. Furthermore, the corticosteroids endow the organism with the capacity to resist many types of noxious stimuli and environmental changes. In the absence of the adrenal cortex, survival is possible but only under the most rigidly prescribed conditions; for example, food must be available regularly, sodium chloride ingested in relatively large quantities, and environmental temperature maintained within a suitably narrow range.

A given dose of corticosteroid may be physiological or pharmacological, depending on the environment and the activities of the organism. Under favorable conditions, a small dose of corticosteroid maintains the adrenalectomized animal in a state of well-being. Under adverse conditions a rela-

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Natural Steroids	
Cortisol	1
Cortisone	0
Corticosterone	15
11-Desoxycorticosterone	100
Aldosterone	3000
Synthetic Steroids	
Prednisolone	<1
Triamcinolone	0

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	CORTISOL	ALDOSTERONE
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tively large dose is needed if the animal is to survive. This same large dose given repetitively under optimal conditions induces hypercorticism—that is, signs of corticosteroid excess. The fluctuations in the secretory activity of a normal subject are presumed to reflect the body's varying requirements for corticosteroids.

The actions of corticosteroids are often complexly related to the functions of other hormones. For example, in the absence of lipolytic hormones, cortisol even in large concentrations has virtually no effect on the rate of lipolysis in adipose tissue *in vitro*. Likewise, a sympathomimetic amine has only a slight effect on the rate of lipolysis if there is a deficiency of glucocorticoids. However, if a necessary minimal amount of cortisol is added, the lipolytic effect of the sympathomimetic amine becomes evident. The necessary but not sufficient role of corticosteroids acting in concert with other regulatory forces has been termed "permissive."

Estimates of the potencies of naturally occurring and synthetic corticosteroids in the categories of Na^+ retention (reduction of Na^+ excretion by the kidney of the adrenalectomized animal); hepatic deposition of glycogen in fasted, adrenalectomized animals; and antiinflammatory effect (inhibition of the action of an agent that induces inflammation) are presented in Table 60–2. It should be noted that such values are not fixed ratios but vary considerably with the conditions of the bioassays used. Potencies of steroids as judged by their ability to sustain life in the adrenalectomized animal closely parallel those determined for Na^+ retention. Potencies based on deposition of liver glycogen, antiinflammatory effect, work capacity of skeletal muscle, and involution of lymphoid tissue closely parallel one another. Dissociations exist between potencies based on Na^+ retention and on hepatic glycogen deposition; traditionally, the corticosteroids have thus been classified into *mineralocorticoids* and *glucocorticoids*, according to potencies in the two categories. Desoxycorticosterone, the prototype of the mineralocorticoids, is highly potent in regard to Na^+ retention but without effect on hepatic glycogen deposition. Cortisol, the prototype of the glucocorticoids, is highly potent in regard to liver glycogen deposition but weak in regard to Na^+ retention. The naturally occurring corticosteroids cortisol and cortisone, as well as synthetic corticosteroids such as prednisolone and triamcinolone, are classified as glucocorticoids. However, corticosterone is a steroid that has modest but significant activities in both categories. In contrast, aldosterone is exceedingly potent with respect to Na^+ retention but has only modest potency for liver glycogen deposition. At rates secreted by the adrenal cortex or in doses that exert maximal effects on electrolyte balance, aldosterone has no significant effect on carbohydrate metabolism; it is thus classified as a mineralocorticoid.

Table 60–2. RELATIVE POTENCIES OF CORTICOSTEROIDS

	NA^+ RETENTION	HEPATIC GLYCOGEN DEPOSITION	ANTIINFLAMMATORY EFFECT
Natural Steroids			
Cortisol	1 *	1	1
Cortisone	0.8 *	0.8	0.8
Corticosterone	15	0.35	0.3
11-Desoxycorticosterone	100	0	0
Aldosterone	3000	0.3	?
Synthetic Steroids			
Prednisolone	<1 *	4	4
Triamcinolone	0	5	5

* Promotes excretion of Na^+ under certain circumstances.

Mechanism of Action. Corticosteroids, like other steroid hormones, act by controlling the rate of synthesis of proteins. However, their nearly instantaneous inhibition of ACTH release (*see* above) is probably an exception. Corticosteroids react with receptor proteins in the cytoplasm of sensitive cells in many tissues to form a steroid-receptor complex. The complex undergoes a modification, as noted by an increase in the sedimentation constant, and then moves into the nucleus, where it binds to chromatin and regulates transcription of specific genes. In most known examples, transcription is enhanced, as manifest by increased amounts of specific mRNA. Nevertheless, glucocorticoids also decrease transcription of some genes, for example, the pro-opiomelanocortin gene that encodes ACTH.

It is now known that binding of corticosteroids by their receptor results in dissociation of a phosphorylated protein of approximately 90,000-dalton size from the receptor complex in the cytosol. This protein has been identified as a heat-shock protein (hsp90), one of a group of proteins synthesized by

organisms as diverse as bacteria and mammals under conditions of heat or certain other types of stress. It is presumed that the release of this intriguing protein of, as yet, unknown function plays a major part in the transformation of the receptor, enabling the hormone-receptor complex to proceed to its nuclear destination or to interact fruitfully with DNA (*see* Pratt, 1987; Yamamoto *et al.*, 1988).

Molecular biological techniques have recently made the human glucocorticoid receptor available for study and have permitted manipulation of its structure by deletion or substitution of amino acid sequences. The receptor has a central domain that is responsible for binding to glucocorticoid-response elements (GREs)—short sequences of DNA in the promoter regions of genes whose transcription is controlled by glucocorticoids. This segment of the receptor contains a region that is similar to portions of receptors for the thyroid hormones as well as those for other steroids (*see* Chapter 2). The steroid-binding domain, located toward the carboxyl-terminal end of the protein, is now known to repress the functions of the DNA-binding segment. When a glucocorticoid associates with the receptor, DNA binding and enhancement of transcription are no longer inhibited; the effect of the glucocorticoid is thus to disinhibit the activity of the unliganded receptor (*see* Funder, 1987; Hollenberg *et al.*, 1987; Godowski *et al.*, 1988).

Carbohydrate and Protein Metabolism. The effects of adrenocortical hormones on carbohydrate and protein metabolism are epitomized in the teleological view that these steroids have evolved to protect glucose-dependent cerebral functions by stimulating the formation of glucose, diminishing its peripheral utilization, and promoting its storage as glycogen. Adrenalectomized animals exhibit no marked abnormality in carbohydrate metabolism if food is regularly available. Under such circumstances, normal concentrations of glucose in the plasma are maintained and glycogen is stored in the liver. However, a brief period of starvation rapidly depletes carbohydrate reserves. The concentration of glycogen in the liver, and to a lesser extent that in muscle, decreases and hypoglycemia develops. In light of these facts, it is not surprising that the adrenalectomized animal is hypersensitive to insulin. Patients with Addison's disease have similar abnormalities in carbohydrate metabolism.

Administration of a glucocorticoid such as cortisol corrects the defect in carbohydrate metabolism of the adrenalectomized animal; glycogen stores, particularly in the liver, are increased; concentrations of glucose in plasma remain normal during fasting; and sensitivity to insulin returns to normal. Increased excretion of nitrogen accompanies the increased production of glucose, indicating that protein is converted to carbohydrate. Prolonged exposure to large doses of glucocorticoids leads to an exaggeration of these changes in glucose metabolism, such that a diabetic-like state is produced: glucose in the plasma tends to be elevated in the fasting subject, resistance to insulin is increased, glucose tolerance is decreased, and glucosuria may be present.

The mechanism by which the glucocorticoids inhibit utilization of glucose in peripheral tissues is not yet understood. Decreased uptake of glucose has been demonstrated in adipose tissue, skin, fibroblasts, and thymocytes as a result of glucocorticoid action.

Glucocorticoids promote gluconeogenesis by both peripheral and hepatic actions. Peripherally these steroids act to mobilize amino acids from a number of tissues. This catabolic action is reflected in the atrophy of lymphatic tissues, reduced mass of muscle, osteoporosis (reduction in protein matrix of bone followed by calcium loss), thinning of the skin, and a negative nitrogen balance. Amino acids funnel into the liver, where they serve as substrates for enzymes involved in the production of glucose and glycogen.

In the liver the glucocorticoids induce *de-novo* synthesis of a number of enzymes involved in gluconeogenesis and amino acid metabolism. For example, the hepatic enzymes phosphoenolpyruvate carboxykinase, fructose-1,6-diphosphatase, and glucose-6-phosphatase, which catalyze reactions of glucose synthesis, are increased in concentration. However, induction of these enzymes requires a matter of hours and cannot account for the earliest effects of the hormones on gluconeogenesis. For example, when dexamethasone, a synthetic glucocorticoid, is added to isolated rat hepatocytes, gluconeogenesis is fully stimulated within 20 minutes, and this effect is not blocked by inhibition of protein synthesis with cycloheximide (Sistare and Haynes, 1985).

Prolonged, but not acute, treatment with glucocorticoids has been found to elevate the concentration of glucagon in the plasma (Marco *et al.*, 1973; Wise *et al.*, 1973). Inasmuch as glucagon itself stimulates gluconeogenesis, the rise in glucagon should also contribute to the enhanced synthesis of glucose. The deposition of glycogen in the liver found after treatment with glucocorticoids is thought to be the consequence of activation of hepatic glycogen synthase. This activation requires the presence of insulin but is not mediated by a rise in the concentration of insulin (*see* Hers, 1985). The effects of glucocorticoids on carbohydrate metabolism have been reviewed by McMahon and colleagues (1988).

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Lipid Metabolism. Two effects of corticosteroids on lipid metabolism are firmly established. The first is the dramatic redistribution of body fat that occurs in the hypercorticoid state. The other is the facilitation of the effect of adipokinetic agents in eliciting lipolysis of the triglycerides of adipose tissue. In rare instances, prolonged exposure to excessive glucocorticoids produces an epidural lipomatosis that can result in neurological disability (Russell *et al.*, 1984). A number of other effects of corticosteroids on lipids have been reported, but in few, if any, instances have they turned out to be direct actions of the corticosteroids themselves.

Prolonged administration of large doses of glucocorticoids to human subjects or the hypersecretion of cortisol that occurs in Cushing's syndrome leads to a peculiar alteration in fat distribution. There is a gain of fat in depots in the back of the neck ("buffalo hump"), supraclavicular area, and face ("moon face") and a loss of fat from the extremities. One hypothesis to explain this phenomenon is that of Fain and Czech (1975), who proposed that the adipose tissue that hypertrophies in Cushing's syndrome responds preferentially to the lipogenic and antilipolytic actions of the elevated concentrations of insulin evoked by glucocorticoid-induced hyperglycemia. According to this hypothesis, adipocytes in the extremities, in contrast to those of the trunk, are less sensitive to insulin and more sensitive to the glucocorticoid-facilitated lipolytic effects of other hormones.

The mobilization of fat from peripheral fat depots by epinephrine, norepinephrine, or adipokinetic peptides of the adenohypophysis is markedly blunted in the absence of the adrenal cortex or the adenohypophysis. Cortisol acts in adipose tissue to facilitate the lipolytic response to cyclic AMP, rather than to enhance its accumulation. Hypophysectomy in rats has only a slight effect on the accumulation of cyclic AMP after exposure of adipose tissue to graded doses of epinephrine (Birnbaum and Goodman, 1973); however, hypophysectomy greatly decreases the lipolytic response of adipose tissue to the cyclic nucleotide. Treatment with cortisol restores the normal response to lipolytic hormones and to cyclic AMP (Goodman, 1968). Plasma lipids are not changed consistently in either hypocorticism or hypercorticism.

Electrolyte and Water Balance. Mineralocorticoids act on the distal tubules and collecting ducts of the kidney to enhance the reabsorption of Na^+ from the tubular fluid into the plasma; they increase the urinary excretion of both K^+ and H^+. The consequences of these three primary effects in concert with similar actions on cation transport in other tissues appear to account for the entire spectrum of physiological and pharmacological activities that are characteristic of the mineralocorticoids. Thus, the primary features of hypercorticism are positive Na^+ balance and expansion of the extracellular fluid volume, normal or slight increase in the concentration of Na^+ in the plasma, hypokalemia, and alkalosis. In contrast, those of the deficient state, hypocorticism, are Na^+ loss, hyponatremia, hyperkalemia, contraction of the extracellular fluid volume, and cellular hydration. A defect of major consequence in adrenocortical insufficiency is the renal loss of Na^+. The renal tubules normally reabsorb practically all the Na^+ filtered at the glomerulus. For example, on an ordinary diet, 99.5% may be reabsorbed to maintain Na^+ balance. Typically, in a patient with Addison's disease with a normal dietary intake, the maximal reabsorption attainable is 98.5%. Since approximately 24,000 mEq of Na^+ is filtered per day, the 1% difference between reabsorption in the normal subject and the patient with Addison's disease amounts to a loss of 240 mEq of Na^+ per day. The gravity of the situation is obvious when one considers that this amount of Na^+ is normally present in 1.7 liters of extracellular fluid. Proportionately more Na^+ than water is lost through the kidney and the concentration of extracellular Na^+ decreases; extracellular fluid becomes hypoosmotic, and water shifts from the extracellular into the intracellular compartment. This shift, together with the renal loss of water, results in a marked reduction in the volume of the extracellular fluid. Cells are hydrated, and the increase in the hematocrit value is due not only to a shrinkage of the plasma volume but also to the swelling of the erythrocytes. Hyperkalemia and the tendency toward acidosis are a result of impairments in the excretion of K^+ and H^+. Without adminis-

tration of mineralocorticoids or sodium chloride solution or both, a rapid downhill course ensues in adrenocortical insufficiency. The shrinkage of extracellular fluid volume, the cellular hydration, and the hypodynamic state of the cardiovascular system combine to cause circulatory collapse, renal failure, and death.

In adrenocortical insufficiency, a basic defect in ion transport occurs in a variety of secretory cells. Not only the kidney but also the salivary glands, the sweat glands, the exocrine pancreas, and the mucosa of the gastrointestinal tract elaborate fluids abnormally high in the concentration of Na^+ and abnormally low in the concentration of K^+. In the patient with Addison's disease, sweating may contribute significantly to the negative balance of Na^+.

Aldosterone is by far the most potent of the naturally occurring corticosteroids with regard to electrolyte balance and plays an important role in the long-term regulation of Na^+ and K^+ balance. Evidence of this is the relatively normal electrolyte balance exhibited by the hypophysectomized animal as a result of continued secretion of aldosterone by the adrenal cortex, and the increased rate of secretion of aldosterone that occurs in man when dietary salt is severely limited. However, changes in the rate of secretion of aldosterone are not the cause of the rapid changes that may occur in Na^+ excretion. The latent period of action of the steroid is too long.

The intravenous administration of aldosterone to a normal subject is followed, after a delay of about an hour, by a decrease in the rate of renal Na^+ excretion and an increase in the rate of K^+ and H^+ excretion. If the administration of relatively large amounts of aldosterone is continued over a period of more than 10 to 14 days, Na^+ excretion again equals Na^+ intake. However, K^+ and H^+ excretion continues at an accelerated rate, resulting in hypokalemic alkalosis. The mechanism of "escape" from acute Na^+ retention is probably the result of the diuretic action of atrial natriuretic peptide, secreted in response to atrial distention. The effects of the mineralocorticoids have been reviewed by Mulrow and Forman (1972).

Aldosterone, like other steroids, acts to initiate transcription of mRNA that serves as template for the synthesis of specific proteins. One hypothetical "aldosterone-induced protein" is thought to facilitate the transport of Na^+ from the lumen of the distal tubules through the tubular cells and into the extracellular fluid. The most widely accepted model to describe the action of aldosterone was put forth by Marver (1980). The Na^+ of the tubular filtrate enters the cells of the distal tubules down a concentration gradient through the cell membrane facing the tubular lumen (apical or mucosal surface). Aldosterone and other mineralocorticoids facilitate this diffusion by increasing the permeability of the apical membrane to Na^+. Thus, Na^+ enters the cells at an accelerated rate and is pumped out into the extracellular space across the basolateral membrane by Na^+,K^+-activated adenosine triphosphatase (Na^+,K^+-ATPase) (Koeppen *et al.*, 1983). After aldosterone acts for a period of time, the amount of the Na^+, K^+-ATPase that is associated with the basolateral membrane increases (*see* Stanton, 1985).

The mechanisms of the enhanced excretion of K^+ and H^+ are less well understood. The exchange of Na^+ for K^+ by Na^+,K^+-ATPase tends to increase the concentration of K^+ in the tubular cells, from which it may escape either into the tubular lumen or back into the interstitial fluid. Diffusion into the tubular fluid results in the urinary excretion of K^+. For practical purposes one may visualize H^+ and K^+ as being "exchanged" for the additional Na^+ that is reabsorbed under the influence of the steroids, because the sum of the equivalents of the additional K^+ and H^+ excreted is equal to that of the additional Na^+ retained.

The glucocorticoids decrease the absorption of Ca^{2+} from the intestine and increase its renal excretion, thus producing a negative balance of the cation. These effects are considered to be the basis of the favorable therapeutic response to glucocorticoids seen in hypercalcemia (*see* Chapter 62).

Desoxycorticosterone is a natural mineralocorticoid of some historical interest for it was the first corticosteroid to be synthesized and made available for the treatment of Addison's disease. Desoxycorticosterone is practically devoid of glucocorticoid effects. Qualitatively, it is identical to aldosterone in its effects on electrolytes; quantitatively, it is about 3% as potent (*see* Table 60–2). Thus, despite the fact that the concentration of desoxycorticosterone in plasma is approximately the same as that of aldosterone, it apparently is of little physiological significance in the normal individual.

Cortisol induces Na^+ retention and K^+ excretion, but much less effectively than does aldosterone. In striking contrast to aldosterone, cortisol, under certain circumstances (especially Na^+ loading), enhances Na^+ excretion. This may be accounted for by the capacity of cortisol to increase the glomerular filtration rate (GFR). Aldosterone and desoxycorticosterone are ineffec-

tive in this regard. Furthermore, cortisol has a significant stimulatory influence on tubular secretory activity.

Impaired water diuresis in response to an administered water load, while not specific for adrenal insufficiency, has been used as a diagnostic criterion. In adrenal insufficiency, the GFR is reduced and the plasma concentration of antidiuretic hormone (ADH) is increased; these factors account for failure to excrete a water load (Ahmed *et al.*, 1967). Administration of cortisol, but not of aldosterone, increases the GFR and restores water diuresis (Gill *et al.*, 1962).

Hypercorticism caused by the administration of large doses of cortisol (or related glucocorticoids) or the excessive secretion of cortisol by the adrenals is sometimes associated with a hypokalemic alkalosis (*see* Chapter 27). However, the changes, particularly the degree of hypokalemia, are moderate in severity and reflect the relatively weak effect on electrolyte balance of cortisol as compared with aldosterone. Muscle weakness associated with glucocorticoid treatment is usually due to a loss of muscle mass rather than of K^+.

An important relationship between cortisol and aldosterone as mineralocorticoids has been discovered recently. The human mineralocorticoid receptor binds aldosterone and cortisol with similar affinity (Arriza *et al.*, 1987). Because the concentration of cortisol in plasma is hundreds of times that of aldosterone (*see* Table 60–1), it might be expected that the human organism would be in a constant state of hypermineralocorticism equivalent to clinical aldosteronism (*see* below). However, some tissues that contain mineralocorticoid receptors, in particular the kidney, colon, and salivary glands, also have a highly active 11-β-hydroxysteroid dehydrogenase that oxidizes cortisol to its inactive 11-keto derivative, cortisone. This reaction effectively shields the mineralocorticoid receptor from most of the cortisol; aldosterone is not a substrate for the dehydrogenase (Funder *et al.*, 1988). In licorice poisoning, the 11-β-dehydrogenase is inhibited by glycyrrhizic acid, a component of licorice. This allows excessive activation of the mineralocorticoid receptor by cortisol, thereby producing a state of hypermineralocorticism (Stewart *et al.*, 1987).

Cardiovascular System. The most striking effects of corticosteroids on the cardiovascular system are those that are the consequence of regulation of renal Na^+ excretion. These effects are seen most vividly in hypocorticism when reduction in blood volume accompanied by increased viscosity can lead to hypotension and cardiovascular collapse. However, the impairment of the cardiovascular system that occurs in patients with adrenocortical insufficiency obviously involves additional, poorly understood processes. The corticosteroids exert important actions on the various elements of the circulatory system, including the capillaries, the arterioles, and the myocardium. In the absence of the corticosteroids, there is increased capillary permeability, inadequate vasomotor response of the small vessels to catecholamines, and reduction in cardiac size and output.

An excess of mineralocorticoids occurs in its purest form in primary aldosteronism, the result of excessive secretion of this steroid. In this disease the major clinical findings are hypertension and hypokalemia. The hypokalemia is an obvious consequence of the renal effects of aldosterone, but the genesis of the hypertension has not been totally clarified. Development of hypertension requires a prolonged excess of mineralocorticoid and retention of Na^+ (Mulrow and Forman, 1972). Plasma renin activity is suppressed. Mineralocorticoid-induced hypertension can be treated by reduction of body stores of Na^+ with diuretics, implying that the hypertension is a result of Na^+ retention. Hypertension occurs in most cases of Cushing's syndrome and sometimes as the result of administration of synthetic glucocorticoids lacking mineralocorticoid activity. One hypothesis proposes that salt retention (or mineralocorticoids themselves) sensitizes blood vessels to pressor agents, in particular angiotensin and catecholamines (Brunner *et al.*, 1972; Yard and Kadowitz, 1972).

Glucocorticoid-induced hypertension has also not been well explained. With agents such as cortisol, retention of Na^+ may play a role. However, in contrast to primary aldosteronism, natriuresis is often not successful in normalizing blood pressure. In addition, plasma renin activity is normal or increased in glucocorticoid-induced hypertension and may have an effect (Krakoff *et al.*, 1975). There is also some evidence that ADH may be involved in the pathogenesis of the hypertension (Share and Crofton, 1982).

Skeletal Muscle. The maintenance of normal function of skeletal muscle requires adequate concentrations of corticosteroids, but excessive amounts of either mineralocorticoids or glucocorticoids lead to abnormalities.

It is well known that one of the outstanding signs of adrenocortical insufficiency is a diminished work capacity of striated muscle. In patients with Addison's disease this is manifested by weakness and fatigue. The most important single factor responsible for this dysfunction appears to be the inadequacy of the circulatory system. Abnormalities in electrolyte balance and carbohydrate metabolism in adrenocortical insufficiency contribute only in small measure to the impairment in skeletal muscle function.

Muscle weakness in primary aldosteronism is in large measure a result of the hypokalemia characteristic of this disease. Glucocorticoids given for prolonged periods in high doses or secreted in abnormal amounts in Cushing's syndrome tend to cause a wasting of skeletal muscle, the mechanism of which is not known. This steroid myopathy is responsible, at least in part, for the weakness and fatigue noted in the syndrome. Steroid-induced myopathy has been reviewed by Ellis (1985); acute myopathy is discussed by Knox and colleagues (1986).

Central Nervous System. The corticosteroids affect the central nervous system (CNS) in a number of indirect ways; in particular, they maintain normal concentrations of glucose in plasma, an adequate circulation, and the normal balance of electrolytes in the body. There is also an increasing recognition of direct effects of corticosteroids on the CNS as understanding of the distribution and function of steroid receptors in the brain has grown (McEwen *et al.*, 1986; Funder and Sheppard, 1987). An influence of the corticosteroids can be observed on mood, behavior, the electroencephalogram (EEG), and brain excitability.

Patients with Addison's disease exhibit apathy, depression, and irritability; some are frankly psychotic. Desoxycorticosterone is ineffective but cortisol is very effective in correcting these abnormalities of psyche and behavior. An array of reactions, varying in degree and kind, is seen in patients to whom glucocorticoids are administered for therapeutic purposes. Most patients respond with elevation in mood, which may be explained in part by the relief of the symptoms of the disease being treated. In some, more definite mood changes occur, characterized by euphoria, insomnia, restlessness, and increased motor activity. A smaller but significant percentage of patients treated with high doses of cortisol become anxious or depressed, and a still smaller percentage exhibit psychotic reactions. A high incidence of neuroses and psychoses has been noted among patients with Cushing's syndrome. The abnormalities of behavior usually disappear when the corticosteroids are withdrawn or the Cushing's syndrome is effectively treated (Lewis and Smith, 1983).

There is usually an increase in the excitability of neural tissue in hypocorticism and a decreased excitability in animals given large doses of desoxycorticosterone; these alterations appear to be related to changes in the concentrations of electrolytes in the brain. In contrast, administration of cortisol increases brain excitability without influencing the concentrations of Na^+ and K^+ in the brain. Thus, it has been concluded that the influence of desoxycorticosterone on excitability is mediated through its influence on Na^+ transport, whereas cortisol acts by a different mechanism, presumably mediated by cytoplasmic receptors (McEwen, 1979; Carpenter and Gruen, 1982).

Formed Elements of Blood. Glucocorticoids tend to increase the hemoglobin and red-cell content of the blood, as evidenced by the frequent occurrence of polycythemia in Cushing's syndrome and a mild, normochromic, normocytic anemia in Addison's disease. The capacity of these steroids to retard erythrophagocytosis may be a factor in the production of polycythemia.

The corticosteroids also affect circulating white cells. Addison was the first to observe the increase in mass of lymphoid tissue that accompanies adrenocortical insufficiency; lymphocytosis also occurs. In contrast, Cushing's syndrome is characterized by lymphocytopenia and decreased mass of lymphoid tissue. The administration of glucocorticoids leads to a decreased number of blood lymphocytes, eosinophils, monocytes, and basophils. A single dose of cortisol produces a decline of about 70% in circulating lymphocytes and a decline of over 90% in monocytes; this reaction occurs in 4 to 6 hours and lasts about 24 hours. The decrease in lymphocytes, monocytes, and eosinophils appears to result from the redistribution of cells rather than from their destruction. The cause of the fall in circulating basophils has not been established. In contrast, the administration of glucocorticoids causes an increase in the number of polymorphonuclear leukocytes in the blood as the result of their increased rate of entrance into the blood from the marrow, diminished rate of removal from the circulation, and increase in release from vascular walls.

After administration of a glucocorticoid, T lymphocytes are decreased proportionately more than are B cells. The profile of cellular responses of the lymphocytes remaining in the blood to various mitogens and antigens is also altered. These findings indicate that subpopulations of lymphocytes are differentially affected by the steroids (*see* Cupps and Fauci, 1982). The altered responsiveness of lymphocytes is an important facet of the antiinflammatory and immunosuppressive actions of the glucocorticoids (*see* below).

While glucocorticoids cause a rapid lysis of lymphatic tissue in rats and mice, evidence of a comparable effect in man is lacking. As noted above, the acute effects of steroids on circulating lymphocytes are due to sequestration from the blood, rather than to lymphocytolysis. However, acute lymphoblastic leukemia cells and, in some cases, cells of other lymphatic malignancies are destroyed by glucocorticoids in a manner presumed to be analogous to that which occurs in lymphoid tissue of rodents.

Antiinflammatory and Immunosuppressive Actions. Glucocorticoids have the capacity to prevent or suppress the devel-

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opment of the manifestations of inflammation. They inhibit the inflammatory response whether the inciting agent is radiant, mechanical, chemical, infectious, or immunological. Although the administration of corticosteroids for their antiinflammatory effects is palliative therapy because the underlying cause of the disease remains, the suppression of inflammation and its consequences has made these agents of great value clinically—indeed, at times lifesaving. The glucocorticoids are also of immense value in treating diseases that result from undesirable immune reactions. These diseases range from conditions that are predominantly the consequence of humoral immunity, such as urticaria, to those that are mediated by cellular immune mechanisms, such as rejection of transplanted organs. The immunosuppressive and antiinflammatory actions of the glucocorticoids are inextricably linked because they both result in large part from inhibition of specific functions of leukocytes. In several instances these effects on leukocytes are a consequence of glucocorticoid-induced inhibition of the elaboration and/or action of lymphokines.

Antiinflammatory Actions. The corticosteroids inhibit not only the early phenomena of the inflammatory process (edema, fibrin deposition, capillary dilatation, migration of leukocytes into the inflamed area, and phagocytic activity) but also the later manifestations (proliferation of capillaries and fibroblasts, deposition of collagen, and, still later, cicatrization). Although of great value in certain circumstances, the suppression of inflammatory manifestations by corticosteroids can invite potential disaster. The signs and symptoms of inflammation are expressions of the disease process that are often used by the physician in diagnosis and in evaluating the effectiveness of treatment. These may be missing in patients treated with glucocorticoids. For example, an infection may continue to progress while the patient superficially appears to improve, or a peptic ulcer may perforate without producing clinical signs.

A number of mechanisms are involved in the suppression of inflammation by the glucocorticoids, and many remain to be elucidated. The ability of glucocorticoids to inhibit the recruitment of leukocytes and monocyte-macrophages into affected areas has been thought for some time to be a very important factor in their antiinflammatory actions (Balow and Rosenthal, 1973; Parrillo and Fauci, 1979). Later investigations have confirmed this idea and have demonstrated that glucocorticoids inhibit the ability of these cells to elaborate a variety of chemotactic substances as well as factors that mediate increased capillary permeability, vasodilatation, and contraction of various nonvascular smooth muscles.

At present, the catalogue of substances whose synthesis and/or release is inhibited by glucocorticoids includes (1) arachidonic acid and its metabolites (*e.g.*, prostaglandins and leukotrienes), through glucocorticoid-induced synthesis of a protein or family of proteins (lipocortin or macrocortin) that inhibits the activity of phospholipase A_2 (DiRosa *et al.*, 1985); (2) platelet activating factor (PAF), apparently also mediated by the induction of lipocortin (Parente and Flower, 1985); (3) tumor necrosis factor (TNF, or cachectin), which incites many of the processes of inflammation and is normally released from phagocytic cells following their stimulation by bacterial endotoxins (Beutler and Cerami, 1987); and (4) interleukin-1 (IL-1), normally elaborated by monocyte-macrophages, which results from a glucocorticoid-induced decrease in the concentration of its mRNA (*see* Dinarello and Mier, 1986, 1987). IL-1 exerts a number of inflammatory actions, including stimulation of the production of PGE_2 and collagenase, activation of T lymphocytes, stimulation of fibroblast proliferation, and enhanced hepatic synthesis of "acute-phase" proteins; it also functions as a chemoattractant for leukocytes and causes neutrophilia (Lew *et al.*, 1988). Glucocorticoids also inhibit the formation of plasminogen activator by neutrophils. This enzyme converts plasminogen to plasmin (fibrinolysin), which is thought to facilitate the migration of leukocytes into sites of inflammation by hydrolyzing fibrin and other proteins (Granelli-Piperano *et al.*, 1977). In addition to inhibiting the release of mediators of inflammation, glucocorticoids can inhibit the actions of humoral regulators, such as PAF (Wallace and Whittle, 1988) and macrophage migration-inhibition factor (MIF), which normally causes the accumulation of nonsensitized macrophages at sites of inflammation (Balow and Rosenthal, 1973).

Immunosuppressive Actions. Although considered to be immunosuppressive, therapeutic doses of glucocorticoids do not significantly decrease the concentration of antibodies in the circulation. Furthermore, during glucocorticoid therapy, patients

exhibit a nearly normal antibody response to antigenic challenge (Butler, 1975). Examination of the cellular immune system also produces seemingly anomalous observations. For example, although guinea pigs previously sensitized to tuberculin do not exhibit responses to tuberculin during treatment with steroids, the introduction of their lymphocytes into untreated recipient animals causes the recipient to become sensitive to intradermal tuberculin (Weston *et al.*, 1973). Thus, glucocorticoids eliminate neither humoral nor cellular hyperimmune states, but rather prevent their manifestations. Nevertheless, they do appear to inhibit early steps in the development of immunity. Thus far, most of the actions that have been elucidated involve disruptions of intercellular communication among leukocytes through interference with the production or function of lymphokines. Although researchers are not in complete agreement as to the sequence of events involved in the production of cell-mediated immunity, many of the current hypotheses are incorporated into the model schematically presented in Figure 60–3, which also includes probable sites of glucocorticoid action.

The immune response is initiated by the interaction of an antigen with macrophages and with surface antibodies on B lymphocytes. The macrophages ingest and process the antigen, which is then displayed on the cell surface of the macrophage together with a major histocompatibility antigen; they also secrete interleukin-1 (IL-1). Glucocorticoids interfere with the function of macrophages in several ways: (1) they inhibit the action of MIF, thereby promoting the egress of macrophages from affected areas; (2) they inhibit the processing and display of antigen by interfering with the facilitating actions of gamma interferon (Gerrard *et al.*, 1984; Mokoena and Gordon, 1985); and (3) they inhibit the synthesis and release of IL-1 (Lew *et al.*, 1988). Although IL-1 participates in the proliferation of B cells and their ultimate synthesis of antibody, glucocorticoids have little effect on antibody production (*see* above). More importantly, IL-1 participates in the activation of resting T lymphocytes when they come in contact with the processed antigen and histocompatibility antigen that is displayed on the surface of activated macrophages; hence, glucocorticoids suppress the activation of T cells by several mechanisms.

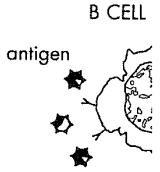
Activated T cells release a series of lymphokines, including interleukin-2 (IL-2), as well as gamma interferon and granulocyte-macrophage colony-stimulating factor. IL-2 directs activated T cells to proliferate, thereby expanding the population of clones of specific T cells; it also induces a particular group of lymphocytes to become cytotoxic ("killer") lymphocytes. Glucocorticoids suppress the amplification of cell-mediated immunity both by inhibiting the expression of the IL-2 gene in T cells and by interfering with the interaction of IL-2 with its receptors on T cells (Horst and Flad, 1987); there is some evidence that the effects on IL-2 synthesis are indirect and are mediated by suppression of the formation of leukotriene B_4 (Goodwin *et al.*, 1986). In addition to effects secondary to the suppression of IL-2 synthesis, glucocorticoids may interfere with the activation of cytotoxic lymphocytes by IL-2 as well as inhibit the function of natural killer lymphocytes (Gatti *et al.*, 1986; Papa *et al.*, 1986). The function of lymphokines in the generation of cell-mediated immunity has been reviewed by Dinarello and Mier (1987). (*See also* Chapter 53.)

Growth and Cell Division. Pharmacological doses of glucocorticoids retard or interrupt the growth of children, indicating an adverse effect on the epiphyseal cartilage. Inhibition of growth is a rather widespread effect of the glucocorticoids on tissues of laboratory animals. For example, glucocorticoids inhibit cell division or the synthesis of DNA in thymocytes; normal, developing, and regenerating liver; gastric mucosa; developing brain; developing lung; and human epidermis. Nevertheless, this effect is somewhat selective, and corticosteroids do not characteristically produce the bone-marrow depression or the enteritis that follows exposure to nonspecific antimitotic agents. How the steroids produce this effect is not known.

ABSORPTION, TRANSPORT, METABOLISM, AND EXCRETION

Absorption. Cortisol and numerous congeners, including synthetic analogs, are effective when given by mouth. Water-soluble esters of cortisol and its synthetic congeners are administered intravenously to achieve high concentrations in body fluids rapidly. More prolonged effects are obtained by intramuscular injection of suspensions of cortisol, its congeners, and its esters. Minor changes in chemical structure may result in large changes in the rate of absorption, time of onset of effect, and duration of action.

Glucocorticoids are absorbed from sites of local application such as synovial spaces, the conjunctival sac, and the skin. When administration is prolonged or when large areas of skin are involved, the absorption may be sufficient to cause systemic effects, including adrenocortical suppression.



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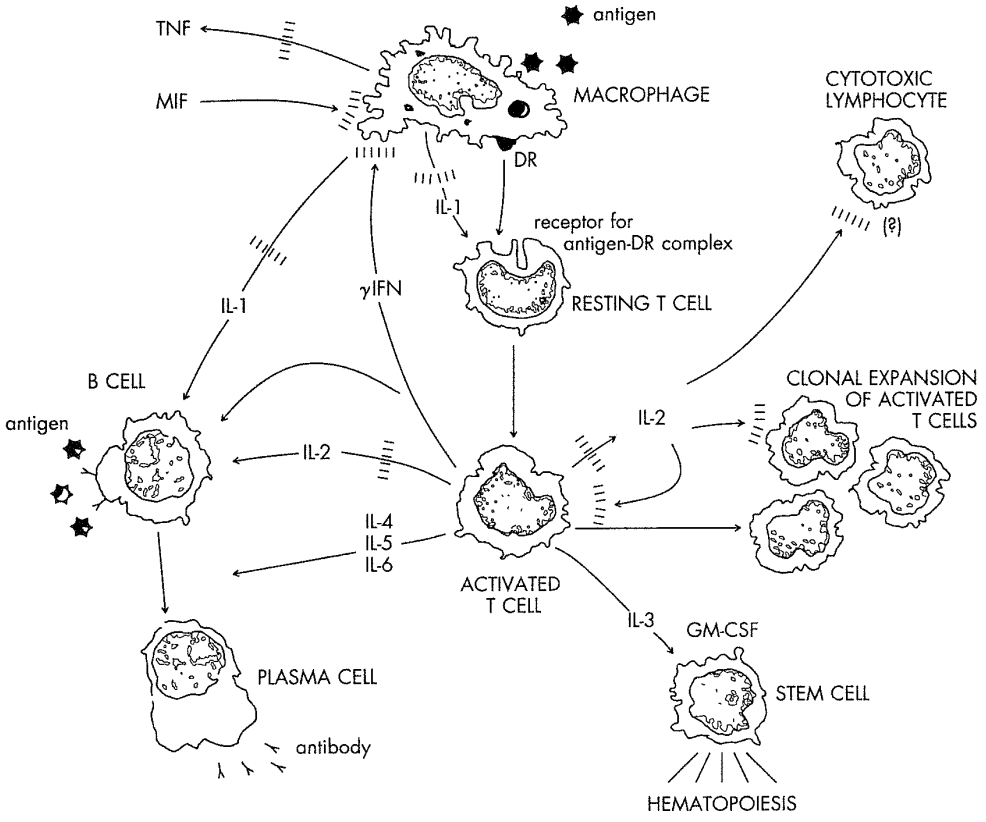


Figure 60–3. *Sites of action of glucocorticoids in the responses of leukocytes during antigenic challenge and inflammation.*

The humoral immune response is initiated by interaction of an antigen with surface antibodies on B cells; cell-mediated immunity begins with the ingestion and processing of an antigen by macrophages. The activated macrophages secrete interleukin-1 (IL-1) and tumor necrosis factor (TNF, cachectin) and display the processed antigen on the cell surface together with a major histocompatibility antigen (DR). Both IL-1 and TNF initiate a number of the processes involved in inflammation (*see* text). Under the influence of IL-1, resting T cells become activated following contact with processed antigen and DR and secrete a series of humoral factors (IL-2 through IL-6, gamma interferon [γIFN], and granulocyte-macrophage colony-stimulating factor [GM-CSF]). The cell-mediated response is amplified by γIFN, which enhances the processing of antigen by macrophages; by macrophage migration-inhibitory factor (MIF), which reduces the egress of wandering monocytes from affected areas; and by IL-2, which causes the clonal expansion of activated T cells. IL-2 also activates a particular group of cells to become cytotoxic (killer) lymphocytes. The inhibitory effects of glucocorticoids (represented by ||||||) are exerted on the release of IL-1 and TNF by activated macrophages, on the release of IL-2 by activated T cells, on the actions of MIF and γIFN on macrophages, and on the actions of IL-2 on activated T cells and perhaps on the precursors of killer lymphocytes. (Adapted from Dinarello and Mier, 1987.)

Transport, Metabolism, and Excretion. In the plasma, 90% or more of the cortisol is reversibly bound to protein under normal circumstances. The binding is accounted for by two proteins. One, corticosteroid-binding globulin, is a glycoprotein; the other is albumin. The globulin has high affinity but low total binding capacity, while albumin has low affinity but relatively large binding capacity. At low or normal concen-

trations of corticosteroids, most of the hormone is bound to globulin. Corticosteroids compete with each other for binding sites on the corticosteroid-binding globulin. Cortisol has high affinity; glucuronide-conjugated steroid metabolites and aldosterone have low affinities.

During pregnancy and during estrogen treatment in both sexes, corticosteroid-binding globulin, total plasma cortisol, and free cortisol increase several-fold. The physiological significance of these facts is not known. In contrast to the protein-bound steroid, the free hormone is biologically active, available for hepatic metabolism, and may be excreted by the kidney.

All the biologically active adrenocortical steroids and their synthetic congeners have a double bond in the 4,5 position and a ketone group at C 3. Reduction of the 4,5 double bond can occur at both hepatic and extrahepatic sites and yields an inactive substance. Subsequent reduction of the 3-ketone substituent to a 3-hydroxyl to form tetrahydrocortisol has been demonstrated only in liver. Most of the ring A–reduced metabolites are enzymatically coupled through the 3-hydroxyl with sulfate or with glucuronic acid to form water-soluble sulfate esters or glucuronides, and they are excreted as such. These conjugation reactions occur principally in liver and to some extent in kidney. Neither biliary nor fecal excretion is of quantitative importance in man.

Reversible oxidation of the 11-hydroxyl group has been demonstrated to occur slowly in a variety of tissues and rapidly in liver, kidney, colon, and parotid. As noted above, inactivation of cortisol by oxidation of the 11-hydroxyl group is thought to suppress the interaction of cortisol with the mineralocorticoid receptor in these organs (Funder *et al.*, 1988). Corticosteroids with an 11-ketone substituent require reduction to 11-hydroxyl compounds for their biological activity. Reduction of the 20-ketone group to a 20-hydroxyl configuration yields a substance having little, if any, biological activity. Corticosteroids with a hydroxyl group at C 17 undergo an oxidation that yields 17-ketosteroids and a two-carbon fragment. These 17-ketosteroids are totally lacking in corticosteroid activity but, in a few instances, have weak androgenic properties.

The metabolism of cortisol has been studied more extensively than that of all other corticosteroids, and it is generally assumed that the metabolism of its congeners and synthetic derivatives is qualitatively similar. Cortisol has a plasma half-life of about 1.5 hours. The metabolism of corticosteroids is greatly slowed by introduction of the 1,2 double bond or a fluorine atom into the molecule, and the half-life is correspondingly prolonged.

STRUCTURE–ACTIVITY RELATIONSHIP

Modifications of the structure of cortisol have led to increases in the ratio of antiinflammatory to Na^+-retaining potency, such that in a number of compounds electrolyte effects are of no serious consequence, even at the highest doses used. However, effects on inflammation and on carbohydrate and protein metabolism have always paralleled one another, and it seems very likely that these effects are mediated by the same type of receptor.

Changes in molecular structure may bring about changes in biological potency as a result of alterations in absorption, protein binding, rate of metabolic transformation, rate of excretion, ability to traverse membranes, and intrinsic effectiveness of the molecule at its site of action. In the following paragraphs, modifications of the pregnane nucleus that have been of value in therapeutic agents are described (*see* Figure 60–4). Table 60–3 lists the effects of the modifications discussed relative to cortisol.

Ring A. The 4,5 double bond and the 3-ketone are both necessary for typical adrenocorticosteroid activity. Introduction of a 1,2 double bond, as in prednisone or prednisolone, enhances the ratio of carbohydrate-regulating potency to Na^+-retaining potency by selectively increasing the former. In addition, prednisolone is metabolized more slowly than cortisol.

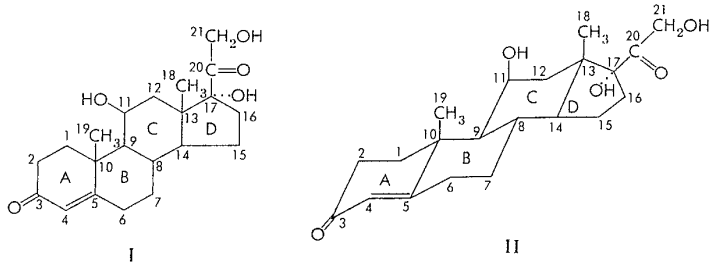
Ring B. 6α-Substitution has unpredictable effects. In the particular instance of cortisol, 6α-methylation increases antiinflammatory, nitrogen-wasting, and Na^+-retaining effects in man. In contrast, 6α-methylprednisolone has slightly greater antiinflammatory potency and less electrolyte-regulating potency than prednisolone. Fluorination in the 9α position enhances all biological activities of the corticosteroids, apparently by its electron-withdrawing effect on the 11β-hydroxy group.

Ring C. The presence of an oxygen function at C 11 is indispensable for significant antiinflammatory and carbohydrate-regulating potency (cortisol versus 11-desoxycortisol) but is not necessary for high Na^+-retaining potency, as demonstrated by desoxycorticosterone.

Ring D. 16-Methylation or hydroxylation eliminates the Na^+-retaining effect but only slightly modifies potency with respect to effects on metabolism and inflammation.

All presently used antiinflammatory steroids are 17α-hydroxy compounds. Although some carbohydrate-regulating and antiinflammatory effects may occur in 17-desoxy compounds (cortisol versus corticosterone), the fullest expression of these activities requires the presence of the 17α-hydroxy substituent.

All natural corticosteroids and most of the active synthetic analogs have a 21-hydroxy group. While some glycogenic and antiinflammatory activities may occur in its absence, its presence is required for significant Na^+-retaining activity.



I II

Figure 60–4. *Structure, stereochemistry, and nomenclature of adrenocorticosteroids, as typified by cortisol (hydrocortisone).*

The four rings—A, B, C, and D—are not in a flat plane, as conventionally represented in I, but have the approximate configuration shown in II. (The planarity of the valence angles about the double bond between C 4 and C 5 prevents the chair form of ring A, as shown, from being an energetically probable conformational state. As a result, ring A is in a half-chair conformation, not easily represented in two dimensions.) Orientation of the groups attached to the steroid ring system is important for biological activity. The methyl groups at C 18 and C 19, the hydroxyl group at C 11, and the two-carbon ketol side chain at C 17 project above the plane of the steroid and are designated β. Their connection to the ring system is shown by full-line bonds. The hydroxy at C 17 projects below the plane and is designated α, and the connection to the ring is shown by a dotted bond.

PREPARATIONS AND ROUTES OF ADMINISTRATION

Organic chemists have synthesized a bewildering number of modified adrenocorticosteroids, many of which share the same properties and differ only with respect to absolute dosage. At the outset it should be reemphasized that, whereas a clear separation has been made between mineralocorticoids and glucocorticoids, there is no member of the latter group that is unique with respect to a separation of therapeutic and toxic effects. A working knowl-

Table 60–3. RELATIVE POTENCIES AND EQUIVALENT DOSES OF CORTICOSTEROIDS

COMPOUND	RELATIVE ANTI-INFLAMMATORY POTENCY	RELATIVE NA^+-RETAINING POTENCY	DURATION OF ACTION *	APPROXIMATE EQUIVALENT DOSE † (*mg*)
Cortisol (Hydrocortisone)	1	1	S	20
Tetrahydrocortisol	0	0	—	—
Prednisone (Δ^1-Cortisone)	4	0.8	I	5
Prednisolone (Δ^1-Cortisol)	4	0.8	I	5
6α-Methylprednisolone	5	0.5	I	4
Fludrocortisone (9α-Fluorocortisol)	10	125	S	—
11-Desoxycortisol	0	0	—	—
Cortisone (11-Dehydrocortisol)	0.8	0.8	S	25
Corticosterone	0.35	15	S	—
Triamcinolone (9α-Fluoro-16α-hydroxyprednisolone)	5	0	I	4
Paramethasone (6α-Fluoro-16α-methylprednisolone)	10	0	L	2
Betamethasone (9α-Fluoro-16β-methylprednisolone)	25	0	L	0.75
Dexamethasone (9α-Fluoro-16α-methylprednisolone)	25	0	L	0.75

* S = Short, or 8- to 12-hour biological half-life; I = intermediate, or 12- to 36-hour biological half-life; L = long, or 36- to 72-hour biological half-life.

† These dose relationships apply only to oral or intravenous administration; relative potencies may differ greatly when injected intramuscularly or into joint spaces.

edge of a small number of preparations is sufficient for nearly every clinical purpose.

Corticosteroids are administered orally, parenterally, and topically. Some absorption into the systemic circulation occurs with all forms of topical administration. In the case of most respiratory aerosols, absorption is virtually equivalent to that from parenteral or oral administration. Adrenocortical suppression can occur with applications of steroids to the conjunctival sac and to the skin. Absorption from the skin is especially marked when the steroid is applied under plastic film over a large surface area.

Information on available steroid preparations is presented in Table 60–4.

TOXICITY OF ADRENOCORTICAL STEROIDS

Two categories of toxic effects are observed in the therapeutic use of adrenocorticosteroids: those resulting from withdrawal and those resulting from continued use of large doses. Acute adrenal insufficiency results from too-rapid withdrawal of corticosteroids after prolonged therapy. Protocols for discontinuing corticosteroid therapy in patients who have been subjected to suppressive therapy for long periods have been described by Harter and associates (1963) and Byyny (1976). A characteristic corticosteroid withdrawal syndrome, consisting of fever, myalgia, arthralgia, and malaise, may be extremely difficult to distinguish from "reactivation" of rheumatoid arthritis or rheumatic fever (Amatruda *et al.*, 1960). Pseudotumor cerebri with papilledema is a rare reaction that follows reduction or withdrawal of corticosteroid therapy (Levine and Leopold, 1973).

The use of corticosteroids for days or a few weeks does not lead to adrenal insufficiency upon cessation of treatment, but prolonged therapy with corticosteroids may result in suppression of pituitary–adrenal function that can be slow in returning to normal. Graber and coworkers (1965) found that the processes of recovery of normal pituitary and adrenal function required 9 months in some patients. During this recovery period and for an additional 1 to 2 years, the patient may need to be protected during stressful situations, such as surgery or severe infections, by the administration of corticosteroids. Dixon and Christy (1980) have discussed the complex clinical problems that can be provoked by withdrawal from steroid therapy.

In addition to pituitary–adrenal suppression, the principal complications resulting from prolonged therapy with corticosteroids are fluid and electrolyte disturbances; hypertension; hyperglycemia and glycosuria; increased susceptibility to infections, including tuberculosis; peptic ulcers, which may bleed or perforate; osteoporosis; a characteristic myopathy; behavioral disturbances; posterior subcapsular cataracts; arrest of growth; and Cushing's habitus, consisting of "moon face," "buffalo hump," enlargement of supraclavicular fat pads, "central obesity," striae, ecchymoses, acne, and hirsutism.

Hypokalemic alkalosis and edema are rarely encountered in patients who are treated with synthetic corticosteroid congeners and almost never in patients taking the 16-substituted compounds. Glycosuria can usually be managed with diet and/or insulin, and its occurrence should not be an important factor in the decision to continue corticosteroid therapy or to initiate it in diabetic patients.

Increased susceptibility to infection in patients treated with corticosteroids is generally considered not to be specific for any particular bacterial or fungal pathogen. However, it should be noted that steroid-induced inhibition of phagocytic killing of *Aspergillus* spores and *Nocardia* is not reversed by gamma-interferon, although the killing of many other microorganisms is restored to normal by such treatment (Schaffner and Schaffner, 1987). If infection develops in a patient treated with corticosteroids, the dose may be maintained or increased and the best available treatment for the infection vigorously administered. Corticosteroid therapy may be initiated in patients having known infections of some consequence if effective, specific chemotherapy can be administered concomitantly with the hormones. However, in these circumstances the physician should be confident that the corticosteroid is needed, that the pathogen has been identified, and that chemotherapy will be effective.

Peptic ulceration is an occasional compli-

NONPROPRIETARY
Fludrocortisone (FLORINEF ACE
Cortisol [3] (hydro (CORTEF, HYDR
Cortisol (hydroco (HYDROCORTON others)
Cortisol (hydroco (CORTEF)
Cortisol (hydroco phosphate (HYDROCORTON
Cortisol (hydrocor succinate (A-HYDROCORT,
Beclomethasone di (BECLOVENT, VA
Betamethasone [2] (CELESTONE)
Betamethasone ben (BENISONE, UTIC
Betamethasone dip (DIPROSONE, othe
Betamethasone sod (CELESTONE PHOS
Betamethasone sodi acetate (CELESTONE SOLU
Betamethasone vale (BETA-VAL, VALIS
Cortisone acetate [2] (CORTONE ACETAT
Dexamethasone [2] (DECADRON, other
Dexamethasone aceta (DECADRON-LA, oth
Dexamethasone sodiu (DECADRON PHOSPH PHOSPHATE, others)
Flunisolide [4] (AEROBID, NASALID

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adrenal suppres-
cations resulting
with corticoste-
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nia and glycosu-
ty to infections,
tic ulcers, which
osteoporosis; a
behavioral dis-
psular cataracts;
shing's habitus,
ice," "buffalo
praclavicular fat
triae, ecchymo-

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Table 60–4. PREPARATIONS OF ADRENOCORTICAL STEROIDS AND THEIR SYNTHETIC ANALOGS *

NONPROPRIETARY NAME (TRADE NAMES)	ORAL FORMS	INJECTABLE FORMS	OTHERS [1]
Fludrocortisone acetate [2] (FLORINEF ACETATE)	0.1 mg	—	—
Cortisol [3] (hydrocortisone) (CORTEF, HYDROCORTONE, others)	5–20 mg	25, 50 mg/ml (susp.)	TA: 0.25–2.5% 100-mg/60-ml enema 1% otic solution
Cortisol (hydrocortisone) acetate (HYDROCORTONE ACETATE, others)	—	25, 50 mg/ml (susp.)	TA: 0.5–1% 25-mg suppositories 10% rectal foam
Cortisol (hydrocortisone) cypionate (CORTEF)	2 mg/ml (susp.)	—	—
Cortisol (hydrocortisone) sodium phosphate (HYDROCORTONE PHOSPHATE)	—	50 mg/ml	—
Cortisol (hydrocortisone) sodium succinate (A-HYDROCORT, SOLU-CORTEF)	—	100–1000 mg (powder)	—
Beclomethasone dipropionate [4] (BECLOVENT, VANCERIL, others)	—	—	I: 42 μg per dose
Betamethasone [2] (CELESTONE)	0.6 mg 0.6 mg/5 ml (syrup)	—	—
Betamethasone benzoate (BENISONE, UTICORT)	—	—	TA: 0.025%
Betamethasone dipropionate (DIPROSONE, others)	—	—	TA: 0.05, 0.1%
Betamethasone sodium phosphate (CELESTONE PHOSPHATE, others)	—	4 mg/ml	—
Betamethasone sodium phosphate and acetate (CELESTONE SOLUSPAN)	—	6 mg/ml (susp.)	—
Betamethasone valerate (BETA-VAL, VALISONE, others)	—	—	TA: 0.01, 0.1%
Cortisone acetate [2] (CORTONE ACETATE)	5–25 mg	25, 50 mg/ml (susp.)	—
Dexamethasone [2] (DECADRON, others)	0.25–6.0 mg 0.5 mg/5 ml (elixir, soln.) 0.5 mg/0.5 ml (soln.)	—	TA: 0.01–0.1% O: 0.1%
Dexamethasone acetate (DECADRON-LA, others)	—	8, 16 mg/ml (susp.)	—
Dexamethasone sodium phosphate (DECADRON PHOSPHATE, HEXADROL PHOSPHATE, others)	—	4–24 mg/ml	TA: 0.1% O: 0.05, 0.1% I: 100 μg per dose
Flunisolide [4] (AEROBID, NASALIDE)	—	—	I: 25 μg per dose (nasal) 250 μg per dose (oral inhalation)

Table 60–4. PREPARATIONS OF ADRENOCORTICAL STEROIDS AND THEIR SYNTHETIC ANALOGS * (Continued)

NONPROPRIETARY NAME (TRADE NAMES)	ORAL FORMS	INJECTABLE FORMS	OTHERS [1]
Methylprednisolone [2] (MEDROL)	2–32 mg	—	—
Methylprednisolone acetate (DEPO-MEDROL, MEDROL ACETATE, others)	—	20–80 mg/ml (susp.)	TA: 0.25, 1%
Methylprednisolone sodium succinate (A-METHAPRED, SOLU-MEDROL)	—	40–2000 mg (powder)	—
Paramethasone acetate [2] (HALDRONE)	1, 2 mg	—	—
Prednisolone [2] (DELTA-CORTEF)	5 mg 3 mg/ml (syrup)	—	—
Prednisolone acetate (ECONOPRED, others)	—	25–100 mg/ml (susp.)	O: 0.12–1%
Prednisolone sodium phosphate (HYDELTRASOL, others)	1 mg/ml (liquid)	20 mg/ml	O: 0.125–1%
Prednisolone tebutate (HYDELTRA-T.B.A., others)	—	20 mg/ml (susp.)	—
Prednisone [2] (DELTASONE, others)	1–50 mg 1 mg/ml (syrup) 1, 5 mg/ml (soln.)	—	—
Triamcinolone [2] (ARISTOCORT, KENACORT)	1–8 mg	—	—
Triamcinolone acetonide (KENALOG, others)	—	3, 10, 40 mg/ml (susp.)	TA: 0.025–0.5% I: 100 μg per dose
Triamcinolone diacetate (ARISTOCORT, KENACORT DIACETATE, others)	2, 4 mg/5 ml (syrup)	25, 40 mg/ml (susp.)	—
Triamcinolone hexacetonide (ARISTOSPAN)	—	5, 20 mg/ml (susp.)	—
Alclometasone dipropionate [4] (ACLOVATE)	—	—	TA: 0.05%
Amcinonide [4] (CYCLOCORT)	—	—	TA: 0.1%
Clobetasol propionate [4] (TEMOVATE)	—	—	TA: 0.05%
Clocortolone pivalate [4] (CLODERM)	—	—	TA: 0.1%
Cortisol (hydrocortisone) butyrate (LOCOID)	—	—	TA: 0.1%
Cortisol (hydrocortisone) valerate (WESTCORT)	—	—	TA: 0.2%
Desonide [4] (DESOWEN, TRIDESILON)	—	—	TA: 0.05% 0.05% otic solution
Desoximetasone [4] (TOPICORT)	—	—	TA: 0.05, 0.25%

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NONPROPRIETARY N

Diflorasone diaceta (FLORONE, MAXIF

Fluocinolone acetor (FLUONID, SYNAL

Fluocinonide [4] (LIDEX)

Fluorometholone [4] (FLUOR-OP, FML)

Flurandrenolide [4] (CORDRAN)

Halcinonide [4] (HALOG)

Medrysone [4] (HMS LIQUIFILM)

Mometasone furoate (ELOCON)

* The preparation abc
[1] TA = topical applica
or aerosols; O = ophthal
[2] *See* Table 60–2 for c
[3] *See* Figure 60–2 for
[4] Beclomethasone, 9α
trihydroxy-16α-methylpr
16,17-acetal with cyclic p
diene-3,20-dione 17-prop
hydroxyprednisolone, cy
diacetate, 6α,9α-difluoro,
diene-3,20-dione cyclic 1
acetal with acetone;
fluorometholone, $\Delta^{1,2}$,9α
16,17-acetal with aceto
acetone; medrysone, 11
1,4-diene-3,20-dione 17-(2

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Table 60–4. PREPARATIONS OF ADRENOCORTICAL STEROIDS AND THEIR SYNTHETIC ANALOGS * (Continued)

NONPROPRIETARY NAME (TRADE NAMES)	ORAL FORMS	INJECTABLE FORMS	OTHERS [1]
Diflorasone diacetate [4] (FLORONE, MAXIFLOR)	—	—	TA: 0.05%
Fluocinolone acetonide [4] (FLUONID, SYNALAR, others)	—	—	TA: 0.01–0.2%
Fluocinonide [4] (LIDEX)	—	—	TA: 0.05%
Fluorometholone [4] (FLUOR-OP, FML)	—	—	O: 0.1, 0.25%
Flurandrenolide [4] (CORDRAN)	—	—	TA: 0.025, 0.05% 4 μg/sq cm tape
Halcinonide [4] (HALOG)	—	—	TA: 0.025, 0.1%
Medrysone [4] (HMS LIQUIFILM)	—	—	O: 1%
Mometasone furoate [4] (ELOCON)	—	—	TA: 0.1%

* The preparation above the double line is intended for use as a mineralocorticoid.

[1] TA = topical application to skin or mucous membranes in creams, solutions, ointments, gels, lotions, pastes (for oral lesions), or aerosols; O = ophthalmic solution, suspension, or ointment; I = nasal or oral inhalation.

[2] *See* Table 60–2 for chemical name.

[3] *See* Figure 60–2 for structure.

[4] Beclomethasone, 9α-chloro,16β-methylprednisolone,17,21-dipropionate; alclometasone dipropionate, 7α-chloro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate; amcinonide, 9α-fluoro,16α-hydroxyprednisolone cyclic 16,17-acetal with cyclic pentanone,21-acetate; clobetasol propionate, 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate; clocortolone, $\Delta^{1,2}$,6α-fluoro,9α-chloro,16α-methylcorticosterone 21-pivalate; desonide, 16α-hydroxyprednisolone, cyclic 16,17-acetal with acetone; desoximetasone, $\Delta^{1,2}$,9α-fluoro,16α-methylcorticosterone; diflorasone diacetate, 6α,9α-difluoro,16β-methylprednisolone, 17,21-diacetate; flunisolide, 6α-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone, hemihydrate; fluocinolone, 6α,9α-difluoro, 16α-hydroxyprednisolone,16,17-acetal with acetone; fluocinonide, 6α,9α-difluoro,16α-hydroxyprednisolone,16,17-acetal with acetone,21-acetate; fluorometholone, $\Delta^{1,2}$,9α-fluoro,6α-methyl, 11β,17-dihydroxyprogesterone; flurandrenolide, 6α-fluoro,16α-hydroxycortisol, 16,17-acetal with acetone; halcinonide, 21-chloro,9α-fluoro,11β,16α,17-trihydroxypregn-4-ene-3,20-dione,16,17-acetal with acetone; medrysone, 11β-hydroxy,6α-methylprogesterone; mometasone, 9,21-dichloro-11β-17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate).

cation of corticosteroid therapy. The high incidence of hemorrhage and perforation in these ulcers and the insidious nature of their development make them serious therapeutic problems. However, researchers disagree about the incidence of these ulcers, and some studies have concluded that the evidence does not support an association between peptic ulcers and treatment with glucocorticoids. It is also not known whether there is an interaction between glucocorticoids and nonsteroidal antiinflammatory drugs, such as aspirin, which, by themselves, can cause ulcers. Messer and associates (1983) concluded from a survey of the literature that steroid therapy approximately doubles the risk of ulcer (*see also* Spiro, 1983).

Myopathy, characterized by weakness of the proximal musculature of arms and legs and of their associated shoulder and pelvic muscles, is occasionally seen in patients taking large doses of corticosteroids. It may occur soon after treatment is begun and be sufficiently severe to prevent ambulation. It is not specific for synthetic corticosteroid congeners, for it is found in endogenous Cushing's syndrome. It is a serious complication and an indication for withdrawal of therapy. Recovery may be slow and incomplete (*see* Ellis, 1985; Knox *et al.*, 1986).

Behavioral disturbances may take various forms, including nervousness, insomnia, changes in mood or psyche, and psychopathies of the manic-depressive or schizophrenic type. Suicidal tendencies are

not uncommon. It is no longer believed that previous psychiatric problems predispose to behavioral disturbances during therapy with glucocorticoids. Conversely, the absence of a history of psychiatric illness is no guarantee against the occurrence of psychosis during hormonal therapy. Psychiatric reactions to glucocorticoid therapy have been reviewed by Lewis and Smith (1983).

Posterior subcapsular cataracts have been reported in children receiving corticosteroid therapy. The majority of patients with rheumatoid arthritis who receive 20 mg of prednisone per day for 4 years develop cataracts (Levine and Leopold, 1973); it is possible that patients with this disease are particularly susceptible to this complication. The problem of corticosteroid-induced cataracts has been reviewed by Urban and Cotlier (1986).

Osteoporosis and vertebral compression fractures are frequent serious complications of corticosteroid therapy in patients of all ages. Ribs and vertebrae, bones with a high degree of trabecular structure, are generally the most severely affected. Glucocorticoids appear to inhibit the activities of osteoblasts directly, and, because of their inhibition of Ca^{2+} absorption by the intestine, glucocorticoids cause an increased secretion of parathyroid hormone (PTH). PTH stimulates the activity of osteoclasts; thus, both decreased formation and increased resorption of bone occur. As noted above, corticosteroids also increase Ca^{2+} excretion by the kidney. Osteoporosis is an indication for withdrawal of therapy and should be looked for regularly in radiographs of the spine in patients taking glucocorticoids for longer than a few months. Unfortunately, significant loss of bone must occur before it is apparent from radiography. The possibility of development of osteoporosis should be an important consideration when initiating and managing corticosteroid therapy, especially in postmenopausal women (*see* Baylink, 1983).

Aseptic necrosis of bone (osteonecrosis) may complicate long-term therapy with glucocorticoids and has also been reported following short courses with high doses. The femoral head is most often involved, but other large joints may be affected. Joint pain and stiffness may be the earliest symptoms, and the syndrome is not reversible. The mechanism of this reaction is not known (Zizic *et al.*, 1985).

Inhibition or arrest of growth can result from the administration of relatively small doses of glucocorticoids to children, and it cannot be overcome with exogenous human growth hormone. The widespread inhibitory effect of the glucocorticoids on DNA synthesis and cell division discussed above is apparently responsible.

THERAPEUTIC USES

With the exception of substitution therapy in deficiency states, the use of corticosteroids and their congeners in disease is largely empirical. From the experience accumulated since the introduction of glucocorticoids for clinical use, at least six therapeutic principles may be abstracted, as follows: (1) for any disease, in any patient, the appropriate dose to achieve a given therapeutic effect must be determined by trial and error and must be reevaluated from time to time as the stage and the activity of the disease change; (2) a single dose of corticosteroid, even a large one, is virtually without harmful effects; (3) a few days of corticosteroid therapy, in the absence of specific contraindications, is unlikely to produce harmful results except at the most extreme dosages; (4) as corticosteroid therapy is prolonged over periods of weeks or months, and to the extent that the dose exceeds the equivalent of substitution therapy, the incidence of disabling and potentially lethal effects increases; (5) except in adrenal insufficiency, the administration of corticosteroids is neither specific nor curative therapy but only palliative by virtue of their antiinflammatory and immunosuppressive effects; and (6) abrupt cessation of prolonged, high-dose corticosteroid therapy is associated with a significant risk of adrenal insufficiency of sufficient severity to be threatening to life.

Translated into the terms of clinical practice, these general principles are equivalent to the following rules. When corticosteroids are to be administered over long periods, the dose must be the smallest one that will achieve the desired effect. This dose must be found by trial and error. Where the

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goal of therapy is relief of painful or distressing symptoms not associated with an immediately life-threatening disease—for example, rheumatoid arthritis—the initial dose should be small and gradually increased until pain or distress has been reduced to tolerable levels. Complete relief is not sought. At frequent intervals the dose should be gradually reduced until the development of more severe symptoms signals that the minimally acceptable dose has been found. When therapy is directed at a state that is immediately life-threatening (*e.g.*, pemphigus), the initial dose should be a large one, estimated to achieve control of the crisis. If some benefit is not observed in a short time, the dose should be doubled or tripled. When potentially lethal disease is controlled by large amounts of corticosteroid, reduction of the dose should be carried out under conditions that permit frequent, accurate observations of the patient. Under these circumstances it is essential to assess constantly the relative dangers of therapy and of the disease being treated.

The apparently innocuous character of a single administration of corticosteroid in amounts within the conventional therapeutic range justifies its use without a definite diagnosis for crises in which there exists some probability that life is threatened by primary adrenal or pituitary insufficiency. If one of these conditions is present, a single intravenous injection of a soluble corticosteroid may prevent immediate death and allow time for diagnostic procedures.

Short courses of systemic corticosteroids in large doses may properly be given for diseases that do not threaten life, in the absence of specific contraindications. The general rule is that long courses of therapy at high dosage should be reserved for life-threatening disease. On occasion, and for definite cause, when the patient is threatened with permanent disability, this rule is justifiably violated.

It is not possible to define the precise dose of glucocorticoids that will produce pituitary and adrenocortical suppression in a given patient, since there is considerable variation. In general, the higher the dose and the more prolonged the therapy, the greater is the likelihood of suppression. Doses of short-acting glucocorticoids administered in the morning (upon waking) have less capacity to suppress the pituitary than do those given in the afternoon or evening; doses taken late in the day suppress the normal surge of ACTH that occurs during sleep.

Harter and associates (1963) suggested that some dissociation of therapeutic effects from certain undesirable metabolic effects can be achieved by the administration of a single large dose of corticosteroid every other day, in contrast to the usual daily multiple-dose schedule. A single dose every other day or at even longer intervals is acceptable therapy for some, but not all, patients with a variety of diseases modified by corticosteroid therapy. When this therapeutic regimen is possible, the degree of suppression of the pituitary and adrenal cortex can be minimized. However, long-acting steroids are not suitable for use by this dosage schedule.

Substitution Therapy. Insufficiency of secretion of the adrenal cortex results from structural or functional lesions of the adrenal cortex itself (primary adrenal insufficiency) or from structural or functional lesions of the anterior pituitary (secondary adrenal insufficiency). In either case, the patient may present with acute, catastrophic adrenal insufficiency (adrenal crisis) or chronic adrenal insufficiency. When the adrenal itself is the site of the lesion, all elements of normal adrenal secretion may be reduced or absent, or the deficiency may be selective for one or more components of secretion.

Acute Adrenal Insufficiency. This life-threatening disease is characterized by gastrointestinal symptoms, dehydration, hyponatremia, hyperkalemia, weakness, lethargy, and hypotension. It is usually associated with disorders of the adrenal, rather than the pituitary, although exceptions occur. It frequently follows abrupt withdrawal of high doses of corticosteroids.

The immediate needs of such patients are water, sodium chloride, glucose, cortisol, and appropriate therapy for precipitating causes, for example, infection, trauma, or hemorrhage. Inasmuch as these patients have a diminished capacity for a water diuresis and have often undergone some degree of cellular hydration, they are susceptible to water intoxication. The principal intravenous fluid should be isotonic sodium chloride solution. Glucose is required for nutrition and to prevent or treat hypoglycemia, but it should be given intravenously in isotonic sodium chloride solution. The total amount of intravenous fluid administered during the first 24 hours should not, in most instances, exceed 5% of ideal body weight. The patient should be monitored for evidence of rising venous pressure and pulmonary edema, because adrenocortical insufficiency reduces the functional capacity of the cardiovascular system. Cortisol (hydrocortisone) sodium succinate or cortisol sodium phosphate must be given intravenously at a rate of 100 mg every 8 hours, following an initial intravenous injection of 100 mg. This provides a quantity of cortisol that is equal to the maximal daily rate of secretion in response to stress. In the period of transition from intravenous fluid therapy to normal diet and activity, intramuscular cortisol sodium succinate or sodium phos-

phate may be used in a dose of 25 mg every 6 or 8 hours.

For the treatment of suspected but unconfirmed acute adrenal insufficiency, 4 mg of dexamethasone sodium phosphate should be substituted for cortisol (because dexamethasone does not interfere with measurements of plasma cortisol concentrations). In addition, cosyntropin (0.25 mg) should be given to test for adrenal responsiveness. Concentrations of cortisol and aldosterone in plasma are determined at the outset and after 30 and 60 minutes. A failure to obtain a response to cosyntropin (stimulation of steroid secretion) is diagnostic of primary adrenal insufficiency. A lack of response in terms of aldosterone indicates failure of the zona glomerulosa. An increase in plasma cortisol that requires prolonged infusion of cosyntropin indicates pituitary insufficiency with secondary adrenal atrophy.

Chronic Primary Adrenal Insufficiency. This disease results from adrenal surgery or destructive lesions of the adrenal cortex. It requires the administration of cortisol, 20 to 30 mg per day in divided doses. A common dose schedule is 20 mg on arising and 10 mg in the late afternoon. Most patients will also require a potent mineralocorticoid. The most convenient drug to use for this purpose is fludrocortisone acetate. The usual adult dose is 0.1 to 0.2 mg daily. Some patients do not need a mineralocorticoid and are adequately treated with cortisone and generous dietary salt. Therapy is guided by the patient's sense of well-being, alertness, appetite, weight, muscular strength, pigmentation, blood pressure, and freedom from orthostatic hypotension.

Adrenal Insufficiency Secondary to Anterior Pituitary Insufficiency. This condition is not usually associated with the dramatic signs and symptoms characteristic of adrenal insufficiency resulting from disease of the adrenal cortex unless there are complicating circumstances, for example, unusual fluid losses, trauma, or starvation. Hypoglycemia is the most frequent cause of symptoms. Quantitation of the electrolytes in plasma often reveals a dilutional hyponatremia. The administration of 20 mg of cortisol on arising and 10 mg in late afternoon is adequate replacement therapy for most patients with anterior pituitary insufficiency. This schedule mimics, to some extent, the normal diurnal cycle of adrenal secretion. Occasional patients require additional doses. When initiating treatment, it is customary to begin cortisol first and to add thyroid replacement therapy after adrenal insufficiency is under some degree of control, on the grounds that the administration of thyroid to a hypopituitary patient may precipitate acute adrenal insufficiency. Additional treatment is necessary during periods of stress. Cortisol, 300 to 400 mg per day, should be given to approximate the normal response to severe stress.

Congenital Adrenal Hyperplasia. This is a familial disorder in which activity of one of several enzymes required for biosynthesis of corticosteroids is deficient. With diminished or absent production of cortisol, aldosterone, or both, and consequent lack of inhibitory feedback, the adrenal cortex is stimulated to overproduce other hormonally active steroids. The clinical presentation, laboratory findings, and treatment depend on which of the six enzyme deficiencies thus far described is responsible. Only the syndrome of 21-hydroxylase deficiency will be described here.

About 90% of the patients with congenital adrenal hyperplasia have a deficiency of 21-hydroxylase activity. When the deficiency is only partial, the usual case, cortisol is secreted at normal rates as a result of continuous hypersecretion of ACTH, with consequent overproduction of adrenal androgens and their precursors. Aldosterone secretion is approximately normal. Female children undergo virilization (female pseudohermaphroditism) and male children show precocious development of secondary sex characteristics (macrogenitosomia). Linear growth is accelerated in childhood, but the height at maturity is reduced by premature closure of the epiphyses.

In about 30% of patients with 21-hydroxylase deficiency, the enzymatic defect is sufficiently severe to compromise increased aldosterone secretion in response to a hypovolemic stimulus. Such patients are unable to conserve Na^+ normally, in addition to manifesting androgenic effects (Bongiovanni *et al.*, 1967).

All patients with congenital adrenal hyperplasia resulting from a 21-hydroxylase deficiency require substitution therapy with cortisol or a suitable congener, and those with a salt-losing tendency require, in addition, a Na^+-retaining steroid. The usual oral dose of cortisol is about 0.6 mg/kg daily in two to four divided doses. The mineralocorticoid usually given is fludrocortisone acetate, 0.05 to 0.2 mg per day. Therapy is guided by gain in weight and height, by excretion of urinary 17-ketosteroids, and by blood pressure. Sudden spurts of linear growth may indicate inadequate pituitary suppression and excessive androgen secretion, whereas growth failure suggests overtreatment.

A number of rare forms of congenital adrenal hyperplasia are known in which enzyme deficiencies of the adrenal cortex, with similar defects of the gonads, result in clinical and laboratory findings very different from those described above for 21-hydroxylase deficiency. The types described thus far are "desmolase" deficiency (Camacho *et al.*, 1968), 3β-hydroxysteroid dehydrogenase deficiency (Bongiovanni *et al.*, 1967), 17α-hydroxylase deficiency (Goldsmith *et al.*, 1968), 11β-hydroxylase deficiency (Bongiovanni *et al.*, 1967), and 18-hydroxylase deficiency (David *et al.*, 1968). The clinical and laboratory findings and the treatment in these rare forms are quite different from those in 21-hydroxylase deficiency. The publications cited should be consulted for details.

Therapeutic Uses in Nonendocrine Diseases. Brief outlines of important uses of corticosteroids in diseases other than those involving the pituitary–adrenal complex are set forth below. The disorders discussed are not inclusive, but rather a representative list of the more common diseases for which the glucocorticoids are used.

The dosage of glucocorticoids varies greatly with the condition being treated. In the following discussion approximate doses of a representative cortico-

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steroid congener, usually prednisone, are suggested. It is not meant to imply that prednisone has peculiar merit in general or for any particular disease over the other congeners. For a comparison of doses of glucocorticoids, *see* Table 60–3.

Arthritis. In rheumatoid arthritis, the criterion for initiating corticosteroid therapy is progressive disease with consequent disability, despite intensive treatment with rest, physical therapy, aspirin-like drugs, gold, and other agents. The decision to embark upon a program of hormone therapy must be made with due consideration for the fact that corticosteroid therapy, once started, may have to be continued for many years or for life, with the attendant risks of serious complications. The initial dose should be small and increased slowly until the desired degree of control is attained. The symptomatic effect of small reductions should be frequently tested to maintain the dose as low as possible. Complete relief is not sought. A regimen of rest, physical therapy, and aspirin-like drugs is continued. The usual initial dose is about 10 mg of prednisone (or equivalent) per day in divided doses. Optimal therapy for some patients with painful symptoms confined to one or a few joints may be intraarticular injection of the steroid into the affected joints. Typical doses are 5 to 20 mg of triamcinolone acetonide or its equivalent, depending upon the size of the joint cavity.

In osteoarthritis, intraarticular injection of corticosteroids is recommended for treatment of episodic manifestations of acute inflammation. Injections for this purpose should be infrequent because, in both rheumatoid arthritis and osteoarthritis, a significant incidence of painless destruction of the joint, reminiscent of Charcot's arthropathy, may be associated with repeated intraarticular injections of corticosteroids.

Rheumatic Carditis. Corticosteroids are reserved for patients failing to respond to salicylates and as initial therapy for patients severely ill with fever, acute congestive heart failure, arrhythmia, and pericarditis; acute manifestations are more rapidly suppressed by corticosteroids than by salicylates, a possibly lifesaving difference in a moribund patient. A dose of approximately 40 mg of prednisone or equivalent is usually given daily, in divided amounts, although much larger doses may on occasion be required. Reactivation of the disease occurs in a number of instances following withdrawal of steroid therapy. For this reason it has been suggested that salicylates be given concurrently with corticosteroids and be continued through and after the period of withdrawal of hormone therapy.

Renal Diseases. Corticosteroids do not modify the course of acute or chronic glomerulonephritis. However, patients with some forms of the nephrotic syndrome attributable to systemic lupus erythematosus or to primary renal disease (except renal amyloidosis) may be benefited by corticosteroid therapy. A typical therapeutic regimen consists in the daily administration, in divided doses, of 60 mg of prednisone or equivalent (2 mg/kg of edema-free body weight in children) for 3 or 4 weeks. If a remission with a diuresis and decreased proteinuria occurs during this period, maintenance treatment is continued for as long as a year. During maintenance therapy, the daily dose of prednisone is given only for the first 3 days of each week (Bacon and Spencer, 1973).

Collagen Diseases. The manifestations of most of the diseases in this group are controlled by glucocorticoids. An exception is scleroderma, which is generally considered refractory to these agents. It is important to distinguish between scleroderma and mixed connective tissue disease syndrome, which is responsive to steroids (Yount *et al.*, 1973). Polymyositis, polyarteritis nodosa, and the granulomatous-polyarteritis group (Wegener's granulomatosis, temporal-cranial arteritis, and polymyalgia rheumatica) are treated with daily doses of prednisone, approximately 1 mg/kg or equivalent, to induce a remission. The dose is then tapered down to the minimally effective level. Glucocorticoids decrease morbidity in all these diseases and prolong the survival times of patients with polyarteritis nodosa and Wegener's granulomatosis. In temporal (giant-cell) arteritis, adequate steroid therapy is necessary to prevent the blindness that occurs in about 20% of untreated cases. Fulminating systemic lupus erythematosus is a life-threatening condition, the manifestations of which should be suppressed by adrenocorticosteroid therapy with doses large enough to produce a prompt effect. Treatment usually consists of a 1-mg/kg daily dose of prednisone or equivalent. Within 48 hours, reduction of fever and improvement in the signs and symptoms of arthritis, pleuritis, or pericarditis should be observed. If not, the dose should be increased in 20-mg increments daily until a favorable response occurs. After the acute episode has been brought under control, corticosteroid therapy should be reduced by small steps, for example, 5 mg of prednisone per week, until signs or symptoms warn against further reductions. Salicylate or related drugs are then introduced and may permit a further reduction of corticosteroid dosage. A combination of glucocorticoids and antimetabolites, such as azathioprine, or the alkylating agent cyclophosphamide, has been used in selected patients with lupus erythematosus, particularly those with renal involvement. The concurrent use of these agents with steroids has been reviewed by Russell and Bretscher (1987).

Allergic Diseases. The manifestations of allergic disease that are of limited duration, such as hay fever, serum sickness, urticaria, contact dermatitis, drug reactions, bee stings, and angioneurotic edema, can, if necessary, be suppressed by adequate doses of glucocorticoids given as a supplement to the primary therapy. It must be emphasized, however, that the effects of the steroids require some time to develop, and severe reactions such as anaphylaxis and angioneurotic edema of the glottis require immediate therapy with epinephrine, 0.3 to 1.0 ml of a 1:1000 solution (0.3 to 1.0 mg) intramuscularly or subcutaneously. In life-threatening situations steroids may be given intravenously; dexamethasone sodium phosphate (8 to 12 mg or equivalent) is appropriate. In less severe diseases, such as serum sickness or hay fever, antihistaminic compounds are the drugs of first choice.

Bronchial Asthma. The corticosteroids should not be used routinely in the treatment of any asth-

matic condition, acute or chronic, that can promptly be brought under moderate control with other measures. However, in status asthmaticus, glucocorticoids should be administered early and in large doses even though their effect is delayed (*see* Chapter 25). Intravenous administration of 60 to 120 mg of methylprednisolone sodium succinate every 6 hours is followed by daily oral doses of prednisone (40 to 60 mg) when the attack has subsided. The dose is then reduced in steps and withdrawal planned for about the tenth day after initiation of the prednisone therapy. Under favorable circumstances, patients can subsequently be managed once again with their prior medication.

Acute exacerbations of asthma are often treated with brief courses of oral corticosteroids. For example, 30 mg of prednisone (in children over 3 years of age) is administered twice daily for 5 days; an additional week of therapy at lower doses may be required. Upon restoration of adequate responses to other medications, the corticosteroid can usually be withdrawn abruptly; any suppression of adrenal function appears to dissipate within 1 or 2 weeks. In the treatment of severe chronic bronchial asthma (or less frequently, chronic obstructive pulmonary disease) that is not controlled by other measures, the administration of a corticosteroid may be necessary. As with other long-term uses of these agents, the lowest effective dose is utilized and care must be exercised when withdrawal is attempted; such therapy is never undertaken without the concurrent use of other medication, such as inhaled β_2-adrenergic agonists and/or oral theophylline.

The incorporation of inhaled corticosteroids in regimens for the treatment of bronchial asthma has increased substantially in recent years. In some patients, the use of inhaled solutions (most frequently beclomethasone dipropionate, triamcinolone acetonide, or flunisolide) can either reduce the duration of courses of oral corticosteroids or replace them entirely. In addition, many physicians recommend replacement of oral theophylline by inhaled glucocorticoids in the treatment of children with moderately severe asthma, in part because of the behavioral toxicity associated with long-term administration of theophylline. When inhaled, glucocorticoids are effective in reducing bronchial hyperreactivity and do not produce appreciable suppression of adrenal function when used at the recommended doses. Dysphonia or oropharyngeal candidiasis may develop, but the incidence of such side effects can be reduced substantially by maneuvers that reduce the deposition of drug in the oral cavity. The current status of glucocorticoids in the therapy of asthma has been reviewed by Cott and Cherniack (1988), and further discussion is presented in Chapter 25.

Ocular Diseases. Corticosteroids are frequently used to suppress inflammation in the eye, and used properly they are often responsible for preservation of sight. Levine and Leopold (1973) list 28 disorders of the eye that respond to corticosteroids. They are administered locally for disease of the outer eye and anterior segment. Both natural and synthetic corticosteroids attain therapeutic concentrations in the aqueous humor following instillation into the conjunctival cul-de-sac. For disease of the posterior segment, systemic administration is required.

A typical prescription is 0.1% dexamethasone sodium phosphate solution (ophthalmic), 2 drops in the conjunctival sac every 4 hours while awake, and 0.05% dexamethasone phosphate ointment (ophthalmic) at bedtime. For inflammations of the posterior segment of the eye, usual daily doses are approximately 30 mg of prednisone or equivalent, administered orally in divided doses.

It has been convincingly demonstrated that topical corticosteroid therapy frequently induces intraocular hypertension in normal eyes and further increases pressure in eyes with initially elevated pressure. The glaucoma has not always been reversible on cessation of corticosteroid treatment. It has been recommended that intraocular pressure be monitored when corticosteroids are applied to the eye for more than 2 weeks.

The local administration of corticosteroids to patients with bacterial, viral, or fungal conjunctivitis may mask evidence of progression of the infection until sight is lost. Corticosteroids are contraindicated in herpes simplex (dendritic keratitis) of the eye, because progression of the disease and irreversible clouding of the cornea may occur. Topical steroids should not be used in the treatment of mechanical lacerations and abrasions of the eye. They delay healing and promote the development and spread of infection. It is generally recommended that the ocular use of glucocorticoids be under the supervision of an ophthalmologist.

Skin Diseases. The development of corticosteroid preparations suitable for topical administration has revolutionized the therapy of the more common varieties of skin disease. Maibach and Stoughton (1973) have divided 20 dermatological disorders that respond to topical corticosteroids into those that are very responsive and those that require higher concentrations of steroids, occlusion of the drug under a plastic film, or intralesional administration. Attention must be paid to the concentration of steroid used; a large number of preparations of various concentrations are available for topical use (*see* Table 60–4). A typical prescription for an eczematous eruption is 1% cortisol ointment applied locally twice daily. Effectiveness is enhanced by application of the cream or ointment under a transparent plastic wrapping. Unfortunately, systemic absorption is also enhanced, occasionally sufficiently to suppress the pituitary–adrenal axis or to produce Cushing's syndrome. Adrenocorticosteroids are administered systemically for severe episodes of acute skin disorders and exacerbations of chronic disorders. The dose is usually 40 mg per day of prednisone or equivalent. Systemically administered corticosteroids may be lifesaving in pemphigus. Up to 120 mg of prednisone or equivalent per day may be required to control the disease. Further discussion of the treatment of skin disorders is presented in Chapter 65.

Diseases of the Intestinal Tract. Patients severely ill with untreated celiac sprue can often benefit from a course of glucocorticoid therapy given at the same time that management with a gluten-free diet is begun. Prednisolone, 30 mg per day or

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Corticosteroid therapy is indicated in selected patients with inflammatory bowel disease (chronic ulcerative colitis and Crohn's disease). Mildly ill patients with bowel symptoms but without disabling systemic symptoms usually can and should be managed with rest, diet, anticholinergic or other antidiarrheal agents, and sulfasalazine or metronidazole. However, patients who do not improve may benefit from corticosteroids. In mild ulcerative colitis, cortisol, 100 mg or equivalent, can be administered as a nightly retention enema in an attempt to induce remission. Alternate-day therapy may be effective. Patients with active Crohn's disease or ulcerative colitis may benefit from oral prednisone (10 to 30 mg daily). Severely ill patients with fever, anorexia, anemia, and malnutrition often improve dramatically when given systemic corticosteroid therapy. Large doses, 60 to 120 mg per day of prednisone or its equivalent, are recommended. Major complications of ulcerative colitis or Crohn's disease may occur despite corticosteroid therapy. Signs and symptoms of intestinal perforation and peritonitis may be difficult to detect during corticosteroid treatment (ReMine and McIlrath, 1980).

Cerebral Edema. Corticosteroids are of value in the reduction or prevention of cerebral edema associated with neoplasms, especially those that are metastatic. In spite of widespread use of glucocorticoids for treatment of the cerebral edema caused by trauma or cerebrovascular accidents, there is no convincing evidence of their value in these conditions (Nelson and Dick, 1975).

Malignancies. Glucocorticoids are used in the chemotherapy of acute lymphocytic leukemia and lymphomas because of their antilymphocytic effects. These diseases are treated in a complex fashion with rigidly scheduled sequences of combined drug therapy. Prednisone is commonly used in conjunction with an alkylating agent such as cyclophosphamide, an antimetabolite, and a vinca alkaloid (*see* Chapter 52).

Glucocorticoids can induce objective tumor regression in carcinoma of the breast in about 15% of patients; prednisolone (30 mg per day) has been the usual treatment. The presumed mechanism by which the corticosteroids act in this disease is through adrenocortical suppression, with an accompanying decrease in production of androgens, which are precursors of tumor-stimulating estrogens. A beneficial response should be expected only when the tumor has estrogen and/or progesterone receptors. Other forms of therapy are usually more effective.

Diseases of the Liver. The use of glucocorticoids in the treatment of hepatic diseases has been the subject of controversy. Careful studies have now indicated several diseases of the liver in which therapy with steroids significantly improves survival rates: subacute hepatic necrosis and chronic active hepatitis, alcoholic hepatitis, and nonalcoholic cirrhosis in women (Lesesne and Fallon, 1973; Copenhagen Study Group for Liver Diseases, 1974). Only certain patients with chronic active hepatitis should receive steroid therapy. Those who benefit have symptomatic disease, histological evidence of severe disease, and a negative reaction for hepatitis B surface antigen (Berk *et al.*, 1976). Treatment of subacute hepatic necrosis and chronic active hepatitis includes prednisolone, 60 to 100 mg per day; the dose is tapered as the disease improves. Treatment of alcoholic hepatitis with corticosteroids is reserved for patients who are severely ill, with evidence of hepatic encephalopathy. Prednisone (40 mg per day) is given for 1 month, followed by withdrawal over a period of 2 to 4 weeks (Carithers *et al.*, 1989). Nonalcoholic cirrhosis in women should be treated with glucocorticoids if the patient does not have ascites. Daily dosages average 15 to 20 mg of prednisone or equivalent when they are adjusted to the needs of the individual patients. The data indicate that steroid treatment lowers survival rates when ascites is present. Treatment of cirrhotic male patients with steroids has not been shown to be beneficial.

Shock. While corticosteroids are often administered to patients in shock, there is no convincing evidence to indicate that such therapy is efficacious.

Miscellaneous Diseases. Sarcoidosis is treated with prednisone, approximately 1 mg/kg per day or equivalent, to induce a remission. Maintenance doses, which are often required for long periods of time, may be 10 mg of prednisone per day or less. In this, as in other diseases treated by prolonged steroid therapy, patients with positive tuberculin reactions or other evidence of tuberculosis should receive prophylactic antituberculosis therapy. In thrombocytopenia, prednisone, 0.5 mg/kg or equivalent, is used to decrease the bleeding tendency. In severe cases and for initiation of treatment of idiopathic thrombocytopenia, daily doses of prednisone, 1 to 1.5 mg/kg, are employed. Hemolytic anemias with a positive Coombs' test are treated with prednisone, 1 mg/kg per day or equivalent. If hemolysis is severe, therapy is initiated with 100 mg of cortisol intravenously; as the disease improves, the dose is decreased. Small maintenance doses may be needed for several months if a positive response is obtained. In organ transplantation, high doses of prednisone (50 to 100 mg) are given at the time of the transplant surgery, usually in conjunction with immunosuppressive agents. Smaller maintenance doses (10 to 20 mg per day) are continued indefinitely, and the dosage is increased if rejection is threatened (*see* Chapter 53). Glucocorticoids have been used to treat aspiration of gastric contents, but no controlled studies have demonstrated their efficacy in this condition, and several uncontrolled studies suggest that steroids do not reduce morbidity or mortality.

DIAGNOSTIC APPLICATIONS OF ADRENOCORTICAL STEROIDS

Potent synthetic congeners of cortisol reduce urinary excretion of cortisol metabolites by inhibition

of pituitary ACTH release. The dose required is so small, in gravimetric terms, that it contributes only negligibly to the urinary steroids. The administration of 0.5 mg of dexamethasone every 6 hours for a total of eight doses results in a marked suppression of excretion of cortisol metabolites in normal persons, but does not suppress urinary steroids in individuals with Cushing's syndrome. This test is useful in distinguishing persons with some nonspecific elevation of steroid excretion, for example, that due to obesity or stress, from patients with Cushing's syndrome. The administration of 2 mg of dexamethasone every 6 hours for a total of eight doses usually causes a suppression of cortisol secretion in most patients with pituitary-dependent hypercorticism, but ordinarily has little if any effect on the urinary steroids of patients with adrenal neoplasms or ectopic ACTH-producing tumors. However, "suppressible" tumors have been reported. The results of these tests are likely to be most definite if the urinary steroids are measured daily for 2 days before and for at least 2 days during administration of the suppressing agent. Variations of this procedure (shorter test period and measurement of plasma cortisol rather than urinary metabolites) have been described (Sawin *et al.*, 1968).

INHIBITORS OF THE BIOSYNTHESIS OF ADRENOCORTICAL STEROIDS

Five pharmacological agents have proved useful as inhibitors of adrenocortical secretion. Mitotane (*o,p'*-DDD), an adrenocorticolytic agent, is discussed in Chapter 52. Metyrapone, aminoglutethimide, ketoconazole, and trilostane are discussed here. The first three agents act by inhibiting those cytochrome P_{450}–containing enzymes that are involved in the synthesis of steroid hormones. As will be discussed below, there is considerable difference in susceptibility of the various reactions to these agents, thus providing some degree of specificity to their actions. Trilostane is a competitive inhibitor of the conversion of pregnenolone to progesterone.

Metyrapone. Metyrapone reduces cortisol production by inhibition of the 11β-hydroxylation reaction. It also inhibits 18-hydroxylation and side chain cleavage to some degree, but the latter effect is largely overcome when ACTH stimulates the gland. The biosynthetic process is terminated at 11-desoxycortisol (*see* Figure 60–2), a compound that has practically no inhibitory influence on the secretion of ACTH. In the normal person, a compensatory increase in ACTH secretion follows, and the secretion of 11-desoxycortisol, a "17-hydroxycorticoid," is markedly accelerated. Consequently, in normal persons, administration of metyrapone induces increases in the concentrations of ACTH and desoxycorticosterone in plasma and elevates the renal excretion of "17-hydroxycorticoids."

Metyrapone is used to test the capacity of the pituitary to respond to a decreased concentration of plasma cortisol. A response that is greater than normal is usually found in patients with Cushing's syndrome of pituitary origin, while in most cases of Cushing's syndrome caused by ectopic production of ACTH there is no response to the drug. Administration of metyrapone to patients with disease of the hypothalamico–pituitary complex who are unable to achieve a compensatory increase in the rate of secretion of ACTH is, of course, not followed by increased renal excretion of 17-hydroxycorticoids or increased plasma desoxycorticosterone.

The ability of the adrenal cortex to respond to ACTH should be demonstrated before metyrapone is employed, for two reasons: (1) administration of metyrapone can be used as a test for normal hypothalamico–pituitary function only if the adrenal glands are capable of responding to ACTH, and (2) the drug may induce acute adrenal insufficiency in patients with reduced adrenal secretory capacity. Metyrapone also inhibits synthesis of aldosterone, which, like cortisol, is an 11β-hydroxylated compound. However, metyrapone does not typically cause a deficiency of mineralocorticoids, with a consequent loss of Na^+ and retention of K^+, because the inhibition of the 11β-hydroxylation reaction results in an increased production of 11-desoxycorticosterone, a mineralocorticoid.

Metyrapone has been used successfully to treat the hypercortisolism that results either from adrenal neoplasms that function autonomously or from ectopic ACTH production by tumors. Its use in the treatment of Cushing's syndrome resulting from hypersecretion of ACTH by the pituitary is controversial (Orth, 1978; Gold, 1979). Long-term treatment with metyrapone can cause hypertension as the result of excessive secretion of desoxycorticosterone.

Metyrapone (METOPIRONE) is 2-methyl-1,2-di-3-pyridyl-1-propanone. The drug is marketed as 250-mg oral tablets. Following two 24-hour control periods, the drug is given orally at a dosage of 750 mg every 4 hours for six doses. Maximal urinary excretion of 17-hydroxycorticoids is observed on the next day.

Aminoglutethimide. This compound, α-ethyl-*p*-aminophenyl-glutarimide, primarily inhibits the conversion of cholesterol to 20α-hydroxycholesterol. This inhibition of the first reaction of steroidogenesis from cholesterol interrupts production of both cortisol and aldosterone.

Aminoglutethimide has been used successfully to decrease the hypersecretion of cortisol in autonomously functioning adrenal tumors and in hypersecretion resulting from ectopic production of ACTH. It has also been used in combination with metyrapone in the treatment of Cushing's syndrome that results from hypersecretion of ACTH by the pituitary (*see* Gold, 1979). Substitution of

physiological doses of cortisol may be required to prevent adrenal insufficiency. It has also been used experimentally for treatment of prostatic and breast cancers (*see* Chapter 52).

Aminoglutethimide (CYTADREN) is marketed as 250-mg oral tablets. The suggested initial dosage is 250 mg every 6 hours. The dose is increased by 250 mg per day at 1- or 2-week intervals until the desired effect is achieved, side effects prohibit further increments, or a daily dose of 2 g is reached.

Ketoconazole. Ketoconazole is an antifungal agent, and this remains its most important role (*see* Chapter 50). In higher doses than those required for antimicrobial therapy, it is an effective inhibitor of steroid biosynthesis in the adrenal cortex and the testis. The most susceptible P_{450} system is apparently the C_{19-20} ligase of the testis, which accounts for its effectiveness in inhibiting the synthesis of testosterone. At higher doses, the drug inhibits the cholesterol side chain–cleavage enzyme system in the adrenal and effectively blocks the synthesis of adrenal hormones. Ketoconazole is a promising agent for management of Cushing's syndrome and carcinoma of the prostate, but the full metabolic consequences of its actions are not known. The use of ketoconazole as an inhibitor of hormone synthesis has been reviewed by Sonino (1987).

Trilostane. This compound ([2α,4α,5α,17β]-4,5-epoxy-17-hydroxy-3-oxoandrostane-2-carbonitrile) is a reversible inhibitor of 3β-hydroxysteroid dehydrogenase (*see* Figure 60–2). Trilostane reduces the synthesis of both cortisol and aldosterone and causes increased urinary excretion of 17-ketosteroids (primarily 3α-hydroxy-17-ketosteroids). The drug has been used in the treatment of Cushing's syndrome when more definitive therapy cannot be utilized. Experimentally, trilostane corrects the hypokalemia and lowers plasma concentrations of aldosterone and systemic blood pressure in patients with primary aldosteronism or in hypertensive patients who become hypokalemic during long-term therapy with diuretics (Winterberg *et al.*, 1985; Griffing and Melby, 1989). Although the drug is not likely to produce adrenocortical insufficiency, it may prevent an adequate response to ACTH during stress. Very few patients have been treated with trilostane for more than 3 months, and its place in long-term therapy has not been established.

Trilostane (MODRASTANE) is available in 30- and 60-mg capsules. Initial dosage is 30 mg four times a day; this is increased gradually at intervals of 3 to 4 days to a maximum daily dose of 480 mg.

ANTIGLUCOCORTICOIDS

A number of steroids have been shown to antagonize the effects of cortisol in systems *in vitro*. However, until recently, none of these agents displayed significant antiglucocorticoid effects *in vivo*. Mifepristone, (11β-4-dimethylaminophenyl)-17β-hydroxy-17α-(propyl-1-ynyl)estra-4,9-dien-3-one, was developed originally as a progesterone antagonist, but it also is a highly effective antagonist of the glucocorticoids. The role of mifepristone in the treatment of Cushing's syndrome caused by ectopic production of ACTH or autonomous corticosteroid secretion by adrenal tumors is currently being investigated. Glucocorticoid antagonists have been reviewed by Agarwal and associates (1987).

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CHAPTER

61 INSUL AND ENDO

C. Ror

INSULIN

History. There are medicine more drama lin. Although approp and Best, there were laborators who prov and techniques that r In 1869, a German m hans, noted that the p groups of cells—the a gestive enzymes, and islands, or islets, whic ond function. Direct came in 1889, when C von Mering showed t exhibit a syndrome si man (*see* Minkowski,

There were numerc pancreatic substance r blood glucose. In the Zuelzer, an internist in dying diabetic patient Although the patient sank back into coma a extract was exhausted. University of Chicago, to isolate an active pri holic extracts of the par those eventually used t treated several diabetic sults; however, he lacke of blood glucose concer considered the experim Between 1916 and 1920, Nicolas Paulesco cond ments in which he foun atic extracts reduced ur diabetic dogs. Although his experiments, their si ciated only many years

Unaware of much of t Frederick G. Banting, a convinced a professor J. J. R. Macleod, to allo tory to search for the ar pancreas. Banting assur secreted insulin, but th stroyed by proteolytic di extraction. Together with dent, Charles H. Best, h the problem by tying the

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