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.

When radioactive-carbon, ring-labeled steroids are injected intravenously in man, most of the radioisotope is recovered in the urine within 72 hours. Neither biliary nor fecal excretion is of any quantitative importance in man. It has been estimated that the liver metabolizes at least 70% of the cortisol secreted.

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.

Clinical laboratories measure urinary cortisol and metabolites with reduced ring A as "17-hydroxycorticosteroids." These compounds and those where the ketone at carbon 20 has been reduced are included in the group referred to as "17-ketogenic steroids." The urinary metabolites that have lost their side chain contribute to the "17-ketosteroids."

STRUCTURE-ACTIVITY RELATIONSHIP

Cortisone was the first corticosteroid used for its anti-inflammatory effect. Modifications of structure have led to increases in the ratio of anti-inflammatory to sodium-retaining potency, such that in a number of presently available compounds electrolyte effects are of no serious consequence, even at the highest doses used. However, in all compounds studied to date, effects on inflammation and on carbohydrate and protein metabolism have paralleled one another. It seems very likely that effects on inflammation and metabolism 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. The molecular sites of alteration are shown in Figure 63–4 in bold lines and letters. Table 63–3 lists the effects of the modifications discussed relative to cortisol. As indicated above, relative potencies vary to some extent with different conditions of bioassay.

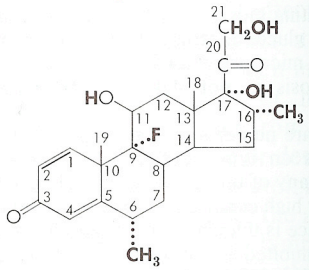

Figure 63–4. *Structure-activity relationship of adrenocorticosteroids.*

Light lines and letters indicate structural features common to compounds having anti-inflammatory action. Bold lines and letters indicate modifications that enhance or suppress characteristic activities. (After Liddle, 1961. Courtesy of *Clinical Pharmacology and Therapeutics*.)

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 sodium-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 anti-inflammatory, nitrogen-wasting, and sodium-retaining effects in man. In contrast, 6α-methylprednisolone has slightly greater anti-inflammatory 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 anti-inflammatory and carbohydrate-regulating potency (cortisol versus 11-desoxycortisol) but is not necessary for high sodium-retaining potency, as demonstrated by desoxycorticosterone.

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

All presently used anti-inflammatory steroids are 17α-hydroxy compounds. Although some carbohydrate-regulating and anti-inflammatory 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 anti-inflammatory activities may occur in its absence, its presence is required for significant sodium-retaining activity.