Drug Treatment of Disease

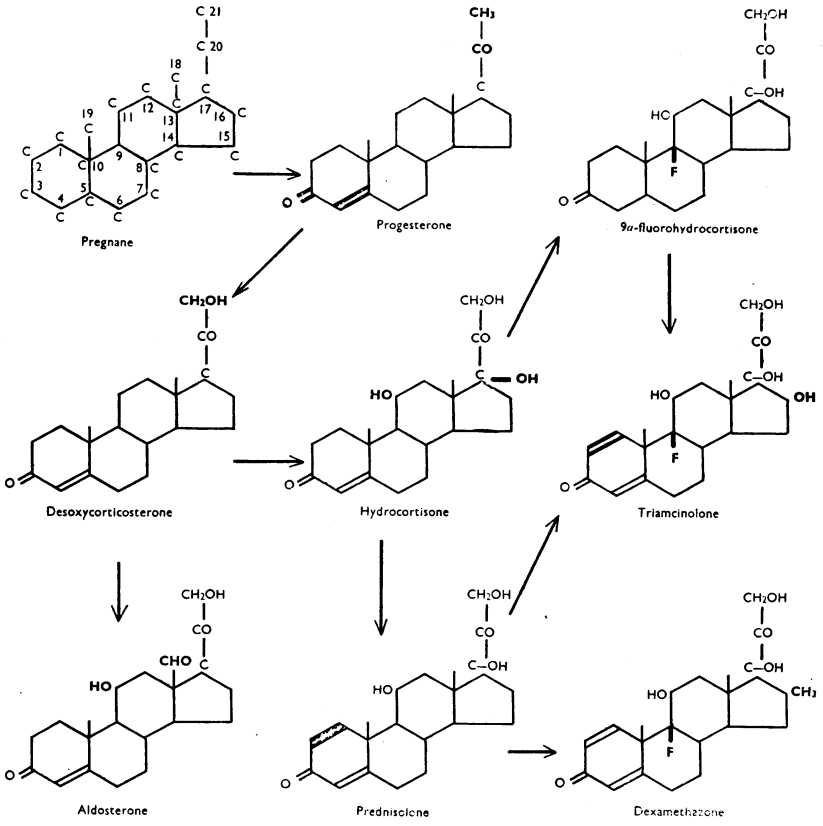
PRINCIPLES OF MODERN STEROID THERAPY: PART I

BY

C. L. COPE, D.M., F.R.C.P.

Physician, Postgraduate Medical School, London

It is only in the last ten to fifteen years that the so-called steroids, after having a rather humble place in biochemistry, have leapt to the greatest interest, mainly because of the dramatic influence they have been found to have in the treatment of a wide variety of diseases. In actual fact the main initial stimulus to interest in these compounds, apart from natural curiosity, was provided by a rumour during the second world war that the German Luftwaffe were using certain steroid extracts from the adrenal cortex to improve the fighting efficiency of their pilots at high altitudes. Although this proved to be untrue, it nevertheless aroused great interest in the U.S.A. and led to research resulting in the synthesis and preparation of several adrenal steroids, including cortisone by Kendall and Reichstein. It was this small accumulation of cortisone which Hench was able to use for his famous trial in patients with rheumatoid arthritis, the results of which led to a Nobel prize for all three investigators. Since then the chemistry and physiology of these compounds have been greatly developed, largely by the enthusiasm and drive of the pharmaceutical industry.



Natural Steroids

All the compounds of this group, the steroids, have the same basic skeleton to the molecule, which consists of three 6-carbon rings linked to one of 5 carbon atoms, the total comprising 17 carbon atoms. The various steroids differ mainly in the types of groupings which are attached at various points to the carbon atoms of this skeleton. For easy reference these carbon atoms are numbered in a uniform manner, so that any type of steroid compound can be described by recording the names of the groupings and the numbers of the carbon atoms to which they are attached.

The natural oestrogens and androgens are variants of this skeleton, possessing respectively one methyl and two methyl groups attached to the carbon skeleton. All the steroids of adrenal origin differ from these 18 and 19 carbon molecules in having a side chain containing two further carbon atoms. From the purely chemical point of view the parent compound of this adrenal cortical series of 21 carbon steroids is pregnane. The basic carbon skeleton of this is shown in the diagram on this page and the carbons are all given their appropriate numbers. It is by various modifications of the structure of this parent steroid that all the natural and synthetic adrenal steroids are formed.

The first change, one which is essential to the production of hormonal activity, is the introduction of a double bond between carbon atoms 4 and 5, a process which involves the loss of two hydrogen atoms. Such a compound would be called Δ^4 pregnene or pregn-4-ene. Destruction of this double bond, a process very readily brought about in the liver, promptly removes all hormonal activity from any adrenal steroid possessing it.

The second major type of change is the introduction of oxygen atoms or of hydroxyl groups at various points in the molecule. All the steroids of adrenal origin have oxygen atoms at carbon 3 and carbon 20. The simplest compound of this type is perhaps the well-known hormone progesterone, which is accordingly called pregn-4-ene-3:20-dione, the suffix -one indicating a ketonic =O grouping. Progesterone is probably not produced in appreciable amount in the adrenal cortex normally. The true adrenal steroids all have an additional hydroxyl group attached to the 21 carbon. The simplest of these adrenal compounds would thus be one described chemically as 21-hydroxy-pregn-4-ene-3:20-dione. This particular compound was one of the

first to be synthesized and has been in use for a long time in clinical medicine as D.O.C. or desoxycorticosterone, commonly used as an acetate in the treatment of Addison's disease.

Possessing in common all these basic modifications, the naturally occurring adrenal hormones have additional groupings. Very important is the attachment of a hydroxyl group to the 11 carbon atom. This results in corticosterone, which in some animals is one of the main hormones of the adrenal cortex, but in man is probably of secondary importance. Corticosterone is thus 11:21-dihydroxy-pregn-4-ene-3:20-dione. It was the introduction of oxygen or hydroxyl at the 11 carbon atom which was the toughest problem that the pharmaceutical industry had to solve in the synthesis of the natural hormones. It led indeed to several exploratory expeditions, notably to West Africa and to Mexico, in search of natural plant sources of steroids already provided with this modification. More recently the grouping has been introduced by microbiological means.

Yet one more hydroxyl group is needed, this time attached to the carbon 17, and we have the main natural hormone of the adrenal cortex, hydrocortisone, the potent drug whose therapeutic effects have provoked such wide interest. Chemically hydrocortisone can be called therefore either 17 hydroxycorticosterone, or more precisely 11:17:21-trihydroxy-pregn-4-ene-3:20-dione.

Cortisone differs from this merely in having an oxygen attached to carbon 11 instead of the hydroxyl group. It is probable that cortisone itself is relatively inactive, but has to be converted first to hydrocortisone before it can exert its pharmacological effects. It has not been detected in the body, though it is present in the urine. It is of interest to recall that cortisone was first synthesized in 1946, but hydrocortisone not until 1950.

The extremely active hormone aldosterone, which is a potent natural controller of sodium and potassium metabolism, was discovered only in 1952, and is yet another variation on the same theme, having an aldehyde grouping on the 18 carbon atom, but no hydroxyl on carbon 17.

These then are the main natural hormones produced in the human adrenal. It seems very likely that further variants remain to be discovered, and these may well have still more diverse pharmacological effects.

Synthetic Steroids

It has been said that the problem of synthesizing cortisone set the pharmaceutical industry its most complex and challenging problem. In its solution vast sums of money were spent on research and large research teams were created. When success was finally achieved and production became sufficiently large to satisfy the big demands, it was natural that the research momentum of these teams should be directed to an effort still further to improve on the pharmacological effects—to improve on nature, in fact. The first modification of this type was the introduction of a second double bond into the first ring, or ring A, giving Δ^{1-4} compounds. When hydrocortisone is modified in this way the result is prednisolone, and a similar change in the cortisone molecule results in prednisone. The pharmacological benefits which these changes introduced will be considered later.

The next important change resulted from the discovery that attachment of a halogen atom to the 9 carbon atom increased greatly the potency of the compound. Comparison of the various halogen derivatives of this type showed that the benefit derived was least with iodine, better with chlorine, but best of all with fluorine. As a result the compound 9α-fluorohydrocortisone has found a valuable place in therapy.

It was a natural further step to study the effects of introducing the 9α-fluoro grouping into prednisolone and some additional benefits have been derived.

The attachment of methyl groups to carbon 2 and to carbon 6 have produced some modifications of therapeutic action, but the attachment of a hydroxyl group to the 16 carbon atom brought major advantages and is present in the steroid now called triamcinolone. Finally, the latest modification to the molecule has been the addition of a methyl group on carbon 16 to 9α-fluoroprednisolone, giving a compound of very high potency whose full chemical name is thus 9α-fluoro:11:17:21-trihydroxy(16-methyl)pregn-1:4-diene-3:20-dione.

All these steroids can be prepared either in the free form, the alcohols, or acetylated to give the so-called acetates, or as other esters such as phosphates or hemisuccinates. The main differences that such esterification makes is in solubility, especially in water. The acetates are in general less soluble than the free alcohols, whereas the hemisuccinate is much more soluble in water. This question of solubility affects very considerably the suitability for various modes of administration.

Production in Adrenal Cortex

Under ordinary conditions hydrocortisone, and probably also some corticosterone, are steadily produced in the adrenal cortex. Until recently the amount of hydrocortisone produced each day was a matter of considerable conjecture and could be estimated only by very indirect means. Recently, however, the introduction of isotope-labelled hormones has made possible the much more direct estimation of production rates. In quiescent males the production varies from 5 to 25 mg. daily, with a mean of about 13 mg.; in females the range is similar, but the mean is about 11 mg. a day.

The hormone pours via the adrenal veins into the general blood stream. The concentration of hydrocortisone in the blood fluctuates during the 24 hours, being lowest during the night. During the day it varies between 5 and 25 μg. per 100 ml., with a mean of about 16 μg. per 100 ml. This is about 1/5,000 of the concentration of glucose in the blood.

The hormone is promptly destroyed in the liver by saturation of the double bond in ring A as the first important stage in the degradation. Destruction probably occurs also in the tissues, but much less is known about this. The level in the blood is thus determined by the balance between formation and destruction. From the blood the hydrocortisone diffuses into the other body fluids, in most of which it has now been identified.

The rate at which hydrocortisone is produced in the resting subject varies under different conditions. Thus exercise probably raises it; so also does any form of stress or trauma such as an infection, an accident, or an operation. Pregnancy causes a rise in output to probably more than twice normal, and labour, itself a serious stress, causes a further rise temporarily. Why

raised plasma levels of hydrocortisone are needed under such varied conditions is not really known, but there is no doubt that they do greatly assist the organism to withstand the effects of an adverse environment.

The general level in the blood is maintained by an automatic control of production in the adrenal, which is brought about by the pituitary hormone corticotrophin. The amount of this which is secreted is determined by the prevailing blood level. A sudden rise in blood level of the hydrocortisone from any cause will promptly cause production of A.C.T.H. to cease, and as a result the adrenal cortex subsides into an inactivity which may indeed be complete. Administration of any appreciable quantity of hydrocortisone, or indeed of any of the steroids having similar pharmacological actions, will promptly inhibit the adrenals and thus stop production of endogenous hydrocortisone.

Types of Product Available

All the ordinary steroids available for therapeutic use are active when taken by mouth and are available as tablets. These include hydrocortisone, cortisone acetate, prednisone, prednisolone acetate, and the other steroids already mentioned. All are rapidly absorbed from the stomach even though some are relatively insoluble in water. They pass through the portal circulation and liver before entering the systemic blood. The level in the blood rises fairly rapidly, and subsides before the next dose, so that a somewhat irregular effect may be obtained. Although this is often effective enough, it is not quite as efficient as the intramuscular route for some purposes. But the oral route is best when treatment is lasting several days or weeks, and when the patients are well enough to ingest and retain the tablets.

The various synthetic steroids differ widely in potency, and in general the dose in each tablet is designed to correspond approximately in activity with a 25-mg. tablet of cortisone acetate.

The intramuscular route is preferable when, for instance, the patient is too ill to swallow, or absorption from the stomach is for any reason impaired. For this purpose special preparations are made which are usually composed of crystals suspended in an aqueous solution. When these are injected intramuscularly they form a depot in the muscle from which absorption is slow and better sustained than from the stomach. The usual preparation for this purpose is cortisone acetate.

When more rapid effects are needed in an emergency, neither oral nor intramuscular routes are adequate, but the intravenous should be used. The intramuscular preparations cannot be used for this purpose, because they consist of insoluble crystals in suspension. Soluble preparations are essential for intravenous injection. The earliest was a solution of hydrocortisone in 10% alcohol, which needs to be introduced as a slow drip into the circulation, but more recently a hydrocortisone hemisuccinate has become available which is readily soluble in water. Ampoules in saline ready for immediate injection, and stab bottles of the dry powder ready for solution when required, are both on the market and both are highly effective preparations.

Local Administration

Apart from these general systemic methods of administering the steroids they may be given more locally to the diseased site itself. Thus they may be injected directly into joint cavities, and many joints besides the knee have been treated in this way. The joint cavity is not able to convert cortisone to hydrocortisone in appreciable quantity, and since cortisone is relatively inactive it is therefore necessary to inject hydrocortisone itself. In order to delay the disappearance from the joint itself and so to prolong the effect, the less soluble acetate is generally used, and ampoules of a suspension of hydrocortisone acetate crystals are available for the purpose.

For direct application to mucous membranes, such for instance as the colon in ulcerative colitis, a soluble form of steroid is desirable, and the preparations made for intravenous injection make also particularly suitable enemata.

For application to the skin topically, a variety of preparations are made. Ointments containing ½, 1, and 2½% of hydrocortisone in a water-miscible cream of vanishing type are made, and so also are lotions containing ½ to 1% of hydrocortisone. Because infection is common in skin diseases, many preparations are offered comprising a mixture of hydrocortisone in ointment base with one or more antibiotics, the ones chosen being usually neomycin sulphate, tetracycline, polymyxin, or bacitracin, it being claimed that local sensitization to these is infrequent.

For the eye, solutions of 1% hydrocortisone acetate are available with or without the addition of neomycin.

For the nose also free hydrocortisone can be administered as a spray, and the acetate in powder form can be insufflated. Nasal drops of a soluble form of prednisolone—the disodium phosphate—are also available.

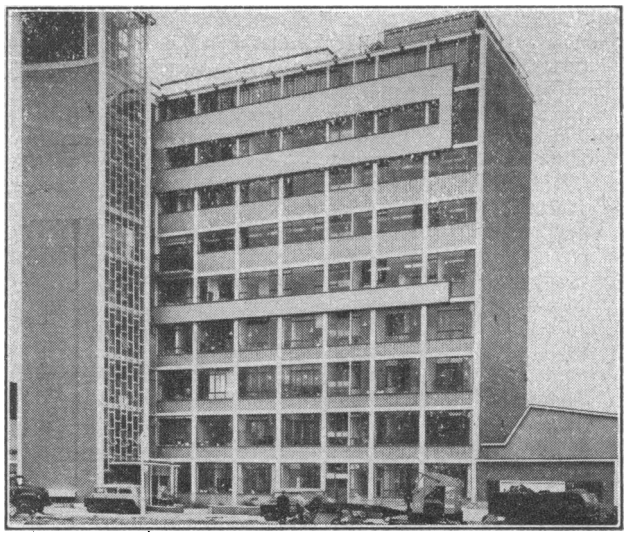
(To be concluded.)

POSTGRADUATE MEDICAL SCHOOL

OPENING OF EXPERIMENTAL SURGICAL UNIT

On Monday the President of the Royal College of Surgeons, Sir JAMES PATERSON ROSS, is due to open a new Experimental Surgical Unit at the Postgraduate Medical School of London.

The Unit is the realization of a 13-year-old dream. Since his appointment to the Chair of Surgery at the



(Continued at foot of next page)