BRITISH PHARMACEUTICAL CONFERENCE BRISTOL, 1957

Chairman: FRANK HARTLEY

CHAIRMAN'S ADDRESS

STEROIDS IN PHARMACY AND MEDICINE

THE term steroid was originally applied to a group of naturally occurring secondary alcohols based upon perhydro*cyclo*pentenophenanthrene. It now has wider usage and embraces not only naturally occurring and synthetic derivatives of perhydro*cyclo*pentenophenanthrene but also related structures derived from the parent ring system by ring enlargement or contraction.

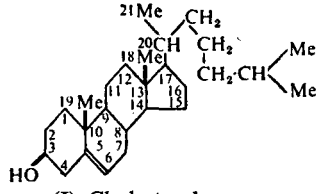
The group comprises not only the adrenocortical and sex hormones, and their synthetic analogues but also the bile acids, antirachitic vitamins, cardiac glycosides, certain alkaloids, saponins and toad poisons. Many steroids have already established their importance therapeutically. I believe that many more will do so with the increasing attention being devoted to chemical, biological and clinical studies of steroids and their derivatives and to their influence on the maintenance of health and even of life itself. And in the application of steroids to medicine there will continue to be need for the integrated efforts of organic and physical chemist, microbiologist, biochemist and pharmacologist as well as of the pharmacist and clinician. For many problems arise in the discovery and utilisation of steroids and many new techniques in consequence have been, and will continue to be, demanded.

Biosynthetic methods have been called forth to aid still further the skill of the organic chemist, as have new physico-chemical techniques. And while the usage and supervision of usage of steroids must be the responsibility of the clinician, the presentation of the materials for effective use rests with the chemist and pharmacist. The necessity for securing delayed or prolonged action in the therapeutic replacement of defective natural secretions, and the seeming versatility of action of many steroids have afforded the pharmacist many opportunities to develop new techniques and new forms of administration. Products suitable for implantation into tissues, microcrystalline suspensions, preparations effective topically without unwanted systemic effects, are some important examples of the contributions of the pharmacist to steroid development and usage. But pharmacy in its wider sense is concerned with all aspects of steroids and it seems appropriate at this Conference to consider some interrelationships in the steroid field, some recent developments and some future possibilities.

THE STEROLS, CHOLESTEROL

The sterols themselves are crystalline alcohols isolated from the unsaponifiable residues of lipoids derived from animals and plants. Most of them are compounds having 27 to 29 carbon atoms and one

secondary alcoholic group; some, like coprostanol, are completely saturated substances, others contain one, two or three double bonds as in cholesterol, stigmasterol and ergosterol respectively. Cholesterol (I) has long been known as the main constituent of human gall stones. It is widely distributed both in the free condition and as its fatty acid esters in the cells of the higher animals, particularly in brain and nerve tissue. Its structure was finally established by 1934 but its complete stereochemistry was not settled until 1947.



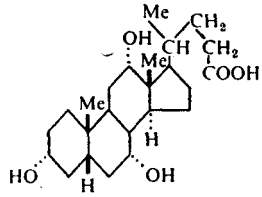
(I) Cholesterol

Cholesterol is of interest both in medicine and in pharmacy. It is elaborated in the liver from acetate. It was for many years regarded as the precursor of the bile acids and sex hormones. Indeed Bloch's isolation[1] of deuterated pregnane-3α:20-diol from the urine of a pregnant woman to whom he had fed deuterocholesterol was regarded as experimental proof that cholesterol was the biochemical precursor of the steroid hormones. It is now known, however, that while cholesterol can be converted into corticoids[2] and into androgens[3] it is not necessarily an obligatory precursor. This follows from experiments in which acetate containing ^{14}C-labelled carboxyl was incubated[4] with or perfused[5] through testis tissue and thereby converted to testosterone and cholesterol. The proportion of ^{14}C present in the testosterone was found to be higher than that present in the cholesterol, thus showing that the hormone did not originate solely from the cholesterol by oxidative degradation. Acetate is likewise a precursor of the oestrogens[6].

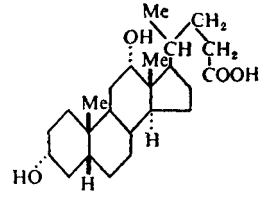
Cholesterol both free and esterified circulates in the blood stream, normal values in whole blood ranging from 20 to 100 mg. per 100 ml. for free cholesterol and from 60 to 200 mg. per 100 ml. for esterified cholesterol. Though the cholesterol level in blood varies within wide limits from one person to another it remains fairly constant in the individual. Its concentration is usually determined in serum or plasma and the values may increase above normal in nephritis, myxoedema, untreated diabetes, pregnancy and atherosclerosis[7]. Though much work has been done to link hypercholesterolaemia with atherosclerosis[8] recent studies reveal other complexities[9,10]. Whatever may be the precise significance of the high content of cholesterol in brain and spinal cord there can be little doubt that its metabolism will continue to engage the attention of biochemical workers for many years. Pharmaceutically cholesterol is used as such (U.S.P. XV) or in the crude form of wool alcohols (B.P. 1953) to increase the hydrophilic properties of soft paraffins, as in Hydrophilic Petrolatum, U.S.P. XV or Hydrous Ointment, B.P. Hadgraft[11] at the Conference in 1947 discussed the value of wool alcohols.

The Bile Acids

The liver transforms cholesterol into the bile acids which are then conjugated with glycine and taurine and the conjugates converted into their sodium salts. These sodium salts are known as the bile salts and are a major constituent of the solid matter of bile. They have the important function of promoting the emulsification and thus the absorption of fats in the intestinal tract. The chief bile acids are cholic acid (II) and deoxycholic acid (III). They occur in bile as the water soluble sodium salts of the peptide conjugates with glycine or taurine which are known as glycocholate and taurocholate, and glycodeoxycholate and taurodeoxycholate respectively.



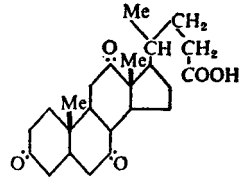
(II) Cholic acid



(III) De(s)oxycholic acid

Deoxycholic acid is of particular interest as it was from this bile acid that cortisone was first manufactured by a method based on the work of Sarett[12,13]. In fact, until microbiological methods for the introduction of hydroxyl at position 11 of progesterone were developed, deoxycholic acid remained the starting material of choice for the manufacture of cortisone. Its use in that way, involving as it did *inter alia*, the removal of a 12-hydroxy group and the introduction of hydroxyl groups at positions 11 and 17 as well as the transformations of the side chain at position 17 still represent an outstanding triumph of chemical skill.

The mixture of bile salts, chiefly sodium taurocholate and sodium glycocholate, are included in the B.P.C., under the title sodium tauroglycocholate, for use in cases of deficiency of biliary secretion to assist emulsification of fats and the absorption of certain water insoluble substances. The triketocholanic acid, dehydrocholic acid (IV), obtained by oxidation of cholic acid is much less toxic than cholic or deoxycholic acid and is preferred as a choleretic.



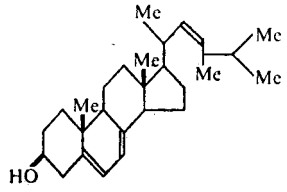
(IV) Dehydrocholic acid

The sodium salt, sodium dehydrocholate N.N.R., is used intravenously for increasing bile flow. It is also employed for the determination of arm-to-tongue circulation time, the time taken from injection into the arm to

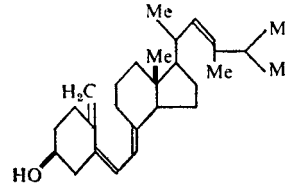
perception of a bitter taste aiding in distinguishing between right and left ventricular failure. Its use in this way, however, has been found to be more hazardous than the use of soluble saccharin.

ANTIRACHITIC VITAMINS

Until thirty years ago cholesterol was regarded as the precursor of the antirachitic vitamin D. The fact that some, but not all, samples of purified cholesterol could be activated by exposure to sunlight or ultra-violet light, however, led to the discovery that a closely related sterol, ergosterol (V), gave on irradiation, a highly potent antirachitic substance named calciferol by its British discoverers[14] and vitamin D_2 almost simultaneously by its German discoverers[15] to distinguish it from an earlier preparation called vitamin D, and subsequently shown to be a molecular compound of vitamin D_2 and an isomer called lumisterol.



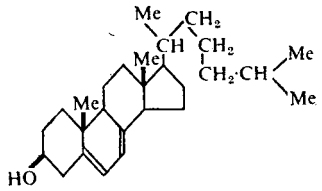
(V) Ergosterol



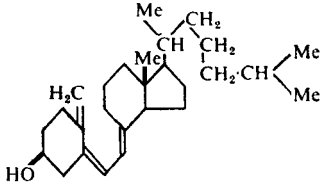
(VI) Calciferol (ergocalciferol)

Calciferol (VI), manufactured by ultra-violet irradiation of ergosterol obtained from yeast, is used in tablets or in oily solution to promote the absorption from foodstuffs of calcium and phosphorus, and in the prevention and cure of rickets in children. Calciferol is also used in the treatment of hypocalcaemia due to parathyroid deficiency. Prolonged high dosage of calciferol causes toxic effects[16] and may lead to hypercalcaemia causing abnormal calcium deposits in the arteries and kidneys, and even death. Calciferol as might be expected from the nature of the unsaturated linkages present, is unstable on exposure to air and light and in the solid form must be stored in sealed containers from which the air has been evacuated or replaced by an inert gas. Although physical constants are available for the standardisation of calciferol these are of little help in the standardisation of its preparations. Until recently only biological methods were recognised for the determination of calciferol and indeed are still the only ones applicable to natural and complex products containing vitamin D. Stross and Brealey at the 1955 Conference[17] however described the applicability of a chemical method for the determination of calciferol in the tablets and oily solution of the British Pharmacopoeia. The method cannot easily be used for the determination of the calciferol content of fish liver oils which still constitute an important source of vitamin D for prophylactic purposes. Calciferol is not the only steroid derivative to exhibit antirachitic activity[18]. Indeed it is only slightly active in the chick. This species, however, responds to a closely related substance called vitamin D_3 (VIII) probably the main form in which the vitamin is present in fish liver oils. Vitamin D_3 is

manufactured by the irradiation of 7-dehydrocholesterol (VII) and differs from cholesterol or vitamin D_2 in having the saturated side chain of cholesterol.



(VII) 7-Dehydrocholesterol



(VIII) Vitamin D_3 (cholecalciferol)

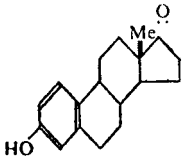
The Commission of Nomenclature of Biological Chemistry of the I.U.P.A.C. has adopted the names Ergocalciferol and Cholecalciferol for vitamin D_2 and vitamin D_3 respectively.

The Steroid Hormones

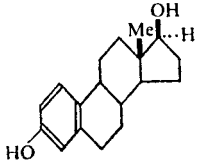
As mentioned already it was for long believed that cholesterol was the precursor of steroid hormones but it is now becoming clear that their biogenesis cannot be so simply explained. Together with cholesterol the steroid hormones form the most important group of phenanthrene derivatives, influencing demonstrably as some of them do the maintenance and propagation of life. They include among others the groups of substances referred to for convenience as androgens, oestrogens, progestational and adrenocortical hormones. Knowledge of their structure and methods for their synthesis followed directly from the final understanding of the structure of the sterols in 1932. Unlike the sterols which occur abundantly in plants and animals the steroid hormones occur in the organism in extremely small amounts and many triumphs of manipulative skill are represented by their isolation.

Oestrogens

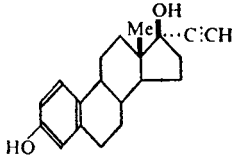
The first steroid hormone to be isolated in crystalline form was the oestrogenic hormone, oestrone (IX), so called[19] to indicate its ketonic nature and its characteristic physiological action exhibited by its ability to induce oestrus in animals. Originally regarded as the primary ovarian



(IX) Oestrone



(X) β-Oestradiol



(XI) Ethinyl oestradiol

hormone it was found that its more oestrogenically active dihydro-derivative is the primary oestrogenic hormone. Usually referred to as oestradiol (X), the more oestrogenically active epimer has been assigned the 17β-hydroxy-configuration[20]. The structure of oestrone was established in 1932[21,22] and the preparation of oestradiol from cholesterol was

accomplished in 1940[23]. Considerable improvements in the partial synthesis have since been effected[24] and total synthesis of natural oestrone was finally accomplished in 1948[25] a remarkable culmination to much brilliant work in this country, in the U.S.A. and in Europe, having regard to the fact that oestrone is one of sixteen possible stereoisomers.

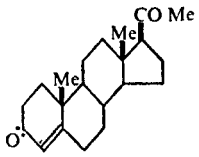
Essential for the proliferation of the uterine endometrium oestrone and oestradiol and their derivatives (e.g., ethinyl oestradiol, XI) have found considerable application in replacement therapy to correct the consequences of defects in the menstrual cycle, in the female climacteric and menopause, and for inhibition of lactation. But the importance of the oestrogens in the maintenance and restoration of health is not limited to their more immediately apparent physiological role. Despite the incidence of side effects, particularly mammary growth, oestrogens have been widely used in the control of prostatic carcinoma since Huggins' discovery of this application[26]. More recently their value in inhibiting the development of secondary metastases following mammary carcinomata, in post-menopausal women, has become established[27–30]. It seems possible that "oestrogens" may have an important role to play in the prevention and treatment of some cardiovascular irregularities[31]. Certain oestrogens also appear capable of influencing favourably the phagocytic activity of the reticulo-endothelial system and hence its role in combatting infection[32]. Though dietary as well as hormonal factors appear to be involved in atherogenesis[10], animal experiments have been sufficiently encouraging for long-term clinical studies to be initiated on the ability of oestrogens to prevent myocardial infarction and prolong life in males under 50 years of age who had recently experienced a proved myocardial infarction. Preliminary results have been considered by Stamler of the American Heart Association to "justify a guarded optimism"[31,33]. The possible value of oestrogens in the reversal of coronary lesions in the male naturally raises the question whether the several oestrogenic properties can be dissociated; that is to say, whether coronary lesions can be prevented without feminisation and alteration of plasma lipids. There are some grounds for believing that transformations of the steroid molecule may result in differentiating between those features of the molecular and stereochemical structures which influence physiology in the female and those features which appear to play an extragonadal role. Thus it now appears[34,35] that oestriol (oestra-1:3:5(10)-triene-3:16α:17β-triol) and its epimer 16-*epi*oestriol (oestra-1:3:5(10)-triene-3:16α:17α-triol) which were formerly considered to be merely excretory or breakdown products of oestradiol and oestrone exert a direct "protective" action against the more active oestrogens in the system. Other oestrane derivatives, particularly those oxygenated at positions 6 and 16, are also able to depress certain effects of oestrone. Such compounds have been called "impeded oestrogens"[35]. So that in addition to the naturally occurring oestrogens and the highly potent partial synthetic oestrogen, ethinyl oestradiol, the simpler synthetic analogues, stilboestrol, hexoestrol and dienoestrol, and related derivatives, we may also expect to see in the future "synthetic" oestrogens which have been "tailored" to accentuate specific biological

manifestations for therapeutic advantage. Dr. V. Petrow and his colleagues, in my own laboratories, in common with workers elsewhere, are actively engaged in such projects.

The value of oestrogen therapy in the treatment of premenopausal and menopausal disorders is well established and the therapy widely used. Its value in the elderly patient for the treatment of symptoms of both physical and psychogenic origin, particularly when used in conjunction with androgen is of more recent recognition[36–38]. Partly this is due to increased knowledge of the anabolic value of the oestrogens and androgens but perhaps more still to the knowledge that the fluid retention properties of the oestrogens can be avoided by the collateral use of androgens in suitable dosage.

Progestational Substances

An important physiological role of the oestrogens is the proliferation of the uterine mucosa; the further development of the uterus in preparation for reception of the fertilised ovum involves a secretory or progestational phase which was shown by Corner and Allen[39] to be stimulated by a hormone or hormones produced by the corpus luteum, a tissue so-called because of its yellow colour which is due to its abundant carotene content. The corpus luteum, developed in the ovary after the ripening and rupture of the follicle, performs the following functions after fertilisation of the ovum has occurred: it suppresses ovulation, it maintains the uterine mucosa in a secretory phase to nourish the developing embryo, it inhibits uterine motility and in conjunction with oestrogen it induces mammary gland development. The pure corpus luteum hormone, progesterone (XII), was isolated in 1934 in dimorphic interconvertible forms, first by Butenandt and almost simultaneously by three other teams. Its structure was established by its partial synthesis from the phytosterols, stigmasterol and sitosterol and it is now manufactured from steroid sapogenins not only for use as such therapeutically, but also as a material which on bio-oxygenation yields 11-hydroxyprogesterone, from which cortisone and its derivatives are manufactured.



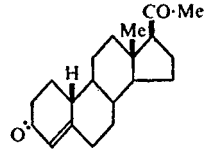
(XII) Progesterone

The characteristic biological properties of progesterone may be enhanced or modified by structural alterations. Thus both 9(11)-dehydroprogesterone and 17α-methylprogesterone are more potent progestational agents than progesterone itself. 17α-Hydroxyprogesterone seems devoid of progestational activity in the human female but is sixty times more active than progesterone in the Hooker-Forbes intra-uterine bioassay employing the mouse as test animal[40]. The hexanoate or caproate ester of 17α-hydroxyprogesterone, in contrast, has recently[41] been introduced

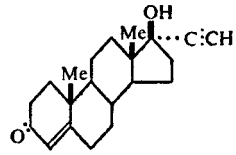
into medicine, as it exerts similar pharmacological responses to those of progesterone including its thermogenic effect, but its ability to induce secretory mucosa is more prolonged. It is therefore of particular value in continuing therapy as in the treatment of habitual and threatened abortion. As they are not active orally, progesterone and the ester of its 17-hydroxy derivative are usually administered by intramuscular injection in oily solutions. Progesterone has also been used by implantation but is liable to be extruded unless implanted deeply into the tissues and its use in this way is often not reliable. For oral use the 17β-hydroxyanhydro derivative, pregneninolone (17β-hydroxy-17α-pregn-4-en-20-yn-3-one or 17α-ethynyl-17β-hydroxytestosterone) or ethisterone (XIV), is widely used particularly in premenstrual tension, in the treatment of functional uterine haemorrhage and in threatened or more particularly habitual abortion.

Recent Development of Progestational Agents

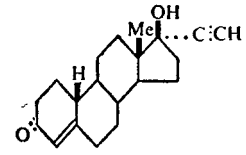
More recently it has been shown that the presence of the C(19) angular methyl group at position 10 is not essential for progestational activity. The 19-nor-steroids are, in fact, engaging attention not only for their progestational, but also for their androgenic and anabolic properties. 19-norprogesterone (XIII) has been shown to be more active than progesterone itself[42,43].



(XIII) 19-Norprogesterone

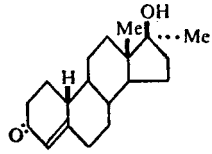


(XIV) Ethisterone

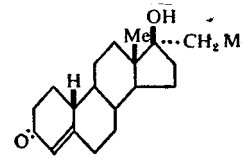


(XV) Norethindrone (19-Norethisterone)

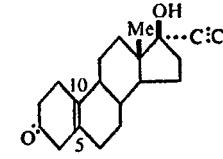
The corresponding 19-norethisterone (17α-ethynyl-19-nortestosterone) (XV) is orally active and of greater activity than ethisterone[44–46]. Other derivatives such as 17α-methyl-19-nortestosterone (XVI) and 17α-ethyl-19-nortestosterone (XVII) (referred to as norethandrolone) also appear to be more active than progesterone in certain respects[47–49] but as



(XVI) 17α-Methyl-19-nortestosterone



(XVII) 17α-Ethyl-19-nortestosterone



(XVIII) 17α-ethynyl-5(10)-oestrenolone

mentioned later they also have pronounced anabolic properties[50]. Another type of progestational agent is represented by 17α-ethynyl-5(10)-oestrenolone (XVIII), in which the unsaturated linkage is no longer $\alpha\beta$- to the 3-oxo group, but located at the juncture of Rings A and B. Surprisingly this material is more active orally than is ethisterone as a progestational agent[49].

From work in my own laboratories it also appears that the presence of alkyl groups at certain other positions can enhance the progesterone-like properties of ethisterone[51,52].

Though the therapeutic application of progesterone and its orally active analogue ethisterone has been mainly to produce a secretory phase in the endometrium and maintain a deciduum after pregnancy and more recently for the treatment of premenstrual tension[53], the ability of progesterone to inhibit ovulation in animals and in women has been recognised. It has now been demonstrated[54] that 17α-ethynyl-19-nortestosterone (norethisterone), 17α-ethynyl-5(10)-oestrenolone, and 17α-ethyl-19-nortestosterone (norethandrolone) on oral administration in dosages of 10 to 50 mg. daily are effective ovulation-inhibitors in women. The possible application of this property raises many interesting aspects and doubtless there will be much discussion of the ethical aspects of this use of these compounds. In the examples so far reported, fertility does not appear to have been impaired, for exposures after cessation of medication resulted in pregnancies in seven instances.

Adrenocortical Hormones

Progesterone is produced in the body not only by the corpus luteum but also by the adrenal cortex where it is almost certainly an intermediate in the biogenesis of the adrenocortical hormones. The importance of the adrenal or suprarenal gland and more particularly the physiological functioning of the adrenal cortex, to the maintenance of life has been known ever since Thomas Addison studied and described, in 1855, "the constitutional and local effects of diseases of the suprarenal capsules". Addison's name has long been associated with the "disease" resulting from adrenal cortical insufficiency. But it is only in the last 25 years that the variety and complexity of the steroids produced by the adrenal cortex, the so-called corticoids, have been recognised. More than twenty steroids have been isolated from extracts of the adrenal glands and though not all of them are biologically active and some may well be intermediate precursors of the biologically active steroids their chemical interrelationships are most interesting to note and are listed in Table I.

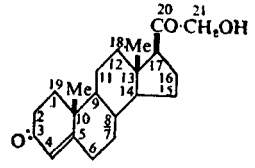
The series of pregnane derivatives, some active, some inactive biologically, which have been isolated indicate the nature of the biosynthetic reactions occurring in the adrenal gland, many of which have been demonstrated by perfusion studies with isolated glands or homogenates using selected steroid substrates[55].

Biogenesis of pregnane derivatives in the adrenals seems to proceed via progesterone which is then hydroxylated at positions 17 or 21. The 17α-hydroxyprogesterone, which has been isolated as such from adrenocortical extracts[56], is then oxidised to hydrocortisone, whilst the 21-hydroxy derivative is converted into corticosterone and presumably into aldosterone. Many of the possible hydroxylations of the pregnane nucleus have been effected by microbiological means. Thus with the aid of appropriate microorganisms, bacteria, yeasts and other fungi, hydroxylations have been effected at positions 6, 7, 8, 11, 14, 16 and 17 in the

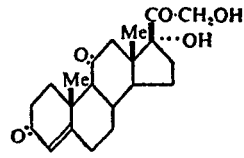
TABLE I

ADRENOCORTICAL STEROIDS

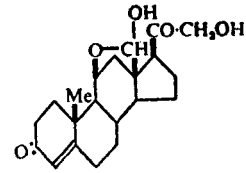
Biologically active steroids:	
Corticosterone	11β:21-Dihydroxypregn-4-ene-3:20-dione (Kendall's compound B; Reichstein substance H)
Cortisone (XX)	17α-Hydroxy-11-dehydrocorticosterone or 17α:21-dihydroxypregn-4-ene-3:11:20-trione (Kendall's compound E)
Deoxycortone (XIX) (deoxycorticosterone)	21-Hydroxypregn-4-ene-3:20-dione
11-Dehydrocorticosterone	21-Hydroxypregn-4-ene-3:11:20-trione (Kendall's compound A)
Deoxycortisol	17α-Hydroxydeoxycorticosterone
	17α:21-Dihydroxypregn-4-ene-3:20-dione
Hydrocortisone (cortisol)	17α-Hydroxycorticosterone
	11β:17α:21-Trihydroxypregn-4-ene-3:20-dione
Aldosterone (XXI)	11:18-Hemiacetal of 11β-21-Dihydroxy-18-oxa-pregn-4-ene-3:20-dione



(XIX) Deoxycortone



(XX) Cortisone

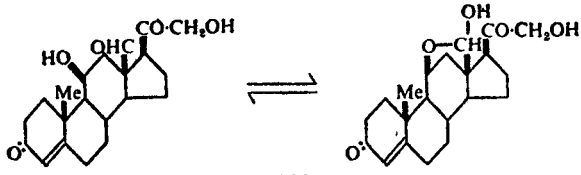


(XXI) Aldosterone

Biologically inactive steroids:		
Reichstein Substance		A: 3β:11β:17α:20:21-Pentahydroxyallopregnane
,,	,,	V: 3β:11β:17α:21-Tetrahydroxyallopregnan-20-one
,,	,,	C: 3α:11β:17α:21-Tetrahydroxyallopregn-20-one
,,	,,	D: 3β:17α:21-Trihydroxyallopregnan-11:20-dione
,,	,,	E: 11β:17α:20:21-Tetrahydroxypregn-4-en-3-one
,,	,,	U: 17α:20:21-Trihydroxypregn-4-en-3:11-dione
,,	,,	K: 3β:17α:20:21-Tetrahydroxyallopregnane
,,	,,	P: 3β:17α:21-Trihydroxyallopregnan-20-one
,,	,,	J: 3β:17α:20-Trihydroxyallopregnane
,,	,,	R: 3β:11β:21-Trihydroxyallopregnan-20-one
,,	,,	N: 3β:21-Dihydroxyallopregnane-11:20-dione
,,	,,	T: 20:21-Dihydroxypregn-4-en-3:11-dione
,,	,,	O: 3β:17α:20-Trihydroxypregnane
,,	,,	L: 3β:17α-Dihydroxyallopregnan-20-one

pregnane nucleus[57]. And by the use of appropriate homogenates hydroxylation has been accomplished in the side chain at position 21 and in the angular methyl groups, that is on carbon atoms C(18) and C(19)[58,59]. These many possibilities of hydroxylation foreshadow the natural existence of a whole galaxy of minor steroids, all pregnane derivatives. Many of them are however as yet of unestablished structure and of unknown function. Hydroxylation at position 6 is perhaps of some interest as it occurs mainly in the liver and may in part explain the relatively low activity of progesterone when administered orally.

The accomplishment of hydroxylation biologically at C(18) is of particular interest in relation to the mode of biogenesis of aldosterone, which is characterised by a unique aldehyde group in place of C(18) methyl group.



(XXI) Aldosterone

The existence of 19-hydroxylating systems[59] portends the possible natural occurrence of the 19-nor-steroids as well as indicating a likely route whereby androgens may be converted into oestrogens.

In addition to the so-called corticoids, other steroids have been isolated from adrenal cortical extracts namely oestrone[60], progesterone[61] and three androgens, derivatives of androsterone: adrenosterone or androst-4-en-3:11:17-trione[62], androstenedione or androst-4-en-3:17-dione, and 3β:11β-dihydroxyandrostan-17-one[63]. While, as stated, progesterone and 17-hydroxyprogesterone seem likely to be biological precursors of the "corticoid" hormones, the androsterone derivatives and oestrone seem likely to arise by subsequent biological oxidations and dehydrogenation of the corticoids.

The physiological functions of the secretions of the adrenal cortex, which are stimulated by the peptide called corticotrophin or adrenocorticotrophic hormone (ACTH) secreted by the anterior lobe of the pituitary gland, are necessary for the preservation of life and the maintenance of health. They are concerned with nitrogen metabolism, carbohydrate metabolism, and the control of electrolyte balance of the blood. But such a simplification scarcely does justice to the remarkable properties and range of therapeutic applications that have been discovered or advocated since manufacture became possible of many of the cortical hormones and their subsequent modifications.

Extract of suprarenal cortex for injection is still included in the B.P.C. and is still used in some cases for the treatment of Addison's disease and other types of adrenal insufficiency. Its continued use reflects the complexity of adrenocortical function. Deoxycortone which, as its acetate, was the first of the corticoids to be manufactured in quantity has not proved adequate for all cases of Addison's disease. It influences electrolyte balance, and is therefore a so-called mineralocorticoid, by controlling loss of sodium, and retention of potassium, with consequent modification of the sodium to potassium ratio, but it has only limited effect on carbohydrate metabolism, the so-called glucocorticoid activity. The expectation at the outbreak of the second world war that the sodium-retaining properties of deoxycortone might be applied to the prevention of fluid loss and the avoidance of secondary shock was not fulfilled. Whether corticosterone itself would have proved much more valuable had it been available in quantity now seems less likely. Although corticosterone, first obtained by partial synthesis by Reichstein in 1941, has a more profound influence on sodium retention than deoxycortone, it too has little effect upon carbohydrate or nitrogen metabolism. Interest in the therapeutic possibilities of corticosterone has waned with the development of cortisone and its derivatives, and with the isolation and investigation of aldosterone.

Aldosterone

Aldosterone (XXI) is the most active electrolyte-regulating hormone secreted by the adrenal cortex having a potency about one hundred times that of deoxycortone when measured by the sodium:potassium urinary

ratio in adrenalectomised rats. Unlike deoxycortone it has an appreciable effect upon organic metabolism having a potency of about one third of that of cortisone in the liver glycogen deposition assay. The isolation of aldosterone, then called electrocortin, by Simpson and Tait in 1953, followed by elucidation of its chemical structure[64] aroused considerable interest matched only by its synthesis in a remarkably short time[65]. Aldosterone was unusually interesting among adrenal cortical hormones not merely because of its uniqueness in possessing an aldehyde group in place of the 18-methyl group which suggested hitherto unsuspected biosynthetic possibilities in the adrenal, but because the daily output (micrograms per day) in normal man was so very much less than that of the corticoids (milligrams per day). Adrenal tumours however cause a considerable rise in the production and excretion of aldosterone and its determination has provided a new diagnostic test for the chemical pathologist. Aldosterone, however, does not merely influence sodium retention. It also accentuates potassium loss. In addition, some kinds of hypertension appear to derive from chronic hypersecretion of aldosterone[66].

Although the therapeutic application of aldosterone now seems likely to be strictly limited, much work continues to be carried out both biologically and clinically to assess the significance of aldosterone output and secretion. A clearer understanding of the part played by the adrenal gland in health and disease seems likely to result. There can be little doubt about the importance of mineralocorticoid activity to health but its control must await further elucidation. In this connection mineralocorticoid antagonists[67] may have their part to play.

The Glucocorticoids

Although the study of steroid hormones has yielded many fascinating and even dramatic results, none of these have so captured the imagination of the scientific world as Hench's revelation in April 1949 of the influence of cortisone on the suppression of rheumatoid arthritis. Following publication of the results of the work at the Mayo Clinic[68] widespread interest in Kendall's compound E subsequently named cortisone was aroused. Its anti-inflammatory, anti-allergic and anti-fibroblastic properties were gradually revealed as also were those other properties which led to undesirable effects during continuing therapeutic use. First obtained by isolation from adrenal extracts, cortisone was subsequently manufactured chemically from deoxycholic acid and later from such steroid sapogenins as diosgenin and hecogenin. The total synthesis of cortisone could formally be said to be based on the Robinson and Woodward synthesis of non-aromatic steroids accomplished in 1951, but the first *de facto* total synthesis of cortisone was accomplished in 1952[69].

Cortisone was found to suppress rheumatoid arthritis but not to reverse or even check the underlying disease. During treatment, however, it afforded much relief to the patient by its anti-inflammatory properties, pain and stiffness being diminished and the patient acquiring a greater range of movement. The use of cortisone for the treatment of rheumatoid

arthritis, however, was found to be not without risk of serious side effects. Electrolyte balance was affected leading even to signs of congestive heart failure in some cases and, in consequence, potassium chloride needs to be given daily during treatment to prevent hypokalaemia. Carbohydrate metabolism was affected leading to glycosuria and increased insulin requirements in diabetes mellitus. Protein metabolism was affected leading with continuing large doses to a negative nitrogen balance. Resistance to bacterial infection was diminished and wound healing delayed. There was found to be a risk of peptic ulceration and of perforation in patients with symptoms of past peptic ulceration. Replacing as it did an important natural secretion of the adrenal, its withdrawal led to the symptoms of adrenal exhaustion which in many cases resulted in worsening of the disease and in some instances proved fatal. Large scale trials organised by the Medical Research Council led to the conclusion that for the treatment of rheumatoid arthritis, cortisone was not significantly more beneficial in longstanding cases than aspirin, and the incidence of side effects circumscribed continuing therapy. Though it might be fair to say that cortisone has not fulfilled the early expectations that its introduction to therapy aroused, it is still a valuable drug and its use has hastened the search for improvements and consideration of the anticortisone properties of steroids[70]. Cortisone is of value and is used as an anti-inflammatory agent in self-limiting conditions, in diseases of the eye, in acute disseminated lupus erythematosus and acquired haemolytic anaemia. It is also valuable in maintenance in Addison's disease and Simmonds' disease with secondary hypoadrenalism and in Addisonian crisis. Its value in acute rheumatic fever is less clear[71].

The corresponding secondary alcohol, hydrocortisone, in which the 11-keto group of cortisone has been reduced, represents the major glucocorticoid secreted by the adrenals. It is now manufactured chemically from bile acids but more commonly from the steroid sapogenins. The application of biooxygenation to convert progesterone into 11α-hydroxyprogesterone has considerably facilitated the accessibility of hydrocortisone. Both this substance and its 21-acetoxy derivative, hydrocortisone acetate, are of considerable value dermatologically and opthalmologically. For topical use there is as yet no general agreement about which form is preferable or what is the most effective ointment base. In addition both forms are of value parenterally. Hydrocortisone acetate in contrast to cortisone acetate is effective when injected intra-articularly. Hydrocortisone is more effective orally than intramuscularly and its use is frequently attended by less risk of the side effects that are encountered with cortisone.

For oral use in rheumatic diseases a considerable advance on cortisone and hydrocortisone appears likely to follow the introduction and usage of the corresponding compounds having an additional unsaturated linkage between carbon atoms 1 and 2 namely the Δ^1 compounds: 17α:21-dihydroxypregna-1:4-diene-3:11:20-trione (Prednisone) and 11β:17α:21-trihydroxypregna-1:4-diene-3:20-dione (Prednisolone)[72–74]. Prednisone and prednisolone appear to be some three to five times more potent

as glucocorticoids than cortisone and hydrocortisone, and seem likely to become, at least for a time, the "glucocoids" of choice for oral use. The availability of the corresponding acetates as well as the free alcohols reflects the use of different routes of manufacture, the free alcohol being directly obtained by one process and the acetate by the other. Conversion of acetate into the free alcohol results in some loss of yield. There appear to be no differences in therapeutic value observable when equivalent molecular quantities of the acetates and free alcohols are used orally.

Recent Developments

Still further advances are likely to result from studies of further modifications of the steroid molecule in the glucocorticoids. For example, the introduction of an unsaturated linkage between C(6) and C(7) into prednisone and prednisolone yields 17α:21-dihydroxypregna-1:4:6-triene-3:11:20-trione and 11β:17α:21-trihydroxypregna-1:4:6-triene-3:20-trione which are stated[75] to be considerably more potent than the parent steroids. Further, halogenation at position 9 by fluorine appears to provide advantages. 9α-Fluorohydrocortisone has received some attention for its value as a glucocorticoid particularly in maintenance therapy in hypoadrenalism. Its mineralocorticoid action, however, leading to fluid retention and to hypertension has limited its value in the treatment of collagen diseases[76,77]. 9α-Fluoro-17α:21-dihydroxypregna-1:4-diene-3:11:20-trione or 9-fluoroprednisone, as it might be termed[78] seems more likely to be valuable and it will be of interest to see whether the corresponding Δ^6 compound proves even more potent. Then again the value of alkylation has been studied and though cortisone derivatives having a methyl group at position 1, 2 or 4 are less active as glucocorticoids than cortisone, enhancement of activity is stated to occur when the methyl group is present at position 6 namely in 6-methyl-11β:17α:21-trihydroxypregna-1:4-diene-3:20-dione or 6-methylprednisolone[79]. But the greatest enhancement of glucocorticoid activity so far reported occurs in the 9α-fluoro derivative of that compound. 9α-Fluoro-6α-methyl-11β:17α:21-dihydroxypregna-1:4-diene-3:20-dione or 9α-fluoro-6α-methylprednisolone is stated to have a glucocorticoid activity some fifty times that of prednisolone and nearly two hundred times that of hydrocortisone[80,81]. Potential glucocorticoids carrying additional hydroxyl groups at position 2[82], position 5[83], position 12[84], position 14[85], position 16[86,87] have been reported. The 19-nor analogues of hydrocortisone and cortisone have also been prepared[88] but surprisingly, loss of the C(19)-angular methyl group is accompanied by marked loss of glucocorticoid activity.

The adrenocortical hormones and their chemical modifications have perhaps suffered to some extent in their therapeutic status by over-enthusiastic use and misuse. Now that the limitations, side effects and definite contraindications for use are becoming accepted, the fields of therapeutic usefulness are becoming more clearly defined. Systemically, the "corticoids" can no longer be regarded as first choice in the treatment

of rheumatoid arthritis or chronic bronchial asthma. They may help prolong life in progressive potentially fatal diseases such as the leukaemias and they are, of course, capable of providing the replacement therapy necessary in Addison's disease and after adrenalectomy. Because of their influence on sodium retention with concomitant potassium loss, their use needs to be linked with restricted sodium chloride intake and with supplementary potassium chloride. For the treatment of skin lesions and of inflammatory conditions of the eye hydrocortisone ointments and drops provide dramatic evidence of the antiphlogistic, anti-allergic, and antipruritic properties of hydrocortisone though when infection is present, specific collateral treatment to eliminate the infection is also required. Whether prednisolone will prove more useful than hydrocortisone dermatologically is at present uncertain, conflicting results having so far been obtained[89,90].

Steroids as Anaesthetics

Another interesting aspect of the properties of cortical hormones and their derivatives arises in connection with their potential anaesthetic properties. It has been known for some time that certain steroids and related compounds were capable of exerting general anaesthetic effect on intraperitoneal injection into animals. In 1942 Selye of McGill University published a paper which attracted much interest, giving the results of his examination of some seventy-five steroid compounds and showing the anaesthetic properties possessed by many of them, and somewhat surprisingly, by the non-steroid, stilboestrol. In his "Correlations between the chemical structure and the pharmacological actions of steroids"[91], Selye drew attention to the molecular features which appeared to lead to increased anaesthetic properties, but at that time the practical application of the results did not seem feasible owing to the corticoid, folliculoid, luteoid or androgenic properties which to greater or less extent were always also exhibited by the active compounds in the dosages required. Recently, however, Selye's pioneer studies have borne fruit and have led to the clinical evaluation of sodium 21-succinoyl-pregnane-3:20-dione as an anaesthetic[92–94]. As a basal anaesthetic, this compound proved acceptable and is now generally available. Its behaviour as an anaesthetic resembles that of thiopentone, though its influence on pulse rate and blood pressure have been commented upon adversely[95]. Whether this reflects mineralocorticoid activity in the compound is not clear.

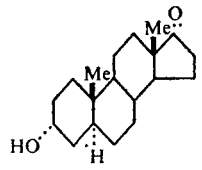
The influence of adrenocortical steroids on brain function and metabolism is attracting increasing attention and it seems reasonable to expect that clarification of neuroendocrinological actions and possibilities will be forthcoming in the near future[96]. The 3:5-*cyclo*steroids are also likely to be of interest in this connection[97].

Androgens

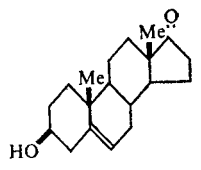
If biogenesis of hydrocortisone in the adrenals proceeds via 17α-hydroxyprogesterone, then it might well be expected that degradation of the latter intermediate to androstane derivatives should take place. This

is indeed found to be the case. It is established that androgens occur not only in the testis but also in the adrenal cortex and ovary. And it has already been mentioned that three androgens androst-4-ene-3 : 17-dione, adrenosterone and androstane-3β : 11β : -diol-17-one have been isolated in crystalline form from adrenal cortical extracts. Furthermore, urinary androgen concentration is considerably increased in certain patients with adrenocortical hyperplasia or tumour, and is diminished in conditions of adrenal hypofunction. The elaboration of androgens by the adrenal gland, irrespective of sex, makes it seem likely that adrenocortical androgens are the biological precursors of oestrogens in the ovary. Though no pure androgen has yet been isolated from ovarian tissue, androgenic extracts have been obtained. There is a great tendency to think of androgens as primarily of importance in a gametogenic function but in fact the biological effects of the androgens include not only effects on sex specific tissues but also on general body mass, kidney, muscle and hair growth, on nitrogen metabolites, on water and electrolyte metabolism and on certain enzyme systems. Not only have androgens an influence on behaviour and characteristics but they play an important part in development, metabolism and ageing. Clinically the androgens have important applications both for male and female use, in correcting deficiencies due to hypogonadism, as anabolic agents both during the menopause and during ageing, and in inhibiting neoplastic developments; proving especially valuable in advanced mammary cancers[98].

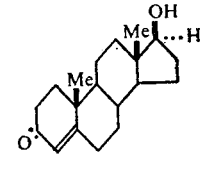
Androgens were first isolated from urine. Androsterone, the first androgenic hormone to be obtained in crystalline form, was isolated in 1931 by Butenandt who used increase of capon comb as a means of measurement of activity to guide the work. The structure of androsterone was deduced by Butenandt in 1932, when only 25 mg. of substance had been available for study and was confirmed by its preparation from cholesterol by Ruzicka, by Butenandt, and by Callow and Deanesly[99]. In currently agreed steroid nomenclature[100] its structure is 3α-hydroxy-androstan-17-one.



(XXII) Androsterone



(XXIII) Dehydroepiandrosterone



(XXIV) Testosterone

A second weakly active androgen, dehydroepiandrosterone, was subsequently isolated from urine in 1934 by Butenandt although this substance which has also been called dehydroisoandrosterone or simply dehydroandrosterone is not itself of importance as an androgen. It is particularly important, however, as it forms an intermediate which is readily obtained by oxidative degradation of cholesterol and of certain sapogenins, and which is widely used for the manufacture of therapeutically important steroids. Molecularly isomeric with dehydroepiandrosterone is the much

more potent androgen, testosterone, which was first isolated from testis tissue in 1935 by Laqueur[101]. The discovery of testosterone stemmed from inexplicable discrepancies in the biologically assayed potencies of androgenic extracts prepared respectively from urines and from testis tissue and provides another reminder of the importance of quantitative biological work in the discovery and development of steroids. Though the original preparative and manufacturing methods for the conversion of 3β-hydroxyandrost-5-en-17-one (dehydroepiandrosterone) into 17β-hydroxyandrost-4-en-3-one (testosterone) involved no fewer than five chemical stages with consequential losses in overall yield, the development of methods of steroid oxidation with the aid of suitable microorganisms has now made it possible to effect the conversion in two stages with but little loss of yield.

Within the last five years the total synthesis of dehydroepiandrosterone has been accomplished independently and by quite different routes by both British and American teams. The structure and stereochemistry of the steroid hormones may consequently be regarded as finally established[69,102–104].

During early studies of the biological properties and clinical applications of testosterone it was found to be relatively inactive on oral administration. That it was absorbed orally and metabolised was shown by recovery of its metabolic products in appropriate yield from the urine[105]. Its relative oral inactivity, as low as one-tenth of that by injection[106] appears to be due to oxidation and esterification on passage through the liver[107] the less active androsterone, among other products, together with the highly stable water soluble sulphates and glycuronates, being formed. Though active on injection in oily solution, testosterone was found to have a less prolonged action than that of its esters[108], and much attention was devoted to the correlation of the nature of the group used to esterify the secondary alcoholic group at position 17 and the resultant potency and duration of action. Among ester groups studied were formate, acetate, propionate, butyrate, *iso*butyrate, valerate, *iso*valerate, palmitate, stearate and benzoate, the most effective clinically being found to be the propionate. In recent years interest has been revived in the modification of the esterifying group and among alternatives to testosterone propionate the esters of the following acids have been advocated as having more prolonged action on intramuscular injection in oily solution, heptanoic or oenanthic ($C_7H_{15}COOH$); decanoic ($C_9H_{19}COOH$); *cyclo*pentylpropionic ($CH_2CH_2CH_2CH_2CH\cdot CH_2CH_2COOH$); *cyclo*hexylpropionic ($CH_2CH_2CH_2CH_2CH_2CH\cdot CH_2CH_2COOH$); phenylpropionic ($C_6H_5\cdot CH_2CH_2COOH$). For water soluble use, the hydrochloride of the testosterone ester of β-diethylaminoethyl carbonic acid ($(C_2H_5)_2N\cdot CH_2CH_2\cdot O\cdot CO\cdot OH$) has been proposed. Hydroxylated testosterones have also been prepared[109].

Testosterone esters have been widely used clinically by intramuscular injection in oily solutions, the choice of oil influencing to some extent the

rate of onset of effect and the duration of action, though greater variations in the duration of action result from varying the ester group. Prolongation of action has also been achieved by the use intramuscularly of suspensions of free testosterone in microcrystalline form in aqueous vehicles. Solutions of testosterone in propylene glycol have been used intravenously in high dosage without ill effects[110] but the absence of clinical advantage has apparently discouraged the routine use of such solutions. Where however considerably prolonged action is required, as for example, in the treatment of advanced mammary carcinoma, free testosterone is implanted, usually in the thigh or abdomen, in up to 300 mg. units in the form of sterile pellets. These are prepared by fusion and extrusion from suitable moulds, or by appropriate compression methods, under aseptic conditions. Implantation therapy, which has been studied with oestrogens, progestational substances, corticoids, as well as with androgens is of course more appropriate when continued steady administration is required. With oestrogens it is not a particularly desirable method of administration because of the risks of excessive absorption and the greater value of interrupted therapy. With androgens, continuous absorption is sometimes necessary. Free testosterone is absorbed from implants more rapidly than is testosterone propionate and is the form commonly preferred, some 3 to 5 mg. being absorbed daily and proving equivalent to 25 mg. of testosterone propionate given by injection three times weekly.

TABLE II

RATE OF ABSORPTION AND DURATION OF ACTION OF IMPLANTED PELLETS OF ANDROGENS

Hormone	µg./ sq. mm. absorbed per day	Pellet weight (mg.)	Mg. absorbed per day per pellet	Proportion absorbed per month (per cent of pellets)	Effective life of pellets (months)	Number of pellets for replacement therapy in man
Testosterone	6–9	<5 30–50 75–225	<0·1 0·5 1·5	>90 40 30	<1 2 3	>50 8–15 3–6
Testosterone propionate	3–4	<10 20–50 100–300	<0·2 0·3 1·0	60 24 16	<2 4 5	>25 15–30 4–10
Methyltestosterone ..	4–5	<5 5–10 40–100	<0·1 0·2 0·7	>90 70 30	<1 1 3	>50 25–50 5–12

The rate of absorption of steroid from an implanted pellet is, of course, dependent not only on the weight of the pellet but on its surface area and Table II, due to Dorfmann[111], has been compiled from studies by various workers. Although early experiments showed that androgens were absorbed through the intact skin and free testosterone was more effective percutaneously than its equivalent concentration of testosterone propionate[112], the use of testosterone ointments has not found any considerable favour in clinical practice; implantation, injection, or oral therapy being preferred.

As already mentioned, testosterone is relatively inactive by the oral route, the 17α-methyl derivative, methyltestosterone, being preferred. Miescher and Tschoff in 1938[113] first discovered the oral activity of methyltestosterone and its clinical applicability was established by Foss in 1939[114].

As an androgen, methyltestosterone by mouth has an activity of about one-third of that of the same dose of testosterone propionate administered by injection. It appeared to be relatively more potent when administered to animals sublingually[115], a study made following the observation that the activity of deoxycorticosterone could be demonstrated after sublingual administration[116]. The observed enhancement of androgenic potency on administering methyltestosterone sublingually in animals has led to clinical usage by this route. Various formulae have been proposed for tablets to enable them conveniently to be used by placing in the groove between the lower cheek and gum (the so-called buccal position). Unfortunately, the arbitrary disintegration time of not more than fifteen minutes at present required by the British Pharmacopoeia was fixed for tablets intended to be swallowed and is not adequate for satisfactory sublingual use. It would appear desirable for a longer time to be allowed to accommodate a choice of route. Free testosterone and its esters have been claimed also to be effective when administered sublingually[117] but to be less potent than methyltestosterone[118].

Anabolic Agents

As already mentioned, androgens play an important part in metabolic processes especially in relation to the ageing process. Their influence on nitrogen metabolism and in consequence on calcium metabolism is being increasingly applied therapeutically and it is possible that their protein-building or anabolic influence may prove to be their most important property. It seems clear that anabolic applications are of value in underdeveloped children, in convalescence and in geriatrics. An important consequence of the anabolic properties of the androgens appears to be their assistance in preventing, and in promoting the healing of, bone fractures in the elderly. The value of androgens in osteoporosis has been considered recently by Wheddon[119]. Understandably the masculinising effects of androgens have somewhat limited hitherto the application of their anabolic properties, a limitation that has to some extent been overcome by the simultaneous use of oestrogen and androgen. The combined use of oestrogen and androgen which is widely preferred for menopausal treatment has, for example, been found effective in the treatment of acute osteoporosis with hypercalcaemia[120]. There seems little doubt that the anabolic properties of the androgens can overcome the demineralisation of bone that accompanies defective protein synthesis. The ability of simple amino acids such as alanine to dissolve calcium phosphate can, of course, readily be demonstrated in the test tube so that anabolic measures to overcome the catabolic processes especially in ageing would be expected to limit the continuing demineralisation of bone.

It is the recognition of the anabolic applications of androgens that has stimulated the search for modified steroids in which the ratio of anabolic to androgenic potency is increased. Androgenic properties which were formerly assessed by comb growth tests in capons are now generally evaluated by their effect on the seminal vesicle and prostate weight in rats or guinea pigs. The anabolic properties manifest themselves by

nitrogen retention and can be evaluated by determining intake and output of nitrogenous materials, or by direct determination of nitrogen content of killed animals compared with controls. But nitrogen retention by enhanced protein synthesis also manifests itself by increased muscle growth and hence the gain in weight of suitably dissectable muscles of test animals compared with those of untreated controls provides a convenient method. The change in weight of the levator ani muscle of the castrated rat has been suggested by Eisenberg and Gordan as a suitable indicator of steroid influence on protein anabolism[121], and has since been widely used in assessing the anabolic properties of recently discovered variants of the testosterone molecule. The levator ani which atrophies in the castrated animal shows marked weight increase in animals receiving an anabolic agent.

17-Methylandrost-5-ene-3β:17β-diol (methylandrostenediol) the penultimate product obtained in the manufacture of methyltestosterone, was among the first alternatives to methyltestosterone to attract some attention as a potentially clinically valuable non-virilising anabolic agent. As an androgen its activity is about one-twentieth only of that of methyltestosterone[122]. Although in animals it appeared to have a somewhat greater anabolic activity than methyltestosterone, and hence a considerably greater anabolic to androgenic ratio than the latter[123], its clinical use as an anabolic agent has generally been disappointing[124]. Greater interest has been aroused in the therapeutic possibilities of derivatives of testosterone lacking the C(19) angular methyl group, namely 19-nortestosterone. 19-Nortestosterone itself, first synthesised by Birch in 1950[125], was stated to have about one-fifth of the androgenic activity of testosterone[126] and was subsequently shown by Hershberger[123] to have about the same anabolic potency as testosterone. It has not yet been made available for therapeutic use though some of its derivatives having the same order of anabolic to androgenic potency ratio, and patented as new products, have been made available. For oral use the 17α-methyl-19-nortestosterone might have been expected to be more active than 19-nortestosterone and this indeed appears to be the case. Other homologues, however, showed a similar activity and ratio[127]. 17α-Ethyl-19-nortestosterone has been judged to be more active orally than the 17α-methyl compound which appeared to inhibit the appetite of the animals used. The 17α-ethyl compound has recently been made available and described as norethandrolone[128]. Although the 17α-methyl compound, first prepared by Djerassi in 1954[129] had first been considered primarily for its potential interest as an oral anabolic agent, clinical studies have revealed its progestational activity[47,48]. As an oral progestational agent, 17α-methyl 19-nortestosterone (also described as methandrone and as methyl-(o)estrenolone) appears to merit closer study. The homologous compound, norethandrolone likewise appears to possess progestational properties[49] and its ability to inhibit ovulation, to cause endometrial proliferation, and the retention of salt and fluid will demand caution in its use as an anabolic agent. In fact, it now seems likely that the 19-nortestosterone derivatives may find their most important clinical application

as oral progestational agents and not as oral anabolic agents. Indeed 17α-methyl- and 17α-ethynyl-19-nortestosterone (19-norethisterone or norethindrone) have already been made available for use as oral progestational agents.

The anabolic action of 19-nortestosterone can be prolonged by esterification, for example by benzoic, *cyclo*pentylpropionic[130] or phenylpropionic acids[131], but the esters so obtained must be administered intramuscularly in oily solution.

In addition, research groups in Europe and the U.S.A. are actively engaged in the preparation of testosterone derivatives containing nuclear substituents such as alkyl, hydroxyl or halogeno[132–134]. Their biological study seems likely to reveal many more compounds of potential therapeutic interest. Thus for example, we already know that 4-chlorination or 6-methylation can increase the anabolic/androgenic index of testosterone derivatives[135]. Furthermore, it is interesting to note that while introduction of a 9α-fluoro substituent into hydrocortisone increases mineralocorticoid and, to a lesser extent, glucocorticoid activity, the introduction of such a substituent into the 11β-hydroxy derivative of methyltestosterone considerably enhances anabolic and androgenic potency. The androgenic activity of 11β:17β-dihydroxy-9α-fluoro-17α-methylandrost-4-en-3-one (fluoxymestrone) is stated to be some ten times greater than that of methyltestosterone[136] and the presence of the 11β-hydroxy group apparently does not give rise to oedema or to hypertension[137].

If it appears that the so-called androgens and their derivatives are at present attracting a disproportionate amount of attention, it must be borne in mind that part of the explanation rests in the fact that the investigation of human steroid metabolism still depends to a considerable extent on knowledge, understanding and interpretation of the 17-ketosteroid output revealed by determination in blood, plasma and urine. Although 17-ketosteroids arise by oxidative degradation of naturally occurring steroids of widely varying physiological significance, nevertheless they are most readily produced from the androgens[138]. Though it is well established that changes in steroid metabolism occur with age[139–141] much remains to be clarified before the full potentialities of the use of steroids in the maintenance of health can be realised. With developments in our knowledge of gerontology[142] and in neuroendocrinology[143] it seems certain that the therapeutic importance of steroids and their synthetic modifications must become increasingly recognised. And with a greater recognition of the importance of steroids there must also be increasing attention devoted to increasing our knowledge of their precise structure, stereochemistry and conformation[144]. The newer applications of spectrology[145,146] and of spectropolarimetry over the wavelength range 230 to 700 mμ[147] are proving extremely valuable in this connection.

Our understanding of the relationship between chemical structure and biological properties seems likely to be increased by the development of newer physical techniques and their physico-chemical application and eventually to replace empirical approaches, however enlightened, by a greater certainty.

Conclusions

An attempt has been made to present some interrelationships in the steroid field, some recent developments and some future possibilities. Steroid chemistry virtually began with the isolation and characterisation of the natural hormones and the preparation of simpler derivatives therefrom. It moved on with the study of their detailed biological properties and the recognition of the multiplicity of their biological properties. Every natural steroid hormone possesses not one but a whole range of biological activities and not all of them are necessary or even desirable in their application therapeutically.

Some of the properties, in fact, seem to be undesirable. The need has thus arisen for steroids "tailored" to a particular therapeutic requirement and this need is now slowly and systematically being met by the various alkyl-, halogeno-, nor- and dehydro-steroids that are being evolved in laboratories throughout the world. Such artificially-created steroids, moreover, are often many times as active, weight for weight, as the natural products they seek to replace. What of the future? The most important future applications of steroids would seem likely to be in the fields of gerontology, neuroendocrinology, and population control. The revolutionary technical advances of this century and even of the past two decades have changed the balance between health and disease and between life and death. The steroid chemist, in collaboration with biologists, pharmacists and clinicians, seems likely to assist in still further alteration of that balance.

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