

THE CHEMISTRY AND THERAPY OF GLANDULAR PRODUCTS*

BY

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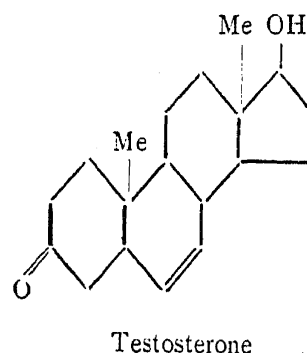
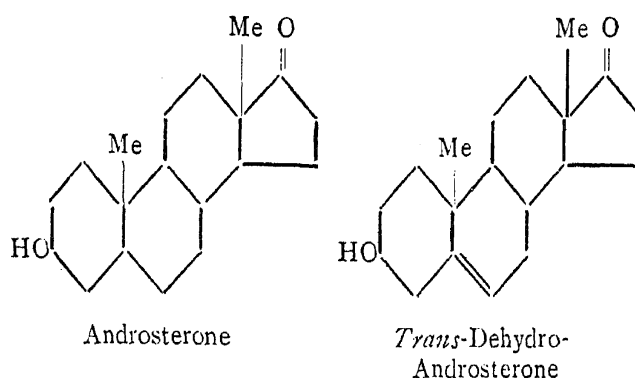
(Presidency College, Madras)

THE researches carried out in the field of hormones in the last two decades have been so extensive that only a cursory glance at the main results can be given in this short review.

Sex Glands.—The sex hormones may be considered to be made up of the testicular, the follicular and the progestational principles. The present-day advance in this field is largely due to the happy discovery that human urine and the serum of pregnant mares form an excellent source of the male and the female hormones, so that sufficient material could be accumulated for chemical as well as therapeutical investigations. Another equally important contributory factor has been the elaboration of two very important methods of biological assay, viz., “The capon-comb test” for the male hormones and the “vaginal smear test” for the oestrogenic hormones. The isolation of these hormones is based on the general principle of extraction by means of fat solvents and concentration by means of selective distribution between suitable organic solvents.

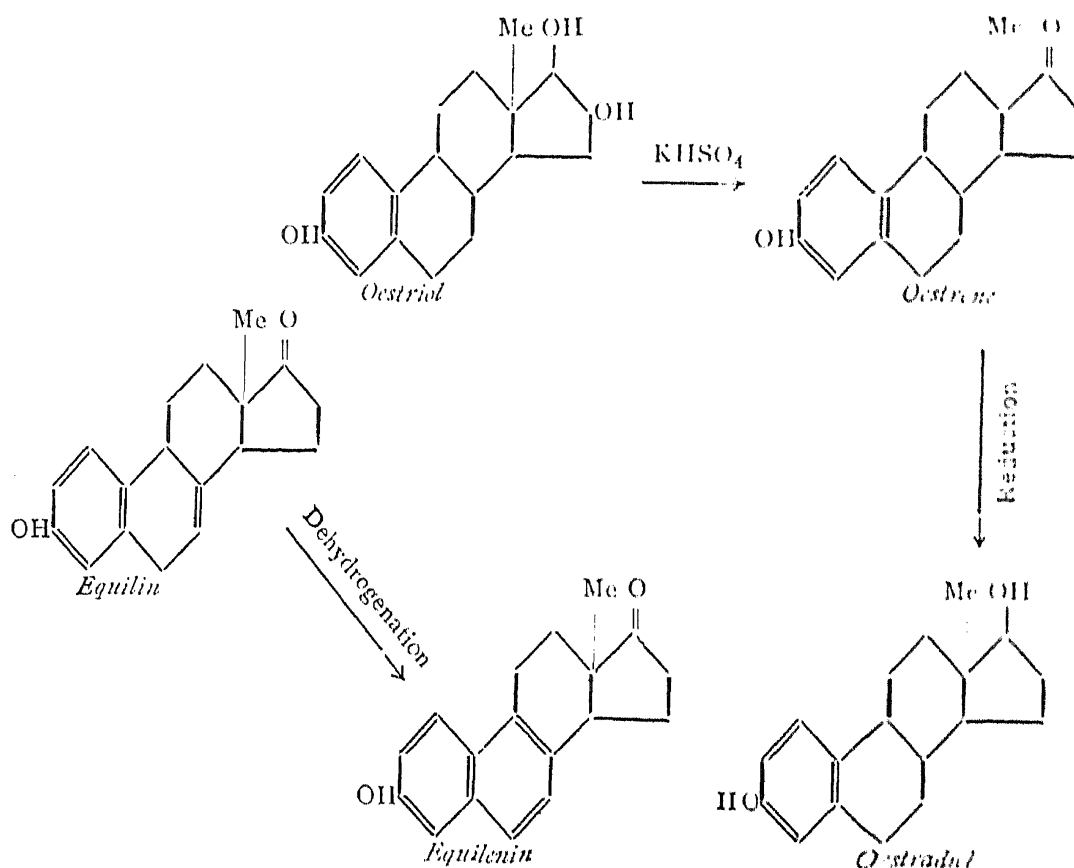
Among the male hormones are Androsterone, Trans-Dehydro-Androsterone and Testosterone, the most potent being Testosterone which is therefore to be considered as the true testicular hormone. All of these hormones have been obtained in a pure crystalline condition and their structures, represented below, have been elucidated by degradation reactions

as well as by partial syntheses from known sterol derivatives.



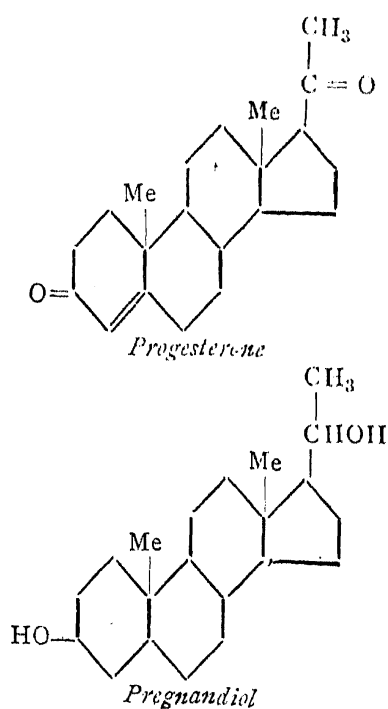
The ovarian hormones play a most important part in the sexual cycle of the female. The “oestrogenic” or the “follicular hormones” induce the development of the uterus, of the vagina and of the mammary glands; the corpus luteum or the “progestational hormones” prepare the uterus for the embedding of the fertilised ovum. Among the oestrogenic hormones are Oestrone, Oestriol, Oestradiol, Equilin, Hippulin and Equilenin. Of these the oestradiols are the most active and should be regarded as the true ovarian hormones. The constitution, as well as the interrelationships of these hormones are brought out in the following scheme:

* A brief summary of a course of four lectures delivered under the auspices of the Madras University.



The structures of these compounds arrived at by degradation reactions have been confirmed by the brilliant total synthesis of Equilenin by Bachmann (1940), the first achievement of its kind in the field of sex hormone synthesis.

Among the corpus luteum hormones are Progesterone and Pregnandiol:



Pregnandiol is inactive and can be derived from Progesterone. The structure of progesterone has been established by its partial syn-

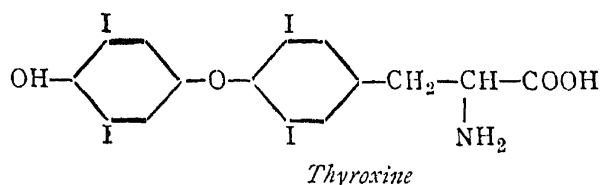
thesis starting from stigmasterol. The drug is now commercially prepared from stigmasterol which in its turn is manufactured from soya beans.

All these sex hormones alike possess the cyclopentenophenanthrene ring structure, which, it will be recalled, is also the basic structure of a wide variety of biologically important products such as sterols, bile acids, heart poisons, saponins, carcinogenic hydrocarbons, cortical hormones and vitamin D.

Several of these products are commercial drugs and are extensively used in the treatment of sex disorders. An important development during the last few years has been the elaboration of the "pellet therapy" wherein pellets of the crystalline hormones are introduced subcutaneously and made to act slowly and steadily, thereby simulating the action of the normal endocrine glands.

The Thyroid Gland.—The endocrine function of the thyroid was recognised very early; in fact Murray laid the foundation of the science of organotherapy in 1891 when he administered extracts of sheep's thyroid glands for the treatment of myxoedema. The gland produces a hormone which catalyses the oxidative

process in the body. The active principle of the gland was isolated by Kendall in 1914 by alkaline hydrolysis of the gland and was termed Thyroxine. Harington worked out its structure by degradation reactions and finally confirmed it by synthesis:



Both the natural and the synthetic products are now available in the market and are used for the treatment of hypothyroidism. For clinical purposes, however, desiccated thyroid (Thyroidium siccum) is the drug of choice. Recent investigations have shown that thyroxine does not account quantitatively for the activity of the whole thyroid and that thyroglobulin itself or a complex peptide of thyroxine is to be regarded as the real thyroïdal hormone. One of the interesting developments of recent years has been the artificial production of iodinated proteins which possess the "thyroïdal activity". It has been shown in several instances that small amounts of thyroxine could be actually isolated from these iodo-proteins.

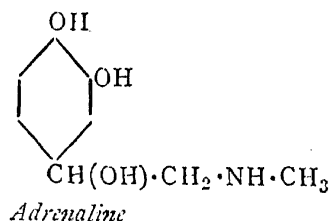
The Parathyroid Gland.—The parathyroids are the smallest of the endocrine glands. They produce an internal secretion,—*viz.*, "parathormone"—which is concerned with the regulation of calcium metabolism and with controlling in some way the concentration of calcium and phosphorus in the blood. Tetany which follows the surgical removal of the parathyroids is due to the lowering of the blood calcium. Recent researches go to show that the primary action of the parathyroid hormone is on the phosphorus metabolism and that changes in the Ca-metabolism are but consequent to alterations of the P-metabolism.

Parathormone is believed to be of the nature of a protein but it has not yet been obtained in a pure crystalline condition. The preparation is based on the fact that the protein can be extracted by means of hot dilute acids. Substitution therapy with parathyroid extracts

to relieve cases of parathyroid deficiency has now fallen out of practice, its place being taken up by irradiated sterols like vitamin D₂ and dihydrotachysterol (A.T. 10).

The Adrenal Gland.—The adrenal gland is made of two structurally different parts, the medulla and the cortex, which are entirely different with regard to the internal secretions elaborated by them.

The Medulla.—The discovery of Oliver and Schafer (1894) that adrenal extracts raised the blood pressure aroused great scientific interest and attempts were carried out in Abel's laboratory to isolate the active principle. Success finally fell to the lot of Takamine and Aldrich (1901) who were able to isolate it in a pure crystalline condition. The name Adrenaline or Epinephrine was given to it and the constitution was established by synthesis. The glandular mass was extracted with acidulated water and after removal of lipoidal contaminants, the pure base was precipitated with ammonia.

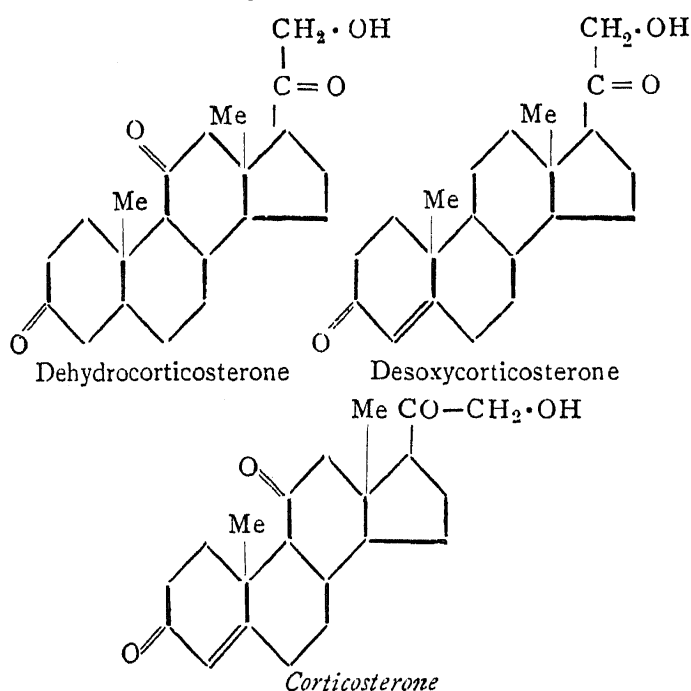


Adrenaline stimulates the action of the sympathetic nervous system and is therefore called a sympathomimetic drug. It raises the blood pressure when injected subcutaneously and also mobilises the liver glycogen and so raises the blood sugar; its action in this respect is therefore antagonistic to that of insulin. For this and other reasons, Adrenaline finds extensive therapeutic usage, such as in the treatment of allergic disorders, in reviving the heart beat when it stops accidentally during surgical operations, in counteracting an over-dosage of insulin and also in admixing with various local anæsthetics for prolonging their action. It is considered by many to be the hormone of emergency.

The Adrenal Cortex.—Researches carried out during recent years go to show that the adrenal cortex may indeed occupy a position in the whole endocrine system second in importance

only to that of the pituitary gland. Stewart and Rogoff (1925) showed that the cortex was essential for life. Hartman prepared active extracts of the cortex for which the name "Cortin" was given. The method consisted in extraction of the minced cortical tissue with alcohol or ether and concentration by selective distribution between various organic solvents. The brilliant investigations carried out during the years 1936-1941 by three groups of workers, Kendall and Wintersteiner in America and Reichstein in Switzerland (Zürich) have resulted in the isolation of about twenty closely related steroid derivatives, some active and others inactive, from the crude extract "cortin".

Among the more important of these cortical hormones are Corticosterone, Desoxycorticosterone and Dehydrocorticosterone.



The structures were established by degradation reactions when steroids of known structure were obtained. Steiger and Reichstein (1937) also succeeded in partially synthesising desoxycorticosterone, starting originally from stigmasterol. Desoxycorticosterone is now available for the treatment of Addison's disease and other ailments traced to cortical deficiency, and is manufactured by the synthetic method.

It is now generally agreed that the cortex does not elaborate any single substance which can be regarded as the true hormone of the gland, but that it produces a surprisingly large

number of closely related compounds which have specific effects differing qualitatively one from the other. These hormones control the metabolism of salt, water, potassium and carbohydrates and also the renal function. Addison's disease, which was recognised as early as 1855, has now been definitely shown to be associated with the adrenal cortex.

The Pituitary Gland.—The pituitary is the most important, complex and interesting of all the ductless glands and has been referred to by Sir Henry Dale as "the conductor of the endocrine orchestra". The gland is made up of two distinct portions—the anterior lobe and the posterior lobe, joined together by the "Pars Intermedia". A battery of hormones is elaborated by the pituitary but none have so far been obtained in a pure condition with certainty. Highly active fractions have been prepared and some placed on the market. The hormones are probably all of a protein nature.

The Posterior Lobe.—An aqueous acid extract of the posterior lobe yields "pituitrin" which raises the blood pressure and stimulates uterine contraction and also controls the renal excretion of water. The work of Kamm has however shown that pituitrin is not a homogeneous substance, but can be resolved into (1) Oxytocin, which causes the contraction of the uterus and (2) Vasopressin, which increases the blood pressure and also exerts an anti-diuretic effect. Active extracts of the posterior lobe of the pituitary find important applications in obstetrics and also in the treatment of "diabetes insipidus".

The intermediary lobe is supposed to secrete a hormone known as "Intermedin"; its definite function in man has not yet been made clear but it has been shown to produce characteristic colour changes in the frog and in certain species of fish.

The anterior lobe produces a very large number of hormones which can be broadly classified under two headings, *viz.*, (1) those which produce general effects in the whole body and of which examples are to be found in the growth-promoting principle which has been

placed in the market under the name "Antuitrin-Growth" and the "Glycotropic principle" or the "Diabetogenic hormone", injections of which raise the blood sugar, and (2) those which produce specific effects on other glands. The anterior lobe of the pituitary is known to control and co-ordinate the endocrinal activities of the other glands and in its turn to be influenced by them. Thus the "Thyreotropic hormone" stimulates the thyroid gland and the "Corticotropic hormone" produces hypertrophy of the adrenal cortex. But much more important are the "Gonadotropic hormones", which have been shown to produce two different effects, *viz.*, follicular stimulation and luteinisation. Recently there have been claims for having isolated the two different principles in a pure condition. It is interesting to note that similar gonadotropic hormones appear in the urine during pregnancy and are produced by the chorionic tissue.

The Pancreas.—The work of Minkowski and Mehring in 1889 definitely established the relation between pancreas and diabetes mellitus. Active extracts of the pancreas which could be successfully employed in the treatment of diabetic patients were first obtained by the Toronto group of workers—Banting, Best, McLeod and Collip. The isolation of insulin created almost a revolution in medical practice for it made the definite control of this disease and the alleviation of the sufferings of the diabetic patients possible. The method of isolation of the hormone consists, in general, in extraction with acidified alcohol, precipitation with ammonium sulphate and final isoelectric precipitation. Of late, methods have been developed to crystallise insulin and they depend on the presence in minute traces of metals like zinc. Insulin has a molecular weight of about 35,000 and is believed to be a pure protein since hydrolysis results in the production exclusively of a number of amino-acids. Recent researches have shown that diabetes may not be due primarily to the

deficiency of the secretion of insulin by the pancreas, but rather to certain other hormonal disturbances, especially of the pituitary. A number of attempts were made to prolong the hypoglycemic action of insulin, so as to avoid the necessity of giving frequent injections: the introduction of "Protamine-Insulin" by Hagedorn in 1935 and its modification by Scott into "Protamine-Zinc-Insulin" in the following year, together constitute a great advance in this direction. Certain groups of workers have recently claimed to have isolated a second internal secretion of the pancreas which has been named "Lipocaic", and which is believed to control fat-metabolism.

The Liver.—In 1929 Minot and Murphy showed that pernicious anæmia could be cured by the inclusion of liver in the diet. Attempts have been made ever since to isolate the anti-anæmic liver principle but up to now no preparation can claim to be homogeneous. Cohn prepared an active fraction—Fraction G—which was further purified by Dakin and West, who used "Reinecke Salt" to precipitate the active fraction and who believed it to be a complex peptide. The more recent researches of Subbarow and Jacobson have shown that the active principle is of a composite nature and that progressive purification leads to a gradual loss of potency due to the elimination of certain "accessory factors". Castle postulated the existence in the stomach of an enzyme—the "intrinsic factor"—which reacted with an "extrinsic factor" present in the food material to give rise to the antianæmic factor which was stored in the liver and sent from there to the bone marrow for haemopoiesis. Pernicious anæmia is therefore due primarily to the deficiency of the intrinsic factor and so the treatment consists in either supplying the intrinsic factor in the form of stomach preparations whereby the elaboration of the haemopoietic principle by the stomach is stimulated, or, by the actual administration of the preformed active principle in the form of liver extracts.