

HORMONES THROUGHOUT HISTORY

SAMIR YAHIA EL-GAMMAL.*

ABSTRACT

Since remote ages man believed that, the different parts of his body and that of the animals, contained therapeutical elements, with effective powers like magic, and that he can fortify his own personality by consuming some parts of the bodies of human beings or animals. He also believed that his organic diseases were due to deficiency in these organs concerning certain ailments, so he treated them with similar organs of different animals.

Since remote ages, man believed that the different parts of his body and that of the animals, contained therapeutical elements with effective powers like magic and that he can fortify his own personality by consuming some parts of the bodies of human beings or animals. The soldiers in time of war, believed that eating the hearts of their enemies will increase their bravery and courage (This belief was existing up to 1873. A.D. when the Scotland soldiers done this act during their wars.)

So man treated the ailment of his hands by eating hands, his brain by eating brains, his kidneys by eating kidneys, his liver by eating livers etc. He also believed that his organic diseases were due to deficiency in these organs concerning certain elements, so he treated them with similar organs of different animals, thus many prescriptions in the ancient Egyptian medical papyri contained such ingredients. Same has appeared in the folkloric medicine of India and China.

Treatment of sexual weakness was done through eating bull's testes, and this theory was adopted by the ancient -

Greeks as was stated by Dioscorides in his famous volume "Materia Medica" where he mentioned cock's testes as an oral intake to increase the sexual powers in man, so did the Arab physicians who mentioned it in their books on medicine.

During the medieval ages in Europe, treatment with animal organs was highly developed and very famous, but in the 18th century, many of these procedures were revolutionarily rejected.

The ancient Egyptians knew that the human body excretions, specially his urine, contained distinctive elements excreted from the internal organs, and going through that famous prescription in Ebers medical papyrus in which detection of the sex of the foetus in pregnant women's urine was carried on germination of either wheat or barley grains. The Greek and Islamic medicines, although adopted the ancient Egyptian medical theories, could not discover the hormones or their glands or their role in the body. The knowledge of these distinctive elements, or hormones of to-day, developed greatly through the extensive and expanded studies of the endocrine glands, and their effective elements that

* Pharmacist, Researcher in History of Medicine and Pharmacy, P.O.No. 136. Maadi, Cairo, Egypt.

they secrete, specially during the second half of the 19th century and the beginning of the 20th century.

It's a common knowledge to-day, that the functions of the human body are controlled by chemical agents, produced by:

a- by stimulation of the autonomic nervous system,

b- by specialised tissues (i.e. the endocrine glands),

c- by non-specialised tissues, e.g. histamine, endocrine secretions that constitute part of the system of chemical control of the body functions. They are a particular group of agents for which a centralised form of production has been evolved.

The manner in which the anterior pituitary gland controls the activity of other endocrine organs indicates the inter-dependence of the glands upon each other. The removal or partial deficiency of one gland produces a very complex series of effects; the action of some endocrine organs is depressed while that of others is augmented. The metabolism of sugar, for instance, is controlled by the pancreas, the thyroid, the anterior lobe of the pituitary and the adrenal glands. The secretion of the last three tend to encourage the breakdown of glycogen into - sugar, and the secretion of the pancreas inhibits this change. So, hyperglycaemia and glycosuria are therefore, produced by increased secretion of the thyroid, of the suprarenal medulla or of the anterior lobe of the pituitary gland, and by deficiency of the pancreatic secretion. A low blood sugar, on the other hand, is produced by deficiency in the secretion of the first three glands and by tumours of the islet cells of the pancreas.

Also, the development of secondary sexual characteristics is controlled by several glands. The interstitial cells of the gonads and the adrenal cortex are the most important organs involved in promoting these changes, whilst deficiency of the anterior lobe of the pituitary or of the thyroid inhibits the development of the secondary sexual characters.

The development of endocrine therapy has been one of the most important advances made in medical science during the present 20th century. The organic chemists have made remarkable advances in the identification and synthesis of a considerable number of the active principles of these endocrine glands. The divergence between scientific knowledge and clinical practice of endocrinology was largely due to the fact that the first endocrine preparation to be successfully employed in practice, namely dried thyroid, was unique in regard to certain important pharmacological properties. Thyroid deficiency produces striking and indeed repulsive effects and these can be fairly and rapidly relieved by eating the gland either in raw state or in the dried form. The reason for this is that, thyroxine happens to be a stable compound, which is absorbed unchanged, and the action of the dried thyroid is also favoured by the fact that the normal thyroid contains large stores of thyroxine. In this case, the discovery that cretinism was due to thyroid deficiency resulted in the discovery of an efficient treatment.

Addison in 1853 discovered that destruction of the suprarenal glands caused the disease named Addison's disease, after him, but an active cortical principal that could be used effectively was first obtained in 1927. This advance was,

however, followed rapidly by the identification of several active principles, and the synthesis of some of these substances was achieved later.

In most cases, the active principles produced by endocrine glands were very unstable, present in minute quantities, and their isolation in a form that could be used in therapeutics was a difficult and expensive problem.

The pituitary gland has been called the dictator or master gland, for it produces a large number of hormones which regulate the activity of other endocrine glands. This gland is composed of two lobes, although closely associated anatomically, yet they differ completely in their origin, structure and function. Removal of the anterior lobe causes a wide variety of deficiency symptoms which can be corrected by administration of extracts of the gland.

The anterior lobe contains the following hormones:

1- Growth, 2- Gonadotrophic, 3- Lactogenic, 4- Thyrotrophic, 5- Adrenocorticotrophic, 6- Metabolic (or Diabetogenic). While the posterior lobe contains:

1- hormones that produces effects on the blood vessels (pressor),

2- hormone that produces effects on the uterus (oxytocic),

3- hormone that produces effects on the kidneys (antidiuretic).

Concerning the growth hormone; Aschner in 1909 showed that, after hypophysectomy (i.e removal of the anterior pituitary regulator), young dogs failed to grow. Later on in 1921, Evans and Long demonstrated that injection of anterior pituitary gland extracts restored the arrested growth of these animals, and that giant rats could be produced by

injecting such extracts into normal young rats. This growth hormone was purified later by Li, Evans and Simpson.

Adrenocorticotrophic hormone (ACTH) was isolated in 1943 by Sayers and also by Li.

In 1929, Loeb and Bassett showed that, the action of the thyrotrophic hormone on the throid gland could not be maintained indefinitely because the animal acquired immunity to the hormone. In 1934, Collip introduced the term "Anti-hormone"; a phenomenon occurs upon repeated administration of the foreign protein, which is the thyrotrophic hormones, which evokes the production of anti-bodies. Same happens with the other anterior pituitary hormones and chorionic gonadotrophic hormone. These anti-hormones disappear soon after the administration of the hormone ceased. No anti-hormones have been demonstrated for insulin, thyroxin, estrogenic substances, progesterone, or testosterone. Over dose of anterior pituitary lobe extracts produced diabetes mellitus.

In 1939, Heller separated different fractions from an extract of the posterior lobe of the pituitary gland, which possessed marked vasopressor and oxytocic activity (which were called vasopressin and oxytocin), and also separated from this vasopressor fraction, an diuretic fraction.

Goitre is a deformity that has been known since classical times. The ancient Egyptians knew the action of the thyroid gland and also the symptoms of hypo- and hyper function of it. They treated the disease with sea water (since it contained iodine salts). The ancient Greeks treated Goitre with the ashes of sponges (which contained also iodine).

In 1820 Coindet instituted iodine therapy for goitre, while A. Chatin published a series of papers between 1850 and 1870 in which he proved conclusively that goitre was associated with a deficiency of iodine. In 1856, Motez Schef showed that guinea pigs died when their thyroid glands were removed, and proved that they could be saved by oral ingestion of thyroid glands, and so deduced that the glands secrete a vital compound and plays an important role in the body.

In 1875, the Swiss surgeon Theodor Kocher observed the enlargement of the thyroid gland (goitre) and the symptoms it produced, also the deficiency of the secretion of the gland. Sir Victor Horsley in 1882 proved the thyroid to be a gland of internal secretion, deficiency of which caused cretinism and myxodema. In 1890 Murray showed that injection of a glycerine extract of thyroid could cure myxodema, or by oral administration of dry thyroid. In 1895 Baumann proved that the thyroid contained an iodine compound, while Kendall in 1925 isolated thyroxine and Harington and Barger in 1927 synthesised it.

Toxicity of thyroid extract was shown when a single dose of it produced less toxic effects than the same quantity given in divided doses, which indicated that any large excess of thyroxine was cleared relatively quickly. In moderate over-dosage, 1/20 of the drug present was cleared daily and this slow excretion coupled with the delayed action favoured the production of cumulative toxic effects; this took about a month, which necessitated the cautious alteration of the dosage of thyroid extract.

Over-dosage of thyroid causes the

following symptoms: palpitation with a rapid and often irregular pulse, nervousness with insomnia, headache and muscular tremors, dilatation of the skin vessels, increases sweating, a temperature above normal and occasionally disturbance of digestion with vomiting and diarrhoea. At the same time, there is loss of weight.

Thyroid extract is frequently used as a remedy to reduce obesity and anti-fat remedies, but this is now prevented by its inclusion in the poison's schedule, since loss of weight will frequently result in hyperthyroidism (this prevention has been executed in the U.S.A. but is going on sale in many countries).

The parathyroid glands are small vascular glands, the size of an apple seed, situated near the dorsal surface of the thyroid gland. Overdosage of the parathyroid extracts or by adenomata of the parathyroid glands will make the bones brittle and fragile, associated with an increase in calcium excretion, resulting in that the calcium deposit in the bones becomes depleted and osteitis fibrosa results.

Pancreas and Diabetes mellitus goes back to thousands of years ago. Pancreas was mentioned in Gardener medical papyrus (2000 B.C.) as a body at the back of the abdomen with no mention of its secretions. In Ebers papyrus, prescription no. 197, Diabetes mellitus was treated with mixture of ground dragon's blood, flaxseed, colocynth, all boiled with oil and honey, then taken for four mornings... so that his thirst perishes and the decay of his inside may be expelled. Diabetes was referred to as honey ruine and a melting away of the flesh. They detected the presence of sugar in the

urine by tasting it. In 1670 A.D., Regner de Graaf of Holland was the first to study pancreas and its secretions.

In 1776, Matthew Dobson discovered a chemical method of proof that the sweetness of diabetic urine was due to the presence of glucose. In 1857 Claude Bernard discovered glycogen in the liver and referred to it as animal starch. Ten years later, Langerhans discovered the islet tissue in the tail of the pancreas. In 1899 von Mering and Minkowski showed that removal of the pancreas produced diabetes in dogs, and this effect was prevented by pancreatic grafts. Diamare suggested in 1889 that the islets of Langerhans were responsible for the internal secretion of the pancreas. In 1921 Banding and Best produced active extracts from the pancreas and crystalline Insulin was produced by Abel in 1926.

Normal carbohydrate metabolism depends upon a balance between the activities of the anterior pituitary and the islet tissue. So diabetes may be caused by either deficient output of insulin or excessive activity of the anterior pituitary gland.

Overdosage of insulin preparations may lead to hypoglycaemia and coma, which can be relieved quickly by the administration of glucose by mouth or by intravenous injection.

In 1855 Addison showed that destruction of the adrenal glands produced a syndrome which was known after his name "Addison's disease", characterised by great muscular weakness, bronzing of the skin, arterial hypotension and gastrointestinal disturbance which may be manifested by vomiting or diarrhoea. In 1901 adrenalin was isolated in crystalline form from the adrenal medulla.

In 1931, Swingle and Pfifner prepared an extract of the adrenal cortex which restored to almost normal health those animals which were dying after adrenalectomy. The two main types of activity in adrenal cortex extracts: 1-maintenance of renal function and inorganic metabolism due to cortical steroids such as desoxycorticosterone.

2-glycogen deposition in fasting animals, associated with steroids such as cortisone, corticosterone and 17 - hydroxy-corticosterone.

Synthetic steroids have been produced on a large industrial scale which could cure Addison's disease such as Deoxycortone acetate (DOCA), Dehydrocorticosterone and cortisone.

In 1935 Kendall and co-workers isolated a compound E from the adrenal cortex and identified it as 17-hydroxy-11-dehydro-corticosterone (later called Cortisone), and its acetate was later synthesised .

Hench, Kendall, Slocumb and Polley in 1948 showed that patients with rheumatoid arthritis were improved rapidly after the administration of cortisone, which later was used to cure various inflammatory and allergic conditions such as rheumatic fever, acute inflammatory disease of the eyes and asthma. But like insulin treatment, cortisone treatment is a form of replacement and it is usually found that within a short time of ceasing cortisone therapy, the patient relapses to his former state.

Prolonged administration of ACTH or of cortisone suppresses the endogenous secretion of various pituitary hormones, thus causing water and salt retention, a rise in blood sugar and an aggravation of diabetes mellitus and hypothyroidism.

ACTH exerts a profound effect upon many of the somatic metabolic processes. It might cause the further spread of tuberculosis, increase in the non-protein nitrogen of the blood, acute psychoses might be aggravated, Cushing's syndrome is worsened, active peptic ulcer perforates, sodium retention, while in diabetes patients insulin requirements might be increased.

In individuals with rheumatoid arthritis and other collagen conditions under ACTH treatment, several side effects have been observed such as acne, keratosis pilaris, muscular weakness, oedema, amenorrhea, impairment of carbohydrate tolerance, negative nitrogen balance, alkalosis, etc.

Unlike ACTH, cortisone when administered, it does not stimulate the adrenal cortex, and so serves as a replacement therapy (ACTH stimulates the adrenal cortex to secrete cortisone). A marked immediate reduction of the eosinophil count is caused by cortisone administration, together with a lesser reduction in the lymphocyte count and an increased total leucocytic count. Also elicits a mild hyperglycemia, alters fat distribution and produces mental changes of a varying degree.

Many synthetic cortisone derivatives have been produced with milder side effects such as insomnia, gastric distress and ulcers.

Concerning the suprarenal glands, the English physician George Oliver made in 1893 a drug which he said that if a minute dose of it was given to a person, then his state will turn upside down, acquiring severe fright, pale face, rapid pulse, excessive sweating, followed by tremors and elevation in his blood pres-

sure. That compound was an extract of the suprarenal gland. In 1903 adrenalin was isolated from this extract, thus becoming the first known hormone, and was prepared synthetically from coal tar.

Reproductive processes are regulated by a system of hormonal control which is complex in the male and very complex in the female. The effects produced by castration of males have been known since the dawn of history. The ancient Egyptians knew a great deal about the sexual organs in both the male and the female and the way pregnancy occurs and a lot about the foetus, as could be understood from Ebers medical papyrus.

In 1849 Berthold discovered that grafting (i.e. transplantation of the testes) produced noticeable growth in the capon's comb (i.e. the castrated cock) during his experiments on chicken, whereas C. Brown Sequard in 1885 stated that the injection of testicular extracts produced remarkable beneficial effects in old men. Their work helped of start endocrine therapy. Voronoff stated that remarkable rejuvenation could be produced by grafting anthropoid testicles into elderly gentlemen.

The term androgen was applied to substances which causes development of the secondary sex characteristics in immature or castrated males. Many androgens have been isolated and synthesised, but the two most important are testosterone and androsterone.

Testosterone is the most active and was first isolated from Bull's testes, and excreted in the urine as androsterone (it was also isolated from male and female urine and also from the adrenal (glands)). Later, it was found that testosterone and

androsterone were chemically related to corticosterone and progesterone.

In 1929 Harrow and Funk could detect the presence of the male sex hormones in men's urine, while Coach could in the same year calculate the physiological quantity of the androgens. In 1931 Butenandt could prepare androsterone in a crystalline form. Overdosage of androgens produces water retention and edema. Concerning the female sex hormones, they are of two types, associated with ovarian function: oestrogenic substances and substances with progesterone activity.

Oestrogens produce oestrus (or heat) in ovariectomised animals. They occur naturally, the most important being oestradiol and oestrone. In 1900 Steinach tried to cure infertility in women by injecting them with an extract of the ovaries. Adler was able in 1912 to increase the development of the uterus using ovaries extract. In 1922 Frank showed that the secretion of the ovaries contains a hormone, and finally in 1923 Allen Indisi was able for the first time to calculate the oestrogenic proportions. Also in 1923 Allen and Doisy observed that an alcoholic extract of the ovaries was capable of producing oestrus. Aschheim in 1927 together with Zondek discovered that the oestrus-producing hormone was excreted in the urine during mammalian pregnancy. Doisy et al in 1929 in

America and Butenandt also in 1929 in Germany independently and almost simultaneously announced the crystallisation of estrone.

It is of interest to note the relationship between the structures of the female sex hormone, the bile acids, cardiac glycosides, carcinogenic hydrocarbons, vitamin D and the male sex hormone.

In 1938 Dodds and his co-workers synthesised diethylstilbestrol, having the same therapeutic effects as the natural oestrogens. Also other oestrogens have been synthesised such as hexoestrol, dienestrol and many other ethylene derivatives with oestrogenic activity such as triphenylchloroethylene with prolonged action.

Large doses of oestrogenic substances cause an inhibition of pituitary activity and this is the mechanism by which lactation is suppressed. Stilboestrol, hexoestrol and dienestrol produce nausea and vomiting.

Concerning progesterone, it is liberated by the corpus luteum and its chief function is to prepare the uterus for the fertilised ovum, thus when pregnancy occurs, progesterone stabilizes the uterus and renders the uterine muscle insensitive to oxytocin and inhibits further ovulation. Thus defective progesterone production causes abortion in the early stages of pregnancy.

REFERENCES

- | | | |
|-------------------------|------|--|
| 1- Krantz & Carr | 1958 | Pharmacologic principles of Medical Practices, 4th Edn', Baltimore, U.S.A. |
| 2- Wilson & Schild | 1955 | Clark's Applied Pharmacology, 8th Edn., London. |
| 3- Sir Stanley Davidson | 1958 | The Principles and Practice of Medicine; 4th Edn., London. |
| 4- Hassan kamal | 1967 | Dictionary of Pharaonic Medicine; 1st Edn', Cairo, Egypt. |

सारांश

सम्पूर्ण इतिहास में हारमोन्स (अंतःस्राव)

- समीर याह्या अल गम्माल

प्राचीनतम काल से मानव की यह धारणा रही है कि उसके शरीर के विभिन्न अंगप्रत्यंगों में एवं पशुओं के भी विभिन्न अंगों में चमत्कारी तथा प्रभावशाली रोगोपचारक तत्त्व होते हैं, अतः वह इन विभिन्न अंगों का सेवन करके अपने व्यक्तित्व को संपुष्ट कर सकता है । उस मानव की यह भी धारणा थी कि उसकी कायिक व्याधियां तत्संबंधित अंगों में उन रोगों से संबन्धित कुछ न कुछ न्यूनताओं के कारण उत्पन्न होती हैं । अतः उसने विभिन्न जानवरों के उसी प्रकार के अंगप्रत्यंगों से उन उन व्याधियों का उपचार किया ।