The Endocrine Glands in Health and Disease

BY A. H. FRANK

SOME of the most extraordinary discoveries of modern medicine are those concerned with the endocrine glands and the hormones they secrete. These glands act as a complicated, delicate set of controls over many vital bodily processes. Some of the hormones have remarkable results, both experimentally and in medical practice, and the future will undoubtedly see further developments.

IN A NORMAL BODY the endocrine glands with their secretions function as a very delicately balanced mechanism. An excessive or deficient secretion of one or more of these glands may lead to an abnormal or diseased condition. Many such conditions are now recognized, several of which, such as diabetes, goiter, cretinism, and sexual impotency, may be successfully treated. This is true of man more than of animals. Some secretions are also being studied with the expectation of increasing certain desirable bodily functions beyond what is considered normal.

All animals have endocrine glands. There are nine of them: The pituitary gland, which is located at the base of the brain; the pineal body, also in the brain; the thyroid, parathyroid, and thymus glands, located in the neck; the adrenal glands, in the abdominal cavity near each kidney; the pancreas, also in the abdominal cavity; and the testicles in the male and ovaries in the female. Because the secretions of these glands are emptied directly into blood vessels within themselves, instead of passing through excretory ducts as in ordinary glands, they are also known as ductless glands or glands of internal secretion.

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Each of the endocrine glands secretes one or more substances called endocrines, or hormones. The secretions are usually in very minute quantities and are normally formed as needed through nervous impulse or the direct action of one endocrine upon a gland secreting another endocrine. In particular, the hormones control sexual growth and the various stages of reproduction.2

The functions of some of the endocrine glands have been recognized for years, but only recently have the particular stimulating substances been recovered from them in pure chemical form. The Bible refers to castrated men (eunuchs), and the changes in physical make-up and behavior following castration are commonly known; in animal husbandry it is common practice to castrate young bulls, rams, boars, and roosters to improve the tenderness and tastiness of the meat. But the extraction from the testicles of the hormone responsible for male physical characteristics was first made in chemical form in 1935.3 The action of this substance is proved by the fact that continued treatment of castrated animals and men with it results in the return of male characteristics and conformation.

As will be noted in the following description of the various endocrine glands and their functions, the actions and interactions of the various hormones are very complex. Though much has been learned about the nature of the endocrines during the last 15 years, only a beginning has been made in the discovery and application of remedies involving them. This is due in part to the difficulty of obtaining many of these substances in pure form in sufficient quantities for extended experimentation, since the endocrines are not stored in the glands but are formed as needed and released immediately. Since the various hormones are fortunately identical in all animal species, these substances can be obtained from animals killed in abattoirs.

In view of its past accomplishments and the vast amount of work being done at present, endocrinology holds promise of great achievements in the future, especially in the purification and possible synthetic preparation of hormones and their application in medical treatment.

THE PITUITARY GLAND

The pituitary gland is unquestionably the master gland of the body. It consists of two parts, a larger anterior lobe and a smaller posterior lobe. It is located at the base of the brain in a bony cavity and is surrounded by a rich supply of blood vessels.

In the cow it is about 1 inch in diameter and in the rat about \( \frac{1}{16} \) of an inch. Its secretions are protein in nature and are so complex that chemists have not been able to analyze them. The anterior lobe is the master part. Eleven or more secretions have been attributed to it alone.

2 Allen, Edgar. ed. Sex and Internal Secretions; a Survey of Recent Research. 1348 pp., illus. Baltimore. 1939.
SECRETIONS FROM THE ANTERIOR LOBE

Gonadotropic Hormones

The development of such sex characteristics as body conformation and voice, and in the female the estrus cycle, which includes the ripening of the ovum, or egg, in the ovary and its passage into the uterus, or womb, is directly or indirectly the result of stimulation by hormones secreted by the anterior lobe of the pituitary gland. Two of these are the gonadotropic hormones, so-called because they act on the gonads (ovaries in the female and testicles in the male). They are known as the follicle-stimulating principle, or prolactin A, and the luteinizing principle, or prolactin B.

The ovary contains thousands of minute eggs, and during the first half of each estrus cycle one or more of these is developed through the action of the follicle-stimulating hormone. A covering is formed around the egg, and the whole is called a follicle. As the follicle grows in size its expansion is in the direction of the periphery, or outside of the ovary. Its growth is characterized by an increase in the quantity of fluid, and when mature it has the appearance of a large blister protruding from the surface of the ovary. After ripening, one of two things may happen to the follicle:

1. Normally, the follicle is ruptured by the action of the other gonadotropic hormone, the luteinizing principle, and the ovum is set free to advance into the uterus. After the escape of the ovum from the follicle, the latter becomes filled with yellowish cells and is thereafter known as the corpus luteum, or yellow body. The luteinizing hormone derives its name from the corpus luteum, which it stimulates directly.

2. Abnormally, the follicle may fail to rupture, developing into a cyst. The cyst may remain stationary or increase in size. Other follicles generally develop similarly, and their walls become thickened. The follicular fluid (containing estrogenic hormone, described later) in these cysts may change the normal reproductive cycle to frequent or constant heat. Cystic ovaries, if treated early, may be benefited by the gonadotropic hormones; but chronic cases do not respond satisfactorily to such treatment, and the cysts may have to be broken down mechanically. Sometimes the cysts reform and must again be ruptured. Ovariectomy, or removal of the ovary, is recommended in persistent cases.

An excess of luteinizing hormone may act on an immature follicle to stimulate the production of a corpus luteum before rupture occurs, thus preventing the subsequent release of the egg.

In males the luteinizing principle stimulates the cells in the testicle to secrete the male sex hormone. The luteinizing hormone is predominant in the urine of pregnant women from about the eighth day after missing the last menstrual period to parturition. A test for its presence makes possible the early detection of pregnancy.

After ovulation in the female, if fertilization occurs, the corpus luteum remains active until pregnancy is ended, but if not, it gradually disappears. No further heat periods occur until the corpus
luteum has become inactive. In cattle its disappearance is sometimes sluggish and it must be expelled by pressure of the hand on the ovary before the cow can again come in heat. The luteinizing hormone activates the corpus luteum, and the latter in turn secretes hormones that act directly on the uterus and indirectly on the mammary glands, as described later.

In addition to initiating ovogenesis (ripening of the germ cells in the ovaries of females) and maintaining this ovarian germ-cell activity, the follicle-stimulating principle, prolan A, initiates spermatogenesis (ripening of the germ cells, or spermatozoa, of the testicles) in young males and maintains this activity in mature males. It is used in man and animals to overcome some types of sterility.

When extracts containing this follicle-stimulating hormone are injected into sexually immature animals, precocious sexual maturity is produced. Ovaries of infantile female rats may be increased in weight 10 to 20 times in 96 hours. Young children who suffer from a tumor involving the pituitary, which causes an excessive secretion of this hormone, may reach sexual maturity at 5 years of age or younger.

Between the 42d and 120th days of pregnancy, the blood of pregnant mares is rich in this principle, and a physiological test of their blood serum for the presence of this hormone may be used to determine whether pregnancy exists.

Various preparations rich in gonadotropic principles have been used to overcome sexual sluggishness, especially inactive gonads, in mature animals. Ewes may be brought into estrus with serum from pregnant mares or with pituitary extracts and bred during their nonbreeding season. Some types of sterility in women and animals can be successfully treated with this extract. Overdosage may result in the ripening of abnormally large numbers of eggs. This is undesirable, as there is not enough space in the female reproductive tract for a large number of fetuses to develop, and abortion or mummification of a number of them may follow.

Mammogenic Hormone

The gonadotropic hormones indirectly stimulate the pituitary to secrete other hormones. As already noted, their action upon the ovary stimulates the growth of the follicle and the corpus luteum, and these in turn secrete the two female sex hormones. One action of the female sex hormones is the direct stimulation of the pituitary to secrete the mammogenic principle. The mammogenic principle directly stimulates the growth and development of the mammary gland, in which milk is secreted and stored. The hormone is secreted during each estrus cycle and produces some growth of the mammary gland; but following conception it is secreted continuously and stimulates the complete development of the mammary gland for that gestation period. If an unlimited supply of this hormone were available, it might be possible to grow large udders on all cows.

Lactogenic Hormone

At parturition, or delivery of young, there is a rapid reduction in the secretion of the sex hormones. This may furnish the stimulus
which activates the pituitary to secrete the lactogenic, or milk-stimulating, principle.

The lactogenic hormone initiates milk secretion in the completely developed mammary gland. Both males and females of most species of mammals may be brought to full lactation by injections of this hormone when their mammary glands have been experimentally developed. The stimulus for continued milk secretion is maintained by this hormone. Injections into cows in declining lactation resulted in a pronounced increase in milk and butterfat, but this added stimulus is only of short duration.

**Growth Hormone**

Experimental evidence and observations of certain disease conditions indicate that the pituitary directly influences the growth of animals. By injecting pituitary extracts that contain the active growth principle into growing mice, it is possible to double the normal mature size of the animals.

Pathological conditions of the pituitary, such as tumorous growths, may result in an excessive secretion of the growth hormone. When this occurs in immature animals they grow abnormally large. If it occurs before maturity in man, gigantism (abnormal tallness, 8 feet or over) may be the result. In adults, it produces the condition known as acromegaly, a chronic disease characterized by enlargement of the bones and soft parts of the hands, feet, and face. Retardation of pituitary activity or the destruction of the gland by X-ray checks these conditions, and the injection of sufficient pituitary extract will maintain normal life.

It is fairly evident that the secretion of the growth hormone in normal individuals is controlled through heredity. Inherited characters are transmitted through genes in the female egg and the male sperm cell. The gene responsible for growth of the cells of the pituitary that secrete this hormone may be absent, as has been shown in a colony of dwarf mice. The dwarfism was shown to be due to a single recessive character, dependent upon a single gene. Through microscopic study of the pituitary tissues of these mice in comparison with those of normal mice, it was found that certain cells of the pituitary were absent in the dwarfs. When pituitaries from normal mice were transplanted into these dwarfs they made normal growth. Growth also occurred when the growth hormone extract was injected into the dwarfs. This condition can occur in both man and animals. Cases of human pituitary infantilism or dwarfism occur frequently where the pituitary has been destroyed by disease processes. The injection of pituitary extracts containing the growth principle in proper amounts restores normal growth in these individuals.

The importance of careful selection of individual animals for breeding purposes is clearly seen, since the quantity of growth hor-
Mone secreted by an immature animal evidently determines the rate and extent of its growth. In the future it may be possible to run a quantitative test for the growth hormone and eliminate undesirable animals at birth.

**Other Anterior-Lobe Hormones**

There is evidence that the anterior lobe of the pituitary gland may secrete an active principle (parathyrotrropic hormone) that influences the activity of the parathyroids in calcium metabolism.

The outer, or cortical, portion of the adrenal glands (to be described later), which is essential to the maintenance of life, is under the influence of the adrenotropic hormone of the pituitary gland. In animals with the pituitary removed, the cortical portion of the adrenal glands becomes inactive.

Carbohydrate metabolism is known to be influenced by a hormone secreted by the pituitary. Following injections of active pituitary extracts the blood sugar increases considerably, while removal of the pituitary causes the blood sugar to fall 50 percent below normal. Some forms of obesity (those in which people weigh 600 pounds or more) are attributed to glandular dysfunctions or upsets, especially dysfunctions of the anterior pituitary.

There are indications that the digestion and assimilation of fats and proteins may be influenced by anterior-pituitary hormones.

An anterior-pituitary principle (the thyrotropic hormone) activates the thyroid gland to secrete the thyroid hormone, thyroxine, described later. In men and animals with the pituitary removed the thyroid becomes inactive.

The secretion of insulin by the pancreas is influenced by the pituitary. In most animals and in man, the disease diabetes mellitus, with its characteristic symptoms of an increased excretion of urine of high sugar content, can be artificially produced by removal of the pancreas. If the pituitary is also removed, the sugar level approaches normal; but if pituitary extract is injected into an animal without the pancreas or pituitary the original condition of excess sugar is again produced. The addition of pituitary extract to insulin has improved the general well-being of some diabetic people.

**Secretions From the Posterior Lobe**

**Pituitrin Hormone**

The posterior lobe of the pituitary secretes the hormone pituitrin. Pituitrin may be split into two active principles, both of which act to contract the smooth muscles of the body. One, oxytocin, stimulates the uterus to contraction. Its action is variable, and it is effective in some mammals only near the end of pregnancy. It is used in difficult labor cases to initiate or to increase the power of uterine contractions. If too much is given, the contractions may be too severe and persistent.
The other principle, vasopressin, activates the muscular tissue of the capillaries and arterioles, or small blood vessels, and thus induces a rise in blood pressure. It increases peristalsis, the wavelike motion of the intestines, by contracting the intestinal muscles. In the dairy cow, it is responsible for the letting down of the milk. Manipulation of the udder and teats at the beginning of milking stimulates the release of this hormone. By contracting the muscles of the udder, it forces the milk into the larger milk channels and cisterns, where it can be readily removed. Its stimulus is short-lived, so a fast milker can obtain more milk than a slow one.

The kidneys are influenced directly by the posterior lobe through its stimulation of the filtering mechanism. Removal or destruction of the posterior pituitary leads to the disease diabetes insipidus, a chronic condition marked by great thirst and passage of large amounts of urine with no excess of sugar.

THE TESTICLE

The testicle has two major functions: (1) Production of spermatozoa, which is seasonal in the majority of animals but continuous in man, monkey, and most of the domestic animals; and (2) the secretion of the male sex hormone, testosterone. In most species, with the exception of birds, the testicles are located in the scrotum, which is outside of the body cavity proper. As previously stated, their activities are under the direct influence of the pituitary.

TESTOSTERONE HORMONE

The testicles begin to secrete testosterone actively at the time of puberty, or sexual maturity. This hormone induces the development of secondary sex characters and stimulates the accessory male sex glands, the prostate, seminal vesicles, and Cowper’s gland. Small or infantile genitalia of immature and mature men may be grown to normal size or larger by the injection of this hormone, and in some cases fertility is restored in sterile males by the simultaneous injection of prolan A.

Sexual desire may be enhanced in subnormal and castrated males by the injection of this hormone. Its continuous injection into castrates enables them to perform the copulatory act successfully and restores the characteristic secondary sex characters in long-standing cases. It also tends to correct the castration atrophy (drying up) of the adrenal glands and restores them to normal condition.

Testosterone has been chemically analyzed and synthesized, so that it is available in pure form. It has been used successfully in correcting cryptorchidism (failure of the testicle to descend into the scrotum) in boys and young men; testicles not descending during such treatment are generally retained by mechanical impediments. It is antagonistic to the female sex hormone, estrogen, which induces heat and female characteristics in the female. The injection of testosterone will prevent heat, and prolonged injections produce male characteristics in normal females.
OVARIES

The ovaries, two in number, are the reproductive glands of the female. They are located in the abdominal cavity, one on each side, and are connected to the uterus, or womb, by a tube which serves as a passage channel for the eggs, or ova. Their functions are threefold: (1) Production of the egg; (2) production of the follicle, which secretes the female sex hormone, estrogen; and (3) production of the corpus luteum, which secretes the other female sex hormone, progesterone. In normal females ovarian activity, which is under the influence of the anterior pituitary, is exhibited in rhythmic cycles, subject to interruption by pregnancy.

ESTROGEN HORMONE

The fluid within the ovarian follicles of normal females and the blood, urine, and amniotic fluid (contained in the sac that surrounds the embryo) of pregnant mammals are rich sources of estrogen. Small traces have also been detected from other sources. Estrogen has been analyzed chemically and prepared synthetically.

In the nonpregnant female estrogen is secreted by the developing follicle, previously described, during half of the estrus cycle (the changes that take place from the beginning of one heat period to the beginning of the next). Ripening of the follicle and the height of estrogen production is characterized by the onset of heat in the female. It also induces a new growth of the epithelium, or lining cells, of the uterus and vagina. A deficiency of estrogen is manifest in some animals. A large percentage of mares are known to pass through estrus cycles without showing signs of heat, although ovulation (releasing of the egg) occurs at the normal time, as proved by mares becoming pregnant following artificial insemination. Estrogen induces the development of the secondary sex characters of the female, about the most noticeable of which are the characteristic plumage of birds and a certain refinement of stature and features in some mammals. During the cycle, as already indicated, it stimulates the pituitary to secrete mammorgen to a limited extent.

In most animals the egg or eggs are expelled from the ovary during or immediately following estrus. Primates (man and monkey) do not outwardly express estrus, but their reproductive tracts pass through similar cyclic changes. Estrus may be induced by the injection of estrogen in both normal females that do not come into heat and those with their ovaries removed. It acts directly upon the vagina and uterus, inducing a new epithelial growth similar to that of the normal cycle.

Because of its action on the epithelium, estrogen is used to treat gonorrhea in young girls, and it should be beneficial in diseases that affect the epithelium of the vagina and the uterus of animals. Large injections immediately following conception (fertilization of the egg) will terminate pregnancy. The presence of this hormone during pregnancy inhibits the pituitary from secreting the follicle-stimulating principle.
PROGESTIN HORMONE

Immediately following rupture of the follicle, the corpus luteum begins to grow into the follicular cavity under the stimulus of the luteinizing hormone (prolan B) of the pituitary. It immediately begins to secrete progestin, which stimulates an increase in blood supply and further development of the epithelium of the uterus in preparation for implantation or embedding of the egg, if fertilized. Small amounts of estrogen are also secreted, which act with the progestin to further stimulate the pituitary to secrete mammogen. When the male sperm cell unites with the ovum, the latter becomes attached to the wall of the uterus. This implantation of the fertilized egg furnishes a stimulus to the pituitary to secrete prolan B and maintain the corpus luteum for the duration of pregnancy. With advancement of pregnancy, an increase of estrogen, together with the progestin, stimulates the maximum secretion of mammogen, and the mammary gland is completely developed.

In sterile cycles the corpus luteum is short-lived, and the stimulus from estrogen and progestin soon ceases. This is followed by menstruation in primates, while there is no outward sign in other mammals. A new cycle begins with the growth of a new follicle.

Abortions and resorptions (absorption of the embryo) that occur during early pregnancy may be due to a deficiency of progestin. The corpus luteum may be slow to develop and thus fail to prepare the uterus for implantation.

THE PARATHYROID GLANDS

The parathyroids are ductless glands that in large animals are about as large as a grain of wheat. They are two to four in number and are located one or two under each lobe of the thyroid gland. Parathormone is produced by the parathyroids and maintains the equilibrium between the insoluble calcium and phosphorus compounds in the skeleton and the soluble compounds of these essential minerals in the blood. Extracts are used in treating cases of reduced secretion of the hormone (hypoparathyroidism).

THE ADRENAL GLANDS

The two adrenal glands are located in the abdominal cavity, one in front of each kidney. They are ductless and consist of two parts, the medullary (inner) and cortical (outer) portions.

The hormone adrenin is secreted by the medullary part of the adrenal glands. Its action is similar to that of pituitrin. It is used extensively in cases of shock as an indirect heart stimulant and to check hemorrhages by contracting the muscles of the small blood vessels.

The hormone cortin, which is essential to the maintenance of life, is contained in the cortical portion of the gland. Extracts of this portion have been used to maintain life in animals after the glands are removed. This hormone is similar to testosterone in its chemical
make-up and its antagonistic reaction to estrogen. When tumorous
growths of the adrenal glands in young girls cause an excessive secre-
tion, this antagonism to estrogen is demonstrated by the produc-
tion of male characteristics, such as growth of beard on the face,
coarseness of voice, cessation of menstruation, and decreased modesty.
The condition is alleviated when the tumor is removed.

Addison’s disease, which is characterized by bronzelike pigmentation
of the skin, severe prostration, progressive anemia, low blood pressure,
diarrhea, and digestive disturbances, is due to a decreased secretion
or functioning of the cortical portion of the adrenal gland. The
disease can be corrected in most cases by injections of cortin.

THE THYROID

The thyroid is a ductless gland resembling a tiny shield in shape.
It is located in front and on both sides of the windpipe. The familiar
enlargement in the neck called goiter is an enlargement of this gland.

The thyroid, as stated previously, is stimulated by the pituitary to
secrete the hormone thyroxin, which controls the energy output, or
metabolism, of the body. Chemical analysis shows that thyroxin
contains large amounts of iodine. An increased production of thy-
roxin gives the individual an excessive amount of energy. The met-
abolic rate may be doubled by injection of thyroxin. Its injection
into rams has been found to activate their sexual functioning and
enhance the production of fertile semen during the nonbreeding sea-
son, summer. Practical use of the method would materially increase
the possibility of getting early lamb crops by rendering the rams
fertile at an earlier date than their normal breeding season. In
hibernating animals the thyroid diminishes in size and practically
ceases activity during hibernation. The injection of thyroxin inter-
rupts the hibernal sleep. An overactive gland may be corrected in
part by surgical removal of a portion of the tissue.

A decreased secretion of thyroxin makes the individual sluggish.
The metabolic rate may be decreased at least half by removal of the
gland. Animals born without the thyroid or those in which it be-
comes inactivated during infancy fail to develop normally in men-
tal, physical, and sexual activity. In children this is known as
cretinism. A similar condition in adults is known as myxedema, a
disease characterized by the decreased function of the thyroid gland
and marked by dropylike swelling, especially of the face and hands,
and a general slowing-down or sluggishness. In this condition the
gland may become quite small. All cases of cretinism and myxedema
are benefited and most cases may be cured by the continuous adminis-
tration of thyroxin. Feeding the dried gland provides a satisfactory
supplement for the normal gland. In some cases of cretinism the
addition of the growth principle from the pituitary may prove
beneficial.

A deficiency of iodine in the diet may result in a decreased func-
tioning of the thyroid gland. This is discussed in the articles on nutri-
tional diseases in this volume.
THE PANCREAS

The pancreas is located in a loop of the small intestine adjacent to the stomach. It has a twofold function. It secretes digestive juices, which enter directly into the intestine, and the hormone insulin, which enters the blood stream. Insulin is secreted by small islets of cells scattered throughout the connective tissue of the pancreas.

When the secretion of insulin falls below the normal level or ceases, diabetes mellitus is produced. The carbohydrate metabolism is badly upset, and the patient is unable to utilize sugars, large amounts of which appear in the blood and are eliminated in the urine, which is decidedly increased in volume. Insulin for the treatment of the disease is now available in both crystalline form and water solution.

An oversecretion or an injection of insulin into normal animals results in a decrease of sugar in the blood and if continued will lead to coma. An increase in the blood-sugar concentration appears to be a stimulus for insulin secretion.

THE PINEAL GLAND

The pineal is a ductless gland located in the central part of the brain. Injection of pineal extracts and implants of the gland have no effect on growth and development of normal animals. There is some indication, however, that daily administration of 1 cubic centimeter of pineal extracts to successive generations of rats has resulted in an increase in the frequency of breeding and a retardation in the rate of growth of the offspring.

THE THYMUS GLAND

The thymus is an irregular glandular mass extending from the thyroid gland to the thorax or chest; it is very prominent and well-developed in young animals, especially calves, in which it is called sweetbread. It becomes degenerate at the time of maturity. Experiments performed to establish the action of the thymus on growth and sexual development have led to conflicting results. The majority of workers have found it to be negligible. There is some indication that the offspring of successive generations all of which have received injections of thymus extracts may grow to maturity at a faster rate but do not exceed normal size.

ANTIHORMONES

Certain experimental evidence indicates that the hormones may be held in check or inactivated by antihormone principles. For instance, after long-continued injection of prolan B into an animal, the blood serum is found to contain antibodies to this hormone, and the injection of blood from this animal into a normal female will prevent ovulation and the growth of the corpus luteum.
This should be a warning that the wholesale, repeated injection of animals with hormones may aggravate rather than alleviate certain troubles. To apply any hormone treatment successfully, it is first essential to determine the cause of the condition that needs to be corrected and then choose the appropriate treatment. The diagnosis of any hormonal difficulty may be complicated by an unbalanced condition among various hormones as well as by the presence of antibodies.